The National Clinical Guideline Centre

acute and chronic conditions

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Unstable Angina and NSTEMI:

the early management of unstable angina and non-ST-segment-elevation myocardial infarction

Clinical guideline 94

Royal College of Physicians

Setting higher medical standards

CONTENTS

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GUIDELINE DEVELOPMENT GROUP MEMBERS

Professor John Camm (Chair)
BHF Professor of Clinical Cardiology, St. George's University of London

Dr Huon Gray
Clinical Advisor, NCGC; Consultant Cardiologist, Southampton University Hospital

Mr Sotiris Antoniou
Principal Cardiac Pharmacist, Barts and the London NHS Trust and Lead Pharmacist for North East London Cardiac and Stroke Network

Ms Jenny Cadman
Cardiac Rehabilitation Service Manager, Senior Nurse in Cardiology, Luton and Dunstable

Dr Emily Crowe
Senior Research Fellow, from May 2008

Dr Mark de Belder
Consultant Cardiologist, Middlesbrough

Dr Jose Diaz
Research Fellow, until May 2008

Mr David H. Geldard
Patient/Carer representative; Immediate Past president, Heart Care Partnership (UK)

Ms Lina Gulhane
Senior Information Scientist

Dr Robert Henderson
Consultant Cardiologist, Nottingham University Hospitals

Professor Marjan Jahangiri
Professor of Cardiac Surgery, London

Ms Taryn Krause
Senior Project Manager, from November 2008

Miss Kate Lovibond
Health Economist, NCGC

Mr Gavin Maxwell
Patient/Carer representative, Patient and Carer Network, RCPL

Dr Francis Morris
Accident and Emergency Physician, Sheffield

Mr Alun Roebuck
Cardiology Nurse Consultant, Sunderland

Ms Nicola Sloan
Research Fellow, July 2008-March 2009

Ms Claire Turner
Senior Project Manager, until November 2008

Professor S. Richard Underwood
Professor of Cardiac Imaging, London

Mr Mark Whitbread
Clinical Practice Manager/Senior Paramedic/Cardiac Lead Medical Directorate, London Ambulance Service NHS Trust

Declaration of interests

Professor John Camm
- Chaired a session at the AHA meeting supported by Sanofi Aventis relating to Clopidogrel (2008)
- Received travel grant from Sanofi Aventis to travel to the US (2008).

Dr Huon Gray
- Received honoraria from Lily advisory board (11/07)
- Received honoraria from Medicines company for advisory board on STEMI, not UA or NSTEMI (12/2008)

Mr Sotiris Antoniou
- Attended Advisory Board for Sanofi Aventis (re: Clopidogrel) and Lilly (re: Prasugrel) (2007)
- Received a grant from Takeda to undertake a diabetes study (2008)
- Received several travel grants from pharmaceutical companies for unrelated areas (2007)
- Wrote an editorial response to OASIS-5 trial (unpublished).
- Attended advisory boards regarding anticoagulant therapy prior to joining NICE GDG for both Sanofi Aventis and GSK.
- Chair of the Cardiac committee of United Kingdom Clinical Pharmacy Association (UKCPA) (2005 – present).

Ms Lina Bakhshi
- None declared.

Ms Jenny Cadman
- None declared.

Dr Emily Crowe
- None declared.

Dr Mark de Belder
- Attended an Advisory Board for Cordis and Conor/Cordis (stent manufactures), Nycomed and Boehringer-Ingelheim (PCI-related pharmaceutical companies) (2005-2009)
- Chaired an Advisory Board for Sanofi-Aventis/Bristol-Myers Squibb (2007-2009)
- Chaired and spoke at a symposium sponsored by Daiichi-Sankyo/Lilly (2007-2009)

- Received payment for professional work done as UK PI for the Finesse (Centocor) Assesnt 4 PCI (Boehringer-Ingelheim) trials (2008)
- Working as UK PI for the REDEEM trial (Boehringer Ingleheim) (present)
- President of the British Cardiovascular Intervention Society (present)
- MDB declared that he had chair a pharmaceutical company sponsored symposium and attended an advisory board for SKF on matters relating to antiplatelet therapy.

Dr Jose Diaz
- None declared.

Mr David H. Geldard
- None declared.

Dr Robert Henderson
- Received honoraria for Advisory Board from Cordis UK (2007) and Abbott Vascular (2009)
- Received travel grants to attend conferences from Cordis UK and Boston Scientific (2008), Daichii Sankyo/Lilly (2008), Abbott Vascular (2009).
- Member of the British Cardiovascular Intervention Society Council (2006 – present)

Professor Marjan Jahangiri
- None declared.

Ms Taryn Krause
- None declared.

Miss Kate Lovibond
- In 2007 worked for a healthcare communications agency on one-off projects:
  - Enoxaparin (Lovenox; Sanofi-Aventis) – non-ACS-related project
  - Fondaparinux (Arixtra; GlaxoSmithKline) – ACS-related health economics project
  - Valsartan (Diovan, Diovan HCT, Exforge; Novartis) – non-ACS-related project

Mr Gavin Maxwell
- None declared.

Dr Francis Morris
- None declared.

Mr Alun Roebuck
- Launched a public and private industry partnership in cardiac genetics involving several educational grants from pharmaceutical companies that go directly to trust and are ACS related.

Ms Nicola Sloan
- None declared.

Ms Claire Turner
- None declared.

Professor S. Richard Underwood
- Lead clinician at Quantum Inhealth (private healthcare section), Nuclear medicine imaging clinic (present)

- Received honoraria for Advisory Board from GE Healthcare (25/06/09)
- Received research funding from GE Healthcare and Cardiovascular Theraputics Inc. (2007-08)
- Received training course funding from CE Healthcare and Bristol Myers Squibb (Feb 2008 + Feb 2009)
- Senate member, ESC Working Group in nuclear cardiology and CT (2005 - current)

Mr Mark Whitbread
- None declared.

Mr Jo Smith (deputy for Mark Whitbread, 26 February 2009)
- None declared.

Professor Keith Fox (attended GDG 8 as an invited expert)
- Received hororaria for lectures from Sanofi-Aventis, GSK, MSD
- Received departmental grants from Sanofi-Aventis, MSD, GSK, Lilly, University of Massachusetts, Duke University

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Mr John Birkhead, MINAP investigator

Mr Gordon Fitzgerald, GRACE investigator

Ms Susan Tann, Co-ordinator, NCGC

Mr David Wonderling, Health Economics Lead, NCGC

ACE Inhibitor	Angiotensin converting enzyme inhibitor
ACC	American College of Cardiology
ACS	Acute Coronary Syndromes
AF	Atrial fibrillation
ARA	Angiotensin receptor antagonist
CI	Confidence interval (95% unless stated otherwise)
CV	Cardio-vascular
ECG	Electrocardiogram
ESC	European Society of Cardiology
GDG	Guideline development group
GPI	Glycoprotein Inhibitor
GRACE	Global registry of acute coronary events
ICER	Incremental cost-effectiveness ratio
IV/iv	Intravenous
LMWH	Low molecular weight heparin
MA	Meta-analysis
MD	Mean difference
MDT	Multidisciplinary team
MHRA	Medicines and Healthcare products Regulatory Agency
MI	Myocardial infarction
NCC–CC	National Collaborating Centre for Chronic Conditions
NCGC	National Clinical Guideline Centre for Acute and Chronic Conditions
NHS	National Health Service; this guideline is intended for use in the NHS in England and Wales
NICE	National Institute for Health and Clinical Excellence
NR	Not reported
NS	Not significant (at the 5% level unless stated otherwise)
NSTEMI	Non-ST-elevation myocardial infarction
OR	Odds ratio
PPV	Positive predictive value
QALY	Quality-adjusted life-year
QoL	Quality of Life
RCT	Randomised controlled trial
RR	Relative risk
SMD	Standardised mean difference
SR	Systematic review
SS	Statistically significant
STEMI	ST-elevation myocardial infarction
TIMI	Thrombolysis in myocardial infarction
UA	Unstable Angina
UFH	Unfractionated heparin
UH	Unfractionated heparin
WMD	Weighted mean differences

Clinically significant improvement

Some trials define a dichotomous outcome of clinically significant pain relief as having been achieved above a specific threshold on a pain score, e.g. pain. However, there is no standard threshold and each such trial should be considered individually.

Cohort study A retrospective or prospective follow-up study. Groups of individuals to be followed up are defined on the basis of presence or absence of exposure to a suspected risk factor or intervention. A cohort study can be comparative, in which case two or more groups are selected on the basis of differences in their exposure to the agent of interest.

Confidence interval (CI) A range of values which contain the true value for the population with a stated 'confidence' (conventionally 95%). The interval is calculated from sample data, and generally straddles the sample estimate. The 95% confidence value means that if the study, and the method used to calculate the interval, is repeated many times, then 95% of the calculated intervals will actually contain the true value for the whole population.

Cochrane review The Cochrane Library consists of a regularly updated collection of evidence-based medicine databases including the Cochrane Database of Systematic Reviews (reviews of randomised controlled trials prepared by the Cochrane Collaboration).

Cost-consequence analysis A type of economic evaluation where, for each intervention, various health outcomes are reported in addition to cost, but there is no overall measure of health gain.

Cost-effectiveness analysis An economic study design in which consequences of different interventions are measured using a single outcome, usually in natural units (for example, life-years gained, deaths avoided, heart attacks avoided, cases detected). Alternative interventions are then compared in terms of cost per unit of effectiveness.

Cost-utility analysis A form of cost-effectiveness analysis in which the units of effectiveness are quality adjusted life-years (QALYs).

Incremental cost The cost of one alternative less the cost of another.

Incremental cost-effectiveness ratio (ICER) The ratio of the difference in costs between two alternatives to the difference in effectiveness between the same two alternatives.

Incremental net benefit (INB) The value, in monetary terms, of an intervention net of its cost compared with a comparator intervention. The INB can be calculated for a given cost-effectiveness threshold. If the threshold is £20,000 per QALY gained then the INB is calculated as: (£20,000 x QALYs gained) – Incremental cost.

Meta-analysis A statistical technique for combining (pooling) the results of a number of studies that address the same question and report on the same outcomes to produce a summary result.

Methodological limitations Features of the design or reporting of a clinical study which are known to be associated with risk of bias or lack of validity. Where a study is reported in this guideline as having significant methodological limitations, a recommendation has not been directly derived from it.

Multivariate Analysis of more than one variable at a time. Takes into account the effects of all variables on the response of interest.

Observational study Retrospective or prospective study in which the investigator observes the natural course of events with or without control groups, for example cohort studies and case-control studies.

Odds ratio A measure of treatment effectiveness: the odds of an event happening in the intervention group, divided by the odds of it happening in the control group. The 'odds' is the ratio of non-events to events.

p values The probability that an observed difference could have occurred by chance. A p value of less than 0.05 is conventionally considered to be 'statistically significant'.

Quality of life (QoL) Refers to the level of comfort, enjoyment and ability to pursue daily activities.

Quality-adjusted life-year (QALY) A measure of health outcome which assigns to each period of time a weight, ranging from 0 to 1, corresponding to the health-related quality of life during that period, where a weight of 1 corresponds to optimal health, and a weight of 0 corresponds to a health state judged equivalent to death; these are then aggregated across time periods.

Randomised controlled trial (RCT) A trial in which people are randomly assigned to two (or more) groups: one (the experimental group) receiving the treatment that is being tested, and the other (the comparison or control group) receiving an alternative treatment, a placebo (dummy treatment) or no treatment. The two groups are followed up to compare differences in outcomes to see how effective the experimental treatment was. Such trial designs help minimize experimental bias.

Sensitivity analysis A measure of the extent to which small changes in parameters and variables affect a result calculated from them. In this guideline, sensitivity analysis is used in health economic modelling.

Stakeholder Any national organisation, including patient and carer groups, healthcare professionals and commercial companies with an interest in the guideline under development.

Statistical significance A result is deemed statistically significant if the probability of the result occurring by chance is less than 1 in 20 ($p < 0.05$).

Systematic review Research that summarises the evidence on a clearly formulated question according to a pre-defined protocol using systematic and explicit methods to identify, select and appraise relevant studies, and to extract, collate and report their findings. It may or may not use statistical meta-analysis.

Technology appraisal Formal ascertainment and review of the evidence surrounding a health technology, restricted in the current document to appraisals undertaken by NICE.

Univariate Analysis which separately explores each variable in a data set.

Utility A number between 0 and 1 that can be assigned to a particular state of health, assessing the holistic impact on quality of life and allowing states to be ranked in order of (average) patient preference.

1 DEVELOPMENT OF THE GUIDELINE

1.1 INTRODUCTION

The development of cholesterol-rich plaque within the walls of coronary arteries (atherosclerosis) is the pathological process which underlies 'coronary artery disease'. However, the clinical manifestations of this generic condition are varied. When the atherosclerotic process advances insidiously the lumen of a coronary artery becomes progressively narrowed blood supply to the myocardium is compromised (ischaemia) and the affected individual will often develop predictable exertional chest discomfort, or 'stable' angina. However, at any stage in the development of atherosclerosis, and often when the coronary artery lumen is narrowed only slightly or not at all, an unstable plaque may develop a tear of its inner lining cell layer (intima), exposing the underlying cholesterol rich atheroma within the vessel wall to the blood flowing in the lumen. This exposure stimulates platelet aggregation and subsequent clot (thrombus) formation.

If the volume of thrombus is sufficient to occlude the lumen of the artery, and this is persistent, then acute ST-elevation (an abnormality of the electrocardiogram) myocardial infarction or 'STEMI' ensues, with progressive death (necrosis) of heart muscle tissue. If the volume of thrombus is insufficient to occlude the artery or does so only temporarily then shortage of blood supply to the affected heart muscle (myocardium) is less severe or is intermittent. In these circumstances there is often some myocardial necrosis, as evidenced by a rise in the cardiac specific serum biomarkers such as troponin; this syndrome is described as 'non-ST elevation myocardial infarction' (NSTEMI). When myocardial ischaemia is present, but without evidence of actual myocardial necrosis (normal serum troponin level), the clinical syndrome is described as unstable angina (UA).

This guideline addresses a variety of issues relating to the management of NSTEMI and UA, conditions which are collectively termed non-ST elevation acute coronary syndromes (NSTEACS). It does not address the management of those with STEMI.

The pathophysiology of coronary atheromatous plaque rupture, described so clearly 30 years ago by Professor Michael Davies[1] and others, underlies most of the advances in the clinical management of those with NSTEACS ever since. It is not surprising that when the importance of platelet aggregation and thrombosis was appreciated research addressed the use of anti-platelet and anti-thrombin drugs, with the number of available agents increasing every year. Also, with the development of coronary artery bypass graft surgery, and subsequently coronary angioplasty with insertion of intracoronary stents, it became possible to improve coronary blood flow and reduce the risk of further coronary ischaemic events.

When the National Service Framework (NSF) for Coronary Heart Disease was published in 2000 it was estimated that in England 1.4 million people suffer from angina, 300,000 have heart attacks, and more than 110,000 die of heart problems every year [2]. Much has improved since then; mortality from myocardial infarction and other cardiovascular causes has declined and inequalities between socioeconomic groups have decreased [3].

However, the number of people admitted with non ST-segment elevation ACS has shown less of a decline and with worrying trends in the incidence of obesity and diabetes, and lifestyles that involve less exercise, the management of these conditions remains a high priority.

Over the last ten years it has become clear that people with acute coronary syndromes of all sorts (STEMI and NSTE- ACS) have quite widely varying outcomes, and much work has gone into defining the clinical components which individually predict this poor outcome (usually defined as mortality in hospital, or at varying periods of follow-up). Scoring systems have been established in an attempt to risk stratify patients and more recent trials of drugs, and other interventions such as coronary angiography and revascularisation, have analysed the effect of an intervention by patient risk group. Broadly speaking, clinical trials have shown that as risk increases the potential for an intervention to give benefit also increases. However, with an increasing number of drugs available that affect blood clotting that with a reduction in ischaemic events has come an increase in bleeding complications, which itself is an important determinant of poor outcome. This has left those managing patients with NSTEACS with a dilemma: should they offer a particular cocktail of drugs, each with individual evidence of benefit, to an individual patient, or will the amount of the cocktail's benefit be offset by the potential for associated complications?

This guideline formally addresses the risk stratification of patients, and the relevance of various clinical trials, to the risk profile of an unselected population with non ST-segment elevation ACS in England & Wales. In this way the guideline defines those who are likely to have a net benefit from an intervention and those where the benefit is either absent, uncertain or not cost-effective.

The optimum outcome for those suffering with ACS depends on them receiving evidence based management throughout the duration of their clinical episode. An episode starts with prompt and accurate diagnosis, and this is addressed as part of the guidance on 'undifferentiated chest pain' (see NICE Clinical Guideline: Chest pain of recent onset: assessment and diagnosis of recent onset chest pain/discomfort of suspected cardiac origin). The episode continues with appropriate care in hospital, the subject of this guidance, but then continues after discharge from hospital with access to rehabilitation, lifestyle changes, secondary preventive medication and maintenance of vascular checks in General Practice. Thus, this guidance addresses an important part of this 'patient pathway' but not the entire pathway itself. Best practice should continue beyond the scope of this guideline and with particular reference to earlier guidance on secondary prevention [4].

1.2 METHODOLOGY

1.2.1 AIM

This piece of guidance was developed by National Collaborating Centre for Chronic Conditions (NCC–CC) whom on 1 April 2009 merged with three other UK collaborating centres to form the National Clinical Guideline Centre for Acute and Chronic Conditions (NCGC). As the evidence for this guideline was reviewed before this merger, the developers will be referred to as the 'NCC–CC' throughout the document for ease of use and remain the same individuals post merger.

The aim of the NCC–CC was to provide a user-friendly, clinical, evidence-based guideline for the National Health Service (NHS) in England and Wales that:

- offers best clinical advice for the management and treatment of acute coronary syndromes (ACS) in adults in primary and secondary care;
- is based on best published clinical and economics evidence, alongside expert consensus;
- takes into account patient choice and informed decision-making;
- defines the major components of NHS care provision for ACS;
- details areas of uncertainty or controversy requiring further research; and
- provides a choice of guideline versions for different audiences.

1.2.2 SCOPE

The guideline was developed in accordance with a scope which detailed the remit of the guideline originating from the Department of Health and specified those aspects of ACS care to be included and excluded.

Prior to the commencement of the guideline development, the scope was subjected to stakeholder consultation in accordance with processes established by NICE[5,6]. The full scope is shown in Appendix A.

1.2.3 AUDIENCE

The guideline is intended for use by the following people or organisations:

- all healthcare professionals
- people with ACS and their carers
- patient support groups
- commissioning organisations
- service providers

1.2.4 INVOLVEMENT OF PEOPLE WITH ACUTE CORONARY SYNDROMES

The NCC–CC was keen to ensure that the views and preferences of people with ACS and their carers informed all stages of the guideline. This was achieved by:

- having two people with ACS as patient representatives on the guideline development group
- consulting the Patient and Public Involvement Programme (PPIP) housed within NICE during the pre-development (scoping) and final validation stages of the guideline project.
- the inclusion of patient groups as registered stakeholders for the guideline

1.2.5 GUIDELINE LIMITATIONS

- NICE clinical guidelines usually do not cover issues of **service** delivery, organisation or provision (unless specified in the remit from the Department of Health).
- NICE is primarily concerned with Health Services and so recommendations are not provided for Social Services and the voluntary sector. However, the guideline may address important issues in how NHS clinicians interface with these sectors.
- Generally, the guideline does not cover rare, complex, complicated or unusual conditions.
- It is not possible in the development of a clinical guideline to complete extensive systematic literature review of all pharmacological toxicity. NICE expect the guidelines to be read alongside the Summaries of Product Characteristics.

1.2.6 OTHER WORK RELEVANT TO THE GUIDELINE

► **Related NICE Technology Appraisals:**

- Clopidogrel in the treatment of non-ST-segment-elevation acute coronary syndrome. NICE technology appraisal guidance 80 (2004). Available from: www.nice.org.uk/TA080

- Myocardial perfusion scintigraphy for the diagnosis of angina and myocardial infarction. NICE technology appraisal guidance 73 (2003). Available from www.nice.org.uk/TA073

- Guidance on the use of coronary artery stents. NICE technology appraisal guidance 71 (2003). Available from: www.nice.org.uk/TA071

- Guidance on the use of drugs for early thombolysis in the treatment of acute myocardial infarction. NICE technology appraisal guidance 52 (2002). Available from: www.nice.org.uk/TA052

- Guidance on the use of glycoprotein IIb/IIIa inhibitors in the treatment of acute coronary syndromes. NICE technology appraisal guidance 47 (2002). Available from: www.nice.org.uk/TA047

- Clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events (review of Technology Appraisal No.90). Publication date to be advised.

- Prasugrel for the treatment of acute coronary syndromes with percutaneous coronary intervention. NICE technology appraisal guidance (October 2009). Available from: http://www.nice.org.uk/nicemedia/pdf/TA182QRG.pdf

- Early high-dose lipid-lowering therapy to avoid cardiac events: a systematic review and economic evaluation. Health Technology assessment 2009; 13(34):1-118

► **Related Interventional Procedures:**

- Off-pump coronary artery bypass (OPCAB). NICE interventional procedure guidance 35 (2004). Available from: www.nice.org.uk/IPG035

►► **Related NICE Clinical Guidelines:**

- Acute chest pain: assessment, investigation and management of acute chest pain of suspected cardiac origin. NICE clinical guideline (publication anticipated December 2009).

- MI: secondary prevention. Secondary prevention in primary and secondary care for patients following a myocardial infarction. NICE clinical guideline 48 (2007). Available from: www.nice.org.uk/CG048

1.2.7 BACKGROUND

The development of this evidence-based clinical guideline draws upon the methods described by the NICE Guideline Development Methods manual [5,6] (see www.nice.org.uk). As of 1 January 2009, the guideline was developed in accordance with the updated NICE Guideline Development Methods manual[6].

The developers' role and remit is summarised in Table 1 below.

Table 1. Role and remit of the developers

National Collaborating Centre for Chronic Conditions (NCC–CC)	The NCC–CC was set up in 2001 and is housed within the Royal College of Physicians (RCP). The NCC–CC undertakes commissions received from the National Institute for Health and Clinical Excellence (NICE). A multiprofessional Partners' Board inclusive of patient groups and NHS management governs the NCC–CC. The NCC–CC merged with three other UK collaborating centres on 1 April 2009 to become the National Clinical Guideline Centre for Acute and Chronic Conditions (NCGC-AC)
Technical Team	The technical team met approximately two weeks before each Guideline Development Group (GDG) meeting and comprised a GDG Chair, GDG Clinical Advisor, Health Economist, Information Scientist, Project Manager, and Research Fellows
Guideline Development Group (GDG)	The GDG met monthly (March 2008 to September 2009) and comprised a multi disciplinary team of health professionals and people with acute coronary syndromes, who were supported by the technical team. The GDG membership details including patient representation are detailed at the front of this guideline.
Guideline Project Executive (PE)	The PE was involved in overseeing all phases of the guideline. It also reviewed the quality of the guideline and compliance with the DH remit and NICE scope. Prior to 1 April 2009 the PE comprised the NCC–CC Director, NCC–CC Assistant Director (operations), NCC–CC Assistant Director (implementation), NICE Commissioning Manager, and the NCC–CC Technical Team. Post 1 April 2009 the PE comprised the NCGC Clinical Director, NCGC Operations Director, NICE Commissioning Manager and the NCGC Technical Team
Formal consensus	At the end of the guideline development process the GDG met to review and agree the guideline recommendations.

1.2.8 THE PROCESS OF GUIDELINE DEVELOPMENT

The basic steps in the process of producing a guideline are:

- Developing clinical questions
- Systematically searching for the evidence
- Critically appraising the evidence
- Incorporating health economics evidence
- Developing a health economic model
- Distilling and synthesising the evidence and writing recommendations
- Grading the evidence statements
- Agreeing the recommendations
- Structuring and writing the guideline
- Updating the guideline

► Developing evidence based questions

The technical team drafted a series of clinical questions that covered the guideline scope. The GDG and PE refined and approved these questions, which are shown in Appendix F.

► Searching for and identifying the relevant evidence

The Information Scientist developed a search strategy for each question. Key words for the search were identified by the GDG.

Systematic literature searches were undertaken to identify evidence within published literature in order to answer the clinical questions. Clinical databases were searched using relevant medical subject headings, free-text terms and study type filters. Non-English studies were not reviewed and were therefore excluded from searches.

Each database was searched up to 18th June 2009. One initial search was performed for the whole guideline topic which looked for systematic reviews, guidelines and economic papers in the non-STEMI acute coronary syndrome populations.

The clinical questions were formulated using the PICO (Population, Intervention, Comparison, and Outcome) format and this was used as a basis for constructing a search strategy. Quality assurance of search strategies were approached by checking relevant key papers were retrieved, and amending search strategies if appropriate. The questions, the study types applied, the databases searched and the years covered can be found in Appendix F.

When looking for health economic evidence a whole guideline search looking for economic evidence relating to an ACS population was undertaken on the NHS economic evaluation database (EED) and health technology assessment (HTA) databases with no date restrictions. Additionally, it was run, with a specific economic filter, on Medline and Embase from 2007 to present, to ensure recent publications that may have not yet been indexed by these databases were identified. This was supplemented by an additional search that looked for economic papers specifically relating to revascularisation (PCI or CABG) on the

NHS EED and HTA database as it became apparent that some papers in this area were not being identified through the first search. Additionally, ad hoc searches were carried out for individual questions as required.

Titles and abstracts of retrieved papers were reviewed by the Research Fellow or Health Economist and full papers were ordered for studies potentially relevant to each clinical question. The full papers were reviewed against pre-specified inclusion and exclusion criteria.

Where the guideline updated Technology Appraisals on clopidogrel or glycoprotein IIb/IIIa inhibitors, the inclusion criteria for clinical evidence was RCTs published beginning of 2003 (update of clopidogrel TA) or 2002 (update of glycoprotein IIb/IIIa inhibitors TA) with a sample size ≥250 and at least 60% of the people enrolled given the diagnosis of unstable angina or non-ST-segment-elevation ACS. Where possible, results were reported in the subgroup of patients with unstable angina/ non-ST-segment-elevation myocardial infarction. In addition, the trial should report on the six key clinical outcomes agreed for this guideline (30 day survival, reinfarction, LV function, revascularisation, quality of life, and serious complications). Review papers were checked for additional relevant studies which were then ordered. Additional papers identified by the GDG were ordered and reviewed.

For the remainder of the guideline, inclusion criteria were as above, except there was no restriction on sample size. For areas in which there were no RCTs, other evidence (observational studies, diagnostic studies) were included.

From a health economic perspective studies were prioritised for inclusion if they were from a UK perspective, based intervention effectiveness on data from one or more RCT and these met the clinical data population cut offs (e.g. >60% UA/NSTEMI population). A judgement was made on a question by question basis regarding whether to include studies from a non-UK perspective[a], that used observational evidence or that used data that did not meet the clinical data population cut-offs, depending on the availability and quality of the other evidence.

Full economic evaluations (cost-effectiveness, cost-utility and cost-benefit analyses), cost-consequence analyses and comparative costing studies that addressed the clinical question and included UA/NSTEMI adult patients were included.

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[a] Healthcare processes, and therefore resource use, vary between countries as does the cost of healthcare resources. Due to this, and potentially other factors, the applicability and generalisability of non-UK economic studies may be limited. Studies were prioritised by relevance of setting: 1 = UK; 2 = other primarily public healthcare systems in OECD countries (e.g. EU, Canada, Australia); 3 = primarily private healthcare systems in OECD countries (e.g. US, Switzerland). 4 = non-OECD countries – this was an exclusion criteria.

Studies that only reported cost per hospital (not per patient), or only report average cost effectiveness without disaggregated costs and effects were excluded. Abstracts, posters, reviews, letters/editorials, foreign language publications and unpublished studies were excluded. Studies judged to have an applicability rating of 'not applicable' were excluded. A judgement was made on a question by question basis regarding whether to include studies with a quality rating of 'very serious limitations', although these would usually be excluded.

Any publication date cut-offs applied to the clinical evidence were also applied to the economic evidence.

Exclusion lists were generated for each question together with the rationale for the exclusion. The exclusion lists were presented to the GDG.

► *Appraising the evidence*

The Research Fellow or Health Economist, as appropriate, critically appraised the full papers. In general, no formal contact was made with authors however there were *ad hoc* occasions when this was required in order to clarify specific details. Critical appraisal checklists were compiled for each full paper. One Research Fellow undertook the critical appraisal and data extraction. The evidence was considered carefully by the GDG for accuracy and completeness.

All procedures are fully compliant with the:

- NICE methodology as detailed in the 'Guideline Development Methods – Information for National Collaborating Centres and Guideline Developers' Manual[5,6]
- NCC–CC Quality assurance document and systematic review chart.

► Distilling and synthesising the evidence and developing recommendations

The evidence from each full paper was distilled into an evidence table and synthesised into evidence statements before being presented to the GDG. This evidence was then reviewed by the GDG and used as a basis upon which to formulate recommendations.

Evidence tables are available on the NICE website.

► Grading the evidence statements

See Table 1-1 for the levels of evidence for interventional studies and Table 1-2 for the levels of evidence for diagnostic studies.

Table 1-1. Levels of evidence for intervention studies[5]

Level of evidence	Type of evidence
1++	High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1-	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias*
2++	High-quality systematic reviews of case–control or cohort studies High-quality case–control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal
2+	Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal
2-	Case–control or cohort studies with a high risk of confounding, bias, or chance and a significant risk that the relationship is not causal*
3	Non-analytic studies (for example, case reports, case series)
4	Expert opinion, formal consensus

*Studies with a level of evidence '–' should not be used as a basis for making a recommendation (see section 7.4 of guideline development manual)[5]

Table 1-2. Levels of evidence for diagnostic studies[5]

Level of evidence	Type of evidence
Ia	Systematic review (with homogeneity)[a] of level-1 studies[b]
Ib	Level-1 studies[b]
II	Level-2 studies[c] Systematic reviews of level-2 studies
III	Level-3 studies[d] Systematic reviews of level-3 studies
IV	Consensus, expert committee reports or opinions and/or clinical experience without explicit critical appraisal; or based on physiology, bench research or 'first principles'

[a] Homogeneity means there are no or minor variations in the directions and degrees of results between individual studies that are included in the systematic review.
[b] Level-1 studies are studies:
- that use a blind comparison of the test with a validated reference standard (gold standard)
- in a sample of patients that reflects the population to whom the test would apply.

[c] Level-2 studies are studies that have **only one** of the following:
- narrow population (the sample does not reflect the population to whom the test would apply)
- a poor reference standard (defined as that where the 'test' is included in the 'reference', or where the 'testing' affects the 'reference')
- a comparison between the test and reference standard that is not blind
- case-control design

[d] Level-3 studies are studies that have at least two or three of the features listed for level-2 studies.

► Assessing the cost effectiveness of interventions

It is important to investigate whether healthcare interventions are cost effective as well as clinically effective. That is they offer good value for money. This helps us to get the most health gain from available NHS resources. In any healthcare system resources are finite and choices must be made about how best to spend limited budgets. We want to prioritise interventions that provide a high health gain relative to their cost.

Cost-effective analysis compares the costs and health outcomes of two or more alternative healthcare interventions. The criteria applied to an intervention to be considered cost effective were either:

a) The intervention dominated other relevant strategies – that is, it is both less costly in terms of resource use and more clinically effective when compared to other relevant strategies

b) The intervention cost less than £20,000 per quality-adjusted life-year (QALY) gained compare with the next best strategy

Where health outcomes were not expressed in QALYs or economic evidence was not available the GDG made a judgement based on the available evidence.

The GDG agreed a priority area for original health economic modelling for the guideline. The analysis undertaken looked at alternative combined antiplatelet and antithrombin strategies. See Appendix C for the full report. A summary of relevant results is also included in each relevant chapter of the guideline.

The following general principles were adhered to:

- The GDG was consulted during the construction and interpretation of the model.
- The model was based on clinical evidence identified from the systematic review of clinical evidence.
- Model inputs and assumptions were reported fully and transparently.
- Sensitivity analysis was used to explore uncertainties in model inputs and methods.
- Costs were estimated from an NHS perspective.

► Agreeing the recommendations

The GDG employed formal consensus techniques to:

- ensure that the recommendations reflected the evidence-base
- approve recommendations based on lesser evidence or extrapolations from other situations
- reach consensus recommendations where the evidence was inadequate
- debate areas of disagreement and finalise recommendations

The GDG also reached agreement on the following:

- recommendations as key priorities for implementation
- key research recommendations
- algorithms

In prioritising key recommendations for implementation, the GDG took into account the following criteria:

- high clinical impact
- high impact on reducing variation in practice
- more efficient use of NHS resources
- allowing the patient to reach critical points in the care pathway more quickly

Audit criteria for this guideline will be produced for NICE following publication in order to provide suggestions of areas for audit in line with the key recommendations for implementation.

► **Structuring and writing the guideline**

The guideline is divided into sections for ease of reading. For each section the layout is similar and contains:

- *Clinical introduction:* sets a succinct background and describes the current clinical context

- *Clinical methodological introduction:* describes any issues or limitations that were apparent when reading the evidence base. Point estimates (PE) and confidence intervals (CI) are provided for all outcomes in the evidence tables available online at the NICE website. In addition within the guideline PE and CI are cited in summary tables for the evidence that pertains to the key priorities for implementation. In the absence of a summary table PE and CI are provided in the narrative text when the outcome adds something to the text and to make a particular point. These may be primary or secondary outcomes that were of particular importance to the GDG when discussing the recommendations. The rationale for not citing ***all*** statistical outcomes is to try to provide a 'user friendly' readable guideline balanced with statistical evidence where this is thought to be of interest to the reader.

- *Clinical evidence statements:* provides a synthesis of the evidence-base and usually describes what the evidence showed in relation to the outcomes of interest. Where the evidence statements are considerable the GDG have attempted to summarise these into a useful summary.

- *Health economic methodological introduction:* as for the clinical methodological introduction, describes any issues or limitations that were apparent when reading the evidence base.

- *Health economic evidence statements:* presents, where appropriate, an overview of the cost effectiveness evidence-base, or any economics modelling.

- *From evidence to recommendations:* this section sets out the GDG's decision-making rationale and aims to provide a clear and explicit audit trail from the evidence to the evolution of the recommendations.

- *Recommendations:* provides stand alone, action orientated recommendations.

- *Evidence tables:* The evidence tables are not published as part of the full guideline but are available on-line at the NICE website. These describe comprehensive details of the primary evidence that was considered during the writing of each section.

► *Writing the guideline*

The first draft version of the guideline was drawn up by the technical team in accordance with the decisions of the GDG, incorporating contributions from individual GDG members in their expert areas and edited for consistency of style and terminology. The guideline was then submitted for a formal public and stakeholder consultation prior to publication. The registered stakeholders for this guideline are detailed on the NICE website www.nice.org.uk. Editorial responsibility for the full guideline rests with the GDG.

The following versions of the guideline are available:

Table 1-3. Versions of the guideline

Full version:	Details the recommendations, the supporting evidence base and the expert considerations of the GDG.
NICE version:	Documents the recommendations without any supporting evidence.
'Quick reference guide':	An abridged version.
'Understanding NICE guidance':	A lay version of the guideline recommendations

► Updating the guideline

Literature searches were repeated for all of the evidence based questions at the end of the GDG development process allowing any relevant papers published up until 6 April 2009 to be considered. Future guideline updates will consider evidence published after this cut-off date.

Following publication and in accordance with the technical manual, NICE will ask a National Collaborating Centre to determine whether the evidence base has progressed significantly to alter the guideline recommendations and warrant an update.

Disclaimer

Healthcare providers need to use clinical judgement, knowledge and expertise when deciding whether it is appropriate to apply guidelines. The recommendations cited here are a guide and may not be appropriate for use in all situations. The decision to adopt any of the recommendations cited here must be made by the practitioner in light of individual patient circumstances, the wishes of the patient, clinical expertise and resources.

The Nation Collaborating Centre for Chronic Conditions (now a part of the National Clinical Guideline Centre for Acute and Chronic Conditions) disclaim any responsibility for damages arising out of the use or non-use of these guidelines and the literature used in support of these guidelines.

Funding

The National Collaborating Centre for Chronic Conditions (now a part of the National Clinical Guideline Centre) were commissioned by the National Institute for Health and Clinical Excellence to undertake the work on this guideline.

1.3 KEY MESSAGES OF THE GUIDELINE

1.3.1 KEY PRIORITIES FOR IMPLEMENTATION

As soon as the diagnosis of unstable angina or NSTEMI is made, and aspirin and antithrombin therapy have been offered, formally assess individual risk of future adverse cardiovascular events using an established risk scoring system that predicts 6-month mortality (for example, Global Registry of Acute Cardiac Events [GRACE]).

Consider intravenous eptifibatide or tirofiban[b] as part of the early management for patients who have an intermediate or higher risk of adverse cardiovascular events (predicted 6-month mortality above 3.0%), and who are scheduled to undergo angiography within 96 hours of hospital admission.

Offer coronary angiography (with follow-on PCI if indicated) within 96 hours of first admission to hospital to patients who have an intermediate or higher risk of adverse cardiovascular events (predicted 6-month mortality above 3.0%) if they have no contraindications to angiography (such as active bleeding or comorbidity). Perform angiography as soon as possible for patients who are clinically unstable or at high ischaemic risk.

When the role of revascularisation or the revascularisation strategy is unclear, resolve this by discussion involving an interventional cardiologist, cardiac surgeon and other healthcare professionals relevant to the needs of the patient. Discuss the choice of revascularisation strategy with the patient.

To detect and quantify inducible ischaemia, consider ischaemia testing before discharge for patients whose condition has been managed conservatively and who have not had coronary angiography.

Before discharge offer patients advice and information about:

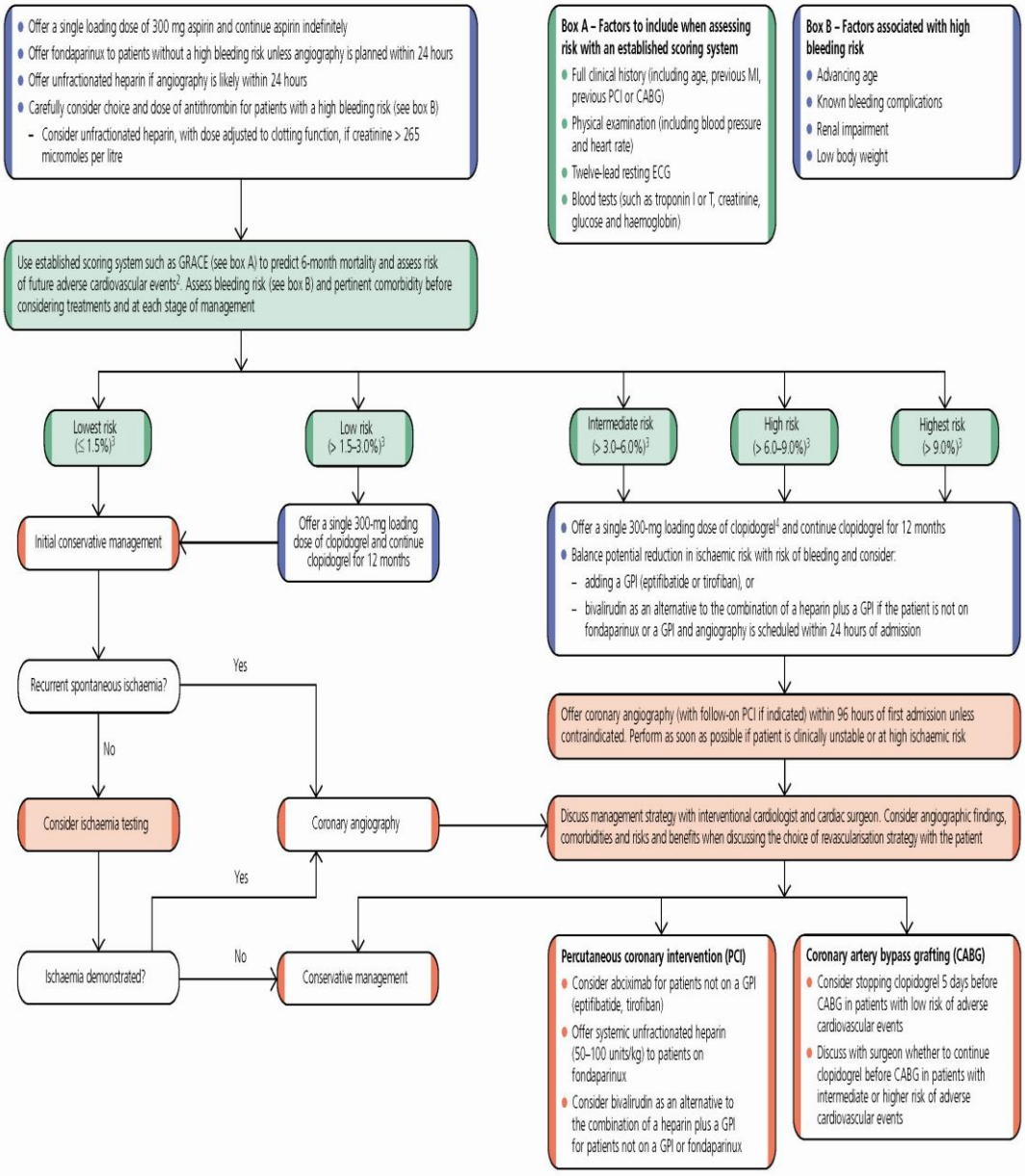
[b] Eptifibatide and tirofiban are licensed for use with aspirin and unfractionated heparin. They do not have UK marketing authorisation for use with clopidogrel. This recommendation is therefore for an off-label use of these drugs. Informed consent should be obtained and documented before they are used in combination with clopidogrel.

- their diagnosis and arrangements for follow-up (in line with 'MI: secondary prevention', NICE clinical guideline 48)
- cardiac rehabilitation (in line with 'MI: secondary prevention', NICE clinical guideline 48)
- management of cardiovascular risk factors and drug therapy for secondary prevention (in line with 'MI: secondary prevention', NICE clinical guideline 48, and 'Lipid modification', NICE clinical guideline 67)
- lifestyle changes (in line with 'MI: secondary prevention', NICE clinical guideline 48)

1.3.2 ALGORITHM

The treatment algorithm is on the following page. Please refer to the Quick Reference Guide available online at http://www.nice.org.uk/nicemedia/live/12949/47924/47924.pdf.

The early management of unstable angina and NSTEMI



[2] Categories of risk are derived from the Myocardial Ischaemia National Audit Process (MINAP) database. More details are in the full guideline which is available at www.nice.org.uk/guidance/CG94/Guidance

[3] Predicted 6-month mortality.

[4] There is emerging evidence about the use of a 600-mg loading dose of clopidogrel for patients undergoing PCI within 24 hours of admission. Clopidogrel does not have UK marketing authorisation for use at doses above 300 mg. The Guideline Development Group was not able to formally review all the evidence for a 600-mg loading dose and was therefore not able to recommend this at the time of publication (March 2010).

2 Assessment of risk

2.1 Assessing an individual's risk of adverse events

2.1.1 CLINICAL INTRODUCTION

The use of the term 'risk' in this guideline refers to an individual's risk of having an adverse outcome (usually cardiovascular mortality, myocardial infarction, stroke or repeat revascularisation). It does **not** refer to the known 'risk factors' associated with the development of cardiovascular disease (such as smoking, family history, hyperlipidaemia, hypertension, diabetes).

Not all patients with UA or NSTEMI have the same risk of an adverse cardiovascular event, either in the short or longer term. An appreciation of absolute individual patient risk is therefore important in clinical management and when assessing which treatment strategies are most appropriate. For instance, the management often involves the use of anti-thrombotic agents that may reduce the rate of adverse cardiovascular events but increase the rate of bleeding complications. The balance between these opposing effects of treatment may be influenced by the individuals' absolute risk of an adverse cardiovascular event. As a generalisation, the greater the absolute cardiovascular risk, as determined by the presence or absence of certain clinical factors, the greater the potential for absolute risk reduction by appropriate pharmacological or invasive intervention. The importance of risk and its management has been highlighted in recent guidelines[7-9].

In addition, the risk of death, re-infarction or other vascular events may impact the cost effectiveness of interventions that reduce the risk of such events. Even if an intervention has the same ***relative*** effect across all risk groups, ***absolute*** benefit will be higher when the absolute risk of an event is higher.

Table 2-1 to the right illustrates this. If the relative risk reduction of a treatment is constant across the population (say 10%), then the absolute number of events avoided is highest for patients at highest risk of an event.

A cost effective treatment intervention, in patients at high underlying risk, may translate into:

- greater QALY gains
- lower cost due to higher number of events avoided
- improved cost effectiveness

Table 2-1. Risk reduction and treatment effect

	Risk (N=1000 people)		
Risk	**Low**	**Medium**	**High**
No. patients	1000	1000	1000
Risk of event	2%	5%	10%
Events (without treatment)	20	50	100
Relative risk reduction with treatment		**10%**	
Events with treatment	18	45	90
Events avoided with treatment	**2**	**5**	**10**

† No. events avoided with treatment = Number of events multiplied by relative risk reduction with treatment

Many individual factors have been shown to be predictors of an adverse outcome. These factors include:

- Advancing age
- Presence and severity of ECG changes of ischaemia
- Magnitude of rise in biomarkers of myocardial injury (e.g. serum troponin)
- Left ventricular dysfunction
- Cardiogenic shock
- Increased heart rate
- Arrhythmias (ventricular, atrial fibrillation)
- Renal impairment
- Diabetes mellitus
- Anaemia
- Cerebrovascular disease
- Peripheral vascular disease

A single risk variable may not provide a reliable assessment of risk. For instance, the serum troponin level (a highly sensitive and specific marker of myocardial injury) has been associated with an elevated risk of future adverse cardiovascular events, and influences the benefit of therapeutic interventions such as anti–platelet therapies and early percutaneous coronary intervention (PCI) (refer to sections 6 & 8.2). In clinical practice there has been a tendency to use this single factor for patient risk stratification, but serum troponin does not accurately measure risk in individual patients, particularly when used as a dichotomous outcome (troponin positive/negative). When compared to a well validated risk scoring system (GRACE, [10]), that uses multiple risk components to predict mortality, a large proportion of troponin positive patients were found to fall into the low and medium risk groups, and conversely some high risk patients were troponin negative (see Figure 2-1. **This** bar chart describes the distribution of (left axis) troponin positive (red bars) and troponin negative (yellow bars) patients according to category of GRACE risk score (ranging from 51 to 226) among 27,406 patients with non-ST elevation acute coronary syndromein the GRACE registry. The blue curve (right axis) depicts the observed hospital mortality rates.

(Figure obtained with permission from The American Journal of Medicine).

A number of risk scoring systems have been developed to predict short and medium term outcome in patients with acute coronary syndromes. Many of these risk scoring systems were derived from clinical trial populations, which generally excluded the highest-risk patients. Other risk scores were derived from large patient databases in an attempt to model a more representative ACS population with a broader spectrum of risk. Most of the risk scores include ECG signs of myocardial ischaemia and cardiac biomarkers of necrosis, as well as other clinical features at presentation.[11] Such observations argue for the use of multiple components for assessing individual patient risk.

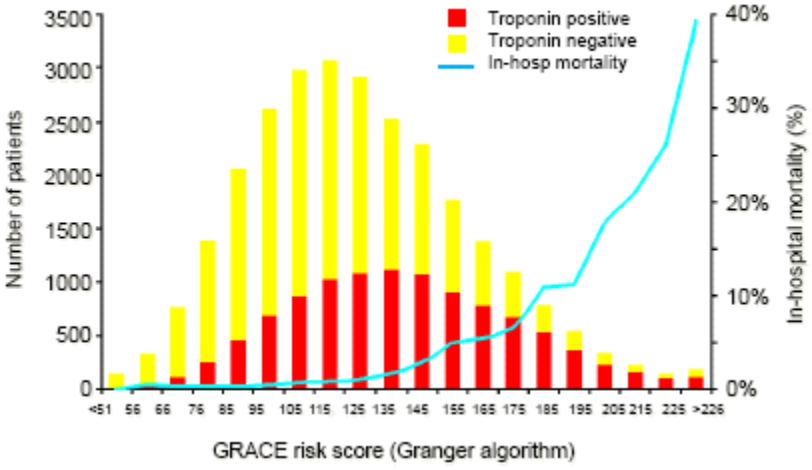


Figure 2-1. This bar chart describes the distribution of (left axis) troponin positive (red bars) and troponin negative (yellow bars) patients according to category of GRACE risk score (ranging from 51 to 226) among 27,406 patients with non-ST elevation acute coronary syndromein the GRACE registry. The blue curve (right axis) depicts the observed hospital mortality rates.

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The purpose of this section is to review the use of these scoring systems, to determine whether one is superior, and whether they should be used routinely in clinical practice.

The clinical question asked, and upon which literature searching was undertaken, was: *'Which tables, equations, engines or scoring systems for patient risk stratification are most predictive of death, re-infarction or other vascular events in patients with UA/non-ST elevation myocardial infarction'?*

2.1.2 CLINICAL METHODOLOGICAL INTRODUCTION

A clinically useful risk model should be able to accurately distinguish high risk from low risk patients (model discrimination; measured with the c-statistic), and estimate the actual risk of adverse outcome (model calibration) [12].

The literature was searched from 1999 to 2009 for systematic reviews (SR), randomised controlled trials (RCT), comparative studies, and observational studies for scoring systems to predict risk in people with non ST segment elevation ACS. The rationale for searching from January 1999 onwards was to reflect current practice, particularly the use of stents for revascularisation. Studies were included if thenon-ST-segment-elevation ACS population was N>500 and if the population contained at least 60% NSTEMI or UA. Outcomes of interest were the ability of the risk scores to predict survival, revascularisation, re-infarction, LV function, quality of life, and serious complications (for example, stroke or bleeding).

Fourteen observational studies [13] [14-16] [12,17,18] [10,19-24] were identified that assessed the utility of various risk scores.

►TIMI risk score

The TIMI risk score was developed to predict the occurrence of the primary end-point (all cause mortality, myocardial infarction, or urgent revascularisation) at 14 days in patients with NSTEMI assigned to treatment with unfractionated heparin in the TIMI-11B trial (N=1957) [13]. The predictive accuracy of the TIMI risk score was assessed in four RCTs: VANQWISH (N= 992; non-Q wave MI) [14], TIMI IIb and ESSENCE (N=7081; NSTEMI/UA) [13], and EFFECT (N=5430; NSTEMI) [15].

The utility of the TIMI risk score to predict death or the composite outcome of death or MI at 28 days was assessed in a registry of people with confirmed MI (N=717; NSTEMI, N=562; STEMI) [17].

The utility of the TIMI risk score to predict in-hospital death was assessed in the Canadian ACS-2 Registry (N= 1728; NSTE ACS) [18].

►PURSUIT risk score

The PURSUIT risk score for death at 30 days or death/MI at 30 days was derived from the PURSUIT RCT (N = 9461; NSTEMI and UA) [19]. The predictive accuracy of the PURSUIT score was assessed in the PURSUIT RCT and in the MINAP database of patients with ACS (Total N=100686; NSTEMI N = 42582; troponin negative ACS N=7369; STEMI N=34986; other diagnoses N=11390) [20].

The utility of the PURSUIT risk score to predict in-hospital death was assessed in the Canadian ACS-1 Registry (N = 2925; NSTE ACS) [12] and Canadian ACS-2 Registry (N = 1728; NSTE ACS) [18]

►GRACE risk score:

The GRACE risk score was derived from the large GRACE registry of patients with ACS (N=43810) to predict death and death or MI, both in-hospital and at six months [10] [21].

The GRACE risk score for predicting in-hospital death was assessed in several ACS patient registries including the MINAP database [20], and the Canadian ACS-1 and ACS-2 Registries [12] [18]. The ability of the GRACE risk score to predict death at 6 months, 1, 2, 3, and 4 years was assessed in a New Zealand ACS registry (N= 1143; all ACS, N=697; non-ST elevation ACS) [22].

The ability of the GRACE risk score to predict death at 6 months and 1 year was evaluated in the NSTEMI population (N=5812) of the EFFECT RCT [16].

►PREDICT risk score

The PREDICT score was developed from a registry of patients hospitalised with UA or acute MI (N=6134) [25]. The ability of this risk score to predict death or the composite outcome of death or MI at 28 days was assessed in people with a confirmed diagnosis MI (N= 717; NSTEMI) [17].

►EMMACE risk score

The EMMACE risk score for death at 30 days was developed from a United Kingdom registry of patients with acute MI [26] (N=2153) and was assessed in the MINAP database of patients with ACS [20].

►Simple Risk Index (SRI)

The SRI risk score was developed from the In-TIME II trial to predict 30 day mortality in patients with ST-elevation MI (N=13253)[27] and was assessed in the MINAP database [20].

►AMIS risk score

The AMIS risk score to predict in-hospital death was derived in the AMIS-Plus database of people with ACS (N=7520) [23].

►UA risk score

Piombo et al. derived a risk score to predict the risk of in-hospital death, acute MI or refractory ischaemia in people with UA (N=715) [24].

►Comparative studies

The GRACE, TIMI, and PURSUIT risk scores were compared in patients with non ST-segment elevation ACS in the Canadian ACS-1 (N = 2925) [12] and ACS-2 (N=1728) [18] registries.

The PURSUIT, GRACE, SRI and EMMACE risk scores were compared in the large MINAP registry of patients with ACS in England and Wales (N=100686).[20].

The TIMI and PREDICT risk scores were compared in patients with confirmed MI (N= 717; NSTEMI) [17].

The AMIS risk score was compared with the TIMI and SRI risk scores to predict in-hospital death in people with NSTEACS (N=2949) in an internal validation cohort (AMIS-plus cohort) and in an external validation cohort of ACS patients treated with a non-invasive strategy. [23].

2.1.3 CLINICAL EVIDENCE STATEMENTS

Derivation of risk scores

For each risk score, multivariate analysis of baseline characteristics was performed to ascertain those characteristics which were most strongly associated with adverse outcomes, typically death, MI, or urgent revascularisation. Risk scores were generated from the coefficients with an appropriate number of points given for the presence of each risk factor.

Age, ST-segment deviation, elevated serum cardiac biomarkers, blood pressure, heart rate, congestive heart failure, and severe anginal symptoms were all associated with adverse outcomes. The PREDICT and GRACE risk scores also identified renal function as an important prognostic factor.

Evidence Level: 3

Table 2-2 and Table 2-3 summarise the discrimination of various risk scores to predict short term and longer term outcomes in populations with non ST-segment elevation ACS

The components of each of the risk scores are shown below:

►**TIMI risk score** for death, new or recurrent MI, or urgent revascularization at 14 days[13]:

- Age ≥ 65 years
- At least three of: family history of CAD, hypertension, hypercholesterolemia, diabetes, or current smoker
- Significant coronary stenosis (for example, prior coronary stenosis ≥ 50%)
- ST segment deviation on ECG
- Severe anginal symptoms (for example, ≥ 2 anginal events in the last 24 hours)
- Use of aspirin in the last seven days
- Elevated serum cardiac markers (CK-MB and/or cardiac-specific troponin level)

►**PURSUIT risk score** for death at 30 days or death/MI at 30 days [19]:

- Age
- Gender

- Worst CCS-class in previous six weeks
- Heart rate
- Systolic blood pressure (SBP)
- Rales
- ST-segment depression on presenting ECG

►**GRACE risk score** for in-hospital death [10]:

- Age
- Killip class[c]
- Heart rate
- SBP
- Serum creatinine
- ST-segment deviation
- Cardiac arrest at admission
- Elevated serum cardiac enzymes

►**GRACE risk score** for death at 6 months [21]:

- Age
- Killip class
- Heart rate
- SBP
- Serum creatinine
- ST-segment deviation
- Cardiac arrest at admission

[c] Killip Class is defined as (1) No evidence of heart failure, (2) Mild-moderate heart failure (third heart sound, rales <one third up lung fields, raised JVP), (3) Overt pulmonary oedema, (4) Cardiogenic shock

- Elevated serum cardiac enzymes

As can be seen above the GRACE scoring systems use the same eight variables to derive a GRACE score. It is important to note that the models for predicting in-hospital mortality and 6-month mortality produce numerically different scores. Therefore, the actual GRACE score (the total number derived after summation of the numbers assigned to each variable) for an individual patient depends on which model is being used. The predictive accuracy of each model though is similar for the time period for which each was derived.

►**PREDICT risk score** for death at 28 days [17]:

- Age
- Prior MI, angina, CABG, cardiac arrest, hypertension, stroke
- Shock
- Congestive heart failure
- ECG severity score
- Charlson index[28]
- Renal function

►**Simple Risk Score** (SRI) for death at 30 days [27]

- Age
- Heart rate
- SBP

►**EMMACE Risk Score** for death at 30 days [20,29]

- Age
- Heart rate
- SBP

►**UA Risk Score** for risk of in-hospital death, acute MI, or refractory ischemia [24]:

- ST-segment deviation
- Age ≥70 years
- Previous CABG
- Serum troponin T ≥ 0.1 ng/mL

►**AMIS Risk Score** for in-hospital death [23]:

- Age
- Killip class
- SBP
- Heart rate
- Pre-hospital cardio-pulmonary resuscitation
- History of heart failure
- History of cerebrovascular disease

Comparative studies

In the MINAP database (N=100,686), the PURSUIT, GRACE, SRI, and EMMACE risk scores showed similarly high discrimination in predicting the likelihood of death [20].

Evidence Level: 3

GRACE risk score versus PURSUIT risk score

Two studies of populations with non ST-segment elevation ACS showed no significant difference in discriminatory performance between the GRACE and PURSUIT risk scores for predicting in-hospital and one year mortality [12] [18]. However, the PURSUIT score had poor calibration (Hosmer-Lemeshow goodness of fit, $p<0.001$) and consistently overestimated risk of in-hospital death compared with GRACE [12].

Evidence Level: 3

►TIMI risk score versus other risk scores

In the Canadian ACS-2 registry, the PURSUIT risk score (c-statistic = 0.80) had significantly better discrimination than the TIMI risk score for 1 year mortality (c-statistic = 0.68; p=0.036 between risk scores). Similarly, the GRACE risk score (c-statistic = 0.81) had significantly better discrimination than the TIMI risk score (c-statistic = 0.68; p=0.02 between risk scores) [18].

Evidence Level: 3

The PREDICT risk score (c-statistic 0.78) had significantly better discrimination than the TIMI risk score (c-statistic 0.59, $p<0.001$ between risk scores) of death at 28 days [17].

Evidence Level: 3

Table 2-2. Summary of discrimination of various risk scores to predict *short term* outcomes in populations with NSTE-ACS.

Study	Population	N	Outcome	Risk Score	Model discrimination c-statistic (95% CI)	Model calibration P value Hosmer-Lemeshow statistic
Yan et al. (2007)[18]	non ST-segment elevation ACS (Canadian ACS-2 Register)	1728	In-hospital death	TIMI	0.68 (0.59 to 0.77)	Not reported (NR)
Kurz et al. (2008)[23]	non ST-segment elevation ACS (AMIS-plus Registry)	1257	In-hospital death	TIMI	0.839 (Not reported)	NR
Granger et al.(2003)[10]	ACS (GRACE register)	11389	In-hospital death	GRACE	0.84 (Not reported)	NR
Granger et al. (2003)[10]	non ST-segment elevation ACS (GRACE register)	NR	In-hospital death	GRACE	0.82 (Not reported)	NR
Gale et al. (2008)[20]	ACS (MINAP register)	85771	In-hospital death	GRACE	0.80 (0.80 to 0.81), p<0.001	NR
Yan et al. (2004)[12]	non ST-segment elevation ACS (Canadian ACS-1 Register)	2925	In-hospital death	GRACE	0.83 (0.77 to 0.89)	0.40
Yan et al.(2007)[18]	non ST-segment elevation ACS (Canadian ACS-2 Register	1728	In-hospital death	GRACE	0.81 (0.73 to 0.89)	

Study	Population	N	Outcome	Risk Score	Model discrimination c-statistic (95% CI)	Model calibration P value Hosmer-Lemeshow statistic
Yan et al.(2004)[12]	non ST-segment elevation ACS (Canadian ACS-1 Register)	2925	In-hospital death	PURSUIT	0.84 (0.79 to 0.89)	<0.001
Yan et al. (2007)[18]	non ST-segment elevation ACS (Canadian ACS-2 Register	1728	In-hospital death	PURSUIT	0.80 (0.71 to 0.88)	NR
Kurz et al. (2008)[23]	non ST-segment elevation ACS (AMIS-plus Registry)	1257	In-hospital death	AMIS	0.851 (NR)	NR
Kurz et al. (2008)[23]		1257	In-hospital death	SRI	0.831 (NR)	NR
Piombo et al. (2003)[24]	UA	715	In-hospital death, AMI or refractory angina	UA risk score	0.72 (0.66 to 0.78)	NR
Antman et al.(2000)[13]	UA/NSTEMI (TIMI IIb RCT-UFH arm)	1957	Death, new or recurrent MI, or urgent revascularization at 14 days	TIMI	0.65 (NR)	0.89
Antman et al. (2000)[13]	UA/NSTEMI (TIMI IIb RCT-enoxaparin arm)	1953	Death, new or recurrent MI, or urgent revascularization at 14 days	TIMI	0.61 (NR)	NR
Antman et al.	UA/NSTEMI (ESSENCE RCT-	1607	Death, new or recurrent MI, or urgent	TIMI	0.59 (NR)	NR

Study	Population	N	Outcome	Risk Score	Model discrimination c-statistic (95% CI)	Model calibration P value Hosmer-Lemeshow statistic
(2000)[13]	enoxaparin arm)		revascularization at 14 days			
Antman et al. (2000)[13]	UA/NSTEMI (ESSENCE RCT-UFH arm)	1564	Death, new or recurrent MI, or urgent revascularization at 14 days	TIMI	0.65 (NR)	NR
Singh et al. (2002)[17]	NSTEMI	717	Death at 28 days	TIMI	0.59 (0.53 to 0.66)	0.61
Singh et al. (2002)[17]	NSTEMI	717	Death at 28 days	PREDICT	0.78 (0.73 to 0.84)	0.36
Bradshaw et al. (2007)[15]	NSTEMI (EFFECT RCT)	5430	Death at 30 days	TIMI	0.80 (0.78 to 0.82)	NR
Boersma et al. (2000)[19]	UA/NSTEMI (PURSUIT RCT)	9461	Death at 30 days	PURSUIT	0.814 (NR)	NR
Gale et al. (2008)[20]	ACS (MINAP register)	49995	Death at 30 days	PURSUIT	0.79 (0.78 to 0.80), p<0.001	NR
Gale et al. (2008)[20]	ACS (MINAP register)	100686	Death at 30 days	SRI	0.79 (0.78 to 0.80), p<0.001	NR
Gale et al. (2008)[20]	ACS (MINAP register)	100686	Death at 30 days	EMMACE	0.78 (0.77 to 0.78), p<0.001	NR
Gale et al.	NSTEMI (MINAP register)	42582	Death at 30 days	EMMACE	0.76 (0.75 to 0.76)	NR

Study	Population	N	Outcome	Risk Score	Model discrimination c-statistic (95% CI)	Model calibration P value Hosmer-Lemeshow statistic
(2008)[20]						
Singh et al. (2002)[17]	NSTEMI	717	Death or MI at 28 days	TIMI	0.59 (0.53 to 0.65)	NR
Singh et al. (2002)[17]	NSTEMI	717	Death or MI at 28 days	PREDICT	0.78 (0.67 to 0.79)	NR
Boersma et al. (2000)[19]	UA/NSTEMI (PURSUIT RCT)	9461	Death or MI at 30 days	PURSUIT	0.670 (NR)	NR
Samaha et al. (2002)[14]	Non-Q wave MI (VANQWISH RCT)	922	Death, nonfatal MI, urgent revascularisation at 30 days	TIMI	0.59 (NR)	0.72

Table 2-3. Summary of discrimination of various risk scores to predict *long term* outcomes in populations with non ST-segment elevation ACS

Study	Population	N	Outcome	Risk Score	Model discrimination c-statistic (95% CI)
Bradshaw et al. (2006)[16]	NSTEMI (EFFECT trial)	5812	Death at 6 months	GRACE	0.78 (0.76 to 0.80)
Fox et al. (2006)[21]	NSTEMI/UA (GRACE validation cohort)	NR	Death at 6 months	GRACE	0.81 (NR)
Fox et al. (2006)[21]	NSTEMI (GUSTO-IIB trial)	8011	Death at 6 months	GRACE	0.76 (NR)
Tang et al. (2007)[22]	ACS	1057	Death at 6 months	GRACE	0.81 (NR)
Bradshaw et al. (2006)[16]	NSTEMI (EFFECT trial)	5812	Death at 1 year	GRACE	0.78 (0.77 to 0.80)
Yan et al. (2007)[18]	non ST-segment elevation ACS (Canadian ACS-2 Register)	1728	Death at 1 year	GRACE	0.79 (0.74 to 0.83)
Tang et al. (2007)[22]	ACS	1057	Death at 1 year	GRACE	0.82 (NR)
Samaha et al. (2002)[14]	Non-Q wave MI (VANQWISH RCT)	922	Death at 1 year	TIMI	0.65, p<0.0001
Singh et al. (2002)[17]	NSTEMI	717	Death at 1 year	TIMI	0.61 (0.56 to 0.66)
Yan et al. (2007)[18]	non ST-segment elevation ACS (Canadian ACS-2 Register	1728	Death at 1 year	TIMI	0.69 (0.64 to 0.74)
Singh et al. (2002)[17]	NSTEMI	717	Death at 1 year	PREDICT	0.81 (0.77 to 0.85)

Study	Population	N	Outcome	Risk Score	Model discrimination c-statistic (95% CI)
Yan et al. (2007)[18]	non ST-segment elevation ACS (Canadian ACS-2 Register	1728	Death at 1 year	PURSUIT	0.77 (0.72 to 0.81)
Tang et al. (2007)[22]	ACS	1057	Death at 2 years	GRACE	0.81 (NR)
Tang et al. (2007)[22]	ACS	1057	Death at 3 years	GRACE	0.81 (NR)
Tang et al. (2007)[22]	ACS	1057	Death at 4 years	GRACE	0.80 (NR)
Fox et al. (2006)[21]	NSTEMI/UA (GRACE validation cohort)	NR	Death/nonfatal MI at 6 months	GRACE	0.73 (NR)
Samaha et al. (2002)[14]	Non-Q wave MI (VANQWISH RCT)	922	Death, nonfatal MI at 1 year	TIMI	0.64, p<0.0001
Singh et al. (2002)[17]	NSTEMI	717	Death, nonfatal MI at 1 year	TIMI	0.62 (0.57 to 0.67)
Singh et al. (2002)[17]	NSTEMI	717	Death, nonfatal MI at 1 year	PREDICT	0.78 (0.74 to 0.82)
Samaha et al. (2002)[14]	Non-Q wave MI (VANQWISH RCT)	922	Death, nonfatal MI, urgent revascularisation at 1 year	TIMI	0.60, p<0.0001

NR = not reported

2.1.4 *HEALTH ECONOMIC METHODOLOGICAL INTRODUCTION*

No relevant economic studies were identified for this question.

2.1.5 *EVIDENCE SUMMARY*

The various risk models reviewed use different components to make up their systems, and none is clearly superior, although PURSUIT, GRACE and PREDICT seem to have better discrimination than TIMI for mortality. Some were derived from populations recruited to RCTs and some from registry data. We found no evidence that risk models have been used prospectively in the management of individual patients and the impact of these scoring systems on clinical decision making and patient outcome is unknown. Prospective use of the GRACE 6-month mortality model was used to categorise patients into risk categories in the recently published TIMACS study[30].

2.1.6 *EVIDENCE TO RECOMMENDATIONS*

Many risk scores have been used in the assessment of risk of an adverse cardiovascular outcome for patients with UA/NSTEMI. Each of the components of these systems is an independent predictor of risk and those caring for patients need to be aware of their importance and additive contributions to overall risk. Whilst the predictor variables each carry differing prognostic weight, generally speaking the greater the number of risk predictors, the greater the individual patient risk. Complex risk scores may be able to refine risk more accurately than simple risk scores, but there is insufficient evidence to allow a strong recommendation about which score would be most appropriately applied in clinical management pathways.

The components of the risk scoring systems have been derived differently:

- Some have come from randomised clinical trials (TIMI, PURSUIT), which have recruited only a minority of the overall potential population, and have generally excluded higher risk groups.
- Some have come from registry data (GRACE, EMMACE), which have the advantage of larger numbers of patients analysed, possibly less case selection and, for some, validation in a UK population [20]. On the other hand, data collection in registries is often less complete than in a RCT.
- Some risk scores were developed to predict mortality but others, such as TIMI, were to predict composite endpoints.

Gale et al.[20] analysed the UK MINAP database containing over 100,000 patients with ACS (including STEMI) and found EMMACE (a simple scoring system comprising three factors: age, heart rate, and systolic blood pressure) to have comparable predictive ability to systems, such as GRACE, that comprise more factors (n=8 for GRACE). The authors commented that "simple models (such as EMMACE and SRI) may be more useful for case mix adjustment, whereas more complex models (such as GRACE) may be more

appropriately used by clinicians making clinical decisions about individual patients" [18,21,29]. An understanding of a patient's underlying risk of an adverse cardiovascular event is important because it may influence the clinician's assessment of the risks and benefits of an intervention, and decisions regarding subsequent management. Assessment of underlying risk is usually not undertaken systematically and may be influenced by the experience and treatment preferences of the clinician, or by the clinician's understanding of best practice guidelines or local protocols. There is evidence that clinical assessment alone may not accurately reflect the patient's risk [31], and lower risk patients may paradoxically be treated more actively than those at higher risk (the so called 'treatment-risk paradox')[32-35]. There is potential for a systematic approach to risk assessment to result in more accurate estimation of risk and more appropriate intervention.

2.2 BALANCING THE RISKS AND BENEFITS OF INTERVENTIONS

Various pharmacological agents (such as anti–thrombin and anti–platelet drugs) and coronary revascularisation (either percutaneous coronary intervention [PCI] or coronary artery bypass graft [CABG] surgery) have been shown to improve the outcome of patients with UA or NSTEMI. These interventions are known to be associated with some treatment hazards (particularly bleeding complications), which for the individual patient must be balanced against any potential treatment benefits. This balance is influenced by the patient's estimated risk of an adverse cardiovascular outcome as a consequence of the ACS, because the absolute magnitude of benefit from an intervention is generally greatest in those with the highest risk. This balancing of risk against benefit was reflected in the previous Technology Appraisals for clopidogrel[36] (where it was recommended for those at moderate or high, but not for those at low, risk) and the glycoprotein IIb/IIIa inhibitors[37] (only recommended for those at high risk of adverse events). A confounding issue is that treatment hazards, such as bleeding complications, are often also greatest in those patients at highest risk of an ischaemic event.

Individual pharmacological interventions and coronary revascularisation are considered in more detail elsewhere in this guideline. This section is concerned with the challenge of balancing the hazards related to, and potential benefits of, an intervention in the context of an individual's underlying risk of an adverse outcome.

To select the most appropriate intervention(s) for an individual, clinicians should consider the:

- individual's risk of an adverse cardiovascular outcome
- potential benefit of the intervention(s)
- potential hazards associated with the intervention(s)

Addressing an individual's underlying risk has been discussed earlier. Measures of risk can be derived from the clinical assessment of a patient and the use of a formal risk-scoring system, such as the GRACE score. The potential benefit and hazards of an intervention are derived from clinical trial data, but trials generally exclude patients who are at high risk of an adverse cardiovascular outcome (such as the elderly, or those with renal or heart failure), and as a consequence the evidence for clinical and cost effectiveness of therapeutic interventions is confined to patients at lower to intermediate levels of risk.

Obtaining more research data in higher risk patient groups presents significant challenges, and unless more becomes available, consensus expert opinion, based on extrapolation of evidence from lower risk cohorts, is the best that can be achieved. These issues provide an additional rationale for a more systematic approach to the assessment of patient risk of adverse cardiovascular outcomes and of complications (such as bleeding), and for the documentation of these data in patient registries. Clinical trials usually do not include a formal risk scoring system, and often have insufficient recorded details of the components of risk within their recruited population to allow a retrospective assessment of the risk profile of the trial. It can therefore be difficult to apply the results of a clinical trial to the wider range of patients with UA or NSTEMI admitted to UK hospitals. For instance, in the RITA-3 Trial an early invasive strategy for patients with UA and NSTEMI was cost effective in the trial's high risk group (quartile 4) and not cost effective in the low risk group (quartile 1), with the intermediate quartiles having clinical benefit but of uncertain cost effectiveness[38,39]. A clinician might reasonably assume that RITA-3 patients have similar risk profiles to those seen in routine clinical practice, and might therefore conclude that an early invasive strategy is appropriate for approximately 25-50% of patients with UA or NSTEMI. However, as is discussed in more detail elsewhere in this guideline (see chapter 5.2), patients recruited to the RITA-3 trial had risk profiles that were at the lower end of the overall risk spectrum seen in patients with UA or NSTEMI. The majority of patients with UA or NSTEMI admitted to hospitals in the UK fall into risk categories at, or higher than those in the high risk quartile in RITA-3. If the benefits seen in the high risk quartile in RITA-3 are extrapolated to the wider unselected UK population with ACS then an early invasive strategy may be cost effective for a much higher percentage of patients. The same argument applies to the interpretation of pharmacological clinical trials, which also require an appreciation of the risk profiles of the recruited patients before their conclusions can be put into the context of a UK population

Assessment of patient risk profiles within clinical trials

An understanding of the relevance of clinical trial results to the wider population of patients with UA or NSTEMI is critical to making clear recommendations about the clinical and cost effectiveness of an intervention. The GDG therefore undertook an assessment of the risk profile of patients within relevant clinical trials to determine the groups of patients (defined by their level of underlying risk of an adverse cardiovascular event) in an unselected UK population who may benefit from a particular intervention. The GDG acknowledged that several risk scoring systems are effective at predicting risk, but selected the GRACE model as the scoring system for this risk assessment because it:

- predicts outcome well and is easy to use
- predicts outcome across all ACS patient groups and at all levels of underlying risk[21].
- Its components have been shown to be an effective tool in an unselected UK population (MINAP)

The GDG aimed to:

a) define clinically relevant risk groups across the spectrum of patients with non ST-segment elevation ACS. These risk groups may then inform clinical management decisions for individual patients.

b) Position the cohorts of patients with non ST-segment elevation ACS enrolled in randomised clinical trials within the much larger unselected population of patients with non ST-segment elevation ACS.

To achieve these aims the GDG undertook the following:

- Creation of a graph ('MINAP-graph') relating risk score to six-month mortality in patients with UA/NSTEMI in the MINAP database (Myocardial Ischaemia National Audit Project database - a registry of patients admitted to hospital with acute coronary syndromes in England & Wales).
- Creation of a graph ('GRACE-graph') relating risk score to six-month predicted mortality in the GRACE international registry.
- Comparison of MINAP derived national data with data from the international GRACE Registry.
- Assessment of the average risk of patients in relevant clinical trials by obtaining data on 6-month mortality in the control and treatment arms of the trials.
- Positioning of the trial populations within the spectrum of risk seen in the MINAP and GRACE registries (achieved by plotting six-month mortality rates from the trials on the 'GRACE-graph').
- Where a formal risk stratification process was included within a clinical trial this was used to help assess the risk profile of patients enrolled in the trial. It is acknowledged that we are assessing 'risk' that may have been modified by treatment; it is impossible to assess 'true risk' in an untreated population. Moreover, the magnitude of treatment effects seen in the randomised trials is relatively small compared with the range of risk seen in unselected ACS populations (MINAP and GRACE registries), so the impact of treatment on the spectrum of risk across such populations is likely to be small.

The GDG selected 6-month mortality as the outcome measure because:

- mortality is a hard endpoint, which is available for most clinical trials
- mortality cannot be misinterpreted (as can an endpoint such as MI, the definition of which has evolved over time, and varies between trials)
- a 6-month time frame captured the majority of clinical events that occur after presentation with UA or NSTEMI, and which may be influenced by an in-hospital intervention (pharmacological or interventional). Shorter follow-up intervals may miss events related to the index acute coronary syndrome event, and longer follow-up may become increasingly influenced by other factors such as the effects of post-discharge secondary prevention interventions. Moreover, trials often do not report findings beyond the six-month follow-up period.

MINAP

The MINAP registry[40]was established in 1998 as a database of patients admitted to hospitals in England & Wales with acute MI (AMI), analysis of which allowed practice in participating hospitals to be measured against standards specified by the National Service Framework for Coronary Heart Disease (NSF)[2].Initially the project focussed on ST-elevation AMI but the dataset was later expanded to cover other ACS. All hospitals in England and Wales that admit patients with ACS contribute data and mortality is periodically tracked using cross-reference to the Office for National Statistics [41], which records all deaths in the UK.

MINAP database of NSTEMI

For the purposes of this assessment, the MINAP investigators created a sub-database of those in the MINAP Registry who had been admitted during the years 2005-7 with UA or NSTEMI (n=75,627 patients). Those with STEMI were excluded. MINAP collects six of the eight components of the GRACE score, and these variables have been shown to predict mortality in an England & Wales population[20]. Using these six components (age, heart rate, systolic BP, ST-deviation on ECG, cardiac arrest at admission, elevated cardiac enzymes) a risk score, termed 'mini-GRACE score', was calculated for each patient in the database. Of the 75,627 patients with UA/NSTEMI a total of 64,312 had all six components of risk recorded and therefore constituted our 'risk cohort' on which all subsequent analysis was undertaken. The risk distribution of these patients is shown in Figure 2-2).

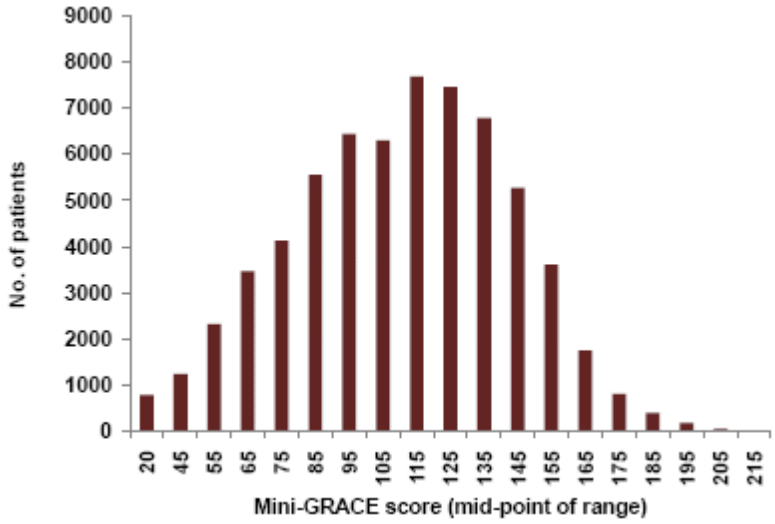

Figure 2-2. Distribution of the mini-GRACE score of patients across the MINAP risk cohort (n=64,312)

Within the MINAP risk cohort six-month mortality (obtained from Office of National Statistics [ONS] mortality tracking) was determined for each 10-point increment of 'mini-GRACE' risk score. Six-month mortality was then plotted against risk score to produce a 'MINAP-graph' (see Figure 2-3).

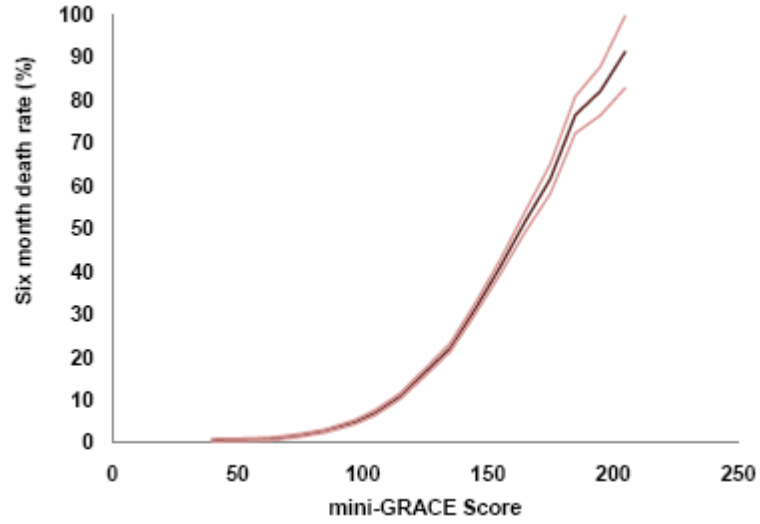

Figure 2-3. Six-month mortality in the MINAP risk cohort plotted against mini-GRACE score. Pale lines show the 95% CI (n=64,312).

The risk cohort of patients was also stratified into quartiles of ascending mini-GRACE score. The two quartiles of lowest risk were further subdivided into four octiles, as most randomised trial evidence relates to patients at these lower levels of risk, and dividing into octiles increased our ability to define the groups of patients (England & Wales

population) to whom the trial evidence applies. Each quartile/octile of risk score was associated with a range of six-month mortality determined by the intercept of the quartile/octile boundary with the MINAP-graph (See Table 2-4, and Figure 2-4). In this way six different risk groups were defined (by ranges of six-month mortality) for the MINAP risk cohort. The upper two quartiles include 50% of the patients in the risk cohort, with a six-month mortality of >9.5%. Patients with NSTEMI at this level of risk are generally not included in randomised clinical trials.

Table 2-4. Risk category and corresponding 6-month mortality

Risk category	Range of mini-GRACE score defined by MINAP quartiles/octiles	Corresponding range of 6-month mortality
1a	<70	<1.6%
1b	71-87	>1.6% ≤3.1%
2a	88-100	>3.1 ≤5.5%
2b	101-112	>5.5% ≤9.5%
3	113-134	>9.5% ≤21.5%
4	>134	>21.5%

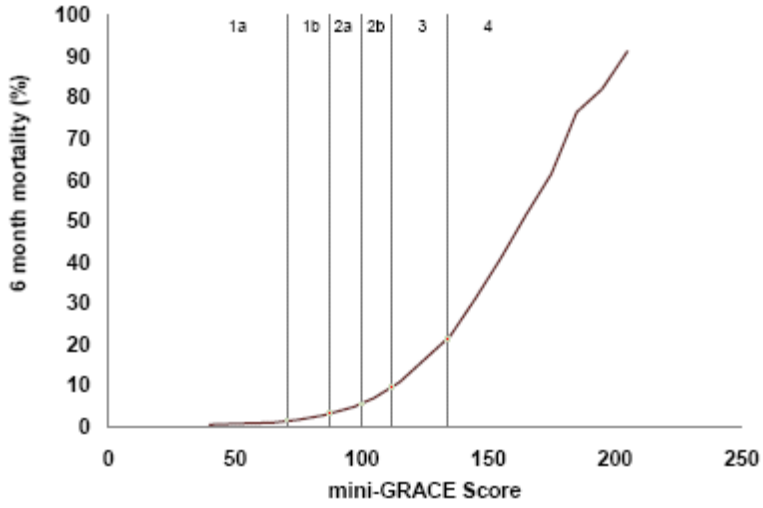

Figure 2-4. Six-month mortality against mini-GRACE score for the MINAP risk cohort. Grey lines show the octiles/quartiles for the MINAP risk population (n=64,312).

A subgroup of the risk cohort prescribed aspirin, clopidogrel, and heparin (UFH or LMWH) was also identified. This subgroup ('drug cohort') was used for the health

economic analysis (see Appendix C). Each patient in the 'drug cohort' retained their individual mini-GRACE score and remained in the risk quartile/octile defined for the 'risk cohort'. Hence the risk groups developed in this risk analysis were also used to risk stratify patients in the economic analysis.

Global Registry of Acute Coronary Events (GRACE)

The multinational GRACE registry is an observational study designed to reflect an unbiased sample of ACS patients within 18 geographic locations. Data from the GRACE registry were used to develop a risk scoring system that could be applied to all ACS (those with and those without ST-elevation on ECG), and across all levels of patients' underlying risk. The GRACE Investigators first determined the variables that predict risk in patients with ACS, and then used a smaller, more manageable, subset of the most predictive variables to develop a scoring tool which could be applied in routine clinical practice.

The methodology behind GRACE has been reported elsewhere [42]. It is an international registry which has enrolled patients with a range of ACS (UA, NSTEMI and STEMI) since 1999, involving a variety of hospital settings (secondary and tertiary care), and used patient surveillance techniques similar to those of the World Health Organization's MONICA Project [43]. To be included in the GRACE registry, an individual had to have the spontaneous onset of symptoms consistent with myocardial ischaemia (not precipitated by surgery, trauma or a significant co-morbidity), and have *at least one* of the following:

- ECG changes consistent with ACS
- Serial increases in serum markers of myocardial necrosis
- Documented coronary artery disease

Separate models were developed for prediction of in-hospital and six-month mortality. For prediction of *in-hospital mortality* the c-statistic of this scoring system was 0.83 for the whole group, and was similar for those patients presenting with (c=0.83) or without (c=0.82) ST-segment elevation, and with (c=0.81) or without (c=0.83) elevation of cardiac biomarkers [10]. The risk model was externally validated using a dataset from the GUSTO-IIb trial[44]. A separate model was also developed to predict *six-month mortality* [45], with a c-statistic of 0.82 for STEMI and 0.81 for UA or NSTEMI [21]. It is the latter six-month model that we have used in our risk assessment exercise within this guideline. It is important to note the models for predicting in-hospital mortality and six-month mortality produce numerically different scores. The widely available GRACE risk calculators (www.outcomes-umassmed.org/grace) provide predicted in-hospital and six-month mortality, rather than GRACE score.

The GRACE investigators provided the GDG with a plot of predicted six-month mortality against GRACE score, based on the GRACE predictive model (the 'GRACE-Graph')[21] (see

Figure 2-5). They also provided data on the distribution of GRACE risk scores of the individuals included in the GRACE registry (see Figure 2-6).

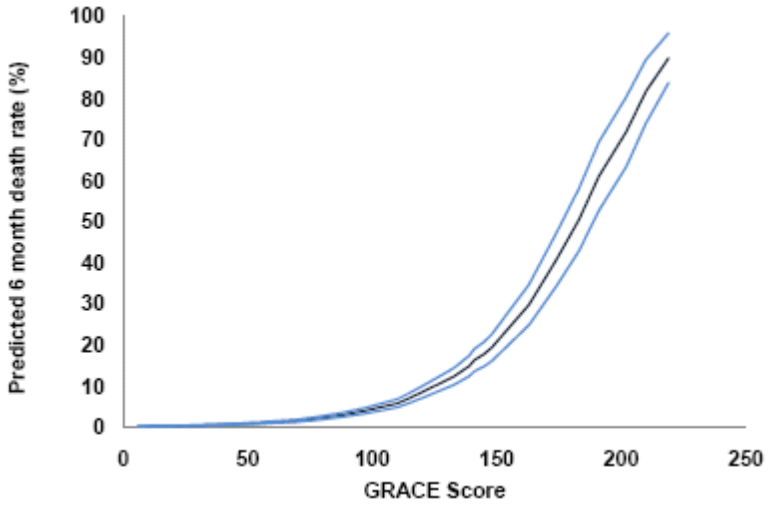

Figure 2-5. The GRACE risk score against the predicted six-month mortality from admission with an acute coronary syndrome (after Fox et al [19]). Pale blue lines show 95% confidence interval.

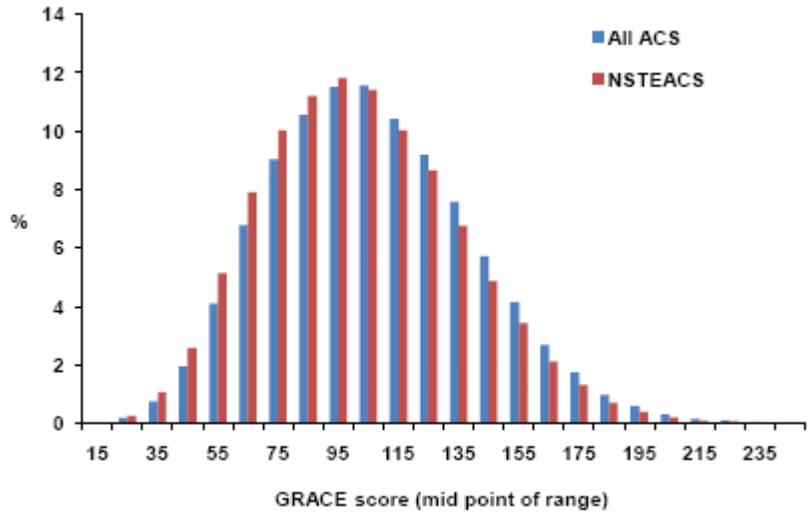

Figure 2-6. The distribution of GRACE scores by 10-point increments in the GRACE registry, for all acute coronary syndromes (ACS) (n=56,771) and those with NSTEMI only (n=35,845). The risk profile of patients in the GRACE Registry when all types of ACS are included is similar to those with NSTEMI, though the distribution for NSTEMI is shifted slightly to the left (Figure provided courtesy of Karen Pieper on behalf of GRACE).

Relating MINAP derived data to GRACE

The superimposition of the curve of risk score versus six-month mortality derived from the MINAP graph, with that derived from the GRACE graph (with 95% confidence interval) is shown below (see Figure 2-7).

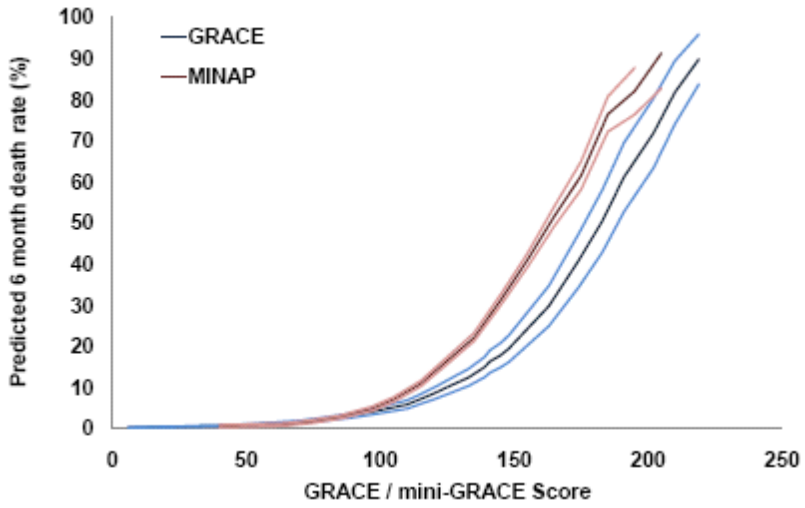

Figure 2-7. Six-month mortality in the MINAP risk cohort against mini-GRACE score (dark line within two 95% CI red curves) and predicted six-month mortality plotted against GRACE score from the GRACE Registry (dark line within two 95% CI blue curves).

The curves are seen to be close to one another at lower levels of risk, but begin to diverge with scores rising above 100 points. As indicated earlier, the mini-GRACE score used for our MINAP risk assessment uses six of the eight components that make up the GRACE score; those absent in mini-GRACE are Killip Class and serum creatinine level. The majority of patients admitted to hospitals in England & Wales with UA or NSTEMI will not have heart failure and would therefore acquire no additional GRACE points above their mini-GRACE score since Killip class I scores zero points. Similarly the majority will also have normal renal function (scored as 1 to 7 points in GRACE thus acquiring a potential maximum of seven additional points). See Table 2.5.

Table 2-5. (*See online GRACE six-month mortality risk calculator :* www.outcomes-umassmed.org/grace)

KILLIP Class	GRACE points	Creatinine (μmol/l)	GRACE points
I	0	0-34	1
II	15	35-70	4
III	29	71-105	7
IV	44	106-140	10
		141-176	13
		177-353	21
		>354	28

For a given six-month mortality, mini-GRACE scores are therefore very similar to full GRACE scores when score values are at the lower end of the risk spectrum, but are less than full GRACE scores when risk scores rise above this level, and are most separated for those at the highest end of the risk spectrum.

'Adjusting' mini-GRACE scores

To make an assessment of the impact of impaired renal function and heart failure on the scores derived from the MINAP risk cohort, an adjustment was made to individual patient risk scores using additional data on these patients. The MINAP database records whether patients are taking a loop diuretic and whether the serum creatinine is above or below 200 μmol/L. These are dichotomous variables (yes/no) and are therefore less sensitive than the continuous variable of creatinine, or four categories of heart failure, recorded in the GRACE registry. Nevertheless, treatment with a loop diuretic was considered to be a surrogate marker for heart failure and was assigned 20 GRACE points (equivalent to a Killip class of around II). Patients with a serum creatinine below 200 μmol/L were assigned 5 additional points and above 200 μmol/L were assigned 20 additional points.

An 'adjusted' mini-GRACE score was then calculated for each patient in the MINAP-derived risk cohort and plotted against six-month mortality (see Figure 2-8 below). The model discrimination c-statistic for the 'adjusted' mini-GRACE score was 0.825 (95%CI 0.82 to 0.83). There was close overlap between the curve of six-month mortality against 'adjusted' mini-GRACE score derived from the MINAP risk cohort, and the curve of predicted 6-month mortality against full GRACE score derived from the GRACE registry, suggesting that both scores are predictive and applicable in an unselected population of patients with NSTEMI in England & Wales.

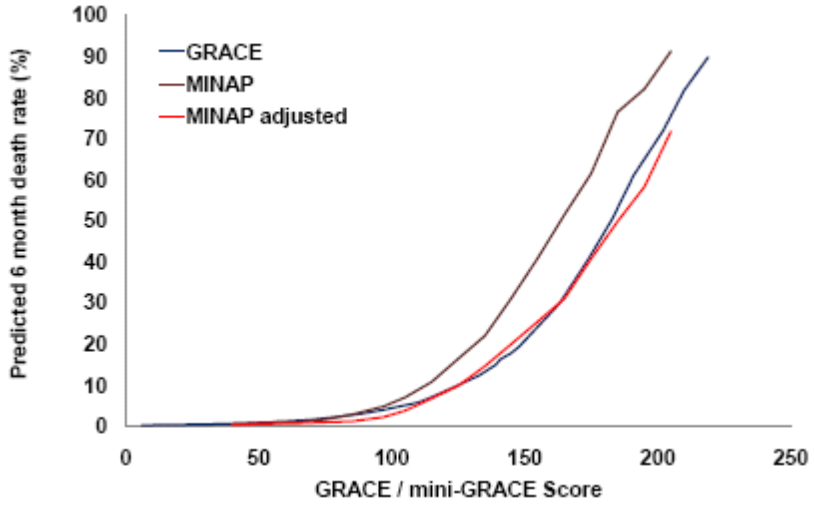

Figure 2-8. Six-month mortality using unadjusted MINAP risk cohort data (brown line) and 'adjusted' MINAP data (red line – see text for adjustment methodology) against mini-GRACE score, and predicted six-month mortality plotted against GRACE score from the GRACE Registry (blue line).

Predicted six-month mortality calculated for individual patients from the GRACE scoring system can therefore be used to stratify patients into one of the risk groups derived from the MINAP database and defined by the mini-GRACE risk quartiles/octiles. Reclassification of the MINAP risk cohort of patients into quartiles/octiles by 'adjusted' mini-GRACE resulted in very little change to their previously determined quartile/octile position using the unadjusted mini-GRACE score (because the impact of 'adjustment' was only significant at higher levels of risk, where only two quartiles exist). Thus only a few patients shifted from quartile 3 to quartile 4 and this had negligible effect on the six-month mortality ranges in these upper quartiles of risk.

The GDG based this risk analysis on six-month mortality data. The analysis suggests that the GRACE scoring system can be used to stratify patients into risk groups defined by the MINAP risk quartiles/octiles, and it is likely that any risk scoring system that predicts six-month mortality also could be used for this purpose.

Extrapolating trial data to a UK population

The absolute risk of adverse cardiovascular events among patients within RCTs is often difficult or impossible to determine from published data. Hence the GDG had difficulty in determining whether the results of any specific RCT can appropriately be extrapolated to an unselected population with UA or NSTEMI in England and Wales, and what proportion of the population should be considered for specific interventions.

The risk assessment described above allowed the GDG to position the RCT patients in the spectrum of risk seen in the wider population of patients with NSTEMI presenting to hospitals in England & Wales, using six-month mortality as an indicator of the overall risk of the RCT patients. In this way the GDG wished to make an assessment of the

proportion of patients for whom an intervention may be appropriate, and those for whom it may not.

To position the RCT within the spectrum of risk seen in unselected populations of patients with UA or NSTEMI the six-month mortality of RCT patients in the intervention and control groups of the trial were plotted onto the 'GRACE-Graph'. For this assessment the GDG selected the GRACE-graph rather than the MINAP-graph (adjusted or unadjusted – see above) because:

- GRACE registry data is well validated for prediction of six-month mortality (which is the prospective categorisation of risk that the GDG has recommended in this guideline)
- The two curves of six-month mortality against GRACE or mini-GRACE scores correlate well, particularly at the lower levels of mortality reported in randomised clinical trials
- The GRACE six-month predictive model is therefore applicable to patients with NSTEMI admitted to hospitals in England & Wales.

For example in the CURE trial of clopidogrel patients were risk stratified by TIMI score (increasing risk levels 0-7) (see Figure 2-9; and Section 3.2):

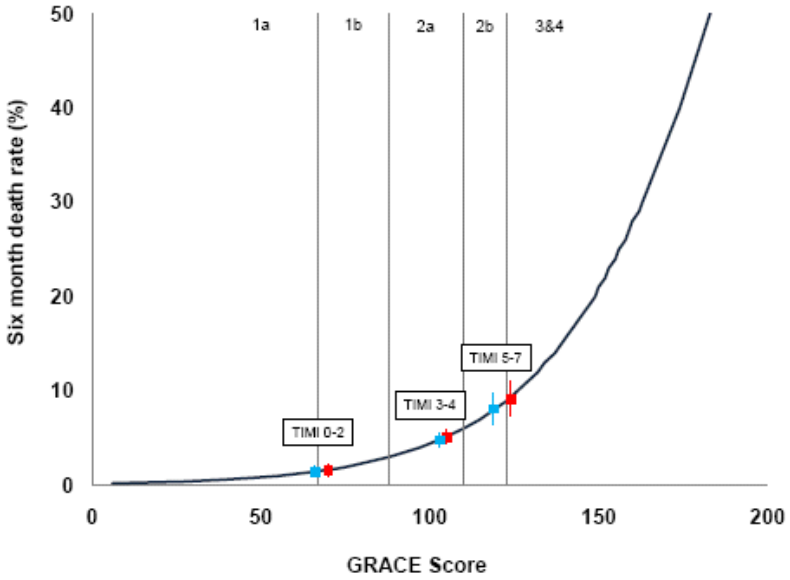

Figure 2-9. 6-month mortality (y-axis) and GRACE score (x-axis) data from the GRACE Registry. Six month mortality in CURE for placebo (red) and clopidogrel (blue) groups shown by TIMI risk stratum on the 'GRACE curve' (dark blue). TIMI risk score 0-2 N=3276, TIMI risk score 3-4 N=7297, TIMI risk score 5-7 N=1989. Bars are 95%CI. Vertical grey lines show risk cohorts (1a, 1b, 2a, 2b, 3 & 4 – see Risk chapter). Risk groups 3 and 4 include approximately 50% of an unselected (England & Wales) population with UA/NSTEMI at highest risk. CURE mortality data provided by Fei Yuan.

From the example above the average underlying risk of patients recruited to the CURE trial can be expressed by their average six-month mortality (around 5%). Of note, the difference in mortality between the treatment (clopidogrel) and placebo arms was relatively small (despite being statistically significant) compared to the potential for large mortality differences between individuals at differing levels of risk of an adverse cardiovascular event

Summary

The risk exercise undertaken led the GDG to conclude:

- Patients with UA/NSTEMI admitted to hospitals in England & Wales can be stratified into ascending risk cohorts (1a, 1b, 2a, 2b, 3 & 4) using a risk scoring system that predicts six-month mortality (such as GRACE [21]).

- Risk and six-month national mortality data derived from MINAP correlated well with six-month predicted mortality from the international GRACE registry.

- Positioning the six-month mortality data from randomised trials relevant to patients with UA/NSTEMI onto the GRACE-graph allows more precise definition of those groups of patients for whom there is evidence of benefit from an intervention. Moreover, this process defines those at higher risk who fall outside clinical trials and for whom recommendations must be made by extrapolation of clinical trial data.

Risk of bleeding

The principle of assessing a patient's baseline risk of an adverse outcome on admission to hospital, and to use this to inform decisions regarding clinical interventions is well established in international guidelines[7,8] and has been further developed by this guideline. Bleeding complications are known to increase the risk of an adverse outcome[7,8] and a number of factors are recognised as predictors of bleeding risk, such as advancing age[46], female gender, renal impairment, and pre-existing anaemia. Guidelines stress the importance of balancing the potential for treatment-related hazards against treatment benefit when making decisions regarding individual patient management, but whilst scoring systems have been developed to assist the clinician in estimating a patient's baseline ischaemic risk the estimation of bleeding risk has largely been left to clinical judgement.

Recently the CRUSADE Investigators have published a quantitative scoring system for estimating the in-hospital risk of bleeding [47]. CRUSADE is a quality improvement initiative and has collected prospective observational data in a registry of over 89,000 patients with non-ST elevation acute coronary syndromes.

As Anderson stresses in an editorial[47] published alongside the CRUSADE publication, the availability of a formal scoring system for bleeding improves the ability of clinicians to balance underlying ischaemic risk against the risk of using pharmacological agents, and interventional procedures, which carry with them a potential hazard. The CRUSADE investigators have made available a web based tool for the calculation of individual patient bleeding risk[d]. Further research will need to be undertaken to integrate ischaemic and bleeding related scoring systems so that an assessment of individual patient net clinical benefit can be refined, particularly as those at highest ischaemic risk (who potentially have the most to gain from interventions) are usually those at highest bleeding risk also. Meantime, clinicians may find the CRUSADE scoring system a useful tool for formal assessment of bleeding hazard, rather than relying on clinical judgement alone.

Conclusion

The assessment of the patient level of risk undertaken in this chapter is an attempt to quantify risk based on predicted six-month mortality for patients admitted to hospital with UA or NSTEMI. In this assessment the GDG has defined risk groups across a spectrum of low-high, which are applicable to a UK population and useful for informing recommendations regarding the clinical indication, and cost effectiveness, of certain interventions (such as GPIs, and early invasive management strategies). These are considered in detail in Sections 0 and 5.1 of the guideline.

For the purpose of this guideline, and *based on the predicted 6-month mortality*, and the quartiles of risk derived from MINAP, the following categorisation of risk was determined (see

[d] See: http://www.crusadebleedingscore.org/index.html

Table 2-6). This categorisation has the advantages of being easily memorable and helpful in positioning the conclusions of clinical trials in a context relevant to a UK population with UA/NSTEMI.

Table 2-6. Guideline risk categorization.

Risk category	Range of mini-GRACE score defined by MINAP quartiles/octiles	Corresponding range of 6 month mortality	% of ACS population	Guideline risk categories	
1a	<70	0-1.6%	12.5%	Lowest	≤1.5%
1b	71-87	1.6%-3.1%	12.5%	Low	>1.5% ≤3.0%
2a	88-100	3.1-5.5%	12.5%	Intermediate	>3.0% ≤6.0%
2b	101-112	5.5%-9.5%	12.5%	High	>6.0% ≤9.0%
3 & 4	>112	>9.5%	50.0%	Very high	>9%

Clinicians should take a more rigorous approach towards the assessment of a patient's underlying risk. This is relevant to decisions regarding appropriate clinical management and for informing patients of the balance between potential risks and benefits of interventions. The GDG used the GRACE score extensively in this risk assessment. Any risk scoring system capable of predicting 6-month mortality with comparable predictive accuracy could be used.

2.2.1 RECOMMENDATIONS

R1 As soon as the diagnosis of unstable angina or NSTEMI is made, and aspirin and antithrombin therapy have been offered, formally assess individual risk of future adverse cardiovascular events using an established risk scoring system that predicts 6-month mortality (for example, Global Registry of Acute Cardiac Events [GRACE]).

R2 Include in the formal risk assessment:

- a full clinical history (including age, previous myocardial infarction [MI] and previous percutaneous coronary intervention [PCI] or coronary artery bypass grafting [CABG])
- a physical examination (including measurement of blood pressure and heart rate)
- resting 12-lead electrocardiography (ECG) (looking particularly for dynamic or unstable patterns that indicate myocardial ischaemia)
- blood tests (such as troponin I or T, creatinine, glucose and haemoglobin).

R3 Record the results of the risk assessment in the patient's care record.

R4 Use risk assessment to guide clinical management, and balance the benefit of a treatment against any risk of related adverse events in the light of this assessment.

R5 Use predicted 6-month mortality to categorise the risk of future adverse cardiovascular events as follows[e]:

Predicted 6-month mortality	Risk of future adverse cardiovascular events
1.5% or below	Lowest
> 1.5 to 3.0%	Low
> 3.0 to 6.0%	Intermediate
> 6.0 to 9.0%	High
over 9.0%	Highest

2.2.2 Research Recommendations

What is the clinical and cost effectiveness of the systematic use of risk scoring systems (in addition to clinical assessment) for ischaemic outcomes and bleeding complications in the management of unstable angina and NSTEMI (at all levels of risk) compared with clinical assessment alone?

For patients with unstable angina and NSTEMI (at differing levels of risk), how do clinical outcome data (adverse cardiovascular events and bleeding complications) collected in cardiac registries compare with data derived from randomised clinical trials?

[e] Categories are derived from the Myocardial Ischaemia National Audit Process (MINAP) database.

3 ANTI–PLATELET THERAPY

Atheromatous plaque within the wall of a coronary artery is usually not exposed to blood flowing within the lumen of the artery because it is covered by cells forming the inner layer (intima) of the arterial wall. When such plaque is chronically progressive it gradually increases obstruction to coronary blood flow and may result in 'stable angina' (a symptom usually comprising chest tightness or discomfort on exertion and eased by rest) (see NICE clinical guideline on Chest Pain, due for publication February 2010). However, if the intimal lining develops a 'rupture', exposing underlying atheroma to intracoronary blood, a process of blood clot formation (thrombosis) is initiated. This acute pathological process is associated with the clinical syndromes of STEMI, NSTEMI or UA which are characterised by the sudden onset or worsening of angina, often occurring at rest, and with or without evidence of heart muscle (myocardial) infarction. A Universal Definition of MI has recently been adopted[48,49].

Circulating blood platelets are involved early in the development of thrombus formation. When stimulated, such as by exposure to sub-intimal atheromatous material rich in lipid and collagen, they aggregate, release various vasoactive substances from their granules, and encourage the development of a blood clot rich in fibrin and red blood cells. Anti–platelet drugs can interfere with a number of different pathways promoting platelet aggregation, release of granule contents, and stimulation of vasoconstriction, and may therefore influence the pathophysiological mechanisms underlying acute coronary syndromes.

3.1 ASPIRIN

3.1.1 CLINICAL INTRODUCTION

Aspirin was the first anti–platelet agent to be investigated and has been prescribed for many years for patients at risk of vascular 'events' such as heart attacks (myocardial infarction, hereafter referred to as MI) and strokes. It blocks cyclooxygenase, an enzyme involved in the pathway of prostaglandin and thromboxane synthesis, agents which are highly vasoactive and prothrombotic. Platelets do not synthesise new cyclooxygenase once exposed to aspirin and so its effect persists for the life of each inhibited platelet.

Given the widespread acceptance of the use of aspirin in current practice the GDG limited the evidence search to systematic reviews to determine the evidence for people with UA or NSTEMI and asked the following clinical question:

> *'What is the efficacy and safety of **aspirin** therapy in the medical management of patients with UA or NSTEMI compared to placebo?'*

3.1.2 *CLINICAL METHODOLOGICAL INTRODUCTION*

The Cochrane database was searched from 1995 to 2009 for systematic reviews comparing aspirin with placebo in the management of people with non ST-segment elevation ACS. For a review to be included, it had to be specific to the non ST segment elevation ACS population (it had to contain > 60% unstable angina/NSTEMI). Studies were included if they reported death, MI, bleeding, stroke, re-revascularisation, left ventricular function, and quality of life.

One well-conducted systematic review compared anti–platelet therapy with placebo in a large group of people at high risk of occlusive arterial disease (195 RCTs; N=135,640). The risk of vascular events (defined as nonfatal MI, nonfatal stroke, or death from a vascular cause or death from an unknown cause) in a sub-population of people with UA was compared in those receiving anti–platelet agents (predominantly aspirin) and those receiving placebo [50].

3.1.3 *CLINICAL EVIDENCE STATEMENTS*

►Vascular events

Compared to those treated with placebo, people with UA treated with anti–platelet agents (predominantly aspirin) had a significantly lower risk of vascular events (12 RCTs, N=5031; RR 0.60 [95% CI 0.51 to 0.71]) [50].

Level 1+

3.1.4 *HEALTH ECONOMIC METHODOLOGICAL INTRODUCTION*

One relevant study was identified. This was a cost-effectiveness analysis that evaluated aspirin versus no aspirin use in UA patients [51].

Fidan et al.[51] reported a cost–effectiveness analysis from a UK NHS perspective. It incorporated the cost of aspirin and life-years gained with treatment to estimate cost effectiveness in terms of cost per life-year gained. Aspirin costs were based on doses from clinical trials and national UK costs (2000). A mortality model (the IMPACT model[52]) was used to estimate deaths prevented/postponed with aspirin treatment in UA over one year and median survival estimates were then applied to extrapolate this impact in terms of life-years gained. The IMPACT mortality model was based on CHD patient numbers, uptake of treatment, median survival in people with and without CHD developed using data from sources describing England and Wales 2000. The effectiveness of aspirin was based on a meta–analysis by the Antithrombotic Trialists' Collaboration (2002)[50]. Results were presented overall and for ten-year age bands.

The study is judged directly applicable to the UK NHS. The key potential limitation of the study is that it only incorporates the cost of aspirin - other relevant events would have cost implications (such as MIs avoided). In addition, the incorporation of treatment-related costs for the full time horizon is recommended NICE methodology and is not included. Other minor limitations include the unclear reporting of methods regarding

the cost calculations – it is unclear if aspirin use is specifically acute use or continued for the whole year – and the lack of incorporation of quality of life (to estimate QALYs).

3.1.5 HEALTH ECONOMIC EVIDENCE STATEMENTS

Fidan et al.[51] reported an incremental cost–effectiveness ratio (ICER) of £58 per life year gained for aspirin use compared to no aspirin use. ICERs in different ten-year age bands ranged between £42 and £85 per life-year gained. Sensitivity analysis was carried out where ICERs were recalculated using minimum and maximum estimates for cost of aspirin, efficacy of aspirin and life-years gained and ranged between £34 and £114 per life year gained.

The lack of inclusion of costs other than the cost of aspirin could potentially be a serious limitation. It is not possible to judge exactly how their inclusion would impact results although it would probably increase some costs (such as bleed costs) while decreasing other cost (such as MI costs due to a reduction in events with aspirin). Nevertheless, as the estimated ICERs are so low it is judged likely that aspirin would remain cost effective if additional costs were incorporated. Incorporation of quality of life is also judged unlikely to change conclusions about cost effectiveness.

3.1.6 EVIDENCE SUMMARY

The meta-analysis involving 197 RCTs with over 135,000 patients randomised to receive an anti–platelet agent versus placebo was accepted as the sole source for review.

The risk of vascular events was considered for various 'at-risk' groups (such as those with coronary artery disease, stroke, or peripheral arterial disease) and for sub-populations such as those with MI, UA, stable angina, and those undergoing coronary revascularisation (angioplasty or coronary bypass grafting). Of the trials analysed aspirin was the predominant anti–platelet agent given.

One of the sub-groups analysed was those with UA but because of the more recently changed definition of MI[49] many of the patients in this previous category will have been those who would currently be classified as having NSTEMI. The GDG were therefore unable to separate those who would currently be regarded as having UA from those with NSTEMI, but in practice this is of little importance because the investigators demonstrated that anti–platelet therapy significantly reduced the number of vascular events in all the relevant coronary disease sub-groups (acute MI, UA, stable angina; range of odds reduction 25 to 46%). The group classified by the previous definition as having UA (n=5031) had a 46% odds reduction of having a vascular event during the follow-up period, which varied between trials (6 days to 18 months).

3.1.7 EVIDENCE TO RECOMMENDATIONS

The GDG concluded that aspirin therapy reduces the risk of a vascular event and should be offered to all patients with UA or NSTEMI unless contraindicated (such as by active

bleeding, current peptic ulceration, or for those considered clinically to be at a high potential risk of the consequences of bleeding, for example, recent neurosurgery or haemorrhagic stroke)[53]. It should be noted that those at higher risk of bleeding, such as those with renal impairment, may have a higher absolute risk of a vascular event and therefore may have a higher potential absolute benefit from aspirin, which may outweigh even the higher bleeding risk associated with their underlying renal impairment. Individual patient circumstances will dictate the advisability of giving aspirin but in only a small minority would it be anticipated that the risk of prescription will outweigh the benefit.

Use of anti–platelet agents has also been associated with about a twofold increase in the rate of major bleeding, but because the background rate of bleeding was low this increased risk was far outweighed by the longer term benefit of anti–platelet treatment, a finding also supported by others[54]. No additional longer term benefit was found from maintenance doses of aspirin higher than 75-150 mg, though the Trialists recommended a loading dose of 150-300 mg in clinical situations where an immediate antithrombotic effect is required "such as MI….and UA".

An aspirin loading dose of 300 mg should be given as soon as possible followed by daily maintenance of 75-150 mg. The use of other anti–platelet agents, such as clopidogrel and the GPIs are considered in this guideline but would normally be given on the background of regular aspirin therapy except where aspirin is considered contraindicated.

3.1.8 RECOMMENDATIONS

R6 Offer aspirin as soon as possible to all patients and continue indefinitely unless contraindicated by bleeding risk or aspirin hypersensitivity.

R7 Offer patients a single loading dose of 300 mg aspirin as soon as possible unless there is clear evidence that they are allergic to it.

R8 For patients with aspirin hypersensitivity, clopidogrel monotherapy should be considered as an alternative treatment. (This recommendation is from 'MI: secondary prevention', NICE clinical guideline 48.)

3.2 CLOPIDOGREL

3.2.1 CLINICAL INTRODUCTION

Clopidogrel was the subject of a NICE TA (TA80) published in July 2004. This made three recommendations:

- the use of clopidogrel with aspirin in the management of NSTEMI considered to be at high or medium risk of MI or death
- the relevance of assessing risk in such patients,
- duration of treatment.

Only the first two recommendations from this TA are pertinent to the scope addressed by this guideline and will be updated in this guidance.

Clopidogrel is an anti–platelet agent and part of the thienopyridine group that block platelets by inhibition of the adenosine diphosphate (ADP) pathway. Clopidogrel has been investigated for its potential to decrease the risk of an adverse cardiovascular outcome in patients with ACS, for reasons which are similar to those described earlier with respect to aspirin therapy. The data reviewed in this chapter refers to clopidogrel hydrogen sulphate; we have not addressed whether other, more recently introduced, clopidogrel salts are equivalent.

Prasugrel[55-57] is an anti–platelet similar to, though with various features different from clopidogrel, but the subject of a separate NICE Appraisal (published 2009) and not considered in this guideline.

The clinical question asked, and upon which the literature searching was undertaken, was:

> *'What is the efficacy and safety of clopidogrel in the medical management of patients with UA or NSTEMI compared to other antiplatelets or placebo?'*

3.2.2 CLINICAL METHODOLOGICAL INTRODUCTION

To look at evidence published since the NICE TA80, the literature was searched for systematic reviews or RCTs published from 2003 to 2009. Because of the high number of randomised trials in this area, the GDG only considered RCTs with a sample size of 250 or more. In addition, for a study to be included at least 60% of patients enrolled needed to have a diagnosis of non ST-segment elevation ACS, and the study had to report on at least one of the six key clinical outcomes agreed for this guideline (30 day survival, re-infarction, LV function, re-vascularisation, quality of life, and serious complications).

Overall, studies identified in this area add some evidence to a number of issues:

- **Timing of clopidogrel**

  The current two approaches are either to initiate treatment early (for example, in A&E, or 'upstream') or wait until the time of cardiac catheterisation when the coronary anatomy can be defined and a decision made on whether revascularisation is deemed appropriate. The advantage of starting treatment early is the potential to reduce early ischaemic events, but the disadvantage is the potential for increased bleeding in patients who subsequently require early CABG[58]. The delayed approach, of using clopidogrel only after cardiac catheterisation, would avoid the increased bleeding risk for patients who undergo CABG.

- **Loading dose of clopidogrel** (300mg versus 600mg)[f]

- **Benefits of clopidogrel with, or without, glycoprotein IIb/IIIa inhibitors (GPIIb/IIIa)**, on a background of aspirin therapy

NICE TA80 assessed the double blind CURE RCT (N= 12562; mean follow-up nine months), in which patients with non ST-segment elevation ACS were randomized to clopidogrel (loading dose of 300 mg followed by 75 mg/day) or placebo and both arms received aspirin (75–325 mg/day) [59] [60] . The primary end-point (cardiovascular death, MI, or stroke) at 30 days was significantly lower in the clopidogrel group. There was also some further benefit which developed later (30 to 365 days). There was no significant excess in life-threatening bleeds in each period.

Since the NICE TA80, two additional subgroup analyses of the CURE study have been published [61,62]. Lewis et al. compared clopidogrel with placebo (on a background of aspirin) in a subgroup of people undergoing PCI (N=2658). Outcomes were assessed in those who received PCI less than 48 hours since randomisation, greater than 48 hours since randomisation, and after hospital discharge. Fox et al. evaluated the benefits and the potential for increased bleeding among the patients who underwent PCI, CABG or medical therapy (no revascularisation) [61].

Two new RCTs [63,64] were identified that compared different doses of clopidogrel (300 mg versus 600 mg) on a background of aspirin. In the Cuisset et al. RCT (N=292 non ST-segment elevation ACS; follow-up 30 days), the timing between the loading dose of clopidogrel and PCI was 12 to 24 hours. In the Yong et al double blind RCT (the PRACTICAL Trial) (N=256; follow-up six months) all patients received 300 mg of clopidogrel 12 hours prior to randomisation. At randomisation, patients received either another 300 mg of clopidogrel (the 600 mg group) or matching placebo (300 mg group). Angiography was performed no sooner than two hours after study drug administration. Mean time between randomisation and the first 300 mg dose of clopidogrel was 12

[f] Currently the 600mg loading dose of clopidogrel is not licensed in the UK.

hours. Mean time between study drug administration and angiography was 13.2 hours (SD=14.4 hours) and between study drug administration and PCI was 16.1 hours (SD=10.9 h) [63].

The CREDO study evaluated the effects of long-term treatment (12 months) with clopidogrel (75 mg once daily) in patients undergoing elective PCI (N=2116; 52.8% UA; 13.7% recent MI; 32.8% stable angina and other) [65]. The CREDO trial was excluded from TA80 on the grounds that the population was undergoing 'elective' PCI; however the GDG included CREDO as the population contained a large proportion of people with UA and recent MI such that it reached the 60% UA/NSTEMI inclusion criterion. The optimal timing for the initiation of clopidogrel (300mg) before PCI was evaluated in a post-hoc analysis of the CREDO RCT [66]. The analysis included 1815 patients who underwent PCI during the index cardiac catheterization procedure, and assessed the effect of the duration of clopidogrel pre-treatment (<15 hours or ≥15 hours before PCI) on the composite outcome of death, MI, or urgent target vessel revascularisation at 28 days. The timing of clopidogrel pre-treatment was not randomised and there was a high (40-50%) concomitant use of GPI.

The TARGET study randomised patients undergoing elective or urgent PCI-stenting to tirofiban or abciximab on a background of aspirin (75 to 325 mg), and heparin (to achieve ACT ≥ 250 seconds). In a post-hoc analysis [67] outcomes were assessed according to whether patients received 300mg of clopidogrel before PCI (N=4477) versus immediately after the procedure (N=332). A limitation of this study is that the timing of clopidogrel administration was at the cardiologist's discretion and thus, was not randomised.

It should be noted that differing study designs, dosing and titration regimens and the differing populations included might limit direct comparisons between studies.

3.2.3 CLINICAL EVIDENCE STATEMENTS

Pre-treatment with clopidogrel in patients receiving PCI, CABG, or medical management[61]

See summary

Table 2-1.

Compared to placebo, clopidogrel significantly reduced the risk of:

- CV death, MI or stroke in people undergoing PCI
- CV death, MI or stroke in people having medical management.

There was a non–significant difference between the placebo and clopidogrel arms for:

- CV death, MI or stroke in people undergoing CABG.
- Major bleeding in people undergoing CABG

- Life threatening bleeding in people undergoing CABG.

This study concluded that clopidogrel use was associated with a lower incidence of the composite endpoint compared with placebo. This trend was similar across different subpopulations undergoing CABG or PCI, and those patients treated medically.

Evidence Level 1+

Table 2-1. Subgroup analysis of the CURE study by type of revascularisation strategy [61]

Outcome	Subgroup	N	Clopidogrel	Placebo	RR(95% CI)	p
CV death, MI, or stroke	CABG	2072	14.5 %	16.2 %	0.89 (0.71 to 1.11)	Not reported
CV death, MI, or stroke	PCI	2658	9.6 %	13.2 %	0.72 (0.57 to 0.90)	0.004
CV death, MI, or stroke	Medical management (no PCI or CABG)	7985	8.1 %	10.0%	0.80 (0.69 to 0.92)	< 0.003
Major bleeding	CABG	2072	9.6%	7.5%	1.27 (0.96, to 1.69)	0.095
CURE life threatening bleeding	CABG	2072	7.0%	5.7%	1.24 (0.89 to 1.73)	0.20

Fox et al. also highlighted that whereas no excess in any bleeding was observed for patients stopping clopidogrel more than five days before surgery, a non–significant excess in major bleeding was seen for those who continued the drug within five days of surgery. However, the study indicates that when using the more stringent TIMI or GUSTO definitions of major bleeding (used in most trials), there was not an increase in major bleeding. These results suggest that the use of clopidogrel within five days before CABG is associated with more mild to moderate bleeding but no excess life-threatening bleeding.

Relationship between pre-treatment with clopidogrel and PCI timing

See Table 2-2 andTable 2-3.

Another subgroup analysis of the CURE RCT [62] (N= 2538 undergoing PCI) showed consistent treatment benefit of clopidogrel over the nine-month follow-up period

regardless of the timing of PCI after randomisation (PCI < 48 hours, PCI ≥ 48 hours, PCI after discharge) for the composite endpoint of CV death or non-fatal MI. The data suggested that the greatest benefit accrued in those patients undergoing earlier intervention, though differences did not reach significance.
Evidence Level: 1+

Table 2-2. CURE study – subgroup analysis by timing of PCI [62]

Outcome	PCI timing	N	Clopidogrel	Placebo	RR (95% CI)	p
Primary endpoint (cardiovascular death or nonfatal MI)	Overall	2658	8.8%	12.6%	0.69 (0.54 to 0.87)	0.002
Primary endpoint (cardiovascular death or nonfatal MI)	< 48 hours	370	6.7%	12.5%	0.53 (0.27 to 1.06)	Not reported
Primary endpoint (cardiovascular death or nonfatal MI)	≥ 48 hours until hospital discharge	1360	8.7%	11.9%	0.72 (0.51 to 1.01)	Not reported
Primary endpoint (cardiovascular death or nonfatal MI)	After hospital discharge	928	9.8%	13.8%	0.70 (0.48 to 1.02)	Not reported

The CREDO trial[65] was undertaken to investigate two principal objectives; first, to evaluate the benefit of long-term (12-month) treatment with clopidogrel after PCI, and second, to determine the benefit of initiating clopidogrel with a pre-procedure 300mg loading dose. Patients were randomly assigned to receive a 300-mg clopidogrel loading dose (n=1053) or placebo (n=1063) three to 24 hours before PCI. Thereafter, all patients:

- received clopidogrel, 75 mg/d, through day 28. From day 29 to 12 months,
- patients in the loading-dose group received clopidogrel, 75 mg/d, and those in the control group received placebo. Both groups received aspirin throughout the study. At one year, long-term clopidogrel therapy was associated with a 26.9% relative reduction in the combined risk of death, MI, or stroke (95% CI 3.9% to 44.4%; *p*=.02; absolute reduction, 3%). Clopidogrel loading pre-PCI overall did not significantly reduce the combined risk of death, MI, or urgent target vessel revascularization at 28 days (reduction 18.5%; 95% CI, −14.2% to 41.8%; *p*=.23). However, in a pre-specified subgroup analysis, patients who received

clopidogrel loading at least six hours before PCI did show a relative risk reduction of 38.6% (95% CI, −1.6% to 62.9%; *P*=.051) compared with no reduction with treatment less than six hours before PCI. Risk of major bleeding at one year increased, but not significantly (8.8% with clopidogrel vs 6.7% with placebo; *p*=.07).

The optimal timing for a 300mg loading dose of clopidogrel before PCI was further evaluated in a post hoc analysis of the CREDO study [66]. All patients received 75 mg of clopidogrel at the time of PCI but some were randomized to receive also a loading dose of clopidogrel (300 mg) 3 to 24 hours before PCI. The incidence of the 28-day combined endpoint of death, MI, or urgent target vessel revascularization, was similar in those patients who simply received 75mg of clopidogrel at the time of PCI and those who received a clopidogrel loading dose less than 15 hours before PCI. The benefit of clopidogrel loading was confined to those patients pre-treated more than 15 hours before the PCI procedure (RR reduction 58.8% [p= 0.028] versus placebo).

Evidence Level: 2+

Table 2-3. CREDO study – Post hoc analysis by timing of pre-treatment with clopidogrel before PCI [66]

Outcome	Clopidogrel ≥15h prior to PCI (N=202)	Clopidogrel < 15H prior to PCI (N=645)	Placebo prior to PCI (N=915)
Death, MI, or urgent target vessel revascularization at 28 days (primary endpoint)	3.5%	7.8%	8.3%
Clopidogrel ≥ 15 hours vs. placebo p= 0.018 Clopidogrel ≥ 15 hours vs. < 15h p= 0.033		Clopidogrel <15 h vs. placebo p=0.72	

Note: The rate of major and minor bleeds was identical in the 3 patient subsets irrespective of treatment allocation.

Loading doses of clopidogrel in patients undergoing PCI (300mg versus 600mg)[g]

Two RCTs [64] [63] addressed the issue of clopidogrel loading dose (600 mg versus 300 mg) prior to PCI or angiography. One (Cuisset, 2006 103 /id) randomized 292 patient with NSTEMI/UA to receive either 300mg or 600mg of clopidogrel at least 12 hours before

[g]Currently the 600mg loading dose of clopidogrel is not licensed in the UK.

undergoing PCI and excluded the use of GPIs. The other {Yong, 2009 4178 /id} randomized 256 patients with UA/NSTEMI to receive either 300mg or 600mg of clopidogrel prior to undergoing coronary angiography. 140 patients then underwent PCI and 68.6% of these received a GPI. See Table 3-4 for a summary of results.

One RCT [64] showed a significant reduction in recurrent ischaemic events in the 600 mg clopidogrel group compared with the 300 mg group with no patient experiencing post-procedural major bleeding or requiring transfusions.

Evidence Level: 1+

By contrast, the PRACTICAL trial [63] showed a non–significant difference between the 600 mg and 300 mg clopidogrel groups for:

- Post-PCI myonecrosis
- Death at six months
- MI at six months
- Stroke at six months
- Death / nonfatal MI / nonfatal stroke / hospitalizations for recurrent ischemia at six months
- TIMI major haemorrhage at one month
- TIMI minor haemorrhage at one month

Evidence Level: 1+

Table 2-4. Clopidogrel loading dose (300mg versus 600mg)

RCT	Outcome	N	Clopidogrel 300mg	Clopidogrel 600mg	RR (95% CI)	P
Cuisset et al. (2006)[64]	Recurrent ischaemic events at 30 days	292	12%	5%	2.57 (1.11 to 5.97)	0.02
Yong et al. (2009)[63]	post-PCI myonecrosis (primary outcome)	140 (PCI subgroup)	39.1%	39.1%	NR	1.0
Yong et al. (2009)[63]	Death at 6 months	256	1.65%	0.78%	2.13 (0.20 to 23.19)	0.51
Yong et al. (2009)[63]	MI at 6 months	256	4.96%	8.59%	0.58 (0.22 to 1.52)	0.26
Yong et al. (2009)[63]	Stroke at 6 months	256	0	0.78%	0.35 (0.01 to 8.63)	0.33
Yong et al. (2009)[63]	Death / nonfatal MI / nonfatal stroke / hospitalizations for recurrent ischemia at 6 months	256	13.2%	13.3%	1.00 (0.53 to 1.89)	0.99
Yong et al. (2009)[63]	TIMI major haemorrhage at 1 month	256	2.42%	1.52%	1.60 (0.27 to 9.40)	0.60
Yong et al. (2009)[63]	TIMI minor haemorrhage at 1 month	256	2.42%	2.27%	1.06 (0.22 to 5.18)	0.94

Triple therapy with clopidogrel

The TARGET trial[68] compared tirofiban and abciximab among PCI patients receiving an intracoronary stent. At six months, the combined endpoint of death, MI, and urgent target-vessel revascularisation was similar for both agents. A post-hoc analysis of the TARGET RCT [67] showed that clopidogrel pretreatment significantly reduced the risk of the primary composite end point of death, MI, or urgent target vessel revascularisation at 30 days (HR 0.63 [95% CI 0.44 to 0.89]; p= 0.009). There were non–significant differences in the incidence of major bleeding (0.8% clopidogrel pre-treatment versus 0.9% no clopidogrel pre-treatment, p=0.754), minor bleeding (3.6% clopidogrel pre-treatment versus 3.3% no clopidogrel pre-treatment, p=0.821), and frequency of transfusion (1.3% clopidogrel pre-treatment versus 0.9% no clopidogrel pre-treatment, p=0.800) in the index hospitalisation. In addition, compared with patients pre-treated for less than 6 hours, those who were clopidogrel-loaded for more than six hours before PCI had a 29% lowering in 30-day events (6.9% vs. 4.9%, p=0.045). However, clopidogrel use in TARGET was not a pre-specified analysis, and clopidogrel use was non-randomised, and so selection bias may have occurred. Also, 93.1% of patients received clopidogrel and only 6.9% did not.**Evidence Level: 2+**

These results suggest that in addition to platelet inhibition provided by aspirin, heparin, and GPIs, early administration of clopidogrel before coronary stenting further reduces ischaemic complications during both elective and urgent PCI procedures.

3.2.4 HEALTH ECONOMIC METHODOLOGICAL INTRODUCTION

Previous NICE TA

The TA80 included a review of the economic literature up to mid-2003. An economic model from the clopidogrel sponsors (Sanofi-Synthelabo, Bristol-Myers Squibb) was also reviewed and the Assessment Group undertook their own analysis.

The model submitted by the clopidogrel sponsors (Sanofi-Synthelabo and Bristol-Myers Squibb) compared clopidogrel + aspirin versus aspirin alone for 12 months followed by aspirin alone. It was a lifetime analysis (40 years). The ICER was found to be £5668 per QALY gained. The Assessment Group noted that, while the sponsor's model was comprehensive and well-presented, there were some methodological concerns.

The model developed by the Assessment Group examined the same comparison and had a similar structure; the main differences were reported in the estimation of resource use and estimates of utility. The resulting ICER was £6078 per QALY gained. Various aspects of uncertainty were also evaluated. It was concluded that clopidogrel in combination with aspirin was cost effective compared to aspirin alone. Different durations of clopidogrel treatment were also evaluated (one, three, six months) – the cost per QALY gained increased as duration of treatment increased (£824 to £13,988). The ICER based on one month of clopidogrel treatment was £824 per QALY gained.

Clopidogrel effectiveness data in both analyses were based on the CURE trial but baseline event and revascularisation rates were taken from UK-specific sources as they differed significantly from the trial data.

New evidence

Three relevant cost-effectiveness analyses from a UK perspective were identified [69-71]. These included two modelling studies and one RCT based evaluation. In addition 17 studies were identified from other perspectives [72-85]; given the availability of good quality UK evidence these were not reviewed.

Karnon et al.[69] reports a lifetime model evaluating the cost effectiveness of clopidogrel (for one year) in combination with aspirin compared to aspirin alone in patients with UA/NSTEMI; the model appears very similar to the manufacturer and Assessment Group models considered in TA80. Clopidogrel effectiveness was based on data from the CURE RCT. Baseline event and revascularisation rates were adjusted using UK-specific data. Cost effectiveness was expressed in terms of cost per QALY gained, and also per life year gained and event avoided (vascular death, MI, stroke).

The evaluation is reported as being part-funded by the clopidogrel sponsors and having informed NICE decision-making; as such it may be a publication based on the manufacturer submission already considered as part of TA80. However, as results do not match it has been considered as new evidence.

Heeg et al.[70] presents a lifetime model with separate cost–effectiveness evaluations of clopidogrel (for one year) in combination with aspirin compared to aspirin alone based on CURE (UA/NSTEMI), PCI CURE (UA/NSTEMI undergoing PCI), and CREDO (PCI – broader than just UA/NSTEMI). Event rates are taken from the international trials i.e. UK—specific baseline rates are not incorporated. There are some concerns regarding methodological quality due to unclear reporting. Cost effectiveness was expressed in terms of cost per life year gained.

The RCT based evaluation reported by Lamy et al.[71] incorporated resource use and outcomes from the CURE study and applied UK unit costs in order to evaluate the cost–effectiveness of clopidogrel in combination with aspirin compared to aspirin alone in patients with UA/NSTEMI. Both costs and outcomes were evaluated for the follow-up of the trial (up to 1 year) and were not extrapolated further. Resource use and event rates were based on an international dataset (only 5.9% from the UK). Cost effectiveness was expressed in terms of cost per event avoided (cardiovascular death, MI, stroke). The CURE study, of which this economic analysis forms part, was funded by the clopidogrel sponsors.

3.2.5 HEALTH ECONOMIC EVIDENCE STATEMENTS

Karnon et al. [69] reported a cost per QALY gained for clopidogrel (for one year) in combination with aspirin compared to aspirin alone in patients with UA/NSTEMI of £7365 that was robust to various sensitivity analyses.

Heeg et al. [70] reported a cost per life year gained of £771 in patients with UA/NSTEMI although there were some methodological concerns regarding the paper which may

account for the more favourable result. Karnon et al. reported a cost of £6991 per life year gained in the same population.

Lamy et al. [71,71] reported a cost per event avoided of £10,366 in patients with UA/NSTEMI (one year analysis based on RCT resource use). Karnon et al. reported a similar cost of £10,599 per event avoided in the same population (lifetime modelling analysis). Lamy et al. reported that at 30 days clopidogrel in combination with aspirin dominated aspirin (that is it reduced costs and improved outcomes).

Heeg et al. [70,70] found that in patients with UA/NSTEMI undergoing PCI and in patients undergoing PCI in general clopidogrel in combination with aspirin was found to dominate aspirin alone (it reduced costs and improved outcomes).

The new economic evidence identified in this literature review supports the recommendation made in TA80 for use of clopidogrel in combination with aspirin in patients with UA/NSTEMI.

The NICE TA80 model, and the manufacturer's model submitted during the development of the TA, were both based on the TA047 glycoprotein IIb/IIIa inhibitor model. Duration of treatment was the main area of uncertainty but long-term treatment is outside the scope of this guideline. The Karnon study [69] assessed the uncertainty around cost effectiveness and found that 77% of simulations were under £20K / QALY and therefore affordable to the NHS. Lamy's 2004 post-hoc stratification of CURE data by TIMI risk [71] showed no change in cost-effectiveness conclusions, though the CURE study recruited patients which the investigators categorised as being medium and high risk patients.

The cost effectiveness of a 600mg loading dose compared to a 300mg loading dose has not been assessed. The additional cost is £5.04[86].

The group noted that clopidogrel will come off patent in 2010/11 and the effect this has on costs may need to be considered (though the likely reduction in cost would increase cost-efficacy).

3.2.6 EVIDENCE SUMMARY

The purpose of reviewing the use of clopidogrel in this guideline was to take account of research published since TA80 and determine whether the previous recommendations should be revised, and particularly to address:

- which people with UA/NSTEMI should be offered clopidogrel
- optimal time of administration
- optimal dosage
- its use peri-operatively in patients undergoing CABG
- its use when possible PCI is planned
- risks associated when combined with other therapies
- whether the previous assessment of cost-effectiveness still applies

Dosage and timing

At the time of the last Technology Appraisal a 300 mg loading dose of clopidogrel had previously been used in clinical trials, but more recently studies have investigated a 600 mg dose, which results in more rapid platelet inhibition. The PRACTICAL trial involved concomitant use of a glycoprotein inhibitor (GPI) in the majority of patients undergoing PCI, and showed no significant benefit of a higher loading dose of clopidogrel, whereas the study by Cuisset showed clear benefit for those scheduled to undergo early angiography of a 600mg loading dose when GPI use was excluded. These findings are in keeping with the post hoc analysis of the CREDO trial[66] which showed that when a 300mg loading dose of clopidogrel was given less than 15 hours before PCI the outcome was no different from a 75mg dose, whereas there was benefit of the higher loading dose (300mg) when this was given at least 15 hours ahead of PCI, suggesting that if PCI may be undertaken early a higher loading dose of clopidogrel should be used. This conclusion is supported by a sub-group analysis of the ISAR REACT trial[87] which suggested a 600mg dose of clopidogrel given at least two hours prior to a PCI procedure resulted in outcomes no different from the same loading dose given further in advance of the procedure.

Bleeding

In CURE, patients treated with both clopidogrel and aspirin had a small increased risk of major bleeding (3.7%) compared to aspirin alone (2.7%) but without an increase in associated mortality. Overall, there was no increased risk of bleeding in the patients who underwent CABG, although clopidogrel was discontinued prior to surgery in 93% of these patients. For those who discontinued clopidogrel more than five days before surgery, there was no increased risk of major bleeding within seven days after surgery (4.4% in the clopidogrel arm and 5.3% on placebo). For those who stopped medication within five days of CABG, the rate of major bleeds was 9.6% in the clopidogrel arm and 6.3% on placebo (relative risk 1.53; p=0.06). Overall, the risk of peri-operative bleeding may be increased in patients taking clopidogrel.

3.2.7 EVIDENCE TO RECOMMENDATIONS

In the previous technology appraisal 'moderate-to-high risk' was determined by "clinical signs and symptoms, accompanied by one or both of the following:

- the results of clinical investigations, such as new ECG changes (other than persistent ST elevation) indicating ongoing myocardial ischaemia, particularly dynamic or unstable patterns
- the presence of raised blood levels of markers of cardiac cell damage such as troponin"

Such clinical determinants of risk were still felt applicable, although the use of single risk components (such as troponin) predict risk poorly, particularly when used in a binary fashion (troponin elevated, or not)[11]. This guideline has addressed the issue of risk in more detail and offers a more comprehensive analysis of factors that clinicians may more accurately use to categorise individual patients into their broad categories of risk, and the use of risk scoring systems (see section 0).

The CURE trial also used a risk scoring system (TIMI 0 to 7; lowest-highest risk) to assess the effect of clopidogrel with increasing levels of baseline risk of an adverse outcome. Our interpretation of the data suggests that most patients enrolled in CURE were at low-medium risk of an adverse cardiovascular outcome, in the context of an unselected population of people with non ST-segment elevation ACS. High risk patients were not enrolled, which is at variance with previous interpretations of the trial's risk profile. See Figure 2-1 below.

The GDG concluded that clopidogrel was likely to be of benefit to those at risk levels 1b and above (six-month mortality >1.5%) by our classification, but that any benefit for those in the lowest risk cohort (1a; six-month mortality 0-1.5%) was likely to be very small and may be outweighed by any additional bleeding caused. In this lowest risk group of people admitted to hospital with UA/NSTEMI in England & Wales the decision regarding whether or not to prescribe clopidogrel may be left to individual physician discretion and based on an assessment of its potential benefit (particularly reducing ischemic events) against bleeding risk.

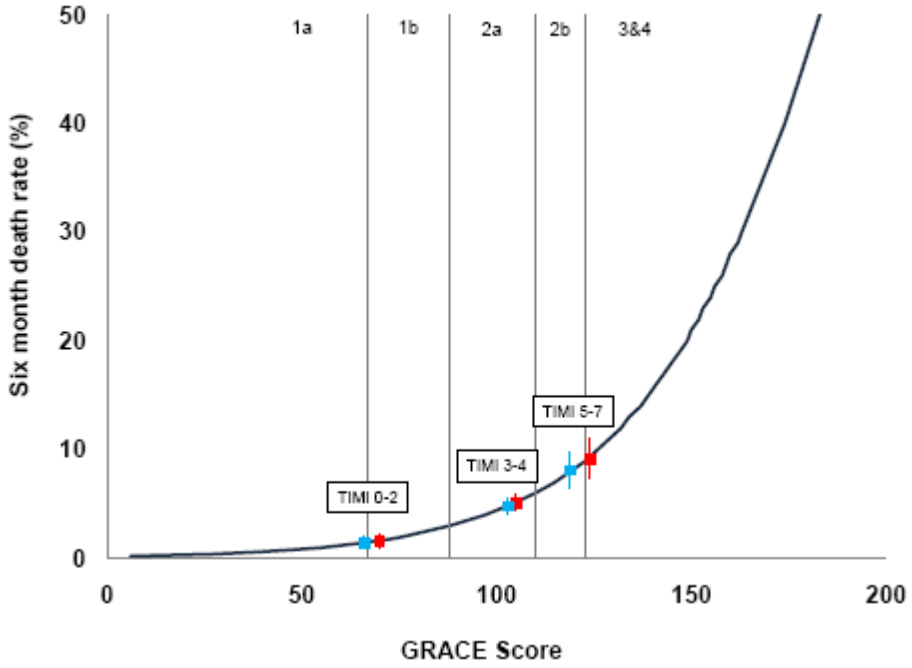

Figure 2-1. Six-month mortality (y-axis) and GRACE score (x-axis) data from the GRACE Registry. Six month mortality in CURE for placebo (red) and clopidogrel (blue) groups shown by TIMI risk stratum on the 'GRACE curve' (dark blue). TIMI risk score 0-2, N=3276, TIMI risk score 3-4 N=7297, TIMI risk score 5-7 N=1989. Bars are 95%CI. Vertical grey lines show risk cohorts (1a, 1b, 2a, 2b, 3 & 4 – see Risk chapter). Risk groups 3 and 4 include approximately 50% of an unselected (England & Wales) population with UA/NSTEMI at highest risk. CURE mortality data provided by Fei Yuan.

The group felt that evidence had now accumulated clearly supporting a loading dose of 300mg of clopidogrel for most people admitted with UA/NSTEMI. Those who are at lowest risk (predicted six-month mortality 0-1.5%; cohort 1a) have least to gain and the decision to prescribe clopidogrel for these patients should be made on an individual basis, depending on circumstances. If a very early (<24 hours) invasive intervention is planned, a higher loading dose should be considered, especially if a patient is

undergoing intervention within six hours. With a standard loading dose of 300 mg, it is likely that some patients will not yet have obtained the full anti-platelet effect of clopidogrel prior to the PCI procedure. The group considered that a higher loading dose for patients in whom a very early (within 24 hours) invasive strategy is planned was reasonable, on the basis that there was no evidence of any increased risk (acknowledging that this is not the same as saying that there is evidence of no increased risk) and the additional cost was modest. As the group were not able to formally review all the evidence for a 600-mg loading dose they were not able to recommend this at the time of publication. The group also stressed that clopidogrel should not be given without a confirmed diagnosis of ACS, because of its potential to increase bleeding risk.

In the circumstance where a cardiac arrest occurs before medical attendance, or where there is no clear clinical indicator of prior ischaemia then decisions about medical therapy should await assessment in hospital (clinical review, ECG, risk assessment, troponin etc.). It would not be appropriate to recommend clopidogrel to all patients who have had a cardiac arrest because clearly other conditions than an ACS may have precipitated the arrest.

After publication of TA80, NICE had clarified the recommendation "up to 12 months" to mean "for 12 months". This guideline is now in a position to formalise this change, along with a reference to the secondary prevention of MI guideline[4] and advising clinical review prior to stopping treatment (because of concerns about prescriptions automatically being stopped at 12 months, sometimes inappropriately, through primary care prescribing software reminders. Some patients, for instance those who have had drug eluting stents as part of complex PCI procedures, or those who have had late stent thrombosis, may be advised to remain on clopidogrel and aspirin indefinitely.

3.2.8 RECOMMENDATIONS

R9 As soon as the risk of adverse cardiovascular events has been assessed, offer a loading dose of 300 mg clopidogrel in addition to aspirin to patients with a predicted 6-month mortality of more than 1.5% and no contraindications (for example, an excessive bleeding risk)[h].

R10 Offer a 300-mg loading dose of clopidogrel to all patients with no contraindications who may undergo PCI within 24 hours of admission to hospital[i].

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[h] In line with 'Prasugrel for the treatment of acute coronary syndromes with percutaneous coronary intervention' (NICE technology appraisal guidance 182), prasugrel in combination with aspirin is an option for patients undergoing PCI who have diabetes or have had stent thrombosis with clopidogrel treatment.

[i] There is emerging evidence about the use of a 600-mg loading dose of clopidogrel for patients undergoing PCI within 24 hours of admission. Clopidogrel does not have UK marketing authorisation for use at doses above 300 mg. The GDG was not able to formally review all the evidence for a 600-mg loading dose and was therefore not able to recommend this at the time of publication (March 2010).

R11 It is recommended that treatment with clopidogrel in combination with low-dose aspirin should be continued for 12 months after the most recent acute episode of non-ST-segment-elevation ACS. Thereafter, standard care, including treatment with low-dose aspirin alone, is recommended. (This recommendation has been incorporated from TA80).

R12 Consider discontinuing clopidogrel treatment 5 days before CABG in patients who have a low risk of adverse cardiovascular events.

R13 For patients at intermediate or higher risk of adverse cardiovascular events, discuss the continuation of clopidogrel before CABG with the cardiac surgeon and base the decision on the balance of ischaemic and bleeding risk.

3.3 GLYCOPROTEIN IIB/IIIA INHIBITORS (GPIS)

3.3.1 CLINICAL INTRODUCTION

This section is intended to update the NICE TA on glycoprotein inhibitors (GPIs) (TA47) published in 2002.

Aspirin was the first anti–platelet therapy to be shown to improve outcome in acute coronary syndromes, and has been followed by other oral antiplatelet agents such as the thienopyridine clopidogrel, and also the intravenously administered GPIs, such as abciximab, eptifibatide or tirofiban. With increasingly aggressive platelet inhibition, and concomitant anticoagulant/antithrombotic therapy, the risk of bleeding has increased. TA47 made recommendations regarding the use of the GPIs in the treatment of ACS, and highlighted the importance of assessment of underlying patient risk because the overall benefit of these agents (the balance of benefit against risk of an adverse event) is greatest in those at highest underlying risk of recurrent myocardial ischaemia or infarction.

GPIIb/IIIa antibodies and receptor antagonists inhibit the final common pathway of platelet aggregation (crossbridging of platelets by fibrinogen binding to the GPIIb/IIIa receptor). Of these, abciximab is a large monoclonal antibody directed against the receptor, whereas tirofiban and eptifibatide are non-antibody receptor (often referred to collectively as "small molecule") inhibitors.

The clinical question asked, and upon which the literature was searched, was:

> *'What is the safety and efficacy of adding a GPI (tirofiban, eptifibatide and abcixmab) to aspirin and heparin therapy as adjunct therapy to patients with UA/ NSTEMI undergoing PCI compared to the combination of aspirin and LMWH?'*

Clinical methodological introduction

The literature was searched for systematic reviews and RCTs published since TA047, from 2002 to 2009. Because of the high number of randomised trials in this area, RCTs with a sample size of 250 or more were included. In addition, for a study to be included at least 60% of patients enrolled must have had a diagnosis of non ST-segment elevation ACS, and the study had to report on at least one of the six key clinical outcomes agreed for this guideline (i.e. mortality, re-infarction, LV function, re-vascularisation, quality of life, and serious complications).

Overall, studies identified add some evidence to the following areas:

- What is the clinical and cost effectiveness of GPIs (tirofiban, eptifibatide and abciximab) in the medical management (conservative) of patients with UA or NSTEMI?
- Triple anti–platelet therapy (aspirin + clopidogrel + GPI)
- Timing of GPIs – two options

  Clinicians who believe that, for individual patients, treatment with a GPI will have little clinical benefit given in advance ('upstream') of possible PCI might

choose to wait until angiography is undertaken before considering their use, whereas others may believe that a treatment benefit exists even without PCI and may therefore choose to give a GPI on the patient's arrival at the hospital.

- Which GPI has the best efficacy/safety profile?

Thirteen studies were identified [88-99] [100]. Of these, four RCTs [90] [89,92,96] were excluded as the population in each trial was less than 60% UA or NSTEMI.

The studies included for review were:

- Two meta-analyses [88,98] evaluating all three GPIs where an invasive strategy was not encouraged.
- The ISAR-REACT 2 [91,94], and ELISA-2 [97] RCTs assessed the addition of a GPI to aspirin, clopidogrel (or ticlopidine) and heparin in people with non ST-segment elevation ACS.
- Three RCTs, ISAR COOL [95] , ACUITY TIMING [99] and EARLY ACS [100], addressed the timing of administration of GPIs.
- One RCT [93] performed a head to head comparison between tirofiban and abciximab.

Overall, the evidence identified was diverse in terms of the study designs, populations included, definitions of MI, inclusion criteria, therapeutic agents, treatment strategies, and access to coronary revascularization.

3.3.2 HEALTH ECONOMIC METHODOLOGICAL INTRODUCTION

TA47 reviewed the economic literature published since the previous appraisal of GPIIb/IIIas, TA12. Economic models from the eptifibatide sponsors (Schering Plough), tirofiban sponsors (MSD), and abciximab sponsors (Eli Lilly) were also reviewed and the Assessment Group undertook their own analysis.

The systematic literature review from TA47 identified the following studies:

- **Medical management of UA/NSTEMI.** Seven studies were identified in the TA12 review; no new studies were found as part of TA47. Of these seven, none were UK based and only one study was considered of interest. This was a US study by Mark et al. that was the only prospective economic analysis undertaken alongside a RCT (PURSUIT, eptifibatide) and was of value only as a source of comparison with the Schering Plough analysis.
- **Alongside PCI.** Seventeen studies were identified in the TA12 review; six new studies were found as part of TA47. While the majority found GPIs to be cost effective in the context of patients undergoing PCI, the studies were not from a UK perspective and most were judged to have serious limitations as inputs to decision making in the UK; these included the use of effectiveness data, disease-specific endpoints (such as CV events avoided), and lack of consideration of down-stream consequences of short-term outcomes from trials.

The model submitted by the eptifibatide sponsors (Schering Plough) for TA12 evaluated the cost effectiveness of eptifibatide in the medical management of UA/NSTEMI. It uses a Western European (n=3697) and UK (n=429) subgroup of the PURSUIT RCT as its main data source for outcomes and resource use (up to six months). Lifetime outcomes are modelled based on these data. The UK analysis found eptifibatide to be dominant (i.e. cost saving and more effective), but this may be considered unreliable due to the small patient group. The Western European analysis, which might be considered more reliable found the incremental cost effectiveness ratio (ICER) to be £8179-£11,079 per life year gained (depending on discount rate used for outcomes). A key limitation is that costs are not extrapolated past six months which would feasibly impact the results.

The model submitted by the tirofiban sponsors (MSD) for TA12 evaluated the cost effectiveness of tirofiban in the medical management of UA/NSTEMI. It uses effectiveness data from the PRISM-PLUS RCT. The primary analysis reports a cost per event avoided (all cause mortality, new MI, refractory ischemia or readmission for UA/NSTEMI) of £8,760 and £9995 using 7-day and 180-day outcomes respectively and the additional cost of tirofiban. A secondary analysis estimates that 22% of additional drug cost is offset by savings due to reduction in events.

The model submitted by the abciximab sponsors (Eli Lilly) for TA12 evaluated the cost effectiveness of abciximab alongside PCI in a UK setting. Baseline event rates and effectiveness of abciximab were based on the EPIC, EPILOG and EPISTENT RCTs. Impact on life years was evaluated by assuming that patients surviving at one year would live a further fifteen. Costs were not extrapolated past one year. The ICER was found to be £3554, £6247 and £12,421 per QALY gained with EPIC, EPILOG and EPISTENT respectively.

The assessment group judged the published and sponsor-driven cost-effectiveness analyses to have significant limitations with regard to UK decision-making. In particular the fact that effectiveness trials used in analyses were undertaken largely or wholly outside of the UK; given the different practice patterns in the UK (e.g. lower rates of PCI), the baseline risks, and possibly the relative risks associated with GPIs, may be different. This may translate to differences in cost-effectiveness. Also many used condition specific endpoints that inhibit interpretation of results in the decision-making context. The Schering Plough analysis was considered the most relevant to UK decision-making.

The model developed by the Assessment Group examined four GPI treatment strategies:

- a GPI used immediately as part of initial management
- a GPI used after making a decision to carry out angiography with a view to PCI
- a GPI used as adjunct to PCI started up to an hour before the procedure
- no use of a GPI

The analysis showed that GPI use immediately as part of initial management was the most cost effective strategy with an ICER of £5738 per QALY gained compared to no GPI use. This conclusion was robust to various sensitivity analyses. Restricting strategy 1 to high risk patients only reduced the cost per QALY gained to £3966 and appeared more

cost effective than treating all ACS patients. The additional benefits in all patients compared to high risk only was at a cost of £91,000 per QALY gained.

New evidence

Two UK studies, each based on a single RCT, were found [101] [102]. Two Canadian and two US studies were also identified but not reviewed given the available UK evidence[103-106]. One Spanish analysis was judged likely to be of limited use to decision making due to the clinical studies it was based on and so was not reviewed[107].

Bakhai et al. report a simple decision analysis based on the PRISM-PLUS trial but using UK event rates. PRISM-PLUS compared tirofiban plus standard therapy compared to standard therapy alone in the initial medical management of UA/NSTEMI. Six-month costs and seven-day health events (death, new MI, refractory ischaemia or rehospitalisation for UA) were included. Cost-effectiveness was expressed in terms of cost per event averted, and is therefore difficult to interpret.

Brown et al. [101] reported a RCT based analysis of eptifibatide plus standard therapy compared to standard therapy alone in the initial medical management of UA/NSTEMI. Six-month outcomes and resource use were obtained from a Western European cohort of the PURSUIT trial. Outcomes were extrapolated past six months to estimate total life years. Costs were not extrapolated, a limitation of the analysis. Cost-effectiveness was expressed in terms of cost per life year gained. A 30-day analysis was also reported which expressed cost effectiveness in terms of cost per event (death or MI) avoided at this time point.

3.3.3 CLINICAL EVIDENCE STATEMENTS

GPIs in conservative & invasive strategies

An individual patient data meta-analysis [88] of six trials (PRISM, PRISM-PLUS, PARAGON-A, PARAGON-B, PURSUIT, and, GUSTO-IV ACS) compared GPIs with placebo or control therapy in 31,402 non ST-segment elevation ACS patients who were not routinely scheduled for early revascularisation (refer to summary). Most of the trials in this meta-analysis were undertaken in the pre-stent era. Also, most patients did not receive a thienopyridine anti–platelet agent (in GUSTO-IV ACS, the most recent of the GPI trials in the Boersma analysis, only 2% received a thienopyridine).

Compared to the control group, the GPI group had a significantly reduced chance of:

- death or MI at 30 days (primary outcome)

Evidence Level 1+

There was a non-significant difference between the control and GPI groups for:

- death at 30 days
- nonfatal MI at 30 days
- revascularisation (CABG or PCI) at 30 days
- intracranial haemorrhage at 30 days.

Evidence Level 1+

Compared to the control group, the GPI group had a significantly increased chance of:

- major bleeding at 30 days.

Evidence Level 1+

Table 2-5 . Summary table of Boersma et al meta-analysis (six RCTs)

Outcome at 30 days	GPI (N=18 297)	Control (N=13 105)	OR (95% CI)	p
Death or MI	1,980 (10.8%)	1,550 (11.8%)	0.91 (0.85 to 0.98)	0.015
Death	631 (3.4%)	485 (3.7%)	0.91 (0.81 to 1.03)	0.14
Nonfatal MI	1349 (7.4%)	1065 (8.1%)	0.92 (0.85 to 1.00)	0.063
CABG or PCI	6862 (37.5%)	5103 (38.9%)	0.99 (0.94, to 1.03)	0.53
Major bleed	445 (2.4%)	180 (1.4%)	1.62 (1.36 to 1.94)	<0.0001
Intracranial haemorrhage	16 (0.09%)	8 (0.06%)	Not reported	0.40

A highly significant interaction with respect to cardiac events was seen between gender and allocated treatment. In men, GPIs were associated with a 19% reduction in the odds of 30-day death or MI compared with placebo or control. By contrast, in women, there was a 15% increase. A further stratification by troponin concentration showed no evidence of a gender difference in treatment response, and a non–significant trend to a risk reduction was seen in men and women with raised troponin (see Table 2-6, Table 2-7 and Table 2-8).

Table 2-6. Meta-analysis by Boersma et al (interaction by gender). All patients.

	Men			Women		
Outcome	**GPI (N= 11886)**	**Control (N=850 2)**	**OR** (95% CI)	**GPI (N=6410)**	**Control (N=4603)**	**OR** (95% CI)
All patients						
Death or MI at 30 days	10.4%	12.6%	0.81 (0.75 to 0.89)	11.5%	10.4%	1.15 (1.01 to 1.30)

Table 2-7. Meta-analysis by Boersma et al (interaction by gender). Patients with normal baseline cardiac troponin T or I <0·1 ug/L

	Men			Women		
Outcome	**GPI (N=2095)**	**Control (N=1449)**	**OR** (95% CI)	**GPI (N=1548)**	**Control (N=1003)**	**OR** (95% CI)
Patients with normal baseline cardiac troponin T or I <0·1 ug/L						
Death or MI at 30 days	7.6%	6.9%	1.10 (0.84 to 1.43)	6.2%	5.3%	1.29 (0.91 to 1.83)

Table 2-8. Meta-analysis by Boersma et al (interaction by gender). Patients with elevated baseline cardiac troponin T or I ≥0·1 ug/L

	Men			Women		
Outcome	**GPI (N=2174)**	**Control (N=1284)**	**OR** (95% CI)	**GPI (N=939)**	**Control (N=567)**	**OR** (95% CI)
Patients with elevated baseline cardiac troponin T or I ≥0·1 ug/L						
Death or MI at 30 days	9.3%	11.3%	0.82 (0.65 to 1.03)	12.7%	13.6%	0.93 (0.68 to 1.28)

Further sub-groups analysis from this meta-analysis reported data on the effect of GPIs in the time period preceding a PCI (medical treatment):

- The authors reported that among patients who received PCI within 5 days (N=4378), the GPI group experienced significantly fewer MIs before the PCI occurred compared with the control group (OR, 0.70 [95% CI, 0.55 to 0.89]).
- For the subgroup of patients who did not undergo an early PCI (N=27024), there was a non-significant difference between the control and GPI group for death or MI at 30 days (OR, 0.95 [95% CI 0.87 to 1.02]).

These subgroup analyses should be interpreted with caution as the specific sub groups had not been randomised to control or GPI a priori. Pieper et al. have highlighted the pitfalls of inappropriate sub-group analyses undertaken in GPI trials and the potential for differing conclusions to be drawn depending on the analytical approach[108].

A second meta-analysis [98] of published data included the same six RCTs pooled by Boersma et al, and analysed the effect of GPIs in 29,570 patients initially managed medically, and then treated with PCI. In this meta-analysis patients were defined according to the procedure received. In PRISMPLUS, the study arm not including heparin (n=345) was discontinued before completion of the trials and was excluded from this analysis. In PURSUIT, the protocol mandated the discontinuation of the lower-dose arm of eptifibatide (N=1487) after documentation of an acceptable safety profile of the higher dose in the interim analysis; thus the lower dose arm was not included in the Roffi et al meta-analysis. Therefore, the Roffi et al. meta-analysis had a total of 29,570 patients compared with the 31,402 included in the Boersma et al meta-analysis.

The findings of the Roffi meta-analysis suggested a gradient of benefit conferred by GPIs depending upon the revascularisation strategy used. Accordingly, patients undergoing PCI while on GPIs derived a significant benefit, while patients undergoing revascularisation after drug discontinuation demonstrated a moderate event reduction that did not reach statistical significance, and only a marginal benefit (non significant) was observed among patients managed medically (see

Table 2-9).

Evidence Level 1+

Table 2-9. Summary of meta–analysis by Roffi et al. [98]

Outcome at 30 days	Population	N=	GPI	Control	OR (95% CI)	p
Death or MI	All patients	29,570	10.7%	11.5%	0.91 (0.85 to 0.99)	0.02
Death or MI	Patients undergoing PCI during index hospitalization	6,337 (21%)	10.7%	12.7%	0.82 (0.71 to 0.96)	0.01
Death or MI	Patients undergoing PCI while still receiving study drug	2,249 (7.6%)	10.5%	13.6%	0.74 (0.57 to 0.96)	0.02
Death or MI	Patients undergoing PCI after drug discontinuation	4,088 (13.8%)	10.9%	12.3%	0.87 (0.72 to 1.06)	0.17
Death or MI	Patients treated medically	20,054 (67.8%)	9.3%	9.7%	0.95 (0.86 to 1.04)	0.27

Triple anti–platelet therapy

The ISAR-REACT 2 [91,94], and ELISA-2 [97] RCTs assessed the addition of a GPI to aspirin, clopidogrel (or ticlopidine) and heparin (i.e. triple antiplatelet therapy) in people with non ST-segment elevation ACS.

These studies differed in several respects such as the GPI evaluated, the baseline risk of population in which they were conducted, the follow-up period and the loading dose of clopidogrel used (see

Table **2-10**).

In ELISA-2 and ISAR-REACT 2, compared with people receiving dual antiplatelet therapy (aspirin + clopidogrel) together with heparin, people randomised to triple antiplatelet therapy (aspirin + clopidogrel + a GPI) with background heparin had a significantly reduced risk of:

- Death, MI, or urgent target vessel revascularisation at 30 days
- Death, MI, or target vessel revascularisation at 1 year

Evidence Level: 1+

There was a non–significant difference between the groups for major bleeding.

Evidence Level: 1+

Table 2-10. Summary of triple antiplatelet therapy studies

Study	N=	Outcome	Triple antiplatelet therapy (% Events)	Dual antiplatelet therapy (% Events)	Effect size
ELISA-2[97]	328	Primary Ischemic outcome: MI at 30 days	Aspirin+Clopidogrel (300mg)+Heparin+ **tirofiban** **46%**	Aspirin+Clopidogrel (600mg)+Heparin+ **placebo** **56%**	P=0.05
ELISA-2[97]	328	Major bleeding at 30 days	Aspirin+Clopidogrel (300mg)+Heparin+ **tirofiban** **12%**	Aspirin+Clopidogrel (600mg)+Heparin+ **placebo** **10%**	**P=0.05**
ISAR-REACT 2[91]	2,022	Primary Ischemic outcome: Death/MI/UTVR at 30 days	Aspirin+Clopidogrel (600 mg) +Heparin + **abciximab** **8.9%**	Aspirin+Clopidogrel (600 mg) +Heparin + **placebo** **11.9%**	RR 0.75 (0.58 to 0.97) p = 0.03
ISAR-REACT 2[91]	2,022	Major bleeding in-hospital	Aspirin+Clopidogrel (600 mg) +Heparin + **abciximab** **1.4%**	Aspirin+Clopidogrel (600 mg) +Heparin + **placebo** **1.4%**	RR 1.00 (0.50 to 2.08)
ISAR-REACT 2[94]	2,022	Primary Ischemic outcome: Death/MI/UTVR at 1 year	Aspirin+Clopidogrel (600 mg) +Heparin + **abciximab** **23.3%**	Aspirin+Clopidogrel (600 mg) +Heparin + **placebo** **28.0%**	**RR 0.80** (0.67 to 0.95) p= 0.012

In the ISAR REACT 2 trial [91], there was non signficant difference in the incidence of death/MI/UTVR at 30 days between the abciximab group (4.6%) and the placebo group (4.6%) in people who had normal troponin concentrations ≤ 0.03 µg/L [N=973; RR, 0.99; (95% CI, 0.56 to 1.76); p= 0.98),]. In patients with an elevated troponin level

(N=1049; troponin > 0.03 µg/L), death/MI/UTVR at 30 days was significantly lower in the abciximab group (13.1%) compared with the placebo group (18.3%) [RR 0.71 (95% CI, 0.54 to 0.95; p=.002) (p=0.07 for interaction).

Evidence Level: 1+

Timing issues

Prospective randomised trial data comparing GPI administration upstream versus in the catheterisation laboratory are limited. Only three RCTs (ISAR COOL, ACUITY TIMING, and EARLY ACS) [95,99 100] addressed this area.

In the ACUITY-TIMING RCT [99] deferred selective vs. routine upstream administration of GPIs was evaluated. Patients assigned to routine upstream GPI received either eptifibatide or tirofiban started at a median time of 35 minutes after randomisation and infused for a median of 4.0 hours before PCI. In contrast, patients randomised to deferred selective GPI use were assigned treatment with either eptifibatide or abciximab started just prior to PCI, approximately 3.9 hours later than GPIs were begun in the upstream use group. The GPI infusion continued during angioplasty and for 12 to 18 hours thereafter. For patients assigned to deferred selective GPI use, the investigator chose whether eptifibatide or abciximab was administered only to patients undergoing angioplasty, begun 5 to 10 minutes prior to first balloon inflation, and continued for 12 hours (abciximab) or 12 to18 hours (eptifibatide) thereafter. It should be noted that people randomized to upstream or deferred GPI had also been randomized to either heparin or bivalirudin, and thus there is a mixture of antithrombin use in the upstream and deferred GPI arms.

In the EARLY ACS trial [100] people with non ST-segment elevation ACS undergoing an early invasive strategy (N=9492) were randomised to either early upstream eptifibatide or to matching placebo. After coronary angiography, but before PCI, investigators could request a 'PCI-study drug kit' for patients who could benefit from eptifibatide on the basis of angiographic evidence. The first bolus of the "PCI-study drug kit" contained eptifibatide for patients who had previously had placebo and placebo for people who previously had eptifibatide. An open label infusion of eptifibatide was started and continued for at least 18 to 24 hours after PCI. During PCI if a thrombotic complication occurred after the catheter guide wire had crossed the lesion, a "bailout drug kit" that contained a bolus therapy opposite to the initial study group drug was given. The median time from randomisation to study drug initiation was 0.5 hours in both groups. The median time from randomisation to angiography was 21.4 hours and to PCI was 22 hours. See

Table 2-11.

Table 2-11. Summary of primary outcomes in people randomised to upstream or deferred GPIs

RCT	N	Primary Outcome	Upstream GPI (% events)	Deferred GPI (% events)	Effect size (95% CI)
Early ACS [100]	9406	Death, MI, recurrent ischemia requiring urgent revascularisation[j], or thrombotic bailout at 96 hours	9.3	10.0	OR 0.92 (0.80, 1.06), p=0.23
ACUITY TIMING [99]	9207	Death, MI, or unplanned revascularisation for ischemia at 30 days [k]	7.1	7.9	RR 0.90 (0.78, 1.03) [l]

Two meta-analyses were performed pooling the outcomes of the ACUITY TIMING and EARLY ACS trials. In the first meta-analysis the entire trial populations of the two RCTs were pooled. This means that for ACUITY TIMING, the upstream and the deferred GPI arms are a mixture of heparin and bivalirudin. Whilst pooling studies increases statistical power, the bivalirudin contamination in the ACUITY TIMING trial is a limitation of this meta-analysis. (see Figure 2-2, Figure 2-3, Figure 2-4, Figure 2-5, Figure 2-6,

[j] In the EARLY ACS trial, recurrent ischaemia requiring urgent revascularisation was defined as an unplanned PCI or CABG following a new episode of myocardial ischemia within hospital, or a readmission within 30 days of randomisation for ischemia requiring cardiac catheterisation and revascularisation before discharge.

[k] In ACUITY TIMING, "unplanned revascularisation" was defined as any further CABG or PCI after the initial treatment (PCI, CABG or medical), excluding planned staged PCI. An unplanned revascularisation was adjudicated as "ischemia driven" if it was associated with either symptoms or signs of myocardial ischemia, or a positive functional study (stress test), or a target lesion with diameter stenosis >70% by quantitative coronary angiography, or operator assessment of >80% in the absence of core lab analysis.

These results are consistent with an increase of up to 29% in the rate of composite ischemic events in the deferred selective treatment group, so that the criterion for non-inferiority was not met.

Figure 2-7, and Figure 2-8).

The meta-analysis was re-run with unpublished data from the ACUITY TIMING RCT [109], in which the upstream and deferred GPI arms were from patients only randomised to heparin (no bivalirudin contamination). This provides a more comparable pharmacological background between the two RCTs, although with fewer patients, the statistical power is decreased. Table 2-12 summarised the two meta-analyses pooling the EARLY ACS and ACUITY TIMING RCTs. (See Figures 2-2, through to 2-15).

Table 2-12 summarises the two meta-analyses pooling the ACUITY TIMING and EARLY ACS RCTs.

Outcome at 30 days	**Original Meta-analysis pooling ACUITY TIMING and EARLY ACS trials (upstream versus deferred GPI arms were on a mixed background of heparin and bivalirudin)** **(Total N=18613)**	**Revised meta-analysis pooling ACUITY TIMING and EARLY ACS trials (upstream versus deferred GPI arms were on a background of heparin only)** **(Total N=14009)**	**Comparison of results from the two meta-analyses**
Death	RR 1.02 (0.84, 1.24)	RR 1.08 [0.87, 1.34]	Very similar results
MI	RR 0.92 (0.83, 1.01)	RR 0.89 [0.79, 0.99]	Results changed and became significant in favour of upstream GPI
Death/MI	RR 0.92 (0.84, 1.01)	RR 0.90 [0.82, 1.00]	Very similar results
Death/MI/unplanned revasc	RR 0.90 [0.83, 0.98]	RR 0.91 [0.83, 1.00]	Results changed and became non-significant
Unplanned revasc	RR 0.78 [0.65, 0.93]	RR 0.81 [0.66, 0.99]	Very similar results
Major TIMI bleed	RR 1.32 [1.08, 1.62]	RR 1.31 [1.04, 1.65]	Very similar results
Minor TIMI bleed	RR 1.52 [1.33, 1.74]; I^2 = 88.3% significantly heterogeneous	RR 1.59 [1.34, 1.89]; I^2 = 87.7% significantly heterogeneous	Very similar results

When the meta-analyses were run without bivalirudin contaminating the ACUITY TIMING arms and compared with deferred GPI use, upstream GPI use)significantly:

- Decreased the risk of MI at 30 days
- Decreased the risk of unplanned revascularisation at 30 days
- Increased the risk of TIMI major bleed
- Increased the risk of TIMI minor bleed

Evidence Level: 1+

There was no significant difference between upstream and deferred GPI use for:

- the composite outcome of death, MI, or unplanned revascularisation at 30 days;
- death at 30 days
- death or MI at 30 days

Evidence Level: 1+

Upstream versus deferred GPI use

Figure 2-2. Death, MI, or unplanned revascularization at 30 days in the entire trial populations (bivalirudin contaminating the ACUITY TIMING arms)

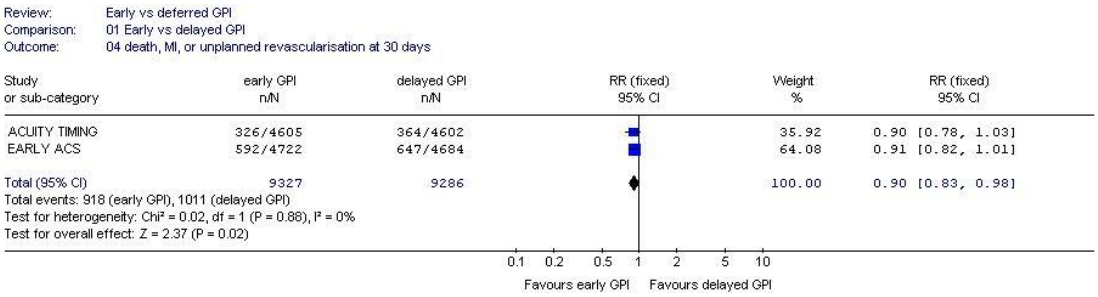


Figure 2-3. Death or MI at 30 days in the entire trial populations (bivalirudin contaminating the ACUITY TIMING arms)

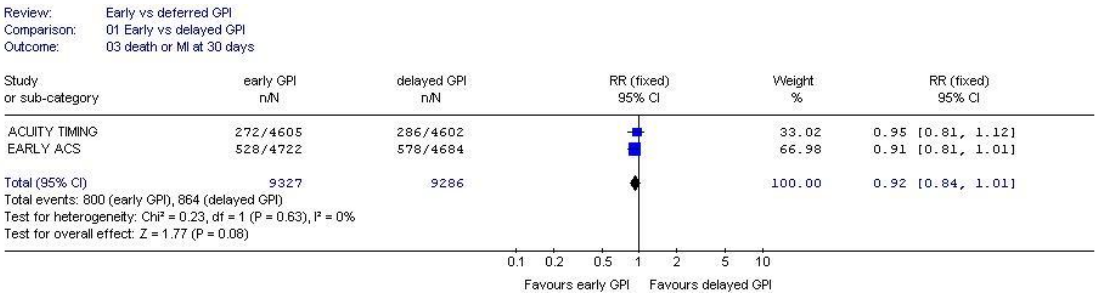


Figure 2-4. Death at 30 days in the entire trial populations (bivalirudin contaminating the ACUITY TIMING arms)

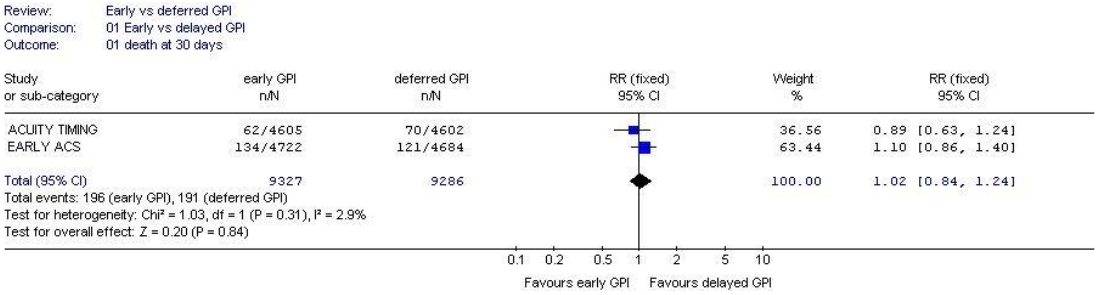


Figure 2-5. MI at 30 days in the entire trial populations (bivalirudin contaminating the ACUITY TIMING arms)

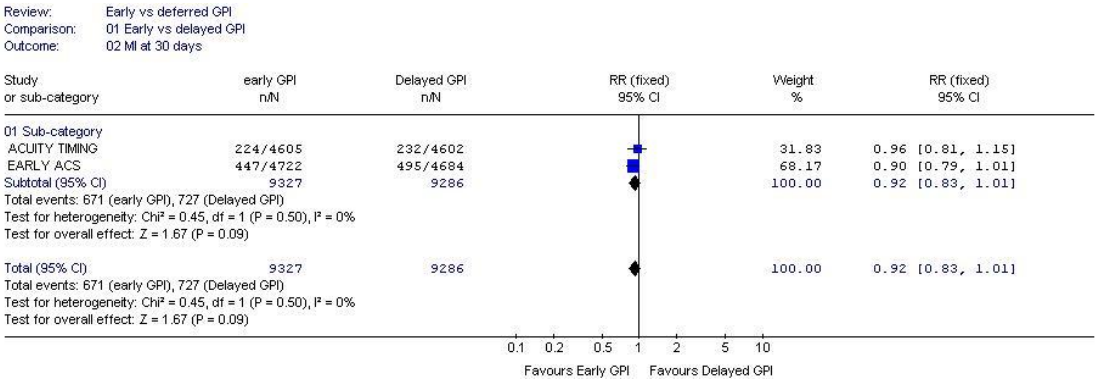


Figure 2-6. Unplanned revascularization in the entire trial populations (bivalirudin contaminating the ACUITY TIMING arms)

Review: Early vs deferred GPI
Comparison: 01 Early vs delayed GPI
Outcome: 05 unplanned revascularisation

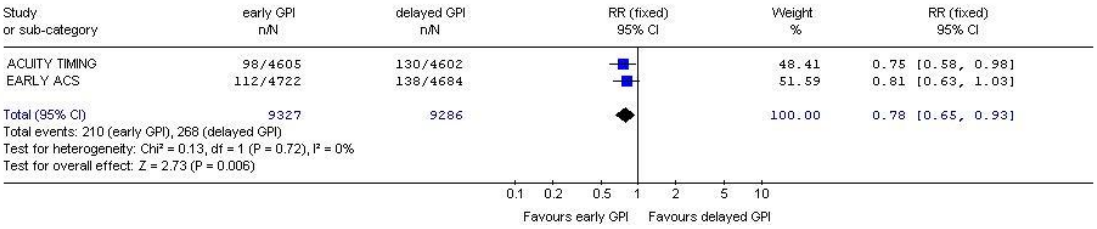


Figure 2-7. TIMI Major Bleed in the entire trial populations (bivalirudin contaminating the ACUITY TIMING arms)

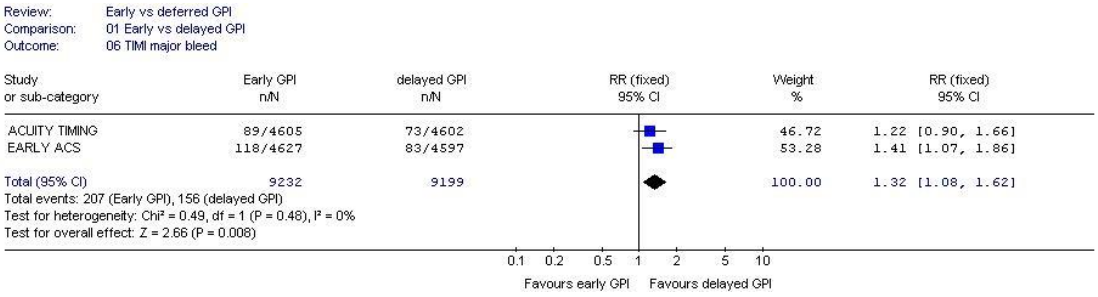
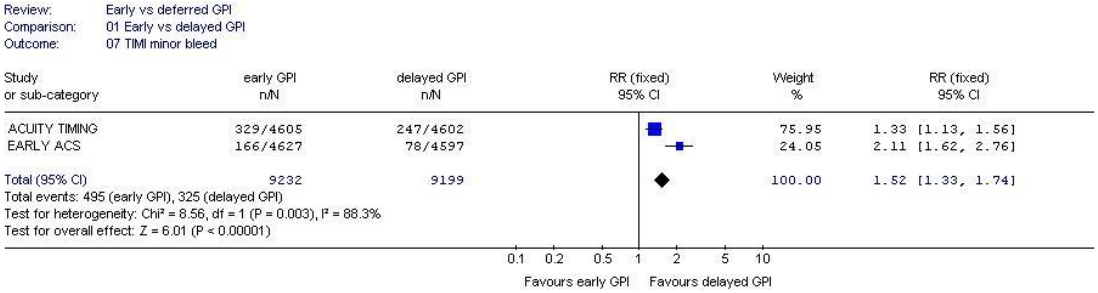


Figure 2-8. TIMI Minor Bleed in the entire trial populations (bivalirudin contaminating the ACUITY TIMING arms)



Revised meta-analyses pooling EARLY ACS and ACUITY TIMING where upstream versus deferred GPI use is on a background of heparin (no bivalirudin contamination)

Figure 2-9. Death, MI, or unplanned revascularization at 30 days (no bivalirudin contaminating the ACUITY TIMING arms)

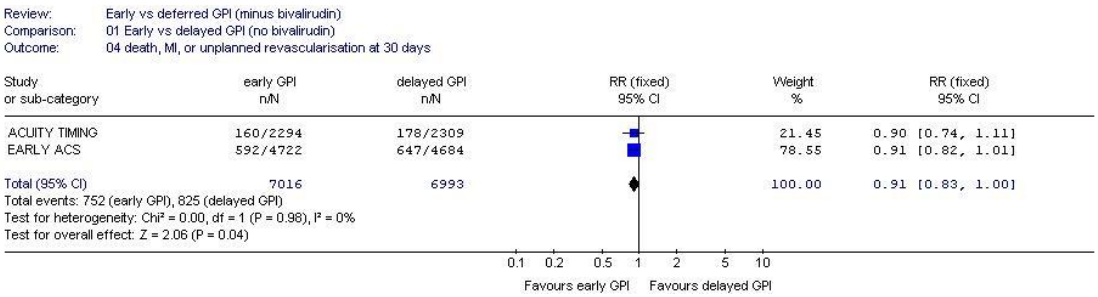


Figure 2-10. Death or MI at 30 days (no bivalirudin contaminating the ACUITY TIMING arms)

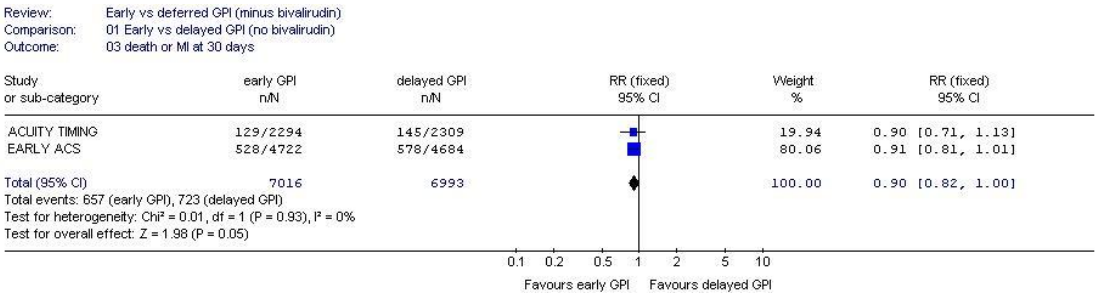


Figure 2-11. Death at 30 days (no bivalirudin contaminating the ACUITY TIMING arms)

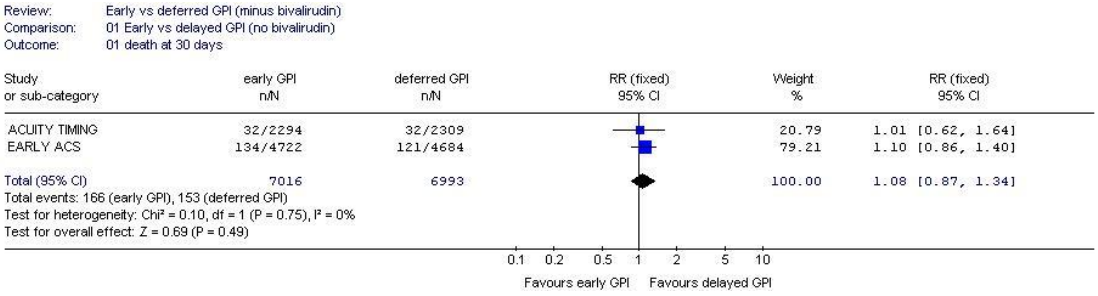


Figure 2-12. MI at 30 days (no bivalirudin contaminating the ACUITY TIMING arms)

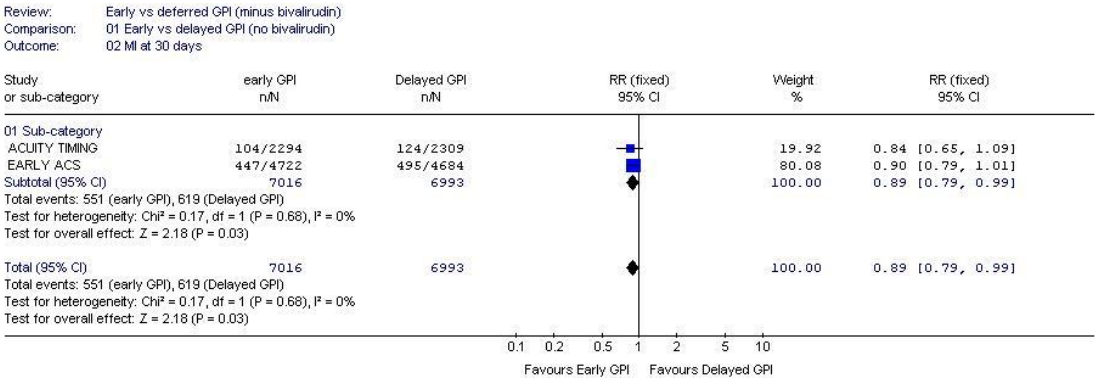


Figure 2-13. Unplanned revascularisation at 30 days (no bivalirudin contaminating the ACUITY TIMING arms)

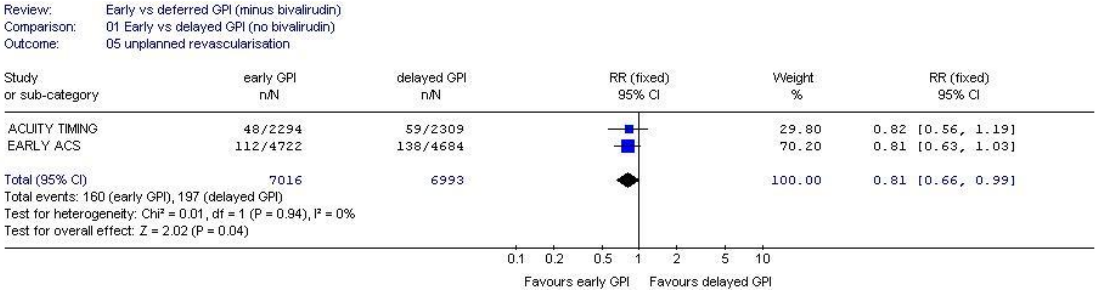


Figure 2-14. TIMI major bleed at 30 days (no bivalirudin contaminating the ACUITY TIMING arms)

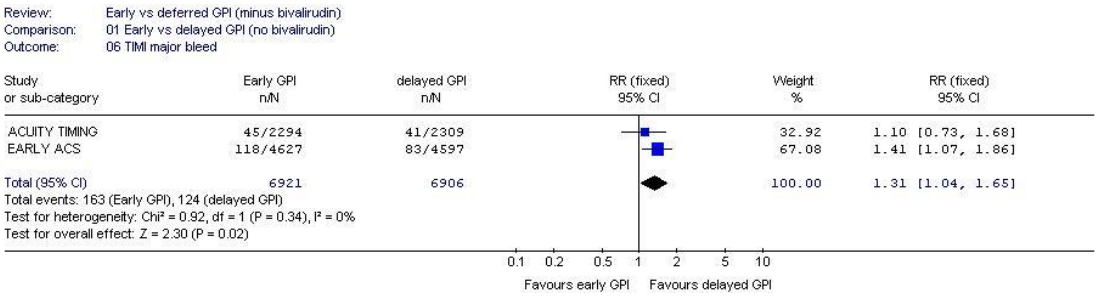
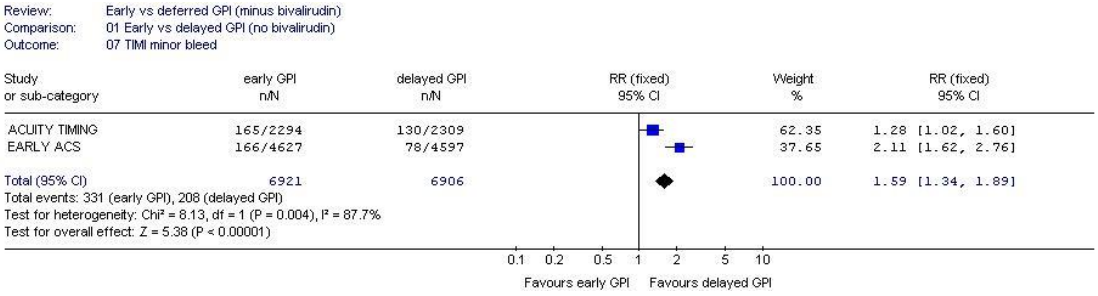


Figure 2-15. TIMI minor bleed at 30 days (no bivalirudin contaminating the ACUITY TIMING arms)



The ISAR-COOL RCT [95] tested the hypothesis that prolonged (three to five days) anti—thrombotic pre-treatment improves the outcome of an intervention (cardiac catheterization) strategy in patients with non ST-segment elevation ACS (N=410) compared with early intervention (pre-treatment for less than six hours). Patients with UA or NSTEMI were randomized within 24 hours of an index episode of myocardial ischaemia. Anti-thrombotic pre-treatment was identical in the two arms (aspirin + heparin + clopidogrel 600mg loading dose + tirofiban). The median time to catheterisation with prolonged anti-thrombotic pre-treatment was 86 hours; only 12 patients (5.8%) were prematurely catheterised in this group according to the pre-specified criteria. Of the patients assigned to early intervention, 87.2% (177/203) underwent coronary angiography within six hours of randomization; the median time to catheterisation was 2.4 hours.

In ISAR COOL, people randomised to prolonged anti thrombotic pre-treatment had a significantly increased risk of death or nonfatal MI at 30 days (primary outcome) compared with the early intervention group (RR, 1.96 [95%CI 1.01, 3.82]; p=0.04). After adjusting for baseline characteristics the difference remained significant (OR, 2.17 [95% CI 1.01 to 4.76]; p=0.047).

Evidence Level 1+

There was a non-significant difference between prolonged antithrombotic pre-treatment versus early intervention groups for:

- Death at 30 days (p=0.25)
- Nonfatal MI at 30 days (RR 1.72 [95% CI 0.87, 3.40], p=0.12)
- Major Bleeding at 30 days (RR 1.31 [95% CI 0.46, 3.70]; p=0.61).

Evidence Level 1+

In sub-group analyses, there was a non–significant effect on death or MI at 30 days when comparing prolonged antithrombotic pre-treatment, with early intervention, either in patients with elevated levels of cardiac troponin T (N=274; OR 1.65 [0.75, 3.64]) or those with ST-depression (N=268; OR 1.50 [0.76, 3.37]). Similarly, in patients undergoing PCI (N=276) there was a non significant difference between prolonged antithrombotic pre-treatment and early intervention (OR 1.64 [0.73, 3.68]).

Head to head comparisons

The TARGET RCT [93] compared tirofiban versus abciximab in patients (N=4812) undergoing non-emergency, stent-based PCI. People with ACS comprised 63% of the total study population (N=3026). People in both arms received treatment with aspirin, heparin and clopidogrel at a loading dose of 300mg. The authors noted that a study limitation was the potential lack of power to detect a difference in mortality at one year.

The TARGET study showed that:

- **At 30 days** the composite endpoint of death, MI or target vessel revascularisation occurred in 7.6% in the tirofiban group and 6.0% in the abciximab group (hazard ratio 1.26 [1.01 to 1.57]; p = 0.038)

- **At six months**, death, MI or target vessel revascularisation occurred in 14.8% in the tirofiban group and 14.3% in the abciximab group (HR 1.04 [0.90 to 1.21]; p=0.591).

- **At one-year** the mortality rate was 1.9% in the tirofiban group and 1.7% in the abciximab group (HR 1.10 [0.72 to 1.67]; p=0.660). In the ACS subgroup (N=3026), death at 1 year was a non–significant difference between tirofiban (2.3%) and abciximab (2.2%) (HR 1.03 [0.64, 1.67]; p=0.897).

Evidence Level: 1+

3.3.4 HEALTH ECONOMIC EVIDENCE STATEMENTS

Bakhai et al.[102] reported an incremental cost-effectiveness ratio of £13,388 per event averted for tirofiban plus standard therapy compared to standard therapy alone in the initial medical management of UA/NSTEMI. Without the estimation of QALYs it is difficult to interpret the results.

Brown et al.[102] reported an incremental cost-effectiveness ratio of £8436 per life year gained for eptifibatide plus standard therapy compared to standard therapy alone in the initial medical management of UA/NSTEMI. Note that costs were not extrapolated past six months. The 30-day analysis produced an ICER of £22,760 per event avoided**.** While reporting slightly different results, this analysis is judged to be consistent with the Schering Plough cos-effectiveness analysis evaluated as part of TA47 and as such does not give cause to change the recommendations made.

The new evidence does not contradict the existing TA model and recommendations.

Health economic modelling

Cost-effectiveness modelling was undertaken for this guideline to look at the use of GPIs taking into account contemporary management. In particular it addressed the use of GPIs in combination with clopidogrel, bivalirudin was included as a possible alternative to heparin plus a GPI and fondaparinux as an alternative to heparin was incorporated.

For the full analysis methods and detailed results and discussion see the report in

Appendix B and Appendix C. A summary is provided below.

Methods

A cost–utility analysis was undertaken with costs and quality-adjusted life-years (QALYs) considered over patients' lifetimes from a UK NHS perspective. The analysis is relevant to patients undergoing an early invasive management approach – that is coronary angiography with revascularisation if indicated – because trial results utilised for GPIs and bivalirudin used in the analysis were only relevant to a population undergoing angiography. This is discussed in more detail in the full report in Appendix C.

This compared the following treatment strategies in the acute management of UA/NSTEMI (heparin baseline):

- Aspirin +clopidogrel +heparin (LMWH or UFH)
- Aspirin +clopidogrel +heparin + GPI during PCI only
- Aspirin +clopidogrel +heparin + GPI upstream of angiography
- Aspirin +clopidogrel +bivalirudin upstream of angiography
- Aspirin +clopidogrel +heparin +bivalirudin during PCI only.

In addition the analysis was run as above but with fondaparinux substituted for heparin in the first three arms (fondaparinux baseline). Fondaparinux was not incorporated in the bivalirudin arms in this analysis as there is no experience with these agents combined and so it was not judged appropriate.

Cost effectiveness was analysed by six risk subgroups, as summarised in Table 2-13 below. The creation and interpretation of these risk groups is discussed in more detail in the Risk chapter of the guideline (section 0) and the report of the analysis of MINAP data for the cost effectiveness analysis (Appendix B).

Table 2-13. Risk groups

Risk group	% population	Corresponding range of 6-month mortality
1a	~12.5%	>1.6%
1b	~12.5%	>1.6 ≤3.1%
2a	~12.5%	>3.1 ≤5.5%
2b	~12.5%	>5.5 ≤9.5%
3	~25%	>9.5 ≤21.5%
4	~25%	>21.5%

The general approach taken was to obtain contemporary UK estimates of events for the aspirin, clopidogrel and heparin arm of the model from recent MINAP (the national audit of ACS management) data. These were stratified by acute management strategy: PCI, CABG, angiography only. Where inputs were not available from the analysis of MINAP data, figures were sourced from the literature or discussion with the GDG. One-year death, MI and post-acute revascularisation, and in-hospital bleeding were incorporated. The effects of different treatment combinations are then modelled by applying relative risks from randomised controlled trials identified by the systematic review of the clinical literature for the guideline – one-year relative risks were used where available except for bleeding. Relative risks were applied to the appropriate part of the population; for example, only PCI patients, if only relevant to these patients.

Lifetime QALYs were estimated based on one-year status: dead, alive having had a new MI, alive without new MI. At one-year patients were attributed a number of life-years based on this status. Those alive at one year with new MI were attributed a lower estimate than those alive without new MI. Life-years were adjusted by a quality of life weight for people with ACS to estimate QALYs. As the rates of death and MI will vary with treatment strategy, so will the QALYs.

Lifetime costs were estimated taking into account initial drug treatment costs, the cost of MI, bleed and post-acute revascularisation events up to one year and average disease-related costs incurred if alive post one-year.

Treatment effects were based on studies identified in the clinical review. Only studies with at least 50% clopidogrel use were used. Relative treatment effects were based on the following studies:

- ISAR-REACT 2[91,94]: GPI versus no GPI in a PCI UA/NSTEMI population
- ACUITY timing (heparin only background, clopidogrel pre-angio/pre-PCI subgroup)[99,109]: upstream GPI versus PCI GPI in an early angiography UA/NSTEMI population
- ACUITY (clopidogrel pre-angio/pre-PCI subgroup)[109-111]: bivalirudin vs LMWH/UFH + GPI in an early angiography UA/NSTEMI population
- REPLACE-2 ACS subgroup[112]: bivalirudin during PCI vs heparin + GPI during PCI in a PCI ACS population
- OASIS-5[113]: fondaparinux vs enoxaparin in a UA/NSTEMI population

The Early ACS trial also compares upstream GPI vs PCI GPI use in an early angiography UA/NSTEMI population[100]. It was published late in the guideline development process and only reports 30-day outcomes, whereas the model had been developed with one-year baseline event rates and effectiveness data. Sensitivity analyses examined the possible impact of this study.

Two analyses were run:

1. Trial aligned analysis (costing based on trial vial usage where pre-angiography treatment period median 4hrs/mean 10hrs; ACUITY management split)
    - Costing based on trial vial usage; ACUITY management split
    - The ACUITY trial which includes 3 of the 5 comparators had a median treatment period pre-angiography of 4hrs (mean 10hrs)
    - This analysis is most aligned with the available trial data
2. Adjusted analysis (costing based on 72hr pre-angiography treatment period; MINAP management split)
    - Costing based on a simulation assuming 72hr pre-angio treatment duration and a 1hr PCI treatment duration; MINAP management split
    - This analysis makes some adjustments to costing and management split that may be more typical for the UK

- Note that this analysis potentially biases against upstream treatments as costs are increased but efficacy remains the same and so should be interpreted carefully with this in mind.

The model was built probabilistically in order to take account of the uncertainty around input parameter point estimates. Probability distributions in the analysis were based on error estimates from data sources, for example confidence intervals around relative risk estimates. Various one-way and scenario sensitivity analyses, where one or more inputs were varied, were undertaken to test the robustness of model assumptions and data sources.

Results

Fondaparinux baseline analysis:

The analysis incorporating a fondaparinux baseline (that is fondaparinux replaces heparin in the aspirin+clopidogrel+heparin, aspirin+clopidogrel+heparin+GPI during PCI, aspirin+clopidogrel+heparin+GPIupstream arms of the model),was considered most relevant to clinical decision making in the majority of cases. Fondaparinux has been found to be cost-effective compared to heparin as shown in the published literature[114]. Fondaparinux is cheaper than enoxaparin and is associated with clinical benefits. In the model Aspirin+clopidogrel+fondaparinux dominated Aspirin+clopidogrel+heparin in all of our analyses (although this comparison was a secondary objective of the analysis).

In the trial aligned analysis (when trial vial usage was used for costings and the ACUITY management split employed) routine addition of upstream GPIs seems to be most cost-effective for patients in risk groups 2 and 3, with selective PCI GPI use the most cost-effective in risk group 4. This is based on these options having the highest mean INB at a £20,000 per QALY threshold. In the adjusted analysis (with treatment costs estimated using a 72hr pre-angiography treatment duration and the MINAP management split employed) selective use of GPIs at PCI was found to be most cost-effective strategy; however, this analysis was considered likely to bias against upstream use of GPIs as treatment costs are increased but efficacy is not adjusted.

There was considerable uncertainty in the results. This is evidenced by differences between the deterministic optimal strategy and probabilistic optimal strategy especially in Groups 1a and 4. Also, there is a wide spread of the probability of cost-effectiveness across different strategies. In places the optimal strategy as based on mean INB is not the one with the highest probability of being cost-effective as based on the highest proportion of simulations. In addition there is uncertainty regarding applicability as the trial aligned analysis may not represent typical treatment durations in the UK; whereas the longer term analysis is limited by the lack of effectiveness data. It was also noted that from a clincal perspective, the longer the wait for angiography the more likely a

patient would need a GPI prior to angiography and deferring use until PCI is undertaken may not be a clinically acceptable option.

Interpretation of results is complicated by the uncertainty in the analysis. Additional clinical considerations should be employed in interpretation and it was considered that it may be reasonable to recommend more than one option to reflect this uncertainty. Risk group 1 is considered least likely to benefit from additional treatment over and above aspirin+clopidogrel+fondaparinux. Dependent on appropriate clinical interpretation, due to the uncertainty it was considered that either GPI use upstream of angiography or selective GPI use in PCI might be considered likely to be cost-effective in higher risk groups. This is due to the fact that different options were found to be most cost-effective in the trial aligned and adjusted analysis but limitations in the analysis mean that a definitive conclusion is not possible based on these model results alone.

Note that the fondaparinux baseline analysis is dependent on the assumption that the relative effect of GPIs will not be impacted by whether heparin or fondaparinux is used as the baseline antithrombin – there were no studies that assessed GPIs against no GPIs in a population using fondaparinux. The OASIS-5 trial addresses this issue somewhat by examining 30-day outcomes for fondaparinux versus enoxaparin in subgroups of patients receiving clopidogrel and GPIs[115]. This analysis suggested that the benefits of fondaparinux are maintained in patients receiving clopidogrel or GPIs.

Heparin baseline analysis:

If fondaparinux is not an appropriate option, then the analysis with a heparin baseline is most appropriate to review. In this analysis, risk group one is least likely to benefit from additional treatment over and above aspirin+clopidogrel+heparin. Heparin use with selective bivalirudin during PCI seems to be most cost-effective in risk groups 2-4. This is based on the mean INB from the heparin baseline analyses in both the trial aligned analysis (reflective of a short time to angiography) and the adjusted analysis (with treatment costs estimated using a 72hr pre-angiography treatment duration and the MINAP management split employed). Bivalirudin use pre-angiography was associated with more QALYs than the selective bivalirudin use but also additional costs and based on the mean INB this use was not cost effective at a £20,000 per QALY threshold.

As in the fondaparinux baseline analysis there was considerable uncertainty in the heparin-baseline analysis. In the trial aligned analysis (reflective of a short time to angiography) bivalirudin PCI was considered the most cost-effective treatment based on mean INB, bivalirudin use upstream of angiography, and upstream GPI use generally also had a high level of simulations where they were optimal. As risk increased the likelihood of bivalirudin initiated upstream of angiography being cost effective increased. It was also raised that there will sometime be a clinical need to give additional treatment upstream of angiography, for example if the patient is actively unstable. Interpretation of results is complicated by the uncertainty in the analysis. Additional clinical rationale should be employed in interpretation and it was considered that it may be reasonable to recommend more than one option to reflect this uncertainty. Dependent on appropriate clinical interpretation, due to the uncertainty it

was considered that use of the following might be considered likely to be cost effective: bivalirudin used selectively during PCI; upstream bivalirudin; heparin plus upstream GPIs.

In the adjusted analysis (where costing was based on a 72hr pre-angiography treatment duration) PCI bivalirudin was also most cost effective, as would be expected as the upstream treatments will have higher costs in the model but the effectiveness was not adjusted. In addition, this analysis was considered the least clinically relevant because if patients were not going for angiography relatively quickly they would be most likely to be considered suitable for fondaparinux.

3.3.5 EVIDENCE SUMMARY

There have been a number of publications investigating the use of GPIs since the last Technology Appraisal (2002). Trial designs, timing of treatments, patient populations and the use of adjunctive therapies and invasive strategies have differed between studies making comparisons difficult.

Triple anti-platelet therapy

When GPIs were first investigated in the management of patients with NSTEMI or UA it was on a background of aspirin but before the widespread use of clopidogrel, and they were found to be beneficial as summarised in a meta analysis [88]. Since these studies, the use of clopidogrel has increased considerably, because of its ease of administration (oral) and evidence of its benefit (reference clopidogrel chapter), when added to aspirin and anti—thrombins. More recent studies investigating the use of GPIs on a background of aspirin, clopidogrel and an antithrombin (ISAR-REACT 2, ELISA-2), have differed significantly in their methodology, and have been relatively underpowered, though have suggested a trend towards benefit by reducing ischaemic end points. In ISAR-REACT 2 this reduction appeared to be in the troponin positive, but not the troponin negative patients.

Bleeding

Trials have differed in the frequency of major bleeding which was, for instance, not significantly increased in ISAR-REACT 2 or ELISA 2 but was significantly increased in CRUSADE [116]. Boersma et al. [88] showed a 1% absolute (9% relative) reduction in odds of death/MI (mainly non-fatal MI) at 30 days, but a corresponding 1% absolute increase in the odds of a major bleed, which is now known to be associated with a significant risk of mortality.

Invasive management

When a strategy of invasive intervention, on a background of aspirin, clopidogrel and an anti-thrombin is pursued the GPIs reduce the risk of urgent revascularisation (and may reduce death/MI) if given in advance (upstream) of the catheter procedure but at the

expense of an increase in bleeding (ACUITY-TIMING). The EARLY-ACS trial suggested that if a GPI is to be given then there may be benefit in doing this upstream rather than delaying until the catheter procedure. Benefit was not seen when treatment with GPIs was deferred until after the procedure [99], or if a strategy of their prolonged use (3-5 days) prior to catheterisation was employed (ISAR-COOL) [95]. Published data from ACUITY and EARLY-ACS do not allow a combined assessment of an upstream GPI by troponin status. When GPIs are used as part of a conservative strategy, pursuing medical therapy, absolute benefit may be limited.

Comparisons between agents

Most studies have compared the use of a single GPI against placebo, in different clinical settings. However, the TARGET trial directly compared tirofiban with abciximab, on a background of treatment with aspirin, clopidogrel and antithrombin, in patients undergoing PCI during the same hospital admission. Abciximab seemed to be superior at 30 days but this difference was lost thereafter.

Effect of gender

Gender differences in efficacy are difficult to interpret because there were fewer women in the trials, and stratification by troponin level may explain some of the differences seen.

Cost-effectiveness

A detailed economic modelling exercise was undertaken in order to update the previous TA47 in light of changes in clinical practice, most notably the widespread use of aspirin, clopidogrel and an antithrombin agent as initial therapy, the greater use of angiography/PCI, the new agents bivalirudin and fondaparinux. The results of this exercise are summarised in detail above. While there was greater uncertainty in the analysis that previsouly, it was considered that the use of GPIs is likely to represent a cost-effective treatment for those at intermediate and above risk (cohorts 2, 3 & 4 in our risk stratification [see risk chapter, and economic analysis above]; predicted 6-month mortality >3%). However, the economic analysis has also highlighted the uncertainty in this area. More information regarding the long term economic consequences of bleeding (other than mortality, which was included), whether relative risks of benefit and harm and differ across risk groups, where relative treatment effects vary across risk groups, longer term follow-up registry data (such as in MINAP), and studies with greater applicability to the UK setting would all help to refine the model and the robustness of its conclusions.

The use of GPIs was shown to represent a cost-effective treatment for those at high levels of risk (cohorts 2b, 3 & 4 in our risk stratification [see risk chapter, and economic analysis above]; predicted 6-month mortality >6%), and likely also to be of benefit, though with greater uncertainty, for those at intermediate levels (cohort 2a, predicted 6-month mortality 3-6%). However, the economic analysis has also highlighted areas of uncertainty and cautions against wholesale application of population data to individual patient management without a clinical assimilation of its findings into the balancing of individual risk of an ischaemic event and bleeding risk. More information regarding the long term economic consequences of bleeding (other than mortality, which was included), whether relative risks of benefit and harm and differ across risk groups, and

longer term follow-up registry data (such as in MINAP), would all help to refine the model and the robustness of its conclusions.

3.3.6 EVIDENCE TO RECOMMENDATIONS

The GDG noted that:

- Whilst GPIs have been shown to reduce the risk of subsequent cardiac ischaemic events, this effect is most apparent when ischaemic risk is high (as judged by formal risk scoring, presence of raised troponins etc.), or if the duration of risk (delays to angiography and revascularisation) is prolonged (suggested by Boersma and Roffi meta-analyses).

- Much of the evidence relating to the use of GPIs preceded the widespread use of clopidogrel in addition to aspirin and an anti-thrombin.

- In the Boersma meta analysis GPIs reduced the 30 day relative odds of the combined endpoint death/MI by 15% (absolute benefit 1.7%) in troponin positive patients, whereas no odds reduction was seen in those who were troponin negative. However, it has also been demonstrated in the GRACE Registry that the presence of an elevated troponin alone does not reliably identify high risk patients, as judged by mortality outcome[11].

- Risk assessed by mortality outcome may not adequately reflect risk of a further ischaemic event. For instance, using the online GRACE risk calculator and a theoretical patient profile[117] it is possible to have a six-month predicted mortality of 4% (which lies in our risk cohort 2a [intermediate], as defined elsewhere in this guideline – see risk assessment chapter), but have a combined risk of death/MI at 6 months as high as 25%. Thus, caution needs to be shown when identifying the levels of risk at which GPIs should or should not be given. This note of caution with regards extrapolation of population data to individual patient decision making has also been highlighted earlier in the section on health economics.

- There may be a gender effect, with females appearing to benefit less from the use of GPIs than males (Boersma et al. [88]), although the subgroup of women with elevated serum troponin do appear to benefit.

No studies that assessed GPIs against no GPIs in a population using fondaparinux. The OASIS-5 trial addresses this issue somewhat by examining 30-day outcomes for fondaparinux versus enoxaparin in subgroups of patients receiving clopidogrel and GPIs[115]. This analysis suggested that the benefits of fondaparinux are maintained when used with GPIs, and the GDG felt it therefore unlikely that fondaparinux would result in a worse outcome than the combination of GPIs and other anticoagulants used in the trials.

Trials have tended to enrol people of low-intermediate, rather than high risk of an adverse outcome. Using methodology described earlier (reference to risk chapter) we plotted the six-month mortalities for ISAR-REACT-2, onto a GRACE graph (6-month predicted mortality by GRACE score – see Figure 2-15 below). The prior risk stratification of people with UA/NSTEMI (England & Wales) into risk cohorts 1a, 1b, 2a, 2b, 3 & 4, allowed us to attempt to position the results from this trial to an unselected population in England & Wales. These plots suggest ISAR-REACT-2 mainly enrolled

people at low to intermediate levels of risk (risk cohorts 1 & 2) relative to the spectrum of risk in the unselected population of people with UA or NSTEMI.

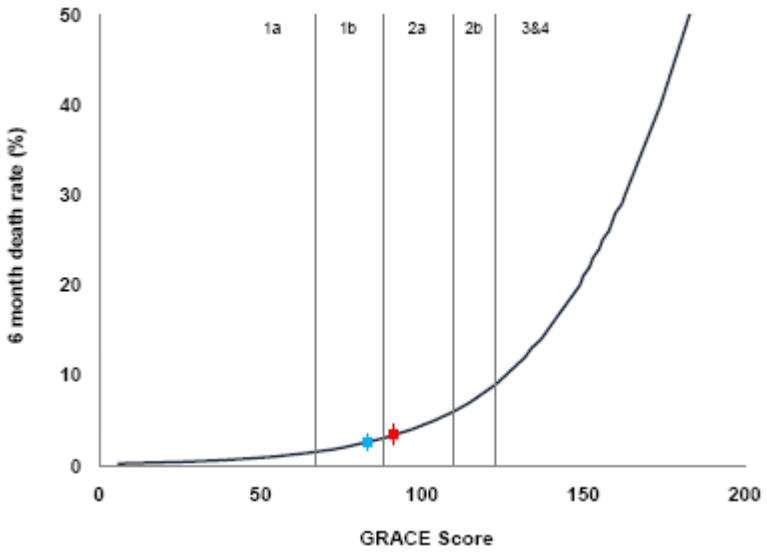


Figure 2-15. 6-month mortality (y-axis) and GRACE score (x-axis) data from the GRACE Registry. Six month mortality in ISAR REACT 2 for placebo (red) and abciximab (blue) groups plotted on the 'GRACE curve' (dark blue). Bars are 95%CI. Vertical grey lines show risk groups. Risk groups 3 and 4 include approximately 50% of the ACS population at highest risk. ISAR REACT-2 mortality data provided by Adnan Kastrati.

The use of GPIs has decreased in the UK since clopidogrel has become so widely used. There has also been a relative lack of evidence relating to the degree to which additional bleeding is associated with adding a GPI to background anticoagulant and antiplatelet therapy, because many trials did not mandate the use of clopidogrel in addition to aspirin. Assuming background triple therapy the GDG felt that the evidence was generally less convincingly in support of the routine use of GPIs in the medical (conservative) management of patients with NSTEMI and UA than was the case when TA47 was published. This was because, with the increased use of early angiography and revascularisation, patients managed conservatively increasingly fall into two categories; those at very low risk of a further ischaemic event, and those at very high risk of a bleeding complication. The evidence does support the use of upstream GPIs in patients at intermediate or high risk who are scheduled to undergo an early invasive strategy, albeit at the expense of some increase in bleeding risk.

GPIs were initially licensed based on clinical trials using unfractionated heparin as the anticoagulant choice. As a result the summaries of product characteristics for GPis state that they are 'indicated as an adjunct to aspirin and heparin' in the case of abciximab or 'intended for use with aspirin and unfractionated heparin' for eptifibatide and tirofiban. In addition, licensing will often state there is limited or no experience with low molecular weight heparins or fondaparinux.

Low molecular weight heparins such as enoxaparin and more recently the synthetic pentasaccharide fondaparinux are licensed for the treatment of UA and NSTEMI. The clinical trials involved the combination with glycoprotein inhibitors as well as aspirin and clopidogrel. Whilst the licensing authorities do not recommend the combination, it has become established practice to prescribe and administer LMWH or fondaparinux in (within their licensed indication) in combination with glycoprotein inhibitors.

3.3.7 RECOMMENDATIONS

R14 Consider intravenous eptifibatide or tirofiban[m] as part of the early management for patients who have an intermediate or higher risk of adverse cardiovascular events (predicted 6-month mortality above 3%), and who are scheduled to undergo angiography within 96 hours of hospital admission.

R15 Consider abciximab as an adjunct to PCI for patients at intermediate or higher risk of adverse cardiovascular events who are not already receiving a GPI.

R16 Balance the potential reduction in a patient's ischaemic risk with any increased risk of bleeding, when determining whether a GPI should be offered.

[m] Eptifibatide and tirofiban are licensed for use with aspirin and unfractionated heparin. They do not have UK marketing authorisation for use with clopidogrel. This recommendation is therefore for an off-label use of these drugs. Informed consent should be obtained and documented before they are used in combination with clopidogrel.

4 ANTI–THROMBIN THERAPY

Instability of coronary plaque is the pathophysiological substrate for the clinical syndromes of UA and NSTEMI, and is associated with activation of local prothrombotic systems. It is therefore not surprising that considerable research has been undertaken to investigate the role of anticoagulant therapy in the management of patients with these conditions. Heparin and the *direct* antithrombin agents inhibit the conversion of fibrinogen to fibrin and therefore reduce the likelihood of clot (thrombus) formation. Prescribers should be aware that advanced age, reduced body weight (<50 kg) and impaired renal function increase bleeding risk associated with anticoagulants.

4.1 HEPARINS

Heparins, both unfractionated and low molecular weight, are *indirect* thrombin inhibitors which form complexes with antithrombin, and inactivate thrombin, clotting factor Xa (and to a lesser extent, factors XIIa, XIa, and IXa). Low molecular weight heparins (LMWH) have a number of potential advantages over unfractionated heparin (UFH):

- They can be administered by subcutaneous injection, rather than having to be given by an intravenous bolus or infusion, and they have greater bioavailability.
- The duration of their anticoagulant effect is greater, allowing once or twice daily administration.
- Their anticoagulant response is more predictable and is correlated with body weight, making dosage calculation easier.
- They do not require monitoring by blood testing, though the dose may have to be adjusted for patients who are very obese or have renal failure.
- They have a reduced risk of causing immune-mediated thrombocytopenia.

UFH has been shown to be superior to placebo in patients with NSTEMI and UA[118] and in a number of trials has been compared to LMWH. A literature search was therefore performed to compare LMWH and UFH in these patients. Thus the clinical question asked, and upon which the literature was searched, was:

> *"What is the efficacy and safety of adding a LMWH compound to aspirin (with or without clopidogrel) in the management of patients with UA or NSTMEMI compared to the combination of unfractionated heparin and aspirin (with or without clopidogrel)?"*

4.1.1 CLINICAL METHODOLOGICAL INTRODUCTION

The literature was searched for systematic reviews or RCTs published in 1999 to 2009. The rationale for searching from January 1999 onwards was to reflect current practice, particularly the use of stents for revascularisation. To be included, the population must contain > 60% people with unstable angina/NSTEMI. Seven RCTs [119-125] were identified which compared low molecular weight heparin (LMWH) and unfractionated heparin (UFH) in non ST-segment elevation ACS patients. The follow up period ranged from 6 to 30 days.

Of these trials, two double blind RCTs, ESSENCE (N=3,171) [122] and TIMI IIB (N=3910) [119], compared enoxaparin and UFH on a background of aspirin.

The open label FRIC RCT [125] (N=1499) compared dalteparin and UFH on a background of aspirin.

The double blind RCT, ACUTE II [121] (N=525), and two open label RCTs, INTERACT [124] (N=746) and A-Z [120] (N=3987) compared enoxaparin and UFH on a background of glycoprotein IIb/IIIa inhibitor and aspirin. The open label RCT, SYNERGY (N=10,027) [123] compared enoxaparin and UFH on a background of aspirin or clopidogrel (62% received clopidogrel) with GPIs recommended, but not mandated (57% received GPIs).

One meta–analysis [126] was rejected because it lacked an explanation of how the studies were searched for and assessed for quality.

The NCC–CC conducted a meta-analysis comparing low molecular weight heparins to unfractionated heparin (7 RCTs: ESSENCE, TIMI IIB, ACUTE II, INTERACT, A to Z, SYNERGY, FRIC). Subsequently, a systematic review [127] comparing enoxaparin with UFH was identified in the literature re-runs. The Murphy et al. systematic review contained an extra outcome (death, nonfatal MI, or nonfatal major bleed). Also, the authors contacted trial investigators for data, and were therefore able to include more studies for the outcome of death or nonfatal MI than the NCC meta-analysis had. The results of the Murphy et al meta-analysis and the NCC meta-analysis were similar for other outcomes.

4.1.2 CLINICAL EVIDENCE STATEMENTS

The NCC–CC meta-analysis (including one dalteparin study) found a non–significant difference between LMWH and UFH for:

- Death (7 RCTs; OR 0.96 [95% CI 0.75 to 1.23])
- Urgent revascularization rates (4 RCTs; OR 0.92 [95% CI 0.79, 1.07])
- Death or MI (4 RCTs; OR 0.88 [95% CI 0.72, 1.06])
- Death or MI or urgent revascularization (4 RCTs; OR 0.88 [95% CI 0.77, 1.02])
- Major bleeding (7 RCTs; OR 1.10 [95% CI 0.85, 1.42]); this analysis had significant heterogeneity I^2 = 49.8%.
- Minor bleeding (6 RCTs; OR 1.58 [95% CI 1.00, 2.50]); this analysis had significant heterogeneity I^2 = 92.7%.

Evidence Level 1+

The NCC–CC meta-analysis (including one dalteparin study) showed that LMWH significantly reduced the odds of:

- MI (7 RCTs; OR 0.87 [95% CI 0.79, 0.95]).

Evidence Level 1+

As the majority of the evidence compared enoxaparin with unfractionated heparin, the meta-analysis results were presented separately for this comparison.
Enoxaparin versus UFH (refer to

Table 4-1):

There was no significant difference between enoxaparin and UFH for:

- Death
- Death, nonfatal MI, or nonfatal major bleed
- Urgent revascularization rates
- Major bleeding (this analysis had significant heterogeneity, I^2 = 58.1%).

Evidence Level 1+

Compared with UFH, enoxaparin significantly reduced the odds of:

- Nonfatal MI
- Death or non fatal MI
- Death or MI or urgent revascularisation

Evidence Level 1+

Compared with UFH, enoxaparin significantly increased the odds of:

- Minor bleeding (this analysis had significant heterogeneity; I^2 = 94.0%)

Evidence Level 1+

Table 4-1. Summary of outcomes for enoxaparin versus UFH from the Murphy et al and NCC meta-analyses

Systematic Review	Outcome	N RCTs	Effect Size (Odds ratio [95% CI]) Enoxaparin versus UFH	Heterogeneity?
NCC–CC	Death	6	0.94 (0.79 to 1.12)	Non–significant
Murphy et al [127]	Death	6	0.99 (0.83 to 1.18)	Not reported
NCC–CC	Non-fatal MI	6	0.87 (0.79 to 0.96)	Non–significant
Murphy et al [127]	Non-fatal MI	6	0.87 (0.79 to 0.96)	Not reported
NCC–CC	Urgent revascularisation	3	0.94 (0.77 to 1.14)	Non–significant
Murphy et al [127]	Death or nonfatal MI	6	0.90 (0.81 to 0.996)	Not reported
Murphy et al [127]	Death, nonfatal MI, or nonfatal major bleed	5	0.97 (0.86 to 1.09)	Non–significant
NCC–CC	Death, MI, or Urgent revascularisation	3	0.84 (0.74 to 0.95)	Non–significant
NCC–CC	Major bleed	6	1.10 (0.83 to 1.46)	Significant I^2 = 58.1%
Murphy et al [127]	Major bleed	6	1.13 (0.84 to 1.54)	Not reported
NCC–CC	Minor bleed	5	1.73 (1.04 to 2.90)	Significant I^2 = 94.0%

Forest plots for NCC–CC meta-analysis comparing LMWH with UFH

See Figure 4-1, Figure 4-2, Figure 4-3, Figure 4-4, Figure 3-5, Figure 3-6.

Figure 4-1. Death

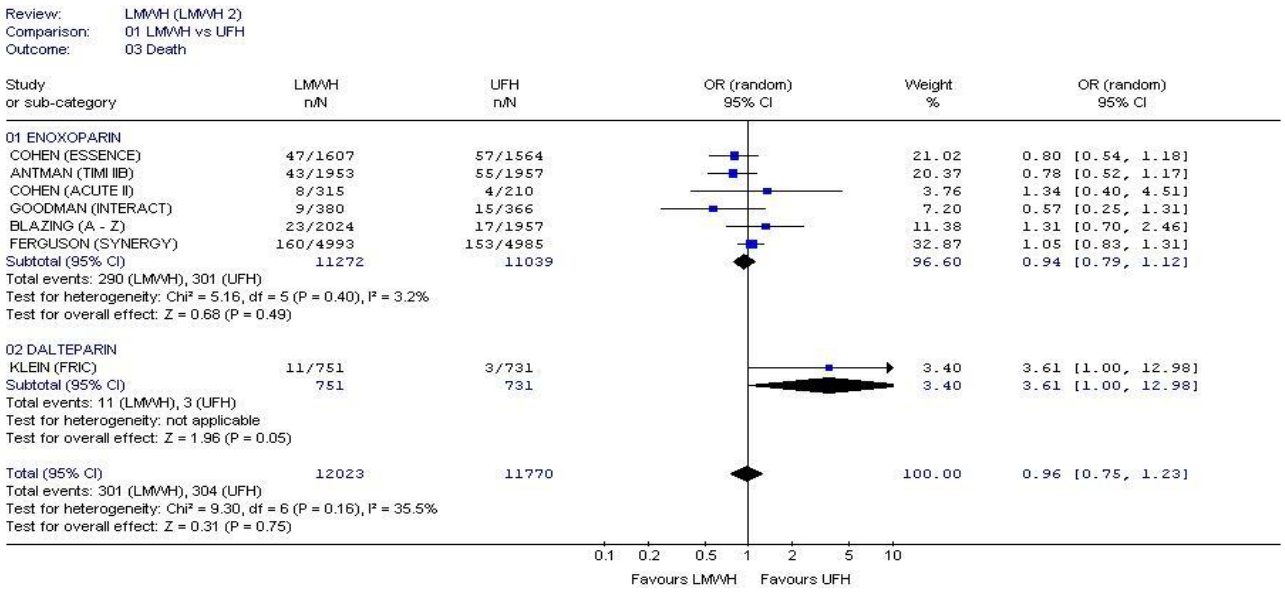


Figure 4-2. Myocardial Infarction

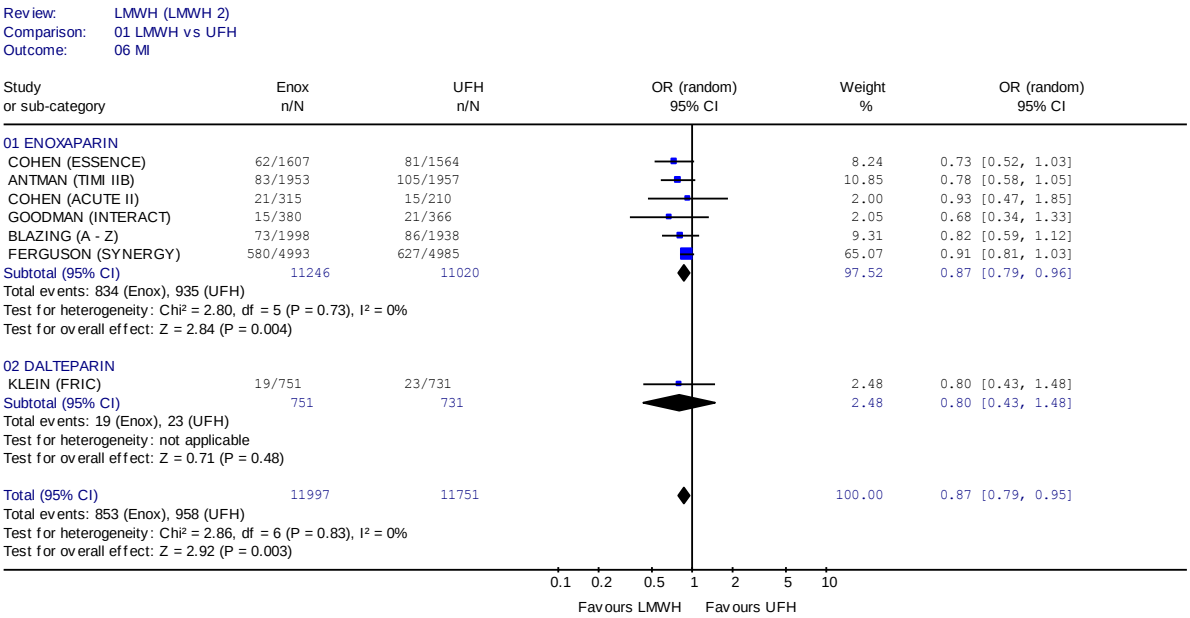


Figure 4-3. Urgent Revascularization

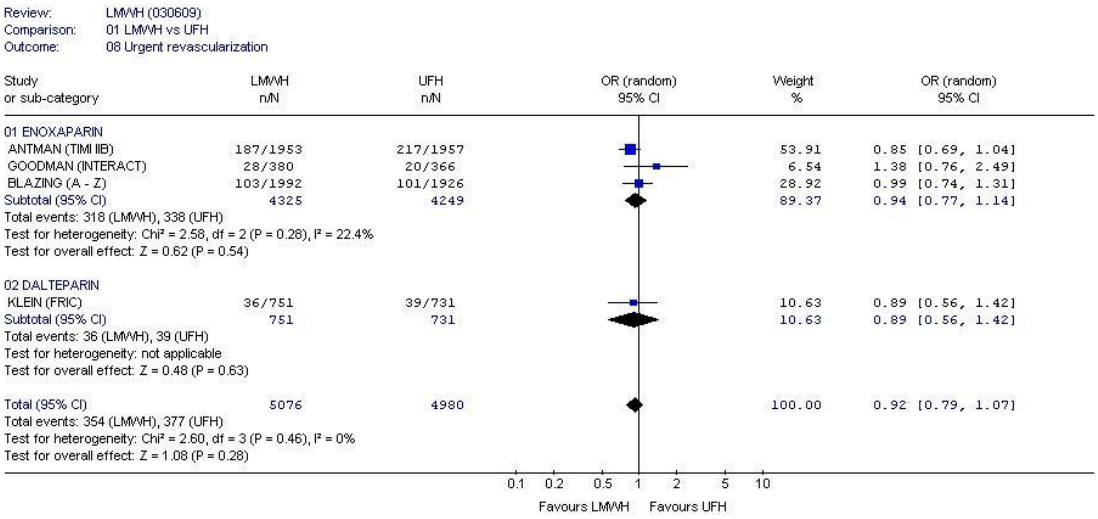


Figure 4-4. Death or MI or Urgent Revascularization

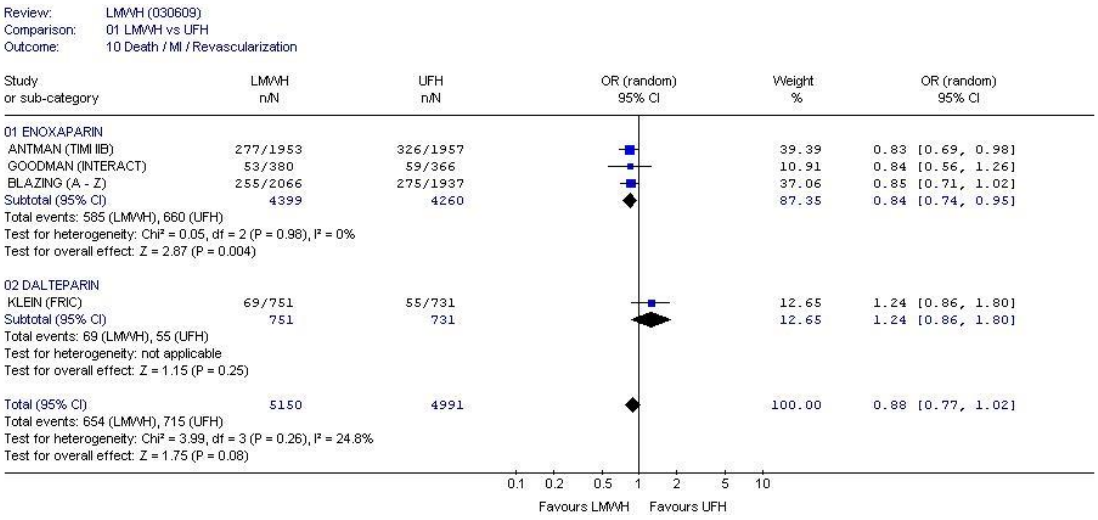


Figure 4-5. Major Bleeding

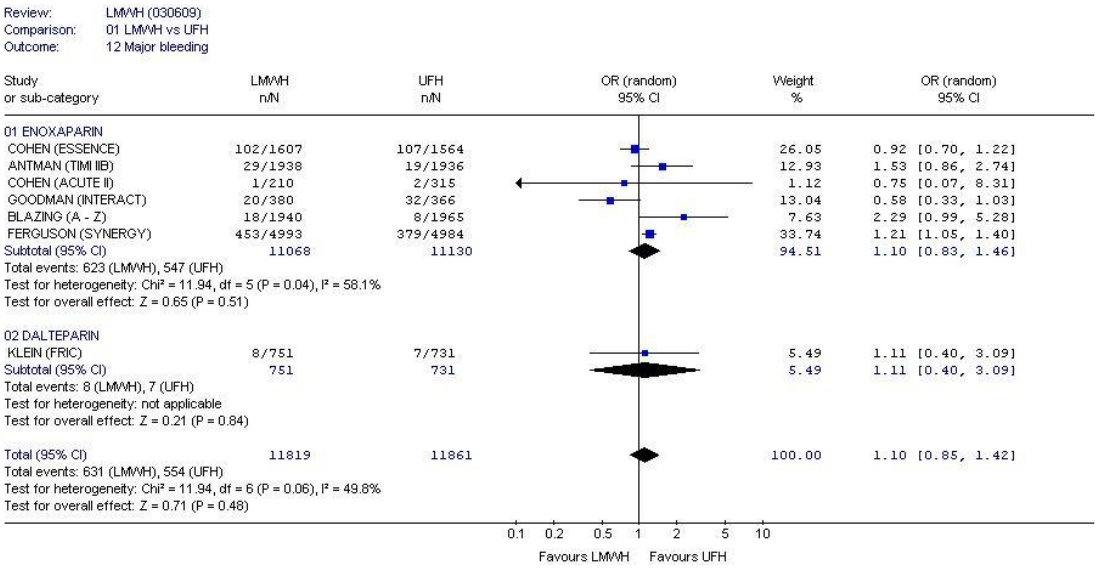
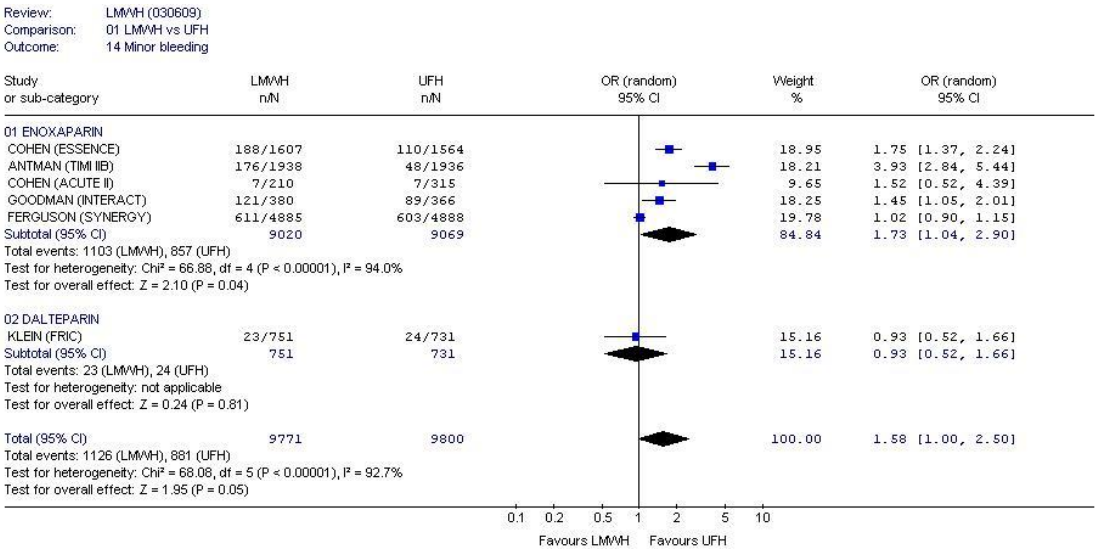


Figure 4-6. Minor Bleeding



4.1.3 *HEALTH ECONOMIC METHODOLOGICAL INTRODUCTION*

One relevant cost-effectiveness analysis from a UK perspective was identified based on clinical effectiveness data from the ESSENCE study [122](with data from TIMI IIB [119] used in sensitivity analysis). Six studies from non-UK perspectives were also identified but as these used the same clinical effectiveness data as the UK analysis were judged to likely to add little additional information for UK decision making and were not reviewed[128-133].

Nicholson et al. [134] reported a decision analysis based primarily on data from the ESSENCE RCT[122] (sensitivity analysis did incorporate data from TIMI IIB[119]). The study compared enoxaparin with UFH in patients with UA or NSTEMI. A UK NHS perspective was taken. Cost and QALYs are estimated at one-year. Outcomes incorporated were death, MI, recurrent angina and quality of life. Costs included were enoxaparin, UFH, drug administration (consumables, IV pump, monitoring, nursing time), hospital length of stay (at 30 days), revascularisation (at one year). An alternative analysis looked at using costs of cardiac events at one year rather than length of stay. Cost effectiveness was expressed in terms of cost per QALY gained. The key potential limitation of the study is the use of data from the ESSENCE trial which reported in 1997 and had a low stent and thienopyridine use relative to current practices. Additionally, a lifetime analysis might be considered more appropriate as mortality was impacted and the quality of life valuation method was not choice-based.

4.1.4 *HEALTH ECONOMIC EVIDENCE STATEMENTS*

Nicholson et al. [134] reported that enoxaparin was dominant compared to UFH in people with UA/NSTEMI – costs were reduced by £317 per person with a QALY gain of 0.013. Additional drug costs of enoxaparin were mostly offset by administration costs of UFH (saline, consumables, iv pump, monitoring, nurse time). Additional cost savings came from reduced length of stay and revascularisation avoided. These results are considered applicable to the UK NHS setting. However, there is a potential serious limitation relating to the use of data from the ESSENCE trial, which reported in 1997 and which is noted to have a low revascularisation rate relative to more recent practice (27% in enoxaparin group, and 32.2% in the unfractionated heparin group). Results are reported as being very sensitive to rates of revascularisation, and duration and cost of length of stay. However, in all but one sensitivity analysis enoxaparin remained dominant – when length of stay was used from a UK sub-group of ESSENCE there was a net cost (due to increased length of stay in the enoxaparin group) with an incremental cost-effectiveness ratio of £3,305 per QALY gained.

4.1.5 *EVIDENCE SUMMARY*

The trials evaluating LMWH in patients with UA or NSTEMI show that enoxaparin is at least comparable, and may be superior, to UFH. Evidence for the use of daltaparin is limited. Enoxaparin reduces the rates of composite end points (death, re-infarction, revascularisation, recurrent myocardial ischaemia) and when analysed separately there

is a reduction in MI but no evidence of a mortality benefit. Also, treatment with enoxaparin is associated with an increased risk of minor, but not major, bleeding.

A UK NHS perspective economic analysis based on the ESSENCE Trial [134] found that enoxaparin was dominant over UFH (more effective and lower cost) in patients with non-ST elevation MI or UA.

4.1.6 EVIDENCE TO RECOMMENDATIONS

The GDG acknowledged that one of the difficulties in analysing the numerous trials which compare LMWH with UFH is that they have occurred over more than a 10-year time period during which the use of adjunctive therapies, such as clopidogrel and GPIs, has changed. The earlier trials, such as FRIC (1997) [125] and ESSENCE (1997) [122] had background therapy of aspirin alone, whereas more recent trials (ACUTE-II [2002] [121], INTERACT [2003] [124], A-Z [2004])[120] had both aspirin and GPIs as adjunctive treatment, and one (SYNERGY [2004][123] had GPIs with aspirin and/or Clopidogrel. In some trials the use of GPIs was mandated, and in others it was left to physician discretion. Given that these agents (aspirin, clopidogrel, GPIs and heparin) can all have an effect on outcome it was difficult for the GDG to dissect out the relative benefits of each individually. All but one of the trials the GDG reviewed involved the use of enoxaparin, and this is reflected in UK clinical practice, where dalteparin is not widely used.

It was noted that the cost of enoxaparin is now lower than used in the ESSENCE trial (£10.80/day versus £12.16/day) and some centres have also reduced the dose of enoxaparin in elderly patients (to 0.75mg/kg as opposed to the usual 1mg/kg) which will also lower drugs costs. It is judged likely therefore that administration costs for UFH will still largely offset the difference in drug costs between enoxaparin and UFH. While the magnitude of the estimates of various clinical effects is lower in the meta–analysis of all enoxaparin studies compared with the ESSENCE study alone, the direction of effect remains the same. As such, it is judged likely that enoxaparin would remain a cost-effective treatment option compared with UFH.

Despite these potentially confounding factors the GDG concluded that: there was insufficient evidence to state that enoxaparin is clearly superior to UFH across an unselected population with UA/NSTEMI, but the following supports its superiority in some respects:

- The meta-analyses showed that enoxaparin is associated with a significant reduction in MI, a composite endpoint (death, MI, urgent revascularisation) or a composite endpoint of death or nonfatal MI.
- The increase in the minor bleeding outcome had significant heterogeneity suggesting that pooled analysis of these studies should be regarded with caution.
- LMWH is easy to administer, has a more predictable anticoagulant effect and does not requiring monitoring.

- The available health economic evidence suggests the use of enoxaparin is cost–effective compared to UFH.
- The patient/carer representatives of the GDG favoured subcutaneous over intravenous route of administration and thus strongly preferred the use of low molecular weight heparin.
- There were insufficient data to allow the GDG to make clear recommendations regarding the use of dalteparin. Therefore, the meta-analysis assessing enoxaparin compared with UFH was used to inform recommendations.

4.2 FONDAPARINUX

4.2.1 CLINICAL INTRODUCTION

Fondaparinux is a synthetic pentasaccharide; the first of a new class of synthetic antithrombotics. It binds to anti–thrombin with greater affinity than either UFH or LMWH, and increases the ability of anti–thrombin to inactivate clotting factor Xa. It has 100% bioavailability after subcutaneous administration and has a half-life much longer than UFH or LMWH. Its effects are not reversed by protamine but may be by recombinant factor VIIa[135]. It has little effect on the activated partial thromboplastin time (aPTT), prothrombin time or bleeding time, and it does not alter fibrinolysis or platelet function (and thrombocytopenia, sometimes seen with UFH and LMWH, is rare). Monitoring can be achieved via an anti-factor Xa assay calibrated with fondaparinux[136].

The standard dose for patients with acute coronary syndromes is considered to be 2.5 mg/day subcutaneously. The majority of an administered dose of fondaparinux is excreted unchanged in the urine, with an elimination half-life of 15 to 17 hours. Patients who had serum creatinine levels >265 μmol/l were excluded from the major ACS clinical trial (OASIS-5); it is contraindicated in those with clearance <20 ml/min[86] .

The clinical questions posed were:

> *"What is the efficacy and safety of adding a factor Xa inhibitor (fondaparinux) to aspirin in the management of patients with UA or NSTEMI compared to the combination of LMWH/ UFH and aspirin therapy?"*
>
> *"What is the efficacy and safety of adding a synthetic pentasaccharide (fondaparinux and enoxaparin) to aspirin as adjunct therapy to patients with UA/ NSTEMI undergoing PCI compared to the combination of LMWH/UFH and aspirin therapy?"*

4.2.2 CLINICAL METHODOLOGICAL INTRODUCTION

The literature was searched from 1999 to 2009 for systematic reviews and RCTs. The rationale for searching from January 1999 onwards was to reflect current practice, particularly the use of stents for revascularisation. Studies were excluded if the population comprised < 60% of people with a diagnosis of non ST-segment elevation ACS. Outcomes of interest were 30 day survival, re-infarction, LV function, re-vascularisation, quality of life, and serious complications. Primary outcomes assessed earlier than 30 days were also reported.

In the OASIS-5 double blind RCT, patients presenting with UA or NSTEMI (mean age 66 years) were randomised to fondaparinux (N = 10057; 2.5 mg s.c., mean treatment duration 5.4 days) or enoxaparin (N= 10021; 1 mg/kg, twice daily, s.c.; mean treatment duration 5.2 days). Aspirin (97%) and clopidogrel (67%) were administered in both trial arms. Primary outcomes included major bleeding at 9 days or death, MI, or refractory ischemia at 9 days. Secondary outcomes were measured at 30 days [113].

A prospectively determined subgroup analysis of the OASIS-5 RCT compared the efficacy and safety of fondaparinux (N=3134) with enoxaparin (N=3104) in people undergoing PCI within the first eight days of randomisation. People in the enoxaparin group received unfractionated heparin (UFH) if their last dose of enoxaparin was greater than six hours before PCI (65-100 iu/kg depending on whether a GPI had also been given or not). People receiving fondaparinux within six hours of PCI received no additional fondaparinux if they were also on a GPI, or an additional 2.5 mg if they were not. Those who had fondaparinux for more than six hours prior to the PCI received an additional dose of 2.5 to 5 mg depending on whether they received a GPI or not. A protocol amendment advised the consideration of open-label UFH prior to PCI in both trial arms for the last 1758 people undergoing PCI [137].

4.2.3 HEALTH ECONOMIC METHODOLOGICAL INTRODUCTION

One relevant cost-effectiveness analysis was identified comparing fondaparinux and enoxaparin in UA/NSTEMI patients[114].

Sculpher et al.[114] reported a cost–utility analysis undertaken from a US direct medical cost perspective based on 180-day effectiveness and resource use data from the OASIS-5 study. A decision analytic model and additional data sources were used to extrapolate beyond the 180-day trial follow-up to estimate lifetime costs and QALYs. The risk of having experienced any of the following key clinical events at 180 days was calculated based on OASIS-5: death, non-fatal MI, non-fatal stroke, combined stroke and MI, major bleed and minor bleed. The cost associated with having each of these key events at 180-days, and of not having any event, were estimated using regression analysis of resource use data from a US subgroup of OASIS-5 (n=759) and US unit costs. Beyond 180 days, long-term mortality rates adjusted for UA/NSTEMI patients were applied in order to estimate life-time costs and QALYs. Higher mortality rates were attributed to those who experienced a non-fatal MI, stroke or both at 180-days. An annual cost of coronary heart disease was applied while patients remain alive. EQ-5D utility weights (US tariff) were applied to life-years in order to calculated QALYs. Lower utility weights were applied to patients who had an MI or a stroke than other patients. Probabilistic sensitivity analysis was used to evaluate uncertainty and a number of other sensitivity analyses were also undertaken.

The study is judged partially applicable to the UK setting. The key issue being the US perspective, in particular there is uncertainty over the applicability of US resource use data and unit costs; although this is at least partially addressed by a sensitivity analysis that used costs based on resource use from all patients instead of only the US subgroup. In addition the US EQ-5D tariff is used and a discount rate of 3%, as opposed to 3.5% recommended by NICE. The study is judged to be of good methodological quality. Catheter-related thrombosis is not incorporated into the analysis but this was judged to be a minor limitation and one that is somewhat addressed by a sensitivity analysis that incorporates an additional cost associated with fondaparinux. This was based on the fact that when randomised treatment was added as a covariate into the cost regression analysis an additional (although non-significant) cost was associated with fondaparinux independent of the clinical events incorporated.

4.2.4 CLINICAL EVIDENCE STATEMENTS

Fondaparinux versus enoxaparin in people with NSTE ACS

Compared with enoxaparin, fondaparinux significantly:

- Reduced the risk of major bleeding at nine days (primary safety outcome) (2.2% in fondaparinux group versus 4.1% in enoxaparin group; HR 0.52 [95% CI 0.44 to 0.61], p <0.001) and at 30 days (3.1% in fondaparinux versus 5.0% in enoxaparin: HR 0.62 [95% CI 0.54 to 0.72], p<0.001). Major bleeding was consistently lower with fondaparinux compared with enoxaparin in all groups assessed, regardless of whether UFH was administered before randomisation or not. [113]

- Reduced the composite risk of death, MI, refractory ischaemia, or major bleeding at nine days (7.3% in fondaparinux group versus 9.0% in enoxaparin group: HR 0.81 [95% CI 0.73 to 0.89], p<0.001) and at 30 days (10.2% in fondaparinux group versus 12.4% in enoxaparin group: HR 0.82 [95% CI 0.75 to 0.89], p<0.001) [113].

- Reduced the risk of death at 30 days (2.9% for fondaparinux versus 3.5% for enoxaparin; HR 0.83 [95% CI 0.71 to 0.97], p=0.02) [113].

Evidence Level: 1++

There was no significant difference between the fondaparinux and enoxaparin groups for [113]:

- Composite risk of death, MI, or refractory ischaemia at 9 days (primary efficacy outcome) (5.8% in fondaparinux group versus 5.7% in enoxaparin group; HR 1.01 [95% CI 0.90 to 1.13])

- Composite risk of death, MI, or refractory ischaemia at 30 days (8.0% in fondaparinux group versus 8.6% in enoxaparin group; HR 0.93 [95% CI 0.84, 1.02])

- Composite risk of death or MI at 30 days (6.2% in fondaparinux group versus 6.8% in enoxaparin group;HR 0.90 [95% CI 0.81, 1.01])

- Risk of MI at 30 days (3.9% in fondaparinux group versus 4.1% in enoxaparin group;HR 0.94 [95% CI 0.82, 1.08])

- Risk of refractory ischaemia at 30 days (2.2% in fondaparinux group versus 2.2% in enoxaparin group;HR 0.99 [95% CI 0.82, 1.19])

- Risk of stroke at 30 days (0.7% in fondaparinux group versus 1.0% in enoxaparin group; HR 0.77 [95% CI 0.57, 1.05])

Evidence Level: 1++

Fondaparinux versus enoxaparin in peoplewith NSTE ACS undergoing PCI within the first eight days of randomisation [137]

In people undergoing PCI, fondaparinux significantly reduced the:

- Composite risk of death, MI, stroke, or major bleeding at nine days (8.2% for fondaparinux versus 10.4% for enoxaparin HR 0.78 [95% CI 0.67, 0.93], p=0.004) and at 30 days (9.5% for fondaparinux versus 11.8 % for enoxaparin: HR 0.80 [95% CI 0.69 to 0.93]) [137].
- Rate of major bleeding at nine days (2.4% for fondaparinux versus 5.1% for enoxaparin; HR 0.46 [95% CI 0.35 to 0.61], p<0.00001) and at 30 days (2.9% for fondaparinux versus 5.4% for enoxaparin; HR 0.52 [95% CI 0.40 to 0.67], p<0.00001) [137].

Evidence Level: 1+

In people undergoing PCI, there was no significant difference between the fondaparinux and enoxaparin groups for: [137]

- Death, MI, or stroke at 9 days (6.3% for fondaparinux versus 6.2% for enoxaparin; HR 1.03 [0.84 to 1.25])
- death, MI, or stroke at 30 days (7.4% for fondaparinux versus 7.4% for enoxaparin; HR 1.00 [0.83 to 1.20])
- Death at 30 days (2.0% for fondaparinux versus 2.1% for enoxaparin; HR 0.94 [0.67 to 1.34])
- MI at 30 days (5.7% for fondaparinux versus 5.5% for enoxaparin; HR 1.04 [0.84 to 1.29])
- Stroke at 30 days (0.6% for fondaparinux versus 0.7% for enoxaparin; HR 0.76 [0.41 to 1.44])

Evidence Level: 1+

An increase in the rate of guiding-catheter thrombus formation was noted with fondaparinux in OASIS-5 (29 episodes [0.9 percent], versus eight episodes with enoxaparin [0.3 percent]; RR 3.59 [95% CI 1.64 to 7.84], p=0.001) - a difference that was observed both before (1.2% vs. 0.3%) and after (0.7% vs. 0.2%) the protocol amendment using unfractionated heparin [113].

Impact of clopidogrel or GPIs on Major Bleeding

In people undergoing PCI, fondaparinux significantly reduced the risk of major bleeding at 30 days compared with enoxaparin when GPIs were used in both groups (N=1198

fondaparinux; N=1263 enoxaparin; HR 0.56 [95% CI 0.39 to 0.81], p=0.002) as well as in the absence of GPIs (N=1874 fondaparinux; N=1842 enoxaparin; HR 0.43 [95% CI 0.30 to 0.63], p<0.0001) [137].

In people undergoing PCI, fondaparinux significantly reduced the risk of major bleeding at 30 days compared with enoxaparin when clopidogrel was used in both groups (N=912 fondaparinux; N=923 enoxaparin; HR 0.45 [0.28-0.72], p=0.001) as well as in the absence of clopidogrel (N=2060 fondaparinux; N=2086 enoxaparin; HR 0.52 [95% CI 0.39 to 0.71], p<0.0001). [137]

Evidence Level: 1+

4.2.5 HEALTH ECONOMIC EVIDENCE STATEMENTS

Sculpher et al.[114] found that fondaparinux was a dominant strategy compared to enoxaparin (that is, it was associated with lower costs and higher QALYs) from a lifetime, US perspective. Mean costs were reduced by £121[n] per person and mean QALYs were increased by 0.04. In probabilistic sensitivity analysis fondaparinux was cost-saving in 82.4% of simulations. At a £32,266 ($50,000) threshold fondaparinux was cost effective in 99.3% of simulations. Costs were also lower with fondaparinux at 180 days at £353.

In sensitivity analysis the model was run for low risk and high risk patients. Fondaparinux was remained a dominant strategy in both groups. The difference in costs and QALYs were smaller in magnitude in low risk patients and bigger in high risk patients. The probability of fondaparinux being cost saving and cost effective were approximately the same as for the overall analysis.

Re-estimating event costs using all patients instead of only US patients increased the 180-day cost-saving to £473[n] with fondaparinux compared to enoxaparin and fondaparinux remained dominant in the lifetime analysis. A 25% reduction in enoxaparin cost did not change conclusions.

Including a randomised treatment covariate in the cost regression showed a non-significant additional cost associated with fondaparinux independent of clinical events. When this was incorporated into the lifetime analysis fondaparinux remained dominant in high risk patients and had an ICER of £1510[n] per QALY gained overall and £4486[n] per QALY gained in low risk patients.

No UK analyses were identified. In terms of drug costs alone: fondaparinux costs £6.41 per day; enoxaparin costs £10.38 per day (assuming dose of 1mg/kg and weight of 80kg)[139]. Given that the clinical evidence suggests a benefit of fondaparinux over enoxaparin, it was judged likely that the conclusion that use of fondaparinux is cost effective compared to enoxaparin would be maintained if a UK perspective were taken.

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[n] Costs are converted from 2006 US dollars using Purchasing Power Parities[138]

Health economic modelling

As drug costs were lower with fondaparinux than enoxaparin, and the clinical evidence supported improved outcomes with fondaparinux, there was considered to be low uncertainty that fondaparinux would be cost effective and it was judged a low priority to conduct a modelling study to analyse this. However, it was of interest to consider how use of fondaparinux instead of enoxaparin might impact the comparisons made in the model regarding use of GPIs and bivalirudin. As such fondaparinux was incorporated into the cost-effectiveness analysis undertaken for the guideline.

A cost–utility analysis was undertaken with costs and quality-adjusted life-years (QALYs) considered over patients' lifetimes from a UK NHS perspective.

This compared the following treatment strategies in the acute management of UA/NSTEMI (heparin baseline):

- Aspirin +clopidogrel +heparin (LMWH or UFH)
- Aspirin +clopidogrel +heparin + GPI during PCI only
- Aspirin +clopidogrel +heparin + GPI upstream of angiography
- Aspirin +clopidogrel +bivalirudin upstream of angiography
- Aspirin +clopidogrel +heparin +bivalirudin during PCI only.

In addition the analysis was run as above but with fondaparinux substituted for heparin in the first three arms (fondaparinux baseline). Fondaparinux was not incorporated in the bivalirudin arms in this analysis as there is no experience with these agents combined and so it was not judged appropriate. The analysis incorporated 1-year death, MI and post-acute revascularisation, and inhospital bleeding.

As comparing fondaparinux and enoxaparin was not the primary objective of the analysis, some issues relating to this comparison may not have been captured fully. For example, catheter-related thrombosis was not incorporated into the model. This however is considered unlikely to impact conclusions. In addition, the six-month relative risks from OASIS-5 were assumed to hold at one year as the studies used for the main comparisons in the model all had one-year follow-up. However, it was possible to compare fondaparinux and enoxaparin in the model – costs were reduced and QALYs increased with fondaparinux. This is consistent with the published analysis based on the OASIS-5 study[114].

For the full analysis methods, detailed results and discussion see the report in Appendix C. A summary is provided in the GPI and bivalirudin chapters.

4.2.6 EVIDENCE SUMMARY

A preliminary investigation (the PENTUA Study[140]) had shown that fondaparinux and enoxaparin had similar efficacy when used in acute coronary syndromes. This finding led to the large OASIS-5 trial[141], which randomised over 20,000 patients with UA or NSTEMI to receive either fondaparinux (2.5 mg, once daily, subcutaneously) or enoxaparin (1 mg/kg, twice daily, subcutaneously (reduced to 1mg/kg once daily if creatinine clearance <30ml/min), for a mean duration of 5.3 days. People were excluded from the trial if their creatinine was >265 μmol/l. Over 60% of patients underwent cardiac catheterisation, and over 30% had PCI. Aspirin was given to 97% of patients, and clopidogrel to 67% in both arms of the trial. GPIs were given to 41% of those undergoing PCI (N=6239). GPI use was not reported for the entire trial population.

At nine days the composite end point of death, MI or refractory ischaemia was no different between the fondaparinux and enoxaparin groups, indicating non-inferiority of fondaparinux with respect to efficacy. However, fondaparinux was associated with a significantly lower rate of major bleeding (2.2% for fondaparinux and 4.1% for enoxaparin; HR 0.52, 95% CI, 0.44 to 0.61, p<0.001), indicating superiority of fondaparinux with respect to safety. This reduction in bleeding occurred irrespective of whether a GPI was administered or not. The composite end point of death, MI, refractory ischemia, or major bleeding occurred in 7.3% of the patients in the fondaparinux group, compared with 9.0% of the patients in the enoxaparin group (HR 0.81; 95% CI 0.73 to 0.89; P<0.001) at nine days and this difference was shown to persist to 180 days.

Regardless of treatment, patients who had major bleeding in hospital had significantly higher rates of death (13.2% vs. 2.8%), re-infarction (11.9% vs. 3.6%), and stroke (3.5% versus 0.7%) at 30 days (P<0.001), than patients without bleeding. The mortality rate among those who had minor bleeding was also higher at 30 days than among those with no bleeding episodes (6.9% vs. 2.8%), and these higher event rates associated with bleeding persisted after the authors adjusted for the various clinical characteristics associated with bleeding.

A US health economic analysis based on OASIS-5 estimated lifetime costs and QALYs and found that fondaparinux reduced costs and increased QALYs[114]. No UK analyses were identified but fondaparinux has lower daily drug costs than enoxaparin and improves clinical outcomes. Modelling undertaken for the guideline also found that fondaparinux is likely to be cost-saving and improve clinical outcomes – although it is noted that this comparison was a secondary objective of the analysis.

Fondaparinux and PCI

In a pre-specified sub-group analysis of over 3,000 patients undergoing PCI in OASIS-5[137] fondaparinux significantly reduced the risk of major bleeding at nine days (HR 0.48 [0.31–0.72], p<0.0005), and minor bleeding at nine days (HR 0.38 [0.25–0.58] p<0.00001) compared to enoxaparin in people who had their PCI within the first 24 hours of randomization. In this PCI sub-group there was no significant difference in risk

of death, MI or stroke at nine days. Major bleeding at 30 days was significantly reduced in the fondaparinux group whether or not clopidogrel, and/or a GPI, were used.

Depending on the timing of the most recent administration of the active agent, some patients in the enoxaparin group of OASIS-5 received additional UFH, with or without a GPI, and some in the fondaparinux group received an additional dose of fondaparinux, the dose of which depended on whether a GPI was given or not. In the enoxaparin group 55% received additional UFH, whereas only 20.8% of the fondaparinux group did so. It is possible that this difference in administration of additional heparin contributed to the observation of higher bleeding in the enoxoparin arm of the trial.

Isolated reports of catheter thrombosis in a small number of cases (0.9% for fondaparinux group vs 0.4% for enoxaparin group) resulted in a protocol amendment that detailed the correct method of administration of the intravenous study drug and emphasized the importance of flushing all catheters and the intravenous line to ensure that the entire bolus of the study drug (which was 0.5 ml for fondaparinux) reached the patient, since it was considered possible that catheter thrombosis may have been due to incomplete administration. In addition, centres were reminded that, at the investigator's discretion, it was permissible to give open-label UFH before PCI in addition to the protocol-mandated study drug[142]. Unlike UFH and enoxaparin, fondaparinux does not inhibit the contact clotting activation pathway (involving clotting factors XII, XI)[143] and this may be a possible explanation for its association with increased catheter thrombosis.

The authors of the OASIS-5 PCI sub-study [142] concluded that upstream fondaparinux is superior to enoxaparin in terms of net clinical benefit, but they recommended that "in fondaparinux-treated patients, UFH rather than intravenous fondaparinux be used as adjunctive therapy at the time of PCI". They also noted that the protection provided against catheter thrombus by adding conventional doses of UFH to fondaparinux or enoxaparin did not increase the risk of major bleeding in either randomized treatment group, and that the substantial benefit of upstream fondaparinux in reducing bleeding was therefore maintained.

4.2.7 EVIDENCE TO RECOMMENDATIONS

The GDG noted that the evidence was dependent on the result of a single randomised controlled trial (OASIS-5). However, this involved over 20,000 patients and was felt to be of high quality. It showed benefit of fondaparinux compared to enoxaparin with an overall reduction in major bleeding and mortality, and the reduction in bleeding risk was apparent in various subsets of patients (those undergoing PCI, those with and without clopidogrel, those with and without treatment with concomitant GPIs). Fondaparinux requires once daily administration and does not require weight adjustment, unlike enoxaparin which requires twice daily administration and is weight dependent. A US perspective analysis based on OASIS-5 found fondaparinux to be associated with lower costs and higher QALYs than enoxaparin. While no UK analyses were identified its current price is lower than enoxaparin (fondaparinux £6.41 per day, enoxaparin approximately £10 per day [assuming an average weight of 80kg, the dose is 80mg twice daily])[139]. One would therefore expect fondaparinux to be dominant over enoxaparin in any cost-effectiveness analysis.

However, the GDG noted the observation that use of fondaparinux alone at the time of a PCI procedure is associated with a small increase in catheter-related thrombosis (that did not translate into an increased risk of clinical events), and the recommendation of the trial's authors to give unfractionated heparin, rather than additional fondaparinux, at the time of a PCI procedure. International guidelines[7] have suggested using a bolus of 50-100 units/kg of UFH for those previously given fondaparinux and undergoing PCI, whereas the OASIS investigators suggested 50 to 60 units/kg. There is insufficient evidence to make a recommendation regarding the exact dose of supplemental UFH that should be used. Operators should regard the range of 50-100 units/kg as a guide and decide the dose on an individual patient basis, considering the timing of the most recent dose of fondaparinux (< or > 6 hours), the concomitant use of a GPI, and the balance between underlying ischaemic risk and potential for bleeding. In routine clinical practice it is common for interventionists currently to miss the morning dose of enoxaparin for patients going to the catheter laboratory and to use UFH during PCI (UFH is used during the procedure in most patients) and therefore the addition of UFH to fondaparinux is unlikely to have a significant impact on any cost-benefit assessment.

OASIS-5 confirmed the importance of bleeding as a predictor of adverse outcome and the need for clinicians to be aware of this association when patients with UA or NSTEMI are offered combinations of anti–platelet and anti–thrombin agents. It excluded people with a creatinine of >265 μmol/l, and renal dysfunction is known both to increase the risk of an adverse cardiovascular event, and also of bleeding[144]. A subsequent analysis of OASIS-5 indicated that the benefit of fondaparinux over enoxaparin was actually greatest in those with the most renal impairment (glomerular filtration rates (GFR) of <58 mls/min)[145]. It would therefore be illogical to use dose-adjusted enoxaparin[146] as an alternative to fondaparinux for those with greater degrees of renal impairment (who were excluded from OASIS-5), especially as it is known that such dose adjustment is often not undertaken appropriately in practice[147]. Unfractionated heparin, with dosage guided by monitoring of blood clotting would be a more logical alternative to fondaparinux where there is particular clinical concern regarding bleeding risk.

The GDG concluded that:

- The use of enoxaparin in patients with UA or NSTEMI is a cost-effective treatment when compared to UFH, and is easier to administer.
- Fondaparinux has been shown to be superior in clinical outcome to enoxaparin, particularly with respect to its lower bleeding risk.
- Clinicians should carefully consider factors (such as renal impairment) which increase bleeding risk. Unfractionated heparin, with dose adjustment guided by monitoring of clotting function, is an alternative to fondaparinux for those with renal impairment excluded from OASIS-5 (creatinine >265 μmol/l).
- People on fondaparinux undergoing PCI should receive unfractionated heparin, and not additional fondaparinux, at the time of the procedure.
- Fondaparinux is likely to be dominant (cost saving and improved health outcomes) compared to enoxaparin.

4.3 BIVALIRUDIN

4.3.1 CLINICAL INTRODUCTION

Hirudin is a naturally occurring substance secreted by leeches which has a powerful anticoagulant effect. It is a natural inhibitor of thrombin and has some potential advantages over heparin; it does not interact with other serum proteins, and it has the ability to lyse existing thrombus, unlike heparin which acts only on soluble thrombin. As it is difficult to extract large amounts of hirudin from natural sources, and hirudin was shown to be associated with a risk of increased bleeding, synthetic analogues were developed. The only one of these analogues that is licensed in the UK for use in acute coronary syndromes is bivalirudin.

Bivalirudin is a direct inhibitor of soluble and clot-bound thrombin. It has a rapid onset of action and has a half-life of 25 minutes, so is given as an intravenous infusion. It is cleared principally by proteolytic cleavage, but a significant component is also cleared by renal excretion.

In current UK practice bivalirudin is used as an anticoagulant during percutaneous coronary intervention (PCI), as an alternative to the combination of heparin and a GPI, (initiated at the time of PCI). It is also approved for use in UA/NSTEMI patients planned for urgent or early invasive intervention (coronary angiography with PCI/CABG/medical management as indicated), and is initiated prior to angiography in combination with aspirin and clopidogrel and continued through PCI in those who undergo this procedure.

When initiated at PCI, recommended dosing is an initial bolus of 0.75mg/kg and an infusion of 1.75mg/kg/hr during the PCI. Following PCI, an infusion of 0.25mg/kg/hr can be optionally continued if clinically appropriate.

When initiated pre-angiography, recommended dosing is a bolus of 0.1mg/kg and infusion of 0.25mg/kg/hr. If the patient continues to PCI following angiography an additional bolus of 0.5mg/kg is administered and an infusion of 1.75mg/kg/hr is used during the PCI. Following PCI, an infusion of 0.25mg/kg/hr can be optionally continued but is generally not required. For patients who are managed medically or go on to CABG following angiography, the infusion can also be optionally continued.

The GDG aimed to assess the clinical and cost-effectiveness of bivalirudin and therefore asked the following questions around which the literature was searched:

> *"What is the efficacy and safety of adding a thrombin inhibitor (bivalirudin) to aspirin, with or without a GPIIb/IIIa inhibitor, in the management of patients with UA or NSTEMI compared to the combination of LMWH/UFH, and aspirin, with or without a GPIIb/IIIa inhibitor?"*
>
> *"What is the efficacy and safety of adding a thrombin inhibitor to aspirin with or without a GPIIb/IIIa inhibitor as adjunct therapy to patients with UA/ NSTEMI undergoing PCI compared to the combination of LMWH/UFH, aspirin, and a GPIIb/IIIa inhibitor?"*

4.3.2 METHODOLOGICAL INTRODUCTION

The literature was searched from 1999 to 2009 for RCTs and systematic reviews comparing direct thrombin inhibitors in combination with aspirin, with or without a GPI compared with the combination of LMWH/UFH, aspirin, with or without a GPI in people with non ST-segment elevation ACS. The rationale for searching from January 1999 onwards was to reflect current practice,, and that bivalirudin is the only licensed direct thrombin inhibitor and was not available before then.

Outcomes of interest were thirty day survival, re-infarction, LV function, re-vascularisation, quality of life, and serious complications. For a study to be included at least 60% of patients enrolled needed to have a diagnosis of non ST-segment elevation ACS or the study had to report outcomes in a non ST-segment elevation ACS subgroup.

Three systematic reviews [148] [149] [150]and four RCTs [151] [44] [152] [110] were identified which compared a direct thrombin inhibitor to heparin in ACS patients. However, one RCT [44] [152] and two meta-analyses [149] [150] assessing hirudin were rejected as this drug does not have a license for ACS. The third systematic review [148] was rejected because study quality was not appraised, and three of the five RCTs included in the meta-analysis (BAT[153] , REPLACE-1 [154], CACHET [155]) had populations containing < 60% unstable angina or NSTEMI.

Two RCTs, ACUITY [110,156]and an ACS subgroup of REPLACE-2 [151] [112], were identified that addressed the use of bivalirudin in people with non ST-segment elevation ACS.

Bivalirudin initiated before angiography: ACUITY RCT

The ACUITY open-label RCT [110] recruited patients (N=13819) with UA (41%) or NSTEMI (59%) who were scheduled for an early invasive strategy (angiography within 72 hours). Following angiography patients were triaged to PCI, CABG or continued medical management alone. In the first randomization, people were randomised to one of three arms:

- Bivalirudin plus GPI
- Heparin (either unfractionated heparin or enoxaparin) plus GPI
- Bivalirudin alone (GPI use allowed for "bail-out" during procedural PCI complications or for suboptimal results; 9% received bail-out GPI).

In the second randomization and only within the heparin plus GPI and the bivalirudin plus GPI arms, patients were randomised to either upstream GPI use (where all patients received early GPI- either tirofiban or eptifibatide) or deferred GPI use (where only patients who went on to PCI received GPI and only during the PCI; patients received abciximab or eptifibatide).

The length of time from antithrombotic study drug to angiography was 4.0 h (median) and to PCI was 4.1 h (median).

All trial participants were given aspirin (daily dose 300-325 mg orally or 250 to 500 mg iv).. Clopidogrel (dose and timing) was left to investigator discretion; although a 300 mg or greater loading dose was required in all people undergoing PCI no later than two hours following their procedure.

Bivalirudin was given as an initial bolus of 0.10 mg/kg, then 0.25 mg/kg per hour continued through angiography. Dosing of bivalirudin beyond angiography depended on the type of management strategy: PCI, CABG or medical management. If PCI followed, an additional bolus of bivalirudin (0.5 mg/kg) was given and the infusion was increased to 1.75 mg/kg per hour and no post-PCI infusion dose was recommended, although 0.25 mg/kg per hour for 4 to 12 hours could be used (in the absence of a GPI) at operator discretion. Full details of the study design and doses of antithrombotic agents were reported in a prior publication [157]

For upstream GPIs, either tirofiban (0.4 microgram/kg/minute infusion for 30 minutes followed by 0.1 microgram/kg/minute infusion) or eptifibatide (180 microgram/kg bolus plus 2.0 microgram/kg/minute infusion) were started immediately. If PCI was to follow, the same GPI was to be used during PCI and discontinued 12-18 hours later. The infusion was typically discontinued in people triaged to CABG or those to medical management, although the infusion could be maintained if clinically indicated.

For those randomised to downstream GPIs, either abciximab (0.25 microgram/kg bolus plus 0.125 microgram/kg/minute infusion, with a maximum of 10 microgram/min) or eptifibatide (180 microgram/kg bolus plus 2.0 microgram/kg/minute infusion, with a second bolus given in ten minutes) were administered only to those people getting PCI, begun 5 to 10 minutes prior to the balloon inflation, and continued for 12 hours (abciximab) or 12 to 18 hours (eptifibatide) thereafter.

A pre-specified subgroup analysis of people undergoing PCI in the ACUITY trial, [156] (N=5170) compared:

- Bivalirudin + GPI blockade, with
- Heparin (unfractionated heparin or enoxaparin) + GPI blockade,

And also:

- Bivalirudin alone, with
- Heparin + GPI blockade.

The current SPC for bivalirudin states that bivalirudin is indicated "for the treatment of adult patients with acute coronary syndromes (unstable angina/non-ST segment elevation myocardial infarction (UA/NSTEMI)) planned for urgent or early intervention. Bivalirudin should be administered with aspirin and clopidogrel". After stakeholder consultation on the draft guideline, it was deemed appropriate to present

unpublished data from the Medicines Company in a subgroup of people who received clopidogrel either before angiography or before PCI (N=8677). The rationale for this was that data from the clopidogrel subgroup was reviewed by the EMEA when it undertook its licensing review of bivalirudin. The EMEA had concerns regarding a numerical increase in ischemic events in the bivalirudin alone arm in certain patient groups in the ACUITY trial and so requested identification of a target group where the benefit/risk profile was clearly positive[158]. A subgroup using aspirin and clopidogrel was identified, with clopidogrel given pre-angiography or pre-PCI. A published subgroup analysis of the ACUITY trial [159]assessed outcomes in people in a different clopidogrel subgroup - people who received clopidogrel any time before angiography or peri-PCI were compared with people who received clopidogrel more than thirty minutes after PCI or not at all. This subgroup analysis was rejected because it was felt that the clopidogrel subgroup on which the EMEA made its licensing decision was the subgroup that was more appropriate and more clinically relevant.

The evidence statements below for the ACUITY trial refer to the group of people who received clopidogrel either before angiography or before PCI. Tables summarise the relative risks in this clopidogrel subgroup as well as in the entire published ACUITY trial population. Three primary 30-day end points were prespecified; a composite ischaemia endpoint (death from any cause, myocardial infarction, or unplanned revascularisation for ischaemia), major bleeding (not related to CABG), and a net clinical outcome endpoint (defined as the occurrence of the composite ischaemia end point or major bleeding).

Bivalirudin initiated after angiography and before PCI: REPLACE-2

In people undergoing PCI, the double blind REPLACE-2 RCT [151] (N=6,010) compared:

- Bivalirudin + provisional use of a GPI (only 7.2% received GPIs), with
- Heparin treatment + planned use of a GPI

The population in REPLACE-2 had a low proportion of people with ACS (defined as unstable angina within preceding 48 h or MI within previous 7 days; N=1351), but was included because results in the ACS subgroup were reported separately [112,151]. The primary outcome was a quadruple composite outcome of death, MI, urgent revascularization or major bleeding by 30 days, but the ACS subgroup is too small (underpowered) to reliably detect a difference in most outcomes.

Bivalirudin dosing in the REPLACE-2 RCT was different from the ACUITY RCT. In REPLACE-2, bivalirudin was given as a bolus of 0.75 mg/kg prior to the start of PCI, followed by infusion of 1.75 mg/kg/hour for the duration of the procedure. The median duration of bivalirudin infusion was 0.73 hours (IQR 0.43 – 1.33 hours).

In the heparin plus planned GPI arm, a heparin bolus (65 U/kg , maximum 7000 U) was given prior to PCI, with either abciximab (0.25 mg/kg bolus, 0.125 microgram/kg/minute infusion for 12 hours) or eptifibatide (two boluses of 180

microgram/kg boluses given ten minutes apart, followed by 2.0 microgram/kg/minute infusion for 18 hours). The median duration of eptifibatide infusion was 18.0 hours (IQR 16.5-18.1 hours) and the median duration of abciximab infusion was 12.0 hours (IQR 11.9-12.2 hours). Aspirin was given to all; pre-treatment with clopidogrel (300 mg loading dose) was encouraged two to twelve hours before the interventional procedure.

4.3.3 CLINICAL EVIDENCE STATEMENTS

Bivalirudin infusion initated before angiography: ACUITY trial

Heparin + GPI versus Bivalirudin + GPI in people who received clopidogrel before angiography or before PCI: Outcomes at 30 days (refer to Table 3-2)

In those who received clopidogrel (before angiography or before PCI) [109], there was no significant difference between people randomised to heparin + GPI versus Bivalirudin + GPI for:

- death/MI/unplanned revascularisation
- death/MI/unplanned revascularisation/major bleeding
- death or MI
- death
- MI
- Unplanned revascularisation
- All major bleeding
- major bleeding not related to CABG
- minor bleeding not related to CABG
- major TIMI bleeding
- minor TIMI bleeding

Evidence Level 1+

Heparin + GPI versus Bivalirudin alone in people who received clopidogrel before angiography or PCI [109]: Outcomes at 30 days (refer to Table 3-3)

In the clopidogrel subgroup and compared with people randomised to heparin + GPI, people randomised to bivalirudin alone had a significantly:

- decreased risk of death/MI/unplanned revascularisation/major bleeding
- decreased risk of all major bleeding

- decreased risk of major bleeding not related to CABG
- decreased risk of minor bleeding not related to CABG
- decreased risk of TIMI major bleeding
- decreased risk of TIMI minor bleeding

Evidence Level 1+

In the clopidogrel subgroup [109] there was no significant difference between people randomised to heparin + GPI versus Bivalirudin alone for:

- death/MI/ unplanned revascularisation
- death/MI
- death
- MI
- unplanned revascularisation

Evidence Level 1+

However, in subgroup analysis of people who did not receive a thienopyridine anti–platelet agent (such as clopidogrel) before angiography (N=3304), the bivalirudin alone group had a significantly increased risk of death/MI/ unplanned revascularisation compared with the heparin + GPI group (RR 1.29 [1.03, 1.63]) [110]

E**vidence Level 1+**

Table 3-2: Outcomes at 30 days in the ACUITY RCT for people with NSTEMI or UA randomised to bivalirudin + GPI or heparin + GPI in the entire trial population, and also in the subgroup of people who received clopidogrel before angiography or before PCI [109] [110]

Population	Entire trial [110]			People who received clopidogrel before angiography or before PCI [109]		
Outcome at 30 days	**Bivalirudin + GPI (N=4604)**	**Heparin + GPI (N=4603)**	**Relative Risk (95% CI)**	**Bivalirudin + GPI (N=2924)**	**Heparin + GPI (N=2,842)**	**Relative Risk (95% CI)**
Death/MI/ unplanned revascularisation/ major bleeding	11.8%	11.7%	1.01 (0.90 to 1.12); p= 0.93	11.4%	11.8%	0.96 (0.84-1.11)
Death/MI/ unplanned revascularisation	7.7%	7.3%	1.07 (0.92 to 1.23) ; p=0.39	7.4%	7.4%	1.00 (0.84-1.21)
Death/MI	NR	NR	NR	6.0%	5.8%	1.02 (0.83-1.25)
Death	1.5%	1.3%	1.13 (0.80 to 1.58); p=0.48**	1.4%	1.4%	1.00 (0.64-1.54)
MI	5.0%	4.9%	1.01 (0.84 to 1.21); p=0.93**	4.9%	4.8%	1.01 (0.80-1.27)
Unplanned revascularisation	2,7%	2.3%	1.17 (0.91 to 1.51); p=0.23**	2.8%	2.6%	1.09 (0.80-1.48)
Major bleeding not related to CABG	5.3%	5.7%	0.93 (0.78 to 1.10); p= 0.38	5.4%	5.9%	0.92 (0.74-1.14)
Minor bleeding not related to CABG	21.7%	21.6%	1.01 (0.93 to 1.09); p=0.84**	23.4%	23.3%	1.00 (0.91-1.10)

All major bleeding	11.1%	11.8%	0.94 (0.84 to 1.06), p=0.31**	10.4%	10.9%	0.96 (0.82-1.11)
Major TIMI bleeding	1.7%	1.9%	0.88 (0.65 to 1.20), p=0.43 **	1.9%	1.9%	1.03 (0.71-1.49)
Minor TIMI bleeding	6.1%	6.4%	0.95 (0.81 to 1.12), p=0.55 **	6.3%	6.0%	1.04 (0.85-1.27)

** effect size calculated by NCC

Table 3-3: Outcomes at 30 days in the ACUITY trial for people with NSTEMI or UA randomised to bivalirudin alone or heparin + GPI in the entire trial population, and also in the subgroup who received clopidogrel before angiography or before PCI [109 110]

Population	**Entire trial [110]**			**People who received clopidogrel before angiography or before PCI [109]**		
Outcome at 30 days	**Bivalirudin alone (N=4612)**	**Heparin + GPI (N=4603)**	**Relative Risk (95% CI)**	**Bivalirudin alone (N=2911)**	**Heparin + GPI (N=2,842)**	**Relative Risk (95% CI)**
Death/MI/ unplanned revascularisation / major bleeding	10.1%	11.7%	0.86 (0.77 to 0.97), p=0.015	9.5%	11.8%	0.81 (0.69-0.94)
Death/MI/ unplanned revascularisation	7.8%	7.3%	1.08 (0.93 to 1.24), p=0.32	7.0%	7.4%	0.95 (0.79-1.15)
Death/MI	NR	NR	NR	5.6%	5.8%	0.96 (0.78-1.19)
Death	1.6%	1.3%	1.19 (0.85 to 1.67); p=0.31**	1.2%	1.4%	0.90 (0.57-1.41)

MI	5.4%	4.9%	1.09 (0.92 to 1.30); p=0.33**	4.7%	4.8%	0.98 (0.78-1.24)
Unplanned revascularisation	2.4%	2.3%	1.05 (0.80 to 1.36); p=0.74**	2.2%	2.6%	0.84 (0.61-1.18)
Major bleeding not related to CABG	3.0%	5.7%	0.53 (0.43 to 0.65); p<0.001	3.1%	5.9%	0.53 (0.41-0.68)
Minor bleeding not related to CABG	12.8%	21.6%	0.60 (0.54 to 0.65); p<0.001**	13.8%	23.3%	0.59 (0.53-0.66)
All major bleeding	9.1%	11.8%	0.77 (0.69 to 0.87), p<0.001 **	7.9%	10.9%	0.73 (0.62-0.86)
Major TIMI bleeding	0.9%	1.9%	0.50 (0.35 to 0.72), p<0.001 **	0.8%	1.9%	0.42 (0.26-0.69)
Minor TIMI bleeding	3.7%	6.4%	0.58 (0.48 to 0.69); p<0.001 **	3.7%	6.0%	0.61 (0.48-0.77)

** effect size calculated by NCC

Subgroup analysis of people undergoing PCI in the ACUITY trial (refer to Table 3-4)

In people undergoing PCI who received clopidogrel (before angiography or before PCI) [109] , there was no significant difference between the bivalirudin + GPI and the heparin + GPI inhibitor groups for:

- death/MI/unplanned revascularisation
- death/MI/unplanned revascularisation/major bleeding
- death
- MI
- Unplanned revascularisation
- major bleeding not related to CABG
- minor bleeding not related to CABG
- major TIMI bleeding
- minor TIMI bleeding

Evidence Level 1+

In people undergoing PCI who received clopidogrel (before angiography or before PCI) [109] , there was no significant difference between the bivalirudin group and the heparin + GPI group for:

- death/MI/unplanned revascularisation
- death/MI
- death
- MI
- Unplanned revascularisation

Evidence Level 1+

In people undergoing PCI who received clopidogrel [109], those randomized to bivalirudin alone (compared with heparin plus GPI) had a significantly decreased risk of:

- death/MI/unplanned revascularisation/major bleeding
- major bleeding not related to CABG
- minor bleeding not related to CABG
- all major bleeding
- major TIMI bleeding
- minor TIMI bleeding

Evidence Level 1+

Table 3-4: Subgroup analysis of the ACUITY trial: Outcomes at 30 days for people undergoing PCI randomised to bivalirudin alone, or bivalirudin + GPI, or heparin + GPI, as well as for the PCI subgroup who received clopidogrel (before angiography or before PCI)[156] [109]

Population	**Entire PCI subgroup** [156]		**PCI subgroup who received clopidogrel before angiography or PCI** [109]	
Outcomes at 30 days	**Bivalirudin + GPI vs Heparin + GPI (N=5170)**	**Bivalirudin alone vs Heparin + GPI (N=5180)**	**Bivalirudin + GPI vs Heparin + GPI (N=3471)**	**Bivalirudin alone vs Heparin + GPI (N=3511)**
Death/MI/urgent revascularization/major bleeding	**15% vs 13%** RR 1.12 (0.98 to 1.28); p= 0.10	12% vs 13%; RR 0.87 (0.75 to 1.00), p=0.057	**14.6% vs 13.9%** RR 1.05 (0.89-1.24)	**11.1% vs 13.9%** RR 0.80 (0.67-0.96)
Death/MI/urgent revascularization	**9% vs 8%** RR 1.14 (0.95 to 1.36); p= 0.16	9% vs 8%; RR 1.07 (0.89 to 1.28), p=0.45	**9.3% vs 8.5%** RR 1.09 (0.88-1.35)	**8.1% vs 8.5%** RR 0.95 (0.76-1.18)
Death/MI	NR	NR	7.5% vs 6.5% RR 1.15 (0.90-1.47)	6.5% vs 6.5% RR 1.01 (0.78-1.29)

death	1% vs 0.9% RR 1.28 (0.75 to 2.20); p=0.37 **	1% vs 0.9% RR 1.19 (0.69 to 2.06); p=0.53 **	1.3% vs 0.9% RR 1.44 (0.75-2.77)	1.0% vs 0.9% RR 1.09 (0.55-2.18)
MI	7% vs 6% RR 1.17 (0.94 to 1.45); p=0.16 **	6% vs 6% RR 1.15 (0.93 to 1.43); p=0.19 **	6.6% vs 5.9% RR 1.12 (0.87-1.45)	5.9% vs 5.9% RR 1.00 (0.77-1.30)
Unplanned revascularisation	4% vs 3% RR 1.16 (0.87 to 1.56); p=0.31 **	3% vs 3% RR 1.03 (0.76 to 1.38); p=0.87 **	3.8% vs 3.4% RR 1.10 (0.78-1.55)	2.6% vs 3.4% RR 0.77 (0.53-1.12)
Major bleeding – non-CABG related	8% vs 7% RR 1.11 (0.91 to 1.35); p= 0.32	4% vs 7%; RR 0.52 (0.40, 0.66), p<0.0001	7.5% vs 7.2% RR 1.04 (0.82-1.32)	3.6 % vs 7.2% RR 0.50 (0.37-0.67)
Minor bleeding – non-CABG related	28% vs 26% RR 1.09 (1.00 to 1.19) p=0.05 **	15% vs 26%, RR 0.57 (0.51, 0.64), p<0.0001 **	29.5% vs 26.5% RR 1.11 (1.00-1.24)	15.3% vs 26.5% RR 0.58 (0.50-0.66)
All Major bleeding	NR	NR	8.1% vs 7.8% RR 1.04 (0.83-1.30)	4.2% vs 7.8% RR 0.55 (0.42-0.72)
TIMI major bleeding	2% vs 2% RR 1.07 (0.75 to 1.52); p=0.72 **	0.8% vs 2% RR 0.37 (0.23 to 0.60); p<0.0001 **	2.7% vs 2.3% RR 1.18 (0.78-1.79)	0.7% vs 2.3% RR 0.29 (0.15-0.55)
TIMI minor bleeding	8% vs 8% RR 1.08 (0.90 to 1.31); p=0.40 **	4% vs 8% RR 0.55 (0.44 to 0.69); p<0.0001 **	8.3% vs 7.3% RR 1.14 (0.91-1.44)	4.1% vs 7.3% RR 0.56 (0.42-0.74)

** effect size calculated by NCC

Bivalirudin initiated after angiography and before PCI: REPLACE-2 (ACS subgroup results only; refer to Table 3-4)

In the ACS subgroup undergoing PCI in the REPLACE-2 RCT, there was no significant difference between patients randomised to heparin plus planned GPI versus those assigned bivalirudin plus provisional GPI for:

- death/MI/urgent revascularization/major bleeding
- death/MI/urgent revascularisation
- death/MI
- death
- MI
- Urgent revascularization
- Major bleeding

Evidence Level 1+

In the REPLACE-2 RCT, people with ACS undergoing PCI who were randomised to bivalirudin plus provisional GPI had a significantly reduced risk of:

- minor bleeding

Evidence Level 1+

Table 3-5: Outcomes at 30 days for people with ACS (defined as unstable angina within preceding 48 h or MI within previous 7 days) undergoing PCI randomised to bivalirudin + provisional GPI or heparin + planned GPI in the REPLACE -2 trial [151 112]

Outcome at 30 days	Bivalirudin + provisional GPI (N=669)	Heparin + planned GPI (N= 682)	RR (95% CI)
Death/MI/urgent revascularization/major bleeding	10%	11%	0.90 (0.66 to 1.23); p=0.50 **
Death/MI/urgent revascularization	8.7%	8.0%	1.09 (0.77 to 1.56); p=0.62 **
Death/MI	7.4%	7.1%	1.04 (0.71 to 1.53); p=0.84**
Death	0.4%	0.4%	1.02 (0.21 to 5.03); p=0.99 **
MI	7.2%	6.9%	1.04 (0.71 to 1.53); p=0.84 **
Urgent revascularisation	2.3%	1.6%	1.39 (0.64 to 3.00); p=0.40 **
Major bleeding	2.7%	4.5%	0.59 (0.33 to 1.05); p=0.07 **
Minor bleeding	13%	27%	0.48 (0.38 to 0.60); p<0.001 **

** effect size calculated by NCC

4.3.4 HEALTH ECONOMIC METHODOLOGICAL INTRODUCTION

Two economic evaluations were identified from the literature that addressed the use of bivalirudin in people with UA/NSTEMI. One based on the ACUITY study[160] and one based on the ACS subgroup of the REPLACE-2 study[112] – the ACUITY study and REPLACE-2 study design and outcomes are described in detail in the clinical evidence section above. One economic evaluation submitted during consultation was also included (this was unpublished but had been presented at conference and submitted for publication); this was based on the ACUITY study with a UK perspective[161]. In addition five studies were identified, taking non-UK perspectives, that examined the clinical question but the population of the clinical studies used to inform effectiveness did not meet the population cut off of >60% UA/NSTEMI and so were not reviewed[162-166]. One study was not reviewed as it was judged to have serious methodological limitations in

terms of the outcome measure used and the method for calculating relative treatment effects[167].

Bivalirudin initiated before angiography: ACUITY-based analyses

Two studies were identified relating to use of bivalirudin initiated before angiography in UA/NSTEMI, based on the ACUITY study[160,161].

Pinto et al. [160] reported an economic evaluation based on resource use and outcomes from a US subgroup of the ACUITY study (n=7,851). A US healthcare system perspective was taken. In-hospital and 30-day costs were estimated based on resource use from the trial and US unit costs. The ACUITY study was an early angiography population (where all patients received angiography and were then triaged to PCI, CABG or continued medical management alone). It had two stages of randomisation: first to bivalirudin monotherapy (provisional GPI use allowed), heparin plus GPI, or bivalirudin plus GPI. In addition, within the heparin plus GPI and the bivalirudin plus GPI arms, patients were further randomised to either upstream GPI use (where all patients received early GPI) or deferred GPI use (where only patients who went on to PCI received GPI and only during the PCI). Resource use and costs were presented for the upstream and deferred PCI patients groups separately in this analysis. Disaggregated costs and events were presented (i.e. there was no cost–effectiveness ratio reported).

The Pinto et al. study is judged partially applicable to the UK with potentially serious limitations. There is uncertainty regarding the applicability of US resource use and costs to the UK. The ACUITY study has short times to intervention that may not represent UK practice. Resource use may also be impacted by the trial setting. The study used a short time-horizon, does not use QALYs and does not estimate a cost-effectiveness ratio.

Schwenkglenks et al.[161] reported an economic evaluation based on a decision analytic model using data from a clopidogrel subgroup of the ACUITY study (defined by clopidogrel use at any point during the index hospitalisation). A UK NHS perspective was taken and lifetime costs and QALYs were estimated. Two analyses were presented: 1) bivalirudin (bailout GPI use allowed) versus heparin plus planned GPI (50% upstream use, 50% deferred selective during PCI); 2) bivalirudin (bailout GPI use allowed) versus heparin plus GPI use during PCI. For each analysis two scenarios were examined a) the whole population and b) a subgroup at high bleeding risk (defined as having at least two of the following risk factors for bleeding: age $\geq$65 years, female gender, renal impairment, baseline haemoglobin <12mg/dL [women] or <13mg/dL [men], weight <60kg, diabetes).

The Schwenkglenks et al. study is judged to be partially applicable to the UK setting. The perspective taken is inline with the NICE base case and as such is more relevant than the Pinto et al. study above. However, there is uncertainty regarding the applicability of the outcomes based on the ACUITY study to the wider UK setting due to short times to intervention in the ACUITY study. The study is generally judged to be of good methodological quality; however there are some potentially serious limitations that may impact results. Differences in QALYs between treatments are only impacted by the

difference in the relative risk of mortality between bivalirudin and heparin+GPI; new non-fatal MI events do not impact QALYs. The relative risk for mortality (which drives the QALY difference) in the clopidogrel subgroup used in this model (clopidogrel at any time during index hospitalisation) is slightly more favourable to bivalirudin and with a narrower confidence interval than that from the pre-angiography/pre-PCI clopidogrel subgroup selected as the most appropriate by the GDG.

Bivalirudin initiated after angiography and before PCI: REPLACE-2 ACS subgroup-based analyses

One study was identified assessing bivalirudin initiated after angiography and before PCI in UA/NSTEMI [112]. Rajagopal et al. reported an economic evaluation based on resource use and outcomes from an ACS subgroup (n=1351) from the REPLACE-2 trial (63% UA, 37% unspecified MI). All patients in the study underwent PCI. A US hospital perspective was taken in terms of costs. The study compared bivalirudin (with provisional GPI) to heparin with planned GPI in patients undergoing PCI with ACS. 30-day costs and 30-day, six-month and one-year outcomes in terms of events (death, MI, revascularisation, major and minor bleeding) were reported. Disaggregated costs and events were presented (i.e. no cost-effectiveness ratio was reported).

The study is judged partially applicable to the UK. There is uncertainty regarding the applicability of international resource use and US costs to the UK. Resource use may also be impacted by the trial setting. The study used a short time-horizon, did not use QALYs and did not estimate a cost–effectiveness ratio. The unit costs used were not reported.

4.3.5 HEALTH ECONOMIC EVIDENCE STATEMENTS

Direct thrombin inhibitors in medical management

Pinto et al. [160] presented disaggregated costs and outcomes. Costs are summarised in Table 3-6 below. Total costs were lowest in the bivalirudin monotherapy arm. A significant difference is reported across all five arms of the trial (this includes the bivalirudin + GPI arm which had the highest costs); pair-wise significance tests were not reported. Only in-hospital health outcomes were reported in this subgroup analysis. These are reported as consistent with the full trial analysis where significant differences are seen in terms of bleeding endpoints with bivalirudin monotherapy but no significant difference is seen across the groups in terms of ischemic endpoints. 30-day results for the US subgroup are reported as 'similar' but not presented. No cost-effectiveness ratio is presented but the authors interpret the evidence to suggest that bivalirudin offers similar ischemic protection with lower bleeding and lower costs.

Table 3-6. ACUITY US subgroup analysis costs

	Heparin + GPI		Bivalirudin + GPI		Bivalirudin mono-therapy	P value across groups
	Upstream GPI	PCI GPI	Upstream GPI	PCI GPI		
Initial hospital stay	£9,053	£8,810	£9,373	£8,888	£8,694	<0.001
Anticoagulant medication	£563	**£323**	**£965**	**£826**	**£613**	**<0.001**
Discharge to 30 days	**£482**	**£538**	£486	£593	£576	0.658
Total 30-day cost	£9,535	£9,347	£9,859	£9,482	£9,270	0.005

Data from Pinto et al. [160] converted from 2005 US dollars using Purchasing Power Parities[138].

Schwenkglenks et al.[161] reported an incremental cost-effectiveness ratio for bivalirudin (bailout GPI use allowed) versus heparin plus planned GPI (50% upstream use, 50% deferred selective during PCI) in patients with UA/NSTEMI undergoing an early invasive strategy of £10,009 per QALY gained. This was reduced to £3750 per QALY gained in a high bleeding risk subgroup. Bivalirudin was cost-effective in 72% and 89% of simulations respectively, at a threshold of £20,000 per QALY gained. The conclusion that bivalirudin is cost effective compared to use of heparin plus GPI was also robust to a range of deterministic sensitivity analyses. A sensitivity analysis was not carried out to address the possibility that non-fatal MI events may have a short-term or long-term impact on QALYs. The parameters with the strongest influence on results were reported as the relative risk of death and the index hospitalisation length of stay.

When bivalirudin (bailout GPI use allowed) was compared to heparin plus GPI use during PCI in an early invasive UA/NSTEMI population only, the incremental cost-effectiveness ratio was lower (that is cost effectiveness was improved) at £4514 per QALY gained in the overall population and £3,416 per QALY gained in the high bleeding risk subgroup.

Bivalirudin initiated after angiography and before PCI: REPLACE-2 ACS subgroup

Rajagopal et al.[112] presented disaggregated costs and outcomes. Taking a 30-day perspective bivalirudin (plus provisional GPI) compared with heparin plus planned GPI reduced costs by £245 and reduced the rate of the composite of death, MI, urgent revascularisation and major bleeding, although not significantly. However, disaggregated results show that MI and urgent revascularisation were numerically, but non-significantly more frequent with bivalirudin, there was no difference in death, major bleeding was non–significantly less frequent and minor bleeding was significantly less frequent. Without extrapolation of these events to overall outcomes (e.g. life years

or QALYs) it is difficult to interpret these results. The US setting limits its UK applicability.

Health economic modelling

Cost effectiveness modelling was undertaken for the guideline to look at the use of GPIs taking into account contemporary management. In particular it addressed the use of GPIs in combination with clopidogrel, bivalirudin was included as a possible alternative to heparin plus a GPI, and fondaparinux as an alternative to heparin was incorporated.

For the full analysis methods, detailed results and discussion see the report in Appendix CAppendix C. A summary is provided below.

Methods

A cost–utility analysis was undertaken with costs and quality-adjusted life-years (QALYs) considered over patients' lifetimes from a UK NHS perspective. The analysis is primarily relevant to patients undergoing an early invasive management approach – that is coronary angiography with revascularisation if indicated – because trial results for GPIs and bivalirudin used in the analysis were only relevant to a population undergoing angiography. This is discussed in more detail in the full report in Appendix C.

This analysis compared the following treatment strategies in the acute management of UA/NSTEMI (heparin baseline):

- Aspirin +clopidogrel +heparin (LMWH or UFH)
- Aspirin +clopidogrel +heparin + GPI during PCI only
- Aspirin +clopidogrel +heparin + GPI upstream of angiography
- Aspirin +clopidogrel +bivalirudin upstream of angiography
- Aspirin +clopidogrel +heparin +bivalirudin during PCI only.

In addition the analysis was run as above but with fondaparinux substituted for heparin in the first three arms (fondaparinux baseline). Fondaparinux was not incorporated in the bivalirudin arms in this analysis as there is no experience with these agents combined.

Cost effectiveness was analysed by six risk subgroups, as summarised in Table 2-13 below. The creation and interpretation of these risk groups is discussed in more detail in the Risk chapter of the guideline (section **0**) and the report of the analysis of MINAP data for the cost effectiveness analysis (Appendix B).

Table 2-12. Risk groups

Risk group	% population	Corresponding range of 6-month mortality
1a	~12.5%	>1.6%
1b	~12.5%	>1.6 ≤3.1%
2a	~12.5%	>3.1 ≤5.5%
2b	~12.5%	>5.5 ≤9.5%
3	~25%	>9.5 ≤21.5%
4	~25%	>21.5%

The general approach taken was to obtain contemporary UK estimates of events for the aspirin, clopidogrel and heparin arm of the model from recent MINAP (the national audit of ACS management) data. These were stratified by acute management strategy: PCI, CABG, angiography only. Where inputs were not available from MINAP, data were sourced from the literature or discussion with the GDG. One-year death, MI and revascularisation, and in-hospital bleeding were incorporated. The effects of different treatment combinations are then modelled by applying relative risks from randomised controlled trials identified by the systematic review of the clinical literature for the guideline – one-year relative risks were used where available except for bleeding. Relative risks were applied to the appropriate part of the population; for example, only PCI patients, if only relevant to these patients.

Lifetime QALYs were estimated based on one-year status: dead, alive having had a new MI, alive without new MI. At one-year patients were attributed a number of life-years based on this status. Those alive at one year with new MI were attributed a lower estimate than those alive without new MI. Life-years were adjusted by a quality of life weight for people with ACS to estimate QALYs. As the rates of death and MI will vary with treatment strategy, so will the QALYs.

Lifetime costs were estimated taking into account initial drug treatment costs, the cost of MI, bleeding and revascularisation events up to one year and average disease-related costs incurred if alive post one-year.

Treatment effects were based on studies identified in the clinical review. Only studies with at least 50% clopidogrel use were used. Relative treatment effects were based on the following studies:

- ISAR-REACT 2[91,94]: GPI versus no GPI in a PCI UA/NSTEMI population pre-treated with clopidogrel

- ACUITY timing (heparin only background, clopidogrel pre-angio/pre-PCI subgroup)[99,109]: upstream GPI versus PCI GPI in an early angiography UA/NSTEMI population
- ACUITY (clopidogrel pre-angio/pre-PCI subgroup)[109-111]: bivalirudin vs LMWH/UFH + GPI in an early angiography UA/NSTEMI population
- REPLACE-2 ACS subgroup[112]: bivalirudin during PCI vs heparin + GPI during PCI in a PCI ACS population
- OASIS-5[113]: fondaparinux vs enoxaparin in a UA/NSTEMI population

The Early ACS trial also compares upstream GPI vs PCI GPI use in an early angiography UA/NSTEMI population[100]. It was published late in the guideline development process and only reports 30-day outcomes, whereas the model was developed with one-year event rates and effectiveness data. Sensitivity analyses examined the possible impact of this study.

The model was built probabilistically in order to take account of the uncertainty around input parameter point estimates. Probability distributions in the analysis were based on error estimates from data sources, for example confidence intervals around relative risk estimates. Various one-way and scenario sensitivity analyses, where one or more inputs were varied, were undertaken to test the robustness of model assumptions and data sources.

Two analyses were run:

3. Trial aligned analysis (costing based on bivalirudin vial usage in the ACUITY trial with a pre-angiography treatment period median 4hrs/mean 10hrs; ACUITY management split)
    - Costing based on trial vial usage; ACUITY management split
    - The ACUITY trial includes 3 of the 5 comparators and had a median treatment period pre-angiography of 4hrs (mean 10hrs)
    - This analysis is most aligned with the available trial data
4. Adjusted analysis (costing based on 72hr pre-angiography treatment period; MINAP management split)
    - Costing based on a simulation assuming 72hr pre-angio treatment duration and a 1hr PCI treatment duration; MINAP management split
    - This analysis makes some adjustments to costing and management split that may be more typical for the UK
    - Note that this analysis potentially biases against upstream treatments as costs are increased but efficacy is not adjusted and so the analysis should be interpreted carefully.

Results

Fondaparinux baseline analysis:

The analysis incorporating a fondaparinux baseline (that is fondaparinux replaces heparin in the aspirin+clopidogrel+heparin, aspirin+clopidogrel+heparin+GPI during PCI, aspirin+clopidogrel+heparin+GPIupstream arms of the model),was considered most relevant to clinical decision making in the majority of cases. Fondaparinux has been found to be cost-effective compared to heparin as shown in the published literature[114]. Fondaparinux is cheaper than enoxaparin and is associated with clinical benefits. In the model Aspirin+clopidogrel+fondaparinux dominated Aspirin+clopidogrel+heparin in all of our analyses (although this comparison was a secondary objective of the analysis).

In the trial aligned analysis (when trial vial usage was used for costings and the ACUITY management split employed) routine addition of upstream GPIs seems to be most cost-effective for patients in risk groups 2 and 3, with selective PCI GPI use the most cost-effective in risk group 4. This is based on these options having the highest mean INB at a £20,000 per QALY threshold. In the adjusted analysis (with treatment costs estimated using a 72hr pre-angiography treatment duration and the MINAP management split employed) selective use of GPIs at PCI was found to be most cost-effective strategy; however, this analysis was considered likely to bias against upstream use of GPIs as treatment costs are increased but efficacy is not adjusted.

There was considerable uncertainty in the results. This is evidenced by differences between the deterministic optimal strategy and probabilistic optimal strategy especially in Groups 1a and 4. Also, there is a wide spread of the probability of cost-effectiveness across different strategies. In places the optimal strategy as based on mean INB is not the one with the highest probability of being cost-effective as based on the highest proportion of simulations. In addition there is uncertainty regarding applicability as the trial aligned analysis may not represent typical treatment durations in the UK; whereas the longer term analysis is limited by the lack of effectiveness data. It was also noted that from a clincal perspective, the longer the wait for angiography the more likely a patient would need a GPI prior to angiography and deferring use until PCI is undertaken may not be a clinically acceptable option.

Interpretation of results is complicated by the uncertainty in the analysis. Additional clinical considerations should be employed in interpretation and it was considered that it may be reasonable to recommend more than one option to reflect this uncertainty. Risk group 1 is considered least likely to benefit from additional treatment over and above aspirin+clopidogrel+fondaparinux. Dependent on appropriate clinical interpretation, due to the uncertainty it was considered that either GPI use upstream of angiography or selective GPI use in PCI might be considered likely to be cost-effective in higher risk groups. This is due to the fact that different options were found to be most cost-effective in the trial aligned and adjusted analysis but limitations in the analysis mean that a definitive conclusion is not possible based on these model results alone.

Note that the fondaparinux baseline analysis is dependent on the assumption that the relative effect of GPIs will not be impacted by whether heparin or fondaparinux is used as the baseline antithrombin – there were no studies that assessed GPIs against no GPIs in a population using fondaparinux. The OASIS-5 trial addresses this issue somewhat by examining 30-day outcomes for fondaparinux versus enoxaparin in subgroups of patients receiving clopidogrel and GPIs[115]. This analysis suggested that the benefits of fondaparinux are maintained in patients receiving clopidogrel or GPIs.

Heparin baseline analysis:

If fondaparinux is not an appropriate option, then the analysis with a heparin baseline is most appropriate to review. In this analysis, risk group one is least likely to benefit from additional treatment over and above aspirin+clopidogrel+heparin. Heparin use with selective bivalirudin during PCI seems to be most cost-effective in risk groups 2-4. This is based on the mean INB from the heparin baseline analyses in both the trial aligned analysis (reflective of a short time to angiography) and the adjusted analysis (with treatment costs estimated using a 72hr pre-angiography treatment duration and the MINAP management split employed). Bivalirudin use pre-angiography was associated with more QALYs than the selective bivalirudin use but also additional costs and based on the mean INB this use was not cost effective at a £20,000 per QALY threshold.

As in the fondaparinux baseline analysis there was considerable uncertainty in the heparin-baseline analysis. In the trial aligned analysis (reflective of a short time to angiography) bivalirudin PCI was considered the most cost-effective treatment based on mean INB, bivalirudin use upstream of angiography, and upstream GPI use generally also had a high level of simulations where they were optimal. As risk increased the likelihood of bivalirudin initiated upstream of angiography being cost effective increased. It was also raised that there will sometime be a clinical need to give additional treatment upstream of angiography, for example if the patient is actively unstable. Interpretation of results is complicated by the uncertainty in the analysis. Additional clinical rationale should be employed in interpretation and it was considered that it may be reasonable to recommend more than one option to reflect this uncertainty. Dependent on appropriate clinical interpretation, due to the uncertainty it was considered that use of the following might be considered likely to be cost effective: bivalirudin used selectively during PCI; upstream bivalirudin; heparin plus upstream GPIs.

In the adjusted analysis (where costing was based on a 72hr pre-angiography treatment duration) PCI bivalirudin was also most cost effective, as would be expected as the upstream treatments will have higher costs in the model but the effectiveness was not adjusted. In addition, this analysis was considered the least clinically relevant because if patients were not going for angiography relatively quickly they would be most likely to be considered suitable for fondaparinux.

4.3.6 EVIDENCE SUMMARY

► Bivalirudin infusion initated before angiography: ACUITY trial

Bivalirudin + GPI versus heparin + GPI

For the entire ACUITY trial population [110] [156], there were no significant differences between people randomised to bivalirudin + GPI versus heparin + GPI for any of the outcomes of interest. In the subgroup that received clopidogrel [109], results were also non-significantly different. Thus, the GDG focused on the comparison of bivalirudin monotherapy versus heparin + GPI.

Bivalirudin vs heparin + GPI (with background aspirin)

In the entire ACUITY trial population, [110] bivalirudin monotherapy was associated with decreased rates of the net clinical outcome (death, MI, unplanned revascularisation, or bleeding) compared with heparin + GPI. The bivalirudin monotherapy group also had significantly decreased major or minor bleeding. . These results were also similar in the subgroup of people who received clopidogrel before angiography or PCI [109]. Angiography was performed in all patients within 72 hours of randomisation. The effect of bivalirudin appeared to be dependent on the use of upstream thienopyridine (such as clopidogrel) use; pre-treatment with clopidogrel was particularly important in the group given bivalirudin alone; without clopidogrel the absolute rate of composite ischaemic endpoints (death, MI, unplanned revascularisation) was 2% higher (9.1% bivalirudin group vs 7.1% heparin + GPI group)[110]. . In keeping with SPC for bivalirudin, the analysis was focussed on those people who received clopidogrel before angiography or PCI.

PCI subgroup analysis

In the ACUITY PCI subgroup who received clopidogrel [109], ischaemic complications were non-significantly different and major bleeding was significantly decreased in the bivalirudin monotherapy arm.

ACUITY showed a reduced bleeding risk for bivalirudin compared to heparin plus GPI, but only when bivalirudin was used alone (without a GPI).

► Bivalirudin initiated after angiography and before PCI: REPLACE-2 ACS subgroup

Bivalirudin vs heparin + GPI (with background aspirin) in patients undergoing PCI

In REPLACE-2, a GPI was mandated in the heparin arm but allowed, if clinically indicated, in the bivalirudin arm. At 30 day follow-up there was no difference in ischaemic endpoints. REPLACE-2 showed bivalirudin to reduce significantly the rate of minor bleeding compared to heparin.

4.3.7 EVIDENCE TO RECOMMENDATIONS

Trials comparing bivalirudin with heparin + GPI suggest that bivalirudin may offer equivalent ischemic protection with reduced bleeding. However, interpretation of bivalirudin trial data is complicated by differences in dosages, duration of therapy, adjunctive therapies (such as clopidogrel and GPIs), trial design, and study populations. Hence, making recommendations regarding the place of bivalirudin in the management of patients in the UK admitted with UA/NSTEMI is difficult.

The ACUITY trial recruited 13,819 patients with UA or NSTEMI who were described as having "moderate or high risk acute coronary syndromes". As commented upon elsewhere in this guideline (see RISK chapter) patients recruited to trials described as being moderate/high risk may nevertheless be lower risk than many patients in unselected registry populations, such as in the MINAP database. For instance, those considered 'high risk' in ACUITY (TIMI risk score 5-7) had 1 year mortalities of 6.1% in the bivalirudin, and 6.7% in the heparin arms of the trial, which puts them into our intermediate (group 2b) or lower risk category (predicted 6-month mortality 3-6%). The overall ACUITY trial concluded that in patients undergoing early angiography (median time from admission to angiography around 19.5 hours, median duration of treatment from randomisation to angiography only 4 hours), the use of bivalirudin alone (but with bail-out GPI if clinically indicated) was associated with rates of ischaemia that were similar to those of patients receiving either heparin+GPI or bivalirudin+GPI, but that the rate of bleeding complications was significantly reduced. Bivalirudin was also found to reduce bleeding complications in the REPLACE-2 trial.

However, achieving this desirable outcome without compromising the risk of ischaemic events, is influenced by the background therapy used, When used in comparison to a combination of heparin given together with a GPI, bivalirudin given alone and without prior treatment with a thienopyridine (most usually clopidogrel) can increase the risk of ischaemic events (ACUITY trial). For this reason the European Medicines Agency (EMEA) now licenses the use of bivalirudin for patients with acute coronary syndromes but states that *"bivalirudin should be administered with aspirin and clopidogrel"*.

The ACUITY trial, on which much of the evidence for the benefit of bivalirudin rests, recruited patients with "moderate and high risk acute coronary syndromes"[o] who were scheduled to undergo angiography. It did not address the use of bivalirudin for those where an early invasive approach was not considered appropriate. In the ACUITY trial the time from hospital admission to angiography (around 19.5 hours), and the duration of treatment prior to angiography (median four hours), was short compare to UK practice. Historically, delays to angiography in the UK have been long (often many days), and although waits for angiography in the UK are declining, they are still longer, than in

[o] Moderate and high risk was defined as being one or more of the following: new ST-segment depression or transient ST elevation of at least 1mm; elevations in troponin-I, troponin-T, or creatine kinase MB levels; known coronary artery disease; or all four other variables for predicting thrombolysis in Myocardial Infarction (TIMI) risk scores for unstable angina (JAMA 2000;284:835-842)

ACUITY. Extrapolation of the results of ACUITY to an unselected UK population of patients with UA or NSTEMI is therefore difficult.

Subsequent publications showed bivalirudin to be of potential benefit for the subset in ACUITY who underwent PCI (ACUITY-PCI[156]) and that at 1-year the rates of composite ischaemia and mortality were similar to patients treated with a heparin together with a GPI[168]. However, ACUITY-PCI has been criticised because randomisation was not stratified by the treatment assigned, different GPIs and heparins were used in the control arm, and the analysis was not powered for non-inferiority testing[169].

What is generally accepted is that any benefit of bivalirudin is predicated on its ability to reduce bleeding in patients who undergo angiography. It has not been shown to reduce ischaemic risk and therefore its potential value is in providing 'net benefit' – reducing bleeding events and being equivalent with regards ischaemic events). This amalgamation of efficacy (ischaemic events) and safety (bleeding events) has also been criticised on principle [169]) because drugs that are ineffective but safe can appear to be better than effective drugs in a non-inferiority trial. Nevertheless, reducing bleeding risk is accepted as important because bleeding is known to be associated with adverse outcomes *(see bleeding risk in risk chapter)* and this association was confirmed in the ACUITY trial [170], particularly in patients of advanced age[46]. However, whilst this association between bleeding and adverse outcomes is generally accepted and has been noted in trials of other antithrombotic and anti-platelet agents such as OASIS-5, the reduction in bleeding associated with bivalirudin did not significantly reduce mortality.

In the REPLACE-2 study bivalirudin (with provisional use of a GPI if clinically indicated) was compared with heparin and GPI in patients undergoing urgent or elective PCI. The trial recruited a mixed population of acute and stable coronary syndromes; however a subgroup was available reporting outcomes in ACS patients where >60% were UA/NSTEMI. Patients were randomised in the catheter laboratory and therefore durations of treatment were shorter than in ACUITY. Again bivalirudin reduced bleeding but had no significant impact on ischaemic outcomes.

No trial has investigated the use of bivalirudin versus fondaparinux. However, as detailed elsewhere in this guideline, fondaparinux is more clinically and cost effective than heparin. Fondaparinux is associated with reduced bleeding risk, and therefore it is possible that the difference in bleeding complications between bivalirudin and fondaparinux+GPI may be less than that seen between bivalirudin and heparin+GPI. Also, whilst switching patients from upstream use of heparin to the use of bivalirudin prior to angiography may be safe[171], there are no data concerning a switch of patients from fondaparinux to bivalirudin. Since this guideline recommends fondaparinux as the baseline antithrombin most patients with UA/NSTEMI admitted in the UK are likely to be on fondaparinux prior to angiography and not heparin.

The difference in bleeding complications seen in ACUITY was largely due to reduced bleeding from the site of arterial access for the angiogram procedure. Other factors may also reduce bleeding risk, such as greater use of a radial rather than femoral arterial access[172], a move towards smaller diameter catheters[173], selective rather than more routine use of GPIs, and lower heparin doses. Differences in the frequency of these

between practice in the USA and UK also add to the need for caution in extrapolating the results of ACUITY to the UK.

Thus, in the light of trial evidence, if bivalirudin were to be considered it would be in patients:

- with acute coronary syndromes who are pre-treated with clopidogrel,
- and who will undergo very early angiography (< 24 hours from admission),
- and who would otherwise be considered appropriate for a GPI
- and who have not already been started on fondaparinux

Health Economics

We undertook a health economic analysis modelled both on **short term** (<24 hours) upstream use of a GPI or bivalirudin prior to angiography, to reflect trial (ACUITY) data, and their use when initiated in the catheter laboratory and given selectively to patients undergoing PCI (REPLACE-2 data). We also modelled **longer term** (72 hours) use of a GPI or bivalirudin (in recognition of the longer average times to angiography in the UK compared to those reported in the ACUITY trial). The cost-effectiveness analysis undertaken for the guideline and its results and limitations are summarised above and described in detail in Appendix C.

Short term upstream bivalirudin
Cost-effectiveness evidence from our analysis of shorter term use of bivalirudin suggested that it may be cost effective when heparin is the antithrombin used in the alternative strategies (heparin + GPI), in patients at intermediate and higher risk (predicted 6-month mortality >3.0). However, when fondaparinux was incorporated into the analysis instead of heparin, results suggested that bivalirudin may no longer be the most cost-effective option. Given the statistical uncertainty in the cost-effectiveness analysis, and limitations such as that associated with the indirect fondaparinux–bivalirudin comparison, it was nevertheless concluded that bivalirudin should be considered as a possible treatment option in patients at intermediate and higher risk of an adverse cardiovascular event. It was considered that either using bivalirudin as an adjunct to PCI (as in REPLACE-2), or as a short term infusion prior to angiography (as in ACUITY) were reasonable. While selective use of bivalirudin during PCI was found to be most cost-effective, there was considerable uncertainty in the analysis.

Longer term upstream bivalirudin
Longer term (72 hours) use of bivalirudin is technically within its license but there is no trial evidence to support its use for this duration upstream of angiography. In addition in the longer term model, the overall cost difference between bivalirudin used upstream of angiography, and other treatment options, increases. This makes bivalirudin less cost effective, although it is acknowledged that the model does not incorporate any

additional potential treatment benefit of longer upstream treatment. Given the lack of clinical evidence for longer use and the additional costs it was concluded that bivalirudin use should be restricted to shorter term (<24 hours) scenarios.

Also, clinically it would be unacceptable to defer the addition of potentially beneficial therapy for 72 hours pending angiography, because if it is judged that a patient requires more than heparin the clinician should be free to offer additional medication ahead of the angiography procedure and not withhold it simply on the basis of this cost-effectiveness modelling.

It is noted that population average risks of events are used in the economic model, based on best available data, but it is possible that clinical assessment may refine risk such that the net benefit (ischaemic risk vs bleeding risk) may be improved for an individual patient over that assumed for the average within a trial population. For this to be fully elucidated improved measures of bleeding risk will need to be incorporated into future clinical trials. In addition it is assumed in the economic model that relative risks of benefit (reduction in mortality or ischaemic events) and of harm (such as bleeding events) are constant across the various patient risk groups (low, intermediate, high, highest). Based on available data this was considered a reasonable assumption, but it is possible that this may vary.

Conclusions

Whilst sensitivity analyses were undertaken to model different assumptions, observations such as the uncertainties listed above, caused the GDG to be cautious about mandating the use of bivalirudin or GPIs, concluding it was more appropriate to recommend that they be "considered" by clinicians for certain patients at intermediate or higher risk (predicted 6-month mortality >3.0%). When such patients are scheduled for very early angiography (<24 hours from admission) and are pre-treated with aspirin and clopidogrel, bivalirudin either used selectively at the time of PCI or for a few hours upstream of angiography, is a reasonable alternative to the combination of heparin+GPI. With potential benefit of earlier angiography reported[30], more patients in future may be considered appropriate for one of these pharmacological strategies.

The lack of data comparing fondaparinux (with or without a GPI) with bivalirudin, and the need for unfractionated heparin to be given at the time of PCI to patients receiving fondaparinux, led the GDG to conclude that if very early angiography was scheduled, upstream unfractionated heparin (with or without a GPI) should be the alternative to bivalirudin. Whilst switching patients from initial treatment with heparin to starting bivalirudin has been shown to be safe [171] there have been no studies of patients being switched from fondaparinux to bivalirudin.

For those patients waiting >24 hours for angiography, fondaparinux is the preferred upstream antithrombin (with or without a GPI), as has been concluded elsewhere in this guideline.

►Bleeding risk

All anticoagulants are necessarily associated with a risk of bleeding complications and weighing this risk against the potential benefits of such agents requires an understanding of the factors associated with bleeding risk, measures by which the magnitude of this risk can be estimated, and the potential for benefit from these agents in reducing the rate of ischaemic events. Close attention to appropriate dosing of these agents is particularly important[174]. This topic is covered in detail in the RISK section of this guideline, to which readers are encouraged to refer (cross reference the bleeding section of the RISK chapter).

4.3.8 RECOMMENDATIONS

R17 Offer fondaparinux to patients who do not have a high bleeding risk, unless coronary angiography is planned within 24 hours of admission.

R18 Offer unfractionated heparin as an alternative to fondaparinux to patients who are likely to undergo coronary angiography within 24 hours of admission.

R19 Carefully consider the choice and dose of antithrombin in patients who have a high risk of bleeding associated with any of the following:

- advancing age
- known bleeding complications
- renal impairment
- low body weight.

R20 Consider unfractionated heparin, with dose adjustment guided by monitoring of clotting function, as an alternative to fondaparinux for patients with significant renal impairment (creatinine above 265 micromoles per litre).

R21 Offer systemic unfractionated heparin (50–100 units/kg) in the cardiac catheter laboratory to patients receiving fondaparinux who are undergoing PCI[p].

R22 As an alternative to the combination of a heparin plus a GPI, consider bivalirudin for patients who:

- are at intermediate or higher risk of adverse cardiovascular events (predicted 6-month mortality above 3%), **and**

[p] Unfractionated heparin is not licensed for use during angiography and PCI. Such use is an off-label use. Informed consent should be obtained and documented before it is used during angiography and PCI.

- are not already receiving a GPI or fondaparinux, **and**
- are scheduled to undergo angiography (with follow-on PCI if indicated) within 24 hours of admission.

R23 As an alternative to the combination of a heparin plus a GPI, consider bivalirudin for patients undergoing PCI who**:**

- are at intermediate or higher risk of adverse cardiovascular events, **and**
- are not already receiving a GPI or fondaparinux.

5 MANAGEMENT STRATEGIES

5.1 EARLY INVASIVE VERSUS CONSERVATIVE MANAGEMENT

5.1.1 CLINICAL INTRODUCTION

People with non ST-egment elevation ACS have a high incidence of recurrent myocardial ischaemia, a similar long term outcome to those with ST elevation MI (STEMI), and a worse outcome than for people with UA[175]. A variety of drug (anti–platelet, anti–thrombin) and coronary revascularisation (PCI or CABG) treatment strategies have been investigated for their potential to reduce the frequency of adverse events (death, MI, recurrent myocardial ischaemia).

However, for PCI or CABG to be considered as treatment options, coronary angiography has to be undertaken first to define the extent and severity of the person's coronary disease. Angiography is an invasive procedure, often requiring further anticoagulation, and therefore potentially has some associated risk. This, together with improving drug therapy, has caused investigators to address whether angiography/revascularisation should be performed, and if so, when in the course of an individual's admission it is best undertaken. Angiography may be undertaken early, deferred until later, or undertaken selectively only if the person has evidence of recurrent ischaemia despite appropriate drug therapy.

Supporters of an early invasive strategy reason that the sooner the coronary anatomy can be imaged, the sooner appropriate therapy (including revascularisation) can be given; thereby avoiding lengthy hospital stays and preventing further events [176]. On the other hand, supporters of a conservative management strategy (involving initial antithrombotic and anti-anginal treatment, and angiography performed only if there is evidence of recurrent ischemia) reason that medical therapy can stabilise people and non-invasive stress testing can identify those who require angiography; thereby reducing costs and complications by using angiography more selectively [176].

A number of clinical trials have been undertaken, but comparison between them is complicated by the:

- era in which they were undertaken (earlier trials involved less aggressive drug therapy and often had a low use of intracoronary stents),
- different time scales used in which angiography could be undertaken,
- frequency of angiography and revascularisation procedures in the conservative arms of the trials, and the
- varying definitions of MI.

In 2007 (the last available year) a total of 77,373 PCI procedures were undertaken in the UK, of which 40.5% were for UA or NSTEMI, and the stent usage overall was 94.7%[177]. The use of glycoprotein IIb/IIIa inhibitors (GPIIbIIIa) for people with UA or NSTEMI was 27% and 39% respectively [178]. Thus, in order to provide evidence close to modern day practice older trials where there was a low use of intracoronary stenting were excluded from our analysis. A separate specific analysis was made of those trials reporting on the use of GPIs.

The clinical question posed, and upon which the literature was searched, was:

> *"In adults with UA or non-ST segment elevation MI does early invasive investigation (i.e. angiography) with intent to assess for (and in those patients deemed suitable, to perform) revascularization improve outcomes in comparison with initial conservative treatment, with or without later angiography?"*

5.1.2 CLINICAL METHODOLOGICAL INTRODUCTION

The literature was searched from 1995 to 2009 for systematic reviews, RCTs, comparative studies, and observational studies comparing conservative management with early invasive management in people with non ST-segment elevation ACS. RCTs were included if they reported on either short (index hospitalisation) or long-term (up to 5 years) outcomes including death, MI, bleeding, stroke, re–hospitalisation.

Four systematic reviews [176] [179] [180,181], one meta–analysis [39] (an update of the Mehta meta–analysis) and two reports from open RCTs [182] [183] analysed the effect of an invasive versus conservative approach on death, nonfatal MI (procedural or non-procedural), quality of life, rehospitalisation, bleeding, and stroke.

The Hoenig et al. systematic review included 5 open RCTs (N=7818) in the stenting eral[178] [q] (FRISC II [184,185] [186,187], TACTICS-TIMI 18 [188], VINO [189], RITA-3 [190] [191], ICTUS [192] [193]). Three analyses were performed pooling trials based on the use of GPIs (stents with GPI use, stents without GPI use, and stents regardless of GPI use). Subgroup analyses were performed according to gender, troponin levels, risk stratification, and ST depression [176].

The Qayyum et al. systematic review included ten open RCTs (N= 10648; TIMI IIIB [194], MATE[195], FRISC II [184,185] [186,187], TACTICS-TIMI 18 [188], VINO [189], RITA-3 [190] [191], ICTUS [192] [193] VANQWISH [196], NQWMI [197], and TRUCS [198]). This meta–analysis was excluded from our analysis as it included three RCTs (VANQWISH [196], TIMI IIIB [194], MATE[195]) that were conducted before the routine use of stents. Also, the inclusion of the TRUCS [198] RCT was controversial because the patient population (Braunwald class IIIb or IIIc UA) was randomised 48 hours after the index episode of myocardial ischaemia and following a

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[q] The 'stent era' was taken to be after 1996, when stent usage had risen to 46% of PCI procedures [from 13.5% in 1994] in the UK. It has increased each year since then to be 90% of procedures in 2003 and 95% in 2007. Source: British Cardiovascular Intervention Society – www.bcis.org.uk/resources/audit [178]

period of stabilization on medical therapy. Thus, these people were managed conservatively for at least 48 hours, making this trial different from the other trials [179].

The Mehta et al systematic review included 7 open RCTs (N=9208 ; VANQWISH [196], TIMI IIIB [194], MATE[195], FRISC II [184,185] [186,187], TACTICS-TIMI 18 [188], VINO [189], RITA-3 [190] [191]) and was also excluded from our analysis because pre–stenting era trials were included, and it lacked the ICTUS trial[180].

The O'Donoghue et al. systematic review compared an early invasive strategy with a conservative strategy in men separately from women (8 RCTs; N total = 10412; N women = 3075; N men = 7075). The NCC–CC performed a modified meta–analysis by excluding three pre-stent trials (VANQWISH, TIMI IIIB, and MATE), which also examined the impact of gender on the comparison of invasive and conservative strategies (5 RCTs; FRISC II [184,185] [186,187], TACTICS-TIMI 18 [188], VINO [189], RITA-3 [190] [191], ICTUS [192] [193]) [181].

The Henriksson et al. meta–analysis was an update of the Mehta et al. meta-analysis. The ICTUS trial and the five year follow-up data from FRISC-II were added. This study was included for consideration by the GDG as it was used in the Henriksson et al. Cost-effectiveness analysis included as economic evidence, although the meta–analysis lacked a rigorous literature search and there was no quality appraisal of the individual trials.

Finally, two open RCTs were appraised that reported quality of life outcomes from the FRISC-II trial[183] (N=2457; follow-up at 3, 6, 12 months) and the RITA-3 trial [182] (N=1810; follow-up at 4 and 12 months). Both trials used validated standardised questionnaires to evaluate quality of life in people randomised to routine invasive versus conservative management strategies.

When considering the evidence it is important to consider the heterogeneity in the studies in terms of patient populations, different definitions of MI, different rates of revascularisation (both within each study arm as well as across the different studies), different stent use (stent use was low in older trials), different pharmacological backgrounds (particularly use of GPIs during PCI), and different mortality rates. All the RCTs that randomised people to routine invasive versus conservative management strategies were open due to the nature of the invasive approach.

Two summary tables (see

Table 5-1 and

Table **5-2**) of the characteristics of the trials with stenting during PCI are presented (adapted from Qayyum et al).

Table 5-1. Summary of characteristics of trials comparing early invasive with conservative management strategies in the stenting era

RCT	Max Follow-up (months)	Elevated cardiac enzymes (%)	ST-depression (%)	N	Use of GP IIbIIIa inhibitors during PCI in invasive/conservative arm (%)	Stent use in invasive arm (%)
FRISC II [184,185] [186,187]	60	68	46	2457	10/10	61
ICTUS [192] [193]	36	100	46	1200	94/75	88
RITA-3 [190] [191]	60	18	37	1810	9/NR	88
TACTICS-TIMI 18 [188]	6	54	31	2220	94/59	83
VINO [189]	6	100	46	131	0	50

In the invasive strategy, (by protocol) time from admission/index pain to randomisation ranged from one to three days and time from randomisation to angiography ranged from four hours to a 'few days'.

The actual time from randomisation to angiography in the trials ranged from an 'average' of 6.2 hours to median of four days and the actual time from randomisation to PCI ranged from an 'average' 8.6 hours to a median of four days (in those who underwent PCI).

Table 5-2. Summary of trial characteristics

Trial	Invasive Group				Conservative Group
	Protocol		Actual		Actual
	Time to randomisation	Time from randomisation to angio.	Time from randomisation to angio.	Time from randomisation to revascularisation	Randomisation to procedure
TACTICS-TIMI 18 [188]	<24 hours from index pain	4-48 hours	97% angio. median 22 hours	41% PCI median 25h; 24% CABG median 89 hours	51% angio. & 36% revasc. during index admission
ICTUS [192] [193]	<24 hours from index pain	Within 24-48 hours	97% angio. <48 hours (98% angio. during index admission)	61% PCI median 23h (53% <2 days); 18% CABG (2%<2 days)	53% angio. during index admission (<48 hours in 11%); median 283 hours to PCI
RITA-3 [190] [191]	<48 hours from index pain	<72 hours	97% angio. median 2 days	35% PCI median 3 days; 20% CABG median 22 days	16% angio., 7% PCI & 4% CABG during index admission
FRISC II [184,185] [186,187]	As soon as possible after admission, <72 hours after the start of open-label anti–thrombin	Angio. within few days of enrolment, aiming for revasc. <7days of the start of open-label anti–thrombin	98% angio. median 4 days (96%<7 days)	43% PCI median 4d (94% ≤7 days); 35% CABG median 7d (82% ≤10 days)	47% angio. median 17 days (10% ≤7 days)
VINO [189]	<24 hours from last rest pain	Angio. as soon as possible: 'first-day strategy'	100% angio. average 6.2 hours	52% PCI average 8.6 hours (47% on admission day); 35% CABG average 34 days	55% angio. average 61 days; 13% PCI average 55 days; 30% CABG average 86 days

5.1.3 CLINICAL EVIDENCE STATEMENTS

Refer to Table 5-3 for a summary of the results from the meta–analyses.

Invasive versus **conservative management strategies: s**hort-term follow-up

One systematic review [176] found a non–significant difference between an early invasive strategy and a conservative management strategy for:

- Death or nonfatal MI during the index hospitalisation (significant heterogeneity; I^2 = 81.0%)
- Death during the index hospitalisation
- Nonfatal MI during the index hospitalisation (significant heterogeneity; I^2 = 83.5%).

Level of evidence 1++

Table 5-3. Summary of outcomes in index hospitalisation: Invasive versus conservative management strategies

Systematic Review	Outcome	N RCTs	Size effect [RR (95% CI)]	Heterogeneity?
Hoenig et al. (2006)[176]	Death or nonfatal MI	4	1.14 (0.59, 2.21)	Significant. I^2 = 81.0%
Hoenig et al. (2006)[176]	Death	4	1.59 (0.96, 2.64)	Non–significant
Hoenig et al. (2006)[176]	Nonfatal MI	4	1.02 (0.44, 2.34)	Significant. I^2 = 83.5%

Invasive versus conservative management strategies: long-term follow-up

Compared to people in the conservative management group, people randomised to an early invasive strategy had a significantly decreased risk of [176]:

- Death or nonfatal MI (follow-up 6-12 months)
- Rehospitalisation (follow-up 6-12 months)
- Death (> 2 years follow-up)
- Nonfatal MI (> 2 years follow-up).

Level of evidence 1++

In one SR [176] people randomised to an early invasive strategy had a significantly increased risk of:

- Procedure-related MI
- Bleeding.

Level of evidence 1++

There was a non–significant risk for stroke between the two groups [176].

Level of evidence 1++

Subgroup analysis: Stent use plus routine GPI use

In two RCTs (ICTUS [192] [193] and TACTICS-TIMI 18 [188]) there was a non–significant difference between invasive and conservative strategy for:

- Death (follow-up 6-12 months) (2 RCTs; RR 0.95 [0.66, 1.39]; p=0.8)
- MI (6-12 months follow-up) (2 RCTs; RR 0.99 [0.48, 2.02]; p=1; significant heterogeneity I^2 = 85.9%)
- Death or nonfatal MI during the index hospitalisation (1 RCT; RR 0.77 [0.51, 1.17]; p=0.2)
- Death or nonfatal MI (at 6-12 months follow-up) (1 RCT; RR 0.77 [0.58, 1.01]; p=0.06)

Level of evidence 1+

In trials (ICTUS [192] [193] and TACTICS-TIMI 18 [188]) that employed the use of stents and routinely used GP IIbIIIa inhibitors an invasive strategy significantly decreased [176]:

- MI during the index hospitalisation (1 RCT; RR 0.61 [0.38, 0.98]; p=0.04)
- MI during follow-up (≤ 4 months) (1 RCT; RR 0.53 [0.35, 0.79], p=0.002)
- Death or nonfatal MI (follow-up ≤ 4 months) (1 RCT; RR 0.67 [0.8, 0.98] 4; p=0.02)
- Rehospitalisation (at 6 to 12 months follow-up) (2 RCTs; RR 0.77 [0.63, 0.93]; p=0.006)

Level of evidence 1+

Subgroup analysis: Stent use with little or no GP IIbIIIa inhibitor use

Three RCTs (FRISC II [184,185] [186,187], RITA-3 [190] , and VINO [189]; use of GPIs ranged from 0-10% in these trials) showed non–significant difference between an invasive and conservative management strategy for [176]:

- death during the index hospitalisation (3 RCTs; RR 1.39 [0.65, 2.96]; p=0.4)
- death during follow-up (6-12 months) (3 RCTs; RR 0.67 [0.33, 1.37]; p=0.3; significant heterogeneity I^2 = 73.5%)
- MI during the index hospitalisation (3 RCTs; RR 1.43 [0.65, 3.12]; p=0.4; significant heterogeneity I^2 = 62.2%)
- death or nonfatal MI during the index hospitalisation (3 RCTs; RR 1.46 [0.75, 2.86]; p=0.3; significant heterogeneity I^2 = 65.3%)
- death or nonfatal MI during follow-up (6-12 months) (3 RCTs; RR 0.74 [0.52, 1.04]; p=0.08; significant heterogeneity I^2 = 59.3%)

Level of evidence 1+

In three trials that employed stents but did not routinely use GP IIbIIIa inhibitors (FRISC II [184,185] [186,187], RITA-3 [190] , and VINO [189]) an invasive strategy significantly decreased [176]:

- death at follow- up (≥ 2 years) [2 RCTs; RR 0.75 (0.62, 0.92); p=0.006]
- MI at follow-up (6-12 months) [3 RCTs; RR 0.72 (0.52, 0.98); p=0.04]
- MI at follow-up (≥ 2 years) [2 RCTs; RR 0.75 (0.61, 0.91); p=0.004]
- re-hospitalisation at follow-up (6 -12 months) [2 RCTs; RR 0.65 (0.59, 0.71); p<0.00001]

Level of evidence 1+

Subgroup analysis in individual RCTs: Invasive versus conservative management in people stratified by risk score

In four RCTs investigators stratified patients by risk score and conducted subgroup analyses on people in different risk groups. It should be noted that the risk groups defined within the trials differ from the risk groups defined elsewhere in this guideline (cross-reference risk chapter).

In the FRISC II RCT [184,185] [186] there was a non–significant difference between an invasive or a conservative strategy for risk of death or MI in low risk groups (FRISC score 0-1; N=369) at two or five year follow-up. By contrast, an invasive strategy significantly reduced the risk of death or nonfatal MI in people with medium/high risk (FRISC score 2-7; N=1714) at two years (RR 0.64 [95% CI 0.51 to 0.80]) and at five years (RR 0.75 [95% CI 0.64 to 0.89]).

In the ICTUS RCT [192] there was a non–significant difference between an invasive or a conservative strategy for risk of death or MI at all levels of FRISC risk score at three years' follow-up (low, medium and high FRISC risk groups are all non–significant).

In the TACTICS-TIMI 18 RCT [188] there was a non–significant difference between an invasive or a conservative strategy for risk of death, MI, or rehospitalisation at six-months in those with a low risk (TIMI risk score 0-2; N=555). An invasive strategy significantly reduced the risk of death, MI, or rehospitalisation at six months in those with an intermediate risk (TIMI risk score 3-4; N=1328; p=0.048) as well as in those with a high risk score (TIMI risk score 5-7; N=337, p value not stated).

In the RITA-3 RCT [190] there was a non–significant difference between an invasive or a conservative strategy for risk of death, or MI at five year follow-up in those at low risk (quartiles 1,2,3, are all non–significant). Those with the highest risk score (4) had a reduced risk of death or MI at five year follow-up but this difference was only statistically significant for the octile at highest risk (4b) (Odd ratio 0.44 (95% CI 0.25 to 0.76]).

Level of evidence 1+

Quality of Life

Two open RCTs [182] [183] showed that people randomised to an invasive strategy had significantly higher quality of life scores at six months and one year follow-up.

Level of evidence 1+

Effect of gender: Invasive versus conservative strategy

In men (5 RCTs, N=5074) an invasive strategy significantly decreased the overall risk of the composite outcome of death, nonfatal MI, rehospitalisation after 12 months, compared with a conservative strategy (RR 0.69 [0.51, 0.93]; significant heterogeneity I^2 = 81.6%).

In women undergoing an invasive versus conservative strategy (5 RCTs, N=2482) there was no significant difference between groups for the risk of the composite outcome of death, nonfatal MI, rehospitalisation at 12 months (RR 0.88 [0.70, 1.09]) [181].

Among biomarker–positive women an invasive strategy was associated with a 33% lower odds of death, MI, or ACS (OR, 0.67; 95% CI, 0.50 to 0.88) and a non–significant 23% lower odds of death or MI (OR, 0.77; 95% CI, 0.47 to1.25). In contrast, an invasive strategy was not associated with a significant reduction in the triple composite end point in biomarker—negative (lower risk) women (OR, 0.94; 95% CI, 0.61to 1.44; *p* for interaction=0.36) and was associated with a non–significant 35% higher odds of death or MI (OR, 1.35; 95% CI, 0.78 to 2.35; *p* for interaction =0.08). Among men the odds-ratio for death, MI, or ACS was 0.56 (95% CI, 0.46 to 0.67) if biomarker—positive and 0.72 (95% CI, 0.51 to 1.01) if biomarker—negative (*p* for interaction=0.09) [181].

When trials were sub-grouped by revascularisation rates in the trial arms an invasive strategy significantly decreased the risk of death, nonfatal MI, rehospitalisation after 12 months compared with a conservative strategy for men in trials where there was >50% difference in revascularisation rates between trial arms (3 RCTs; RR 0.57 [0.48, 0.67]) [181].

Level of evidence 1+

NCC–CC meta–analysis

The NCC–CC conducted a meta–analysis of RCTs with high stent use (range from 50% to 93%) [FRISC II [184,185] [186,187], TACTICS-TIMI 18 [188], VINO [189], RITA-3 [190] [191], ICTUS [192] [193]]. The four year results of the ICTUS trial and the five year results of FRISC II were used to update the Hoenig et al. meta–analysis. Outcomes were death, MI, or composites of death or MI, and death, MI, or hospitalisation. Effect sizes were reported as relative risks with a random effects model. Inter-study heterogeneity was assessed with the I^2 statistic.

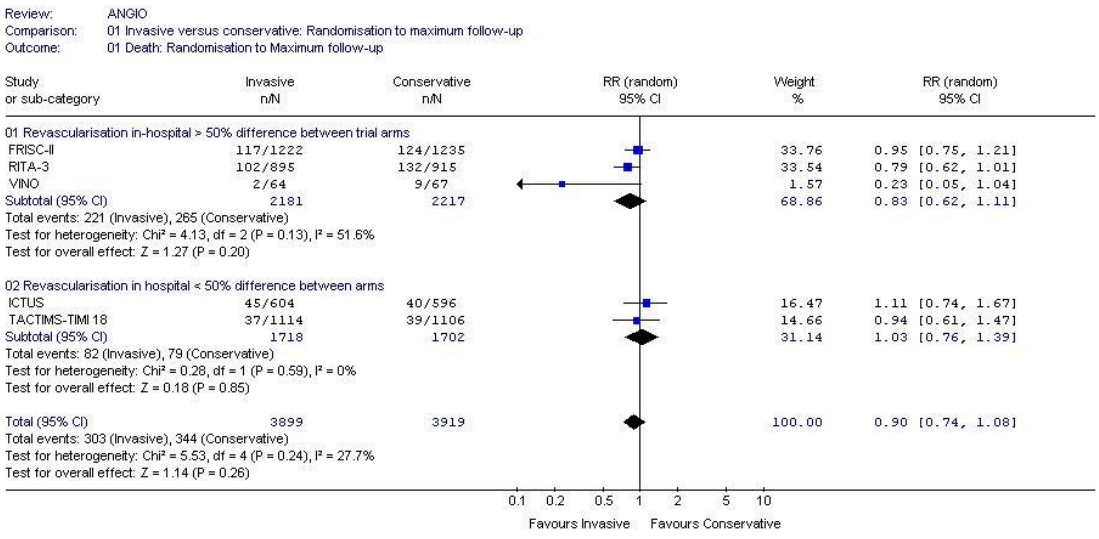
The NCC–CC used three strategies for conducting the meta–analysis:

- All five RCTs from randomisation to maximum follow-up.
- Three RCTs (ICTUS, FRISC II, RITA-3) from randomisation to maximum follow—up for studies that reported > 1 year follow-up. This was done to update the "late" (> two year follow-up) data in the Hoenig meta–analysis.
- All five RCTs from post-discharge period to maximum follow-up for the outcome of death or MI for the health economics analysis. Note that the index events were not reported in the original published studies. The index events reported in the Hoenig meta–analysis (and the Qayyum et al. meta–analysis for the ICTUS index data only) were subtracted from the entire follow-up events to calculate post-discharge to maximum follow-up outcomes.

►Death: Randomisation to maximum follow-up.

The NCC–CC meta–analysis of five RCTs (analysis 1) showed a non-significant difference between in randomised to an invasive versus a conservative approach for the risk for death. Results were similar when trials were grouped by the difference in revascularisation procedures between the two arms (either > or < than 50% difference in revascularisation rates). See Figure 4-1.

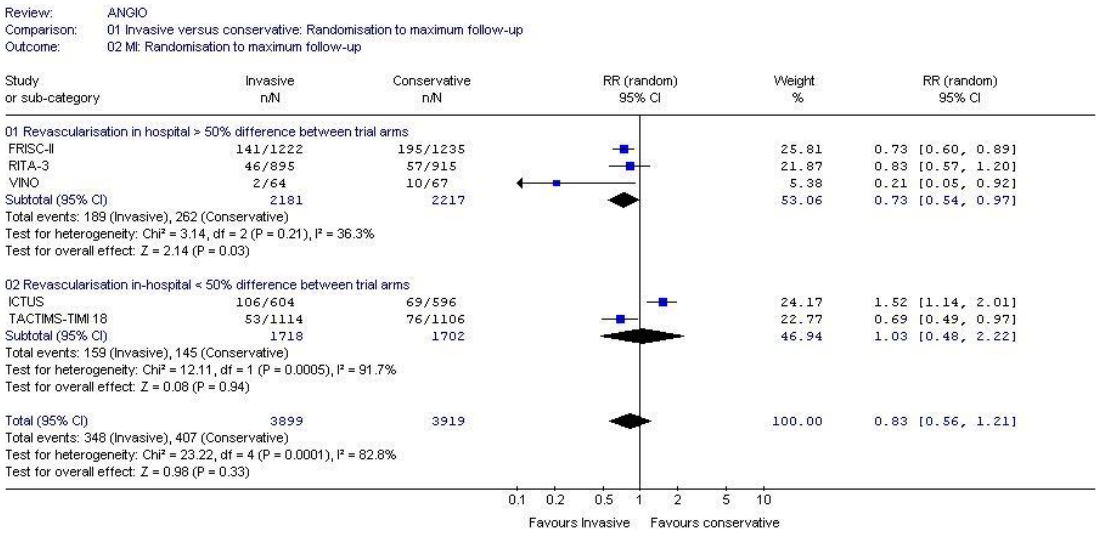
Figure 5-1. Analysis 1.



►MI: Randomisation to maximum follow-up

The NCC–CC meta–analysis (Analysis 2; 5 RCTs) showed no significant difference between those randomised to an invasive versus a conservative approach for the risk of MI at long-term follow-up, however this analysis had significant heterogeneity. An invasive strategy significantly decreased the risk of MI in trials in which there was > 50% difference in revascularisation rates between the two arms (3 RCTs; RR 0.73 [95% CI 0.54 to 0.97], p=0.03). See Figure 5-2.

Figure 5-2. Analysis 2.

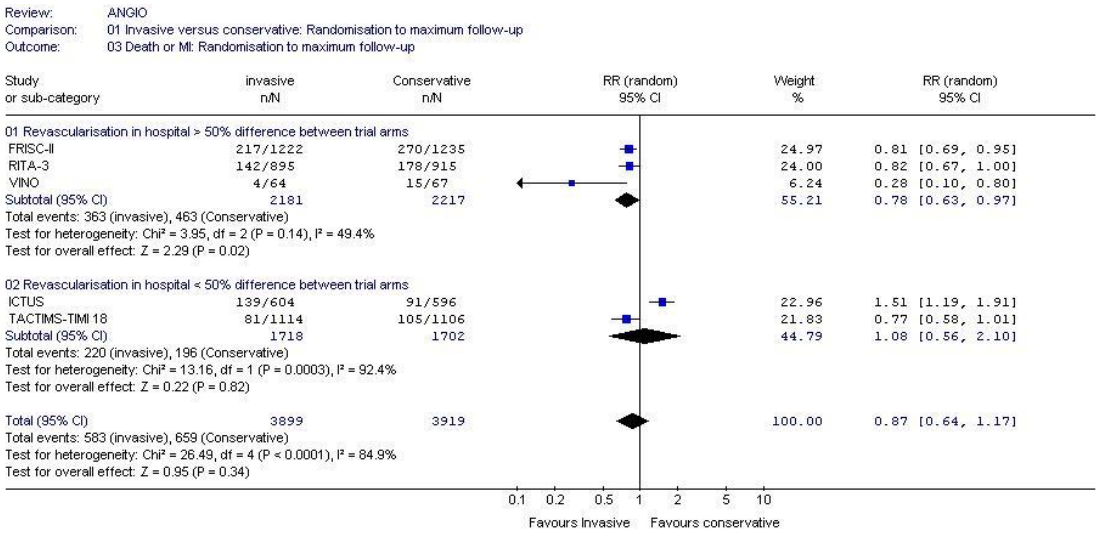


►Death or MI: Randomisation to maximum follow-up

The NCC–CC meta–analysis (5 RCTs; Analysis 3) showed no significant difference between those randomised to an invasive versus a conservative approach for the risk for death or MI at long-term follow-up, however this analysis had significant heterogeneity. An invasive strategy significantly decreased the risk of death or MI in trials in which there was > 50% difference in revascularisation rates between the two arms (3 RCTs; RR 0.78 [95% CI 0.63 to 0.97], p=0.02). There was NS difference between groups for the risk of death or MI in trials with greater than one year follow-up data (FRISC-II, RITA-3, ICTUS), however this analysis had significant heterogeneity. See

Figure 5-3.

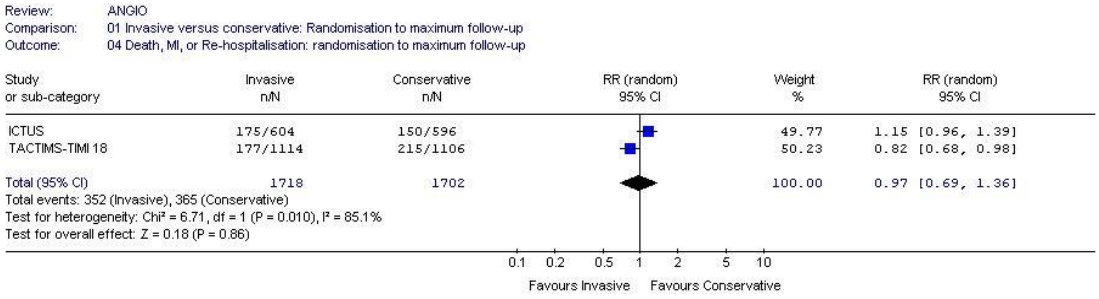
Figure 5-3. Analysis 3.



►Death, MI, or re-hospitalisation: Randomisation to maximum follow-up

The NCC–CC meta–analysis (Analysis 4; 2 RCTs) showed no significant difference between those randomised to an invasive versus a conservative approach for the risk for death, MI, or re-hospitalisation at long-term follow-up, however this analysis had significant heterogeneity. See Figure 5-4.

Figure 5-4. Analysis 4.

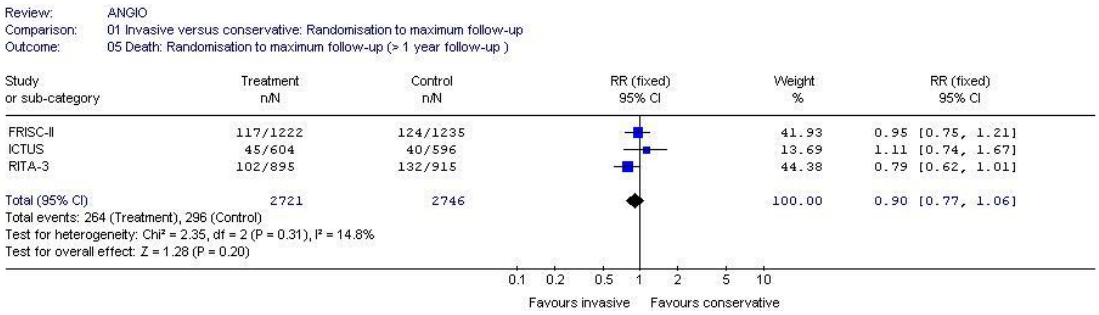


►Update of Hoenig meta–analysis

To update the Hoenig meta–analysis, a meta–analysis was conducted by the NCC-CC on the three RCTs with follow-up greater than one year (Analysis 5: 5 year results from RITA-3, and FRISC II, and 4 year results from ICTUS). There was no significant difference between those randomised to an invasive versus a conservative approach for the risk of death. See

Figure 5-5.

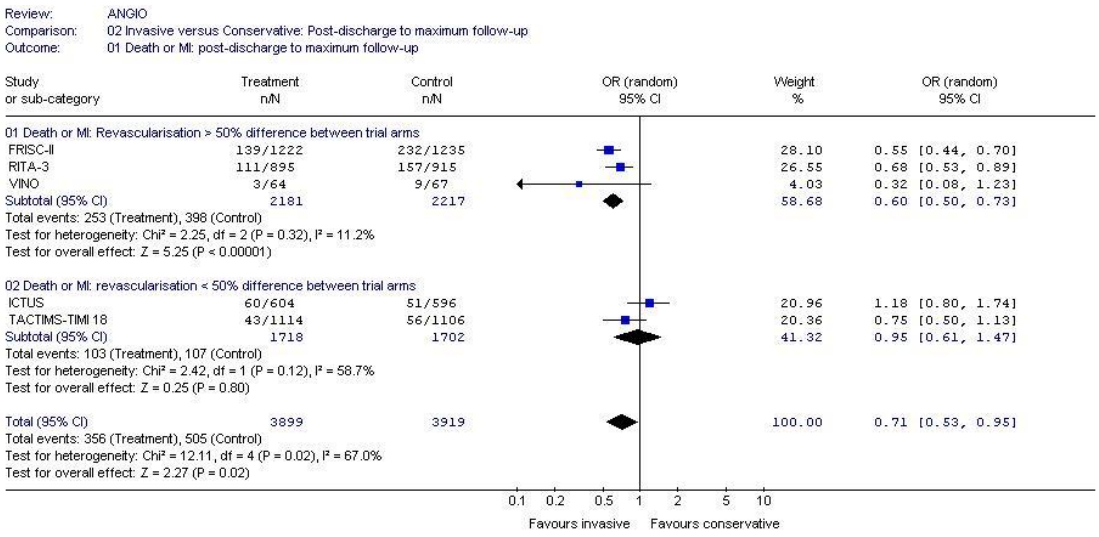
Figure 5-5. Analysis 5.



►Death or MI: Post-discharge to maximum follow-up

A meta–analysis was conducted for death or MI post—hospital discharge to maximum follow-up to compare with the Henriksson meta–analysis (that is used in the Henriksson et al. cost–effectiveness analysis included as economic evidence) (Analysis 6). The pre—stent trials (TIMI IIIB, VANQWISH, MATE) were excluded and updated with the long-term follow-up (three years) of ICTUS. None of the original papers reported events in the index hospitalisation. The index events were extracted from the Hoenig and Mehta meta—analyses (both agreed). However, the ICTUS index event data was only reported in the Qayyum meta–analysis, and the reviewers could not see how these numbers were obtained. Index death or MI for the ICTUS trial were obtained from Henriksson who had a personal communication from R. de Winter of the ICTUS trial. See figure Figure 5-6.

Figure 5-6. Analysis 6.



The NCC–CC meta–analysis showed that an invasive strategy significantly reduced chances of death or MI post-hospital discharge [OR 0.71 (95% CI 0.53 to 0.95), p=0.02], however there was significant heterogeneity in this analysis. The Henriksson meta–analysis reported cardiovascular death and MI post-hospital discharge (or death and MI, if there was no data) and the pooled estimate was similar to ours at OR 0.69 (95% CI 0.54 – 0.88). See Figure 5-7 and Figure 5-8.

Figure 5-7. Invasive versus conservative strategy in men (modified from O'Donoghue et al.)

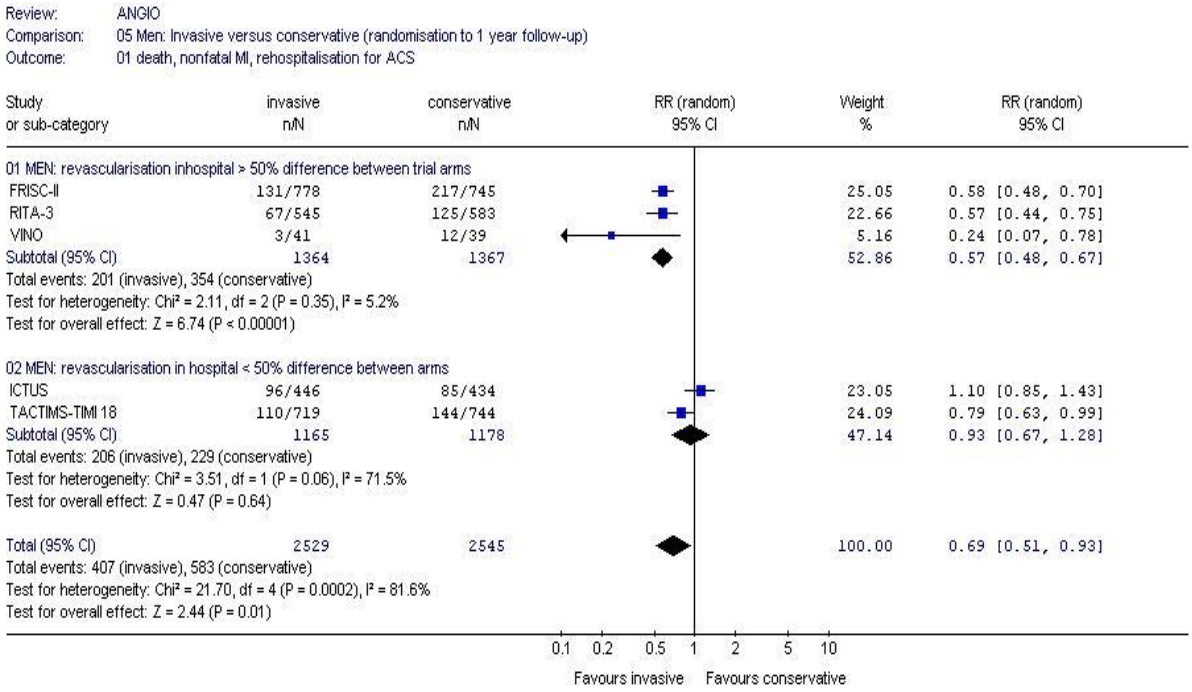
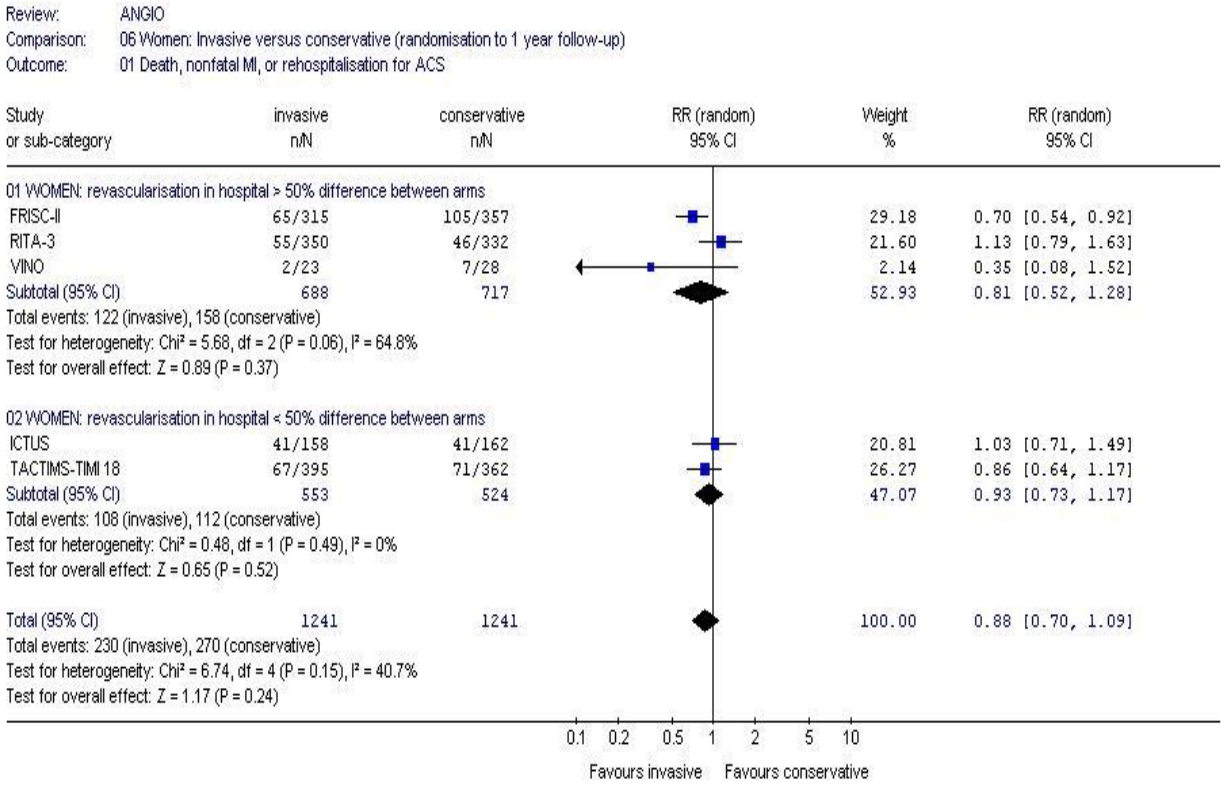


Figure 5-8. Invasive versus conservative strategy in women (modified from O'Donoghue et al)



►Summary of outcomes with long-term follow-up
See Table 5-4.

Table 5-4. Summary of Outcomes with Long-term follow-up: Invasive versus conservative management strategies

Systematic Review	Outcome	N RCTs	Size effect [RR (95% CI)]	Heterogeneity?
Hoenig et al. (2006)[176]	Death or nonfatal MI (6-12 mos)	4	0.76 (0.62-0.94)	Non–significant
NCC–CC	Death or MI (to end of follow-up)	5	0.87 (0.64, 1.17)	Significant. I^2 = 84.9%
Hoenig et al. (2006)[176]	Death (> 2 years)	2	0.75 (0.62-0.92)	Non–significant
NCC–CC	Death (to end of follow-up)	5	0.90 (0.74, 1.08)	Non–significant
Hoenig et al. (2006)[176]	Nonfatal MI (> 2 years)	2	0.75 (0.61, 0.91)	Non–significant
NCC–CC	MI	5	0.83 (0.56, 1.21)	Significant. I^2 = 82.8%
Hoenig et al. (2006)[176]	Re-hospitalisation (6-12 mos)	4	0.67 (0.61-0.74)	Non–significant
Hoenig et al. (2006)[176]	Procedure-related MI	3	2.05 (1.56-2.70)	Non–significant
Hoenig et al. (2006)[176]	Bleeding	4	1.71 (1.34-2.19)	Non–significant
Heonig et al. (2006)[176]	Stroke	2	0.89 (0.34, 2.31)	Non–significant

5.1.4 HEALTH ECONOMIC METHODOLOGICAL INTRODUCTION

One relevant cost–effectiveness analysis from a UK perspective was identified [38,39,199]. In addition, one from a Swedish perspective[200] and three from a US perspective [201-203] were identified but not reviewed due to the availability of a directly applicable UK study with only minor limitations.

Henriksson et al.[38,39] reported a cost–utility analysis undertaken from a UK NHS perspective based on effectiveness and resource use data from the five year follow-up of the RITA-3 trial (UK based, n=1810), with a sensitivity analysis where effectiveness data was based on a meta–analysis of all trials in the area. A decision-analytic model was used comprising a short-term decision tree representing the index hospitalisation followed by a Markov model representing the post-index period. The analysis takes into account death, MI, quality of life (EQ5D) and resource use based on data from RITA-3. Relative treatment effect of an early invasive strategy over a conservative strategy was assumed to last only to five years in line with available follow-up in RITA-3 but the impact of alternative assumptions was assessed. Lifetime costs (£ 2003/2004 prices) and QALYs were estimated and stratified by risk. A multivariate predictive model for MI or death in RITA-3 was used to calculate a risk score defining quartiles of risk, with the 4th quartile subdivided into two groups due to the much higher event rate in the top quartile (risk groups: 1, 2, 3, 4a, 4b).

The primary results of the cost–effectiveness analysis were based on the characteristics of people with the median risk score in each of these five risk groups. Cost effectiveness was expressed in terms of cost per QALY gained. Probabilistic sensitivity analysis was used to evaluate uncertainty. The basecase analysis assumed that the relative effect of an early invasive strategy compared to a conservative strategy was constant across risk groups, but a post hoc analysis of RITA-3 suggested that there was an interaction between treatment effect and risk group. Although the interaction was not statistically significant an alternative analysis was undertaken in which the relative benefit of the early invasive strategy varied with risk group. In another sensitivity analysis pooled effectiveness data were used from a published meta–analysis by Metha et al.[180], which was updated to include results from the ICTUS[192] trial, and the long-term results from RITA-3[191] and FRISC-II [187].

The main potential limitation of the cost–effectiveness analysis is that RITA-3 enrolled 1997-2001 and so may not reflect current practice. Additionally the pooled effectiveness data analysis used in the sensitivity analysis included results from trials where stenting was largely not used (specifically TIMI IIB, VANQWISH and MATE) and does not include all the clinical data identified in the literature review for this guideline.

5.1.5 HEALTH ECONOMIC EVIDENCE STATEMENTS

Henriksson et al.[38,39] found that an early invasive strategy, compared to a conservative strategy, was generally increasingly cost–effective as risk increased and reported cost–effectiveness ratios of £53,760, £22,949, £21,325, £11,957, £12,750 per QALY gained for risk groups 1, 2, 3, 4a and 4b respectively (1 = lowest and 4b = highest risk).

Allowing the relative treatment effect to vary by risk group improved cost effectiveness in the risk groups 4a and 4b while reducing it in risk groups 1, 2 and 3. Cost effectiveness was also considerably impacted by variations in the assumption regarding duration of treatment effect: assuming that treatment effect was maintained beyond the observed trial follow-up of five years improved cost–effectiveness. Using effectiveness inputs from pooled data instead of from only the RITA-3 trial had a modest impact in terms of reducing cost–effectiveness.

Full results for the basecase analysis and selected alternative scenarios are summarised in Table 5-5 below.

Table 5-5. Mean incremental cost–effectiveness ratio for an early invasive strategy compared to a conservative strategy (% of simulations cost–effective at a threshold of £20,000/£30,000)

	Basecase *	Basecase with different assumptions re treatment effect duration			Pooled effectiveness data	Interaction between treatment effect and risk**	Interaction model with different assumptions re treatment effect duration		
		10 yrs	15 yrs	Lifetime			10 yrs	15 yrs	Lifetime
Risk group 1	£53,760 (1%/12%)	£34,901	£27,949	£13,920	£58,490 (0.2%/6%)	Dominated (0.1%/3%)	£187,947	£121,044	£45,130
Risk group 2	£22,949 (33%/75%)	£15,410	£11,652	£7,850	£26,265 (19%/63%)	£50,131 (7%/26%)	£28,163	£21,553	£14,354
Risk group 3	£21,325 (41%/81%)	£15,754	£13,159	£10,473	£24,143 (25%/71%)	£29,711 (17%/51%)	£19,681	£16,218	£12,781
Risk group 4a	£11,957 (95%/98%)	£9,631	£8,446	£7,600	£13,646 (87%/96%)	£11,898 (94%/98%)	£9,450	£8,334	£7,600
Risk group 4b	£12,750 (92%/98%)	£9,707	£8,904	£8,270	£14,673 (83%/96%)	£10,476 (98%/99%)	£7,934	£7,348	£6,906

*RITA-3 effectiveness, no variation in treatment effect by baseline risk, 5-year duration of treatment effect

**RITA-3 analysis

Impact of changes in current practice

The main potential limitation of the study is that RITA-3 enrolled 1997-2001 and so may not reflect current practice. Table 5-6 below summarises the key changes in practice identified by the GDG and their potential impact on the cost effectiveness estimates from the Henriksson et al. study.

Table 5-6. Changes in practice and impact on Henriksson cost effectiveness estimates

Change in practice	Impact on Henriksson cost effectiveness estimates
Increased use of drug-eluting stents	• Will improve outcomes for both the early invasive and the conservative strategy as a proportion of people in both undergo PCI; likely to relatively improve outcomes for the early invasive strategy more, as more people undergo PCI. • While drug-eluting stents are more expensive than bare metal stents, the current average cost of a stent was estimated to be similar to the 2003 price used in the Henriksson analysis due to the considerable reduction in the price of bare metal stents o Henriksson unit cost (2003) = £370 o Estimated average cost (2008) = £397* • Given the above, reported cost–effectiveness estimates may improve.
Reductions in the length of hospital stay	• Will reduce resource use for both the early invasive and conservative strategies • The group considered the reduction likely to be greater in the early invasive group (for example, because time to wait for angiography has reduced considerably, and more people undergo angiography with the early invasive strategy) • Given the above, reported cost–effectiveness estimates may improve
Increases in the rates of angiography and revascularisation	• If this reduces the difference in rates of revascularization, the difference in effects between the early invasive and the conservative strategy also will be reduced. • However, if the difference in rates of angiography and revascularisation between the strategies is reduced, the cost difference will also be reduced • Reduced difference in outcomes will reduce cost–effectiveness, but reduced difference in costs will improve it; the net impact is difficult to judge • To some extent, the use of pooled data effectiveness addresses some of the concerns regarding differences in practice as the trials all had differing rates of angiography with the conservative strategy and rates of revascularisation with both strategies – this analysis had a limited impact on

	reported cost effectiveness estimates
Increased use of clopidogrel and GPIs	• Increased use of clopidogrel and GPIs is likely to improve outcomes and increase costs in both arms • Use and effect of clopidogrel is expected to be the same with a conservative and an early invasive strategy and so cost–effectiveness would not be impacted • GPI use and effect may be higher in the early invasive arm as PCI use is higher – this would be associated with increased costs but also improved outcomes; if GPI use is cost–effective then this should improve reported cost–effectiveness estimates • As above, to some extent, the use of pooled data effectiveness addresses some of the concerns regarding differences in practice as the trials had differing rates of GPI use – this analysis had a minimal impact on cost effectiveness

*Estimated assuming bare metal stents/drug eluting stent 45%/55% use [178] and £232/£532[204,205]

Impact of pooled effectiveness estimate excluding pre-stent trials

The Henriksson analysis uses effectiveness data from the RITA-3 trial in the base case analysis but also investigates the impact of using pooled data. The meta–analysis used included trials in the pre-stent era, which were judged not relevant to current practice by the GDG (specifically TIMI IIB, VANQWISH and MATE). Comparable pooled estimates that excluded pre-stent trials and included all relevant published data were generated as part of the clinical review.

Comparing these numbers to the pooled estimates used by Henriksson show that the relative effect in the index hospitalisation is improved and in the post-discharge period is similar although slightly worsened (see

Table 5-7 below for figures). As these effects are acting in different directions it is difficult to judge the net impact. In the original analysis using the pooled analysis instead of RITA-3 had a modest impact.

Table 5-7. Comparison of composite endpoints of MI or CV death for early invasive versus initial conservative strategy.

	Composite endpoint of MI or CV death for early invasive versus initial conservative strategy	
	Odds ratio during index hospitalisation	**Hazard ratio from hospital discharge to end of trial**
Henriksson et al. RITA-3 analysis	1.52 (0.864, 2.675)	0.621 (0.464, 0.830)
Henriksson et al. Updated meta analysis	1.42 (NR)	0.69 (NR)
Pooled analysis excluding non-stent era trials	1.14 (0.14, 2.21)*	0.71** (0.53, 0.95)

*Hoenig et al. Cochrane review[176] **NCC–CC meta analysis NR = not reported

5.1.6 EVIDENCE SUMMARY

- When all five trials were included and analysed to the end of *the index hospital admission* there was no significant overall difference between the invasive and conservative group with respect to death, stroke or non-fatal MI, but an invasive strategy increased the risk of bleeding (mainly minor). However, an invasive strategy significantly decreased the composite of death and MI at *6-12 months follow-up*, both *late (>2 yrs)* death and *late* MI, and reduced the *long-term* rate of re-hospitalisation. Procedure- related MI was significantly increased in the invasive arm (the denominator in both arms was the total number of people randomised to each arm).

- There was no difference in mortality at any time whether angiography was undertaken very early (<24 hours from randomisation – ICTUS, TACTICS-TIMI 18, VINO) or when undertaken later (>48 hours - RITA-3, FRISC-II).

The NCC–CC meta–analysis analysed the five RCTs from randomisation to end of maximum follow-up (5 years in RITA-3 and FRISC II, 4 years in ICTUS, 0.5 years in VINO and TACTICS-TIMI 18). Overall, there was a non–significant difference between an early invasive and conservative strategy for death, death or nonfatal MI, or MI. An early invasive strategy significantly reduced MI and death or MI in trials in which there was a greater than 50% difference in revascularisation rates between the trial arms.

- When analysis was undertaken of those trials *not involving the routine use of GPIIbIIIa inhibitors* (VINO, RITA-3, FRISC-II -use of GPIs ranged from 0-10% in these trials; compared to 94% use in TACTICS-TIMI 18 and ICTUS) an invasive strategy significantly decreased intermediate (6-12 months) MI and refractory angina, but not death at any time point, nor the index admission MI.

- In the FRISC-II trial, an invasive strategy significantly reduced the composite of death or non-fatal MI in those with either ST depression or troponin elevation (higher risk), but not in those without (lower risk), suggesting that the benefit of an invasive strategy was mostly in higher risk people. The FRISC investigators used a risk scoring system (scores 0-7) and showed worsening outcome (death, recurrent MI) as the score increased but greater benefit form the invasive stratgey[206].

- Similarly, in the RITA-3 trial there was no difference between management strategies for those at lowest risk, but those at highest risk who were managed by an early invasive strategy had a significantly reduced risk of death or MI up to 5 years follow-up.

- By contrast in the ICTUS trial an early invasive strategy did not confer benefit and there was no evidence that treatment effect was influenced by risk at randomization. Interpretation of the ICTUS trial is influenced by a high rate of early angiography and revascularization in the conservative arm of the trial[193].

- When analysis was undertaken of those trials with the routine use of GPIs (mainly based on TACTICS-TIMI 18 but including ICTUS – use of GPIs was 94% in the invasive arms of both trials) an invasive strategy significantly reduced in-hospital non-fatal MI, the composite of death or non-fatal MI (but not death alone), suggesting that appropriate use of GPIs reduces in-hospital MI when added to an invasive strategy. It also reduced rehospitalisation over 6-12 months follow-up.

- When analysed by troponin elevation (TACTICS-TIMI 18) there was no difference between invasive and conservative groups who were troponin negative, but there was a reduction in 30 day death or MI in those managed with an early invasive strategy who were troponin positive, again suggesting that the benefit of an invasive strategy is mostly in higher risk people. The TIMI risk score used in this trial was previously developed to stratify people with UA or NSTEMI according to their risk of an adverse outcome[207] [18]and has been modified to allow stratification before the 12-hour troponin is known[208].

- When trials with large absolute differences in revascularisation rates between early invasive and conservative strategies (FRISC-II, RITA-3, VINO) were pooled, a significant reduction in death was seen, suggesting that if a strategy of conservative management is associated with a high subsequent rate of revascularisation (as in TACTICS-TIMI 18, ICTUS, TRUCS) the benefit of an early invasive strategy diminishes.

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[18] TIMI Risk Score: (score 1 for each factor). Total = 7)
Age ≥ 65 years, Presence of at least three risk factors for CHD, Prior coronary stenosis of ≥ 50 percent, ST segment deviation on admission ECG, At least 2 anginal episodes in prior 24 hours, Elevated serum cardiac biomarkers, Use of aspirin in prior seven days. [208]

A higher TIMI risk score correlates significantly with increased numbers of events (all-cause mortality, new or recurrent MI, or severe recurrent ischemia requiring revascularization) at 14 days: **Score 0/1** - 4.7 %, **2** 8.3 %, **3** - 13.2 %, **4** - 19.9 %, **5** - 26.2%, **6/7** - 40.9%

Alternatively, the greatest difference between strategies is seen when the conservatively managed group has a low rate of intervention.

- Two RCTs were appraised that reported quality of life outcomes from FRISC-II [183] and RITA-3[182] . These showed that people randomised to an early invasive strategy had significantly higher quality of life scores at 6 and 12 months follow-up, than those managed by a conservative approach.

Cost effectiveness

Henriksson et al. found that an early invasive strategy was increasingly cost effective with increasing risk, with the high risk groups (4a, 4b) being definitely cost effective, and the lowest risk group (1) being not cost effective. A degree of uncertainty exists for the intermediate groups (2 & 3) since they lay within the range £20-30,000 per QALY gained.

5.1.7 EVIDENCE TO RECOMMENDATIONS

Using methodology described earlier (reference to risk chapter) the GDG plotted the 6-month mortalities for these risk stratified groups in FRISC and RITA, on GRACE graphs (6-month predicted mortality by GRACE score – see Figure 4.9 and Figure 4.10).

Within the trials the benefits of the routine invasive strategy were mainly seen in people at highest risk. The GDG concluded that an early invasive strategy was likely to benefit those people with a predicted six-month mortality of >3.0% (our risk cohorts 2a, 2b, 3 & 4), although evidence to guide treatment of people at very high risk is limited.

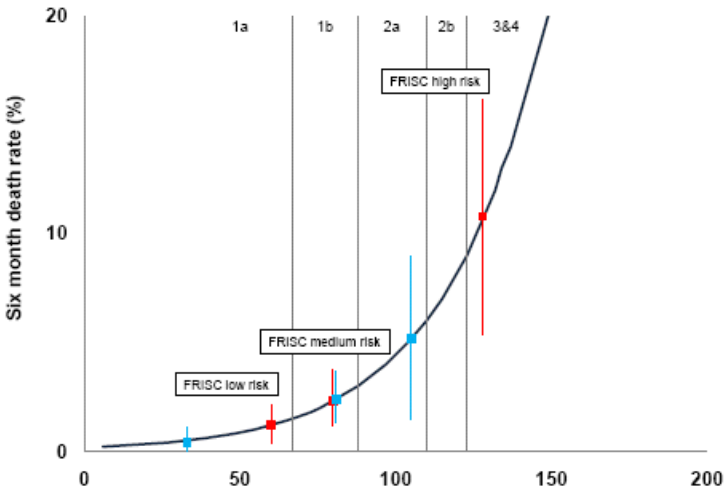

Figure 5-9. 6-month mortality (y-axis) and GRACE score (x-axis) data from the GRACE Registry.
Six month mortality in FRISC-2 for conservative (red) and invasive (blue) groups shown by FRISC risk stratum on the 'GRACE curve' (dark blue). FRISC low risk stratum N=395, FRISC medium risk stratum N=1214, FRISC high risk stratum N=684. Vertical grey lines show risk groups. Risk groups 3 and 4 include approximately 50% of the ACS population at highest risk. FRISC-2 mortality data provided by Bo Lagerqvist.

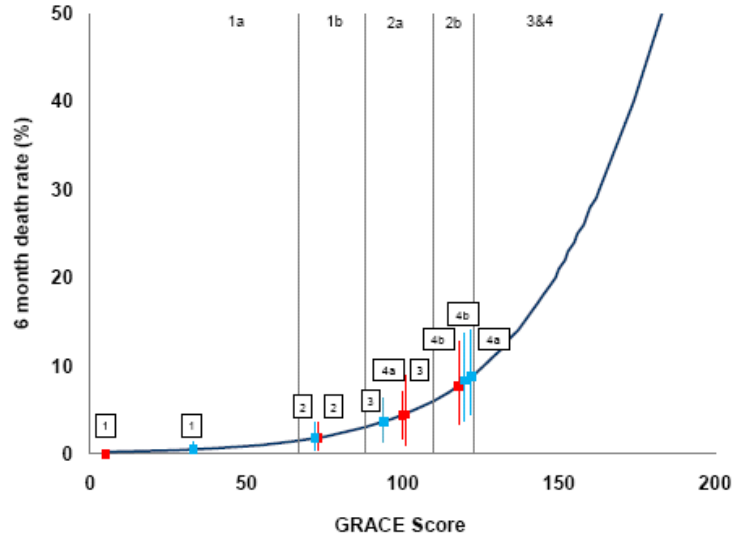

Figure 5-10. 6-month mortality (y-axis) and GRACE score (x-axis) data from the GRACE Registry. Six month mortality in RITA-3 for conservative (red) and invasive (blue) groups shown by RITA-3 risk stratum (boxes) on the 'GRACE curve' (dark blue). RITA risk stratum 1 N=451, RITA risk stratum 2 N=452, RITA risk stratum 3 N=452, RITA risk stratum 4a N=226, RITA risk stratum 4b N=226. Vertical grey lines show risk groups. Risk groups 3 and 4 include approximately 50% of the ACS population at highest risk. RITA-3 mortality data provided by T Clayton.

The GDG considered the Hoenig and NCC–CC meta-analyses and concluded that:

- Various scoring systems have been used in the trials of early invasive vs. conservative strategies to assess an individual's underlying risk and several (TIMI, FRISC, RITA) have stratified people into high, intermediate and lower risk groups.

- Comparison of the trial populations with an unselected population of people with UA or NSTEMI suggests that the trials enrolled people at low to intermediate levels of risk and people at the highest levels of risk are systematically excluded from the evidence base.

- An early invasive strategy does have benefit, mainly in reducing recurrent ischaemia/infarction in the short term, but also in reducing longer term mortality or reinfarction. However, this benefit appears to be greatest in those people at higher absolute risk of such events (with the most benefit seen in those at the highest risk). This has also been demonstrated in the recently published TIMACS trial. Some studies have attempted to see if there is a difference in relative treatment benefit amongst different risk groups. However the GDG concluded that there was not strong evidence to demonstrate such an effect.

- Conversely, those at lowest risk are likely to have a similar outcome whether initially managed with an early invasive strategy, or one where angiography is undertaken only when recurrent ischaemia is present, either clinically apparent or as demonstrated by non-invasive investigations. This is particularly true for women where there may even be net harm from an early invasive strategy in those who are troponin negative.

- The trials reviewed have compared an early invasive strategy against a *selective* invasive strategy, with angiography (and, where appropriate, revascularisation) undertaken if there is subsequent evidence of ischaemia (spontaneous or on non-invasive testing). Those in the conservative limb had a high rate of subsequent angiography (16-55% of those in the conservative management groups of 5 RCTs [TACTICS, ICTUS, RITA-3, FRISC II, VINO] underwent angiography during the index admission). Thus, for those in whom a conservative strategy is adopted many would be expected to undergo angiography (and be considered for revascularisation) at a later stage if the potential benefits of this strategy are to be obtained.

How early should PCI be undertaken?

An 'early' invasive strategy is generally regarded as being angiography, with PCI where appropriate, undertaken within 72-96 hours after the index admission. If an early invasive strategy is proposed then, to some extent, the earlier that this is undertaken the better because coronary anatomy will be defined and decisions regarding revascularisation can be made. In the ISAR-COOL trial[95], people were randomly assigned to a very early versus delayed invasive strategy (median time from randomisation to catheterization 2.4 hours versus 86 hours). The early invasive strategy, when compared with the delayed invasive strategy, was associated with a borderline significant reduction in death or large MI at 30 days (5.9 versus 11.6 percent), suggesting the benefit of a very early invasive strategy compared to waiting three to five days.

However, in a small study, terminated early due to slow recruitment (OPTIMA-trial[209]), a group of similar people underwent early angiography (median two hours from admission). Those who required PCI were then randomised to either immediate PCI (n=73, median time from angiography to PCI 30 minutes) or deferred PCI (median time from angiography to PCI 25 hours). All people having PCI received a bolus dose of abciximab. The incidence of the primary end point (a composite of death, non-fatal MI (MI) or unplanned revascularisation, at 30 days) was 60% in the group receiving immediate PCI and 39% in the group receiving deferred PCI (RR=1.5, 95% CI 1.09 to 2.15; p=0.004). No deaths occurred in either group. MI was significantly more common in the group receiving immediate PCI (60% vs 38%, RR=1.6, 95% CI 1.12 to 2.28, p=0.005). Although the trial was small, and the loading dose of clopidogrel (300 mg) was less than would now be advised (600 mg) for those undergoing such early PCI, it does raise the possibility that PCI undertaken within a few hours of admission, before medical therapy has had time to exert its beneficial effect, may be associated with further infarction.

Summary

Following careful consideration of the limitations of the cost–effectiveness analysis identified in the literature, the GDG agreed that the results of the analysis should be accepted as a basis for decision making. While the RITA-3 study does not wholly reflect current UK practice, the Henriksson et al [38] analysis is a comprehensive, high quality economic evaluation based on patient-level effectiveness, resource use and quality of life data prospectively collected in a UK setting. The UK setting is of particular relevance not only in terms of obtaining applicable resource use estimates but also as previous cost effectiveness analyses in non ST-segment elevation ACS have often noted the problem of differences in practice, and therefore base line event rates, between countries[210,211].

Consideration of changes in practice since the RITA-3 trial found that some are likely to improve the cost effectiveness estimates for an early invasive strategy. Others are less clear cut, but will not necessarily worsen it.

Based on the risk assessment exercise undertaken as part of this guideline (reference RISK chapter and HE appendix) and its use in placing clinical trials in a UK context, the GDG judged that in people with a predicted 6-month mortality of >3.0% (our risk cohorts 2a, 2b, 3 & 4) an early invasive strategy was likely to be both clinically and cost effective.

The GDG concluded that on the basis of the evidence available for review at the time, the definition of 'early angiography' could be interpreted as being within 96 hours of admission to hospital. However, the European Society of Cardiology has recommended that 'early angiography' be regarded as being within 72 hours, although acknowledging that controversy exists over interpretation of the optimum exact timing. The GDG also noted that if angiography were felt to be beneficial (as in those at intermediate or higher risk of an adverse cardiovascular event) then there would be logic in attempting to undertake this sooner rather than later, provided no potential for harm were present in undertaking angiography too early. As further evidence emerges it may be that a shorter recommended time limit can be more strongly supported. Angiography should be expedited for those who are clinically instable or at high ischaemic risk

5.1.8 RECOMMENDATIONS

R24 Offer coronary angiography (with follow-on PCI if indicated) within 96 hours of first admission to hospital to patients who have an intermediate or higher risk of adverse cardiovascular events (predicted 6-month mortality above 3.0%) if they have no contraindications to angiography (such as active bleeding or comorbidity). Perform angiography as soon as possible for patients who are clinically unstable or at high ischaemic risk.

R25 Offer conservative management without early coronary angiography to patients with a low risk of adverse cardiovascular events (predicted 6-month mortality 3.0% or less).

R26 Offer coronary angiography (with follow-on PCI if indicated) to patients initially assessed to be at low risk of adverse cardiovascular events (predicted 6-month mortality 3.0% or less) if ischaemia is subsequently experienced or is demonstrated by ischaemia testing.

R27 Offer patients clear information about the risks and benefits of the treatments offered so that they can make informed choices about management strategies. Information should be appropriate to the patient's underlying risk of a future adverse cardiovascular event and any comorbidities.

5.2 PERCUTANEOUS CORONARY INTERVENTION (PCI) VERSUS CORONARY ARTERY BYPASS (CABG)

5.2.1 CLINICAL INTRODUCTION

For all those presenting with UA or NSTEMI, other than those considered at lowest risk, coronary angiography has been shown to offer benefit and is recommended (see section 5.1). This benefit arises from the value of knowing the extent and severity of the individual's coronary artery disease, and the important contribution this makes in determining optimum therapy. For some, treatment will be based on drug therapy alone, but for most this will be supplemented by coronary revascularisation, involving either percutaneous coronary intervention (PCI) or surgical coronary artery bypass grafting (CABG). Determining the optimum treatment strategy for an individual patient is a complex matter that takes account of the risk associated with their underlying cardiac condition, their left ventricular function, co-morbidity, the distribution of their coronary artery disease and the relative risks of the revascularisation procedure itself. The objectives of both forms of revascularisation are the same - to alleviate symptoms, prolong life and reduce cardiac morbidity – but the two procedures are obviously very different; CABG involves a surgical operation and general anaesthesia, whereas PCI is less invasive and can be done under local anaesthesia.

Broadly speaking, CABG has tended to be preferred for people with more extensive (three vessel), or diffuse, coronary disease (particularly where there is associated poor left ventricular function), and those with significant narrowing of the left main stem coronary artery. PCI, on the other hand, has been favoured for those people with one or more discrete coronary lesions. Thus, randomised trial data comparing PCI and CABG reflect only those people for whom both treatment strategies are felt clinically to be equally appropriate, and therefore address only a subset of all people presenting with coronary disease. Those for whom there are good clinical reasons to favour one treatment strategy over another (for example medical therapy or PCI for those at high surgical risk, PCI for those with single discrete lesions, CABG for those with diffuse triple vessel or complex left main stem disease) have generally not been randomised in trials. However, the interface between revascularisation strategies has changed over the years and has resulted, for instance, in the more recent randomisation of people who would previously have been considered unsuitable for PCI and to require CABG[212] [212] and some who would previously have been considered too old, frail or with too much co-morbidity to undergo CABG. The selection of patient populations, their respective co-morbidity (particularly the prevalence of diabetes and renal disease) and the advances in clinical practice over time complicates data interpretation and trial comparisons.

Considerable clinical trial and registry data comparing PCI and CABG have been used to inform recommendations and guidelines for the management of people with coronary artery disease.

A number of points should be highlighted:

- the data comparing PCI and CABG are predominantly derived from people with stable angina rather than acute coronary syndromes,
- when included in randomised trials those with acute coronary syndromes usually form a minority of the whole group,

- people with ST elevation MI are generally not considered for early CABG because of their high risk, but increasingly undergo immediate (primary) PCI because of its superiority over medical (fibrinolytic) therapy,
- trials have generally not enrolled the elderly (>75 to 80 years) and have varying exclusion criteria, but generally do not include those at highest risk,
- comparisons over time are confounded by advancing surgical and interventional techniques (such as the introduction of coronary stenting, and the use of arterial graft conduits) and changing adjunctive pharmacotherapy (uptake of secondary preventive treatments such as statins and anti–platelet therapy).

The GDG sought data specific to people with UA or NSTEMI in order to determine the place of these two revascularisation procedures (CABG and PCI) in their management. The clinical question posed was:

'In adults with UA or non-ST segment elevation MI does CABG improve outcomes in comparison with PCI?'

5.2.2 CLINICAL METHODOLOGICAL INTRODUCTION

The literature was searched from 1995 to 2009 for systematic reviews, RCTs, and observational studies comparing PCI with CABG in people with non ST-segment elevation ACS. There were few RCTs of PCI versus CABG in people with ACS, thus both RCT and observational studies were included. Studies were included if they reported on either short (index hospitalisation) or long-term (up to 5 years) outcomes including death, MI, bleeding, stroke, repeat revascularisation, angina. Studies of angioplasty without stenting were excluded, as were studies in which the NSTEMI/UA population comprised < 60% of the participants, or if the participants had stable coronary artery disease.

Four open RCTs [ERACI-II [213] [214], AWESOME [215], SoS [216], and ARTS [217]] and five cohort studies [218] [219] [220] [221].[222] compared PCI with CABG in people with multivessel coronary artery disease and UA. Three of the cohort studies [220] [221].[222] were rejected because they had serious limitations due to high dropout rates and/or lack of adjustment for confounding variables.

Caution should be exercised in combining results of the studies as they are a mix of RCTs and cohort studies with different degrees and types of stent usage. The populations differed in the number and type of diseased vessels. Table 5-8 details differences in the participants recruited to the four open RCTs.

The Palmerini et al cohort study compared PCI and CABG in people with de novo ≥ 50% unprotected left main coronary artery stenosis (N=311; 63% NSTEMI/UA; follow-up at 30 and 430 days). Multivariate analysis identified independent predictors of death [218].

The Seung et al cohort study [219] assessed 3 year outcomes in people who had PCI or CABG for unprotected left main coronary artery disease (N= 542 propensity score matched pairs of PCI and CABG people; 57% UA; 11% NSTEMI).

Table 5-8. Summary of baseline characteristics in four RCTs comparing CABG with PCI

RCT	ERACI-II [213 214]	AWESOME [215]	ARTS (UA cohort only) [217]	SoS (ACS cohort only) [216]
Inclusion Criteria	Multivessel CAD and CCS class III-IV angina despite maximal therapy and UA (Brunwald's criteria class II, III –c); angiographic evidence of severe coronary obstruction (≥ 70%) in at least 1 major epicardial vessel and > 50% in other vessels; all lesions amenable to both PTCR or CABG	Medically refractory (defined as anginal symptoms despite ASA and/or heparin and control of HR and BP) UA (defined as rest angina with ECG changes or known CAD; recurrent rest angina; or stabilised rest angina with a subsequent positive stress test). People had to be at high risk for CABG by fulfilling at least 1 criteria of: Age > 70 years; prior CABG; MI within 7 days; LVEF < 0.35; or IABP required to stabilise them.	People with multivessel disease and left ventricular ejection fraction of at least 30%	Symptomatic people with typical angina pectoris and multivessel disease.
Age	62	67	61	62
% UA	91	100	100	62
% 2VD	39	36	65.5	Not reported
% 3VD	56	45	35	45
% LAD	92	88	91	Not reported
% Prior CABG	Excluded	31	Excluded	Excluded
% MI < 7 days	NR	33	Excluded	Not reported
% Prior MI	28	71	47	56

% LVEF < 0.35	Excluded	20	Excluded	Not reported
% IABP needed	Not reported	2	Not reported	Not reported
% Renal disease	Not reported	Not reported	Excluded	Not reported
Definition of MI	Q-wave MI: new pathologic Q-waves or new LBBB with > 3X CK-MB rise	NR; MI was not an outcome	New Q waves with one sampled ratio of CK-MB > 10% or one plasma level of CK-MB > 5 x ULN	New Q waves

5.2.3 CLINICAL EVIDENCE STATEMENTS

Short term outcomes (index hospitalisation to 30 days) for CABG versus PCI:

Refer to summary

Table 5-9 for a summary of short term outcomes in people randomised to PCI or CABG.

►MACCE (Major Adverse Cardiac and Cerebrovascular Event[223]) at 30 days (death, Q-wave MI, stroke, or repeat revascularisation)

One RCT (ERACI-II) showed significantly increased MACE at 30 days in the CABG group compared with the PCI group [213].

Level 1+

►Death (index hospitalisation to 30 days)

In ERACI-II there was a significantly higher death rate in the CABG group compared with the PCI group [213]. However, two RCTs [216] [215] and a cohort study [218] showed non–significant difference for early death.

Level: 1+ and 2+

►MI (index hospitalisation to 30 days)

At 30 days, the ERACI-II RCT [213] showed significantly increased MI in the CABG group compared with the PCI group, whereas SoS [216] and a cohort study [218] showed non–significant difference for early MI.

Level: 1+ and 2+

►Repeat Revascularisation (index hospitalisation to 30 days)

The SoS RCT [216] and one cohort study [218] showed non–significant difference in repeat revascularisations between the PCI and CABG groups.

Level: 1+ and 2+

►Bleeding (in hospital)

One RCT [216] showed a non–significant difference in bleed rates between the PCI and CABG groups.

Level: 1+

►Stroke (index hospitalisation to 30 days)

Three RCTs showed a non–significant difference between PCI and CABG for stroke at 30 days. [214] [215] [216].

Level 1+

Table 5-9. Summary of short-term outcomes in RCTs: CABG versus PCI revascularisation strategies

Reference	RCT	Outcome	N	CABG (% events)	PCI (% events)	P value
Rodriguez et al. (2001)[213]	ERACI-II	MACE (death, Q-wave MI, stroke, or repeat revascularisation) at 30 days	450	12.3	3.6	0.002
Zhang et al. (2005)[216]	SoS	Death in-hospital	242	0.8	0	1.00
Rodriguez et al. (2001)[213]	ERACI-II	Death at 30 days	450	5.7	0.9	0.012
Morrison et al. (2001)[215]	AWESOME	Death at 30 days	454	5	3	Not reported
Zhang et al. (2005)[216]	SoS	MI in-hospital	242	1.6	4.3	0.26
Rodriguez et al. (2001)[213]	ERACI-II	MI at 30 days	450	5.7	0.9	0.012
Zhang et al. (2005)[216]	SoS	Bleeding In-hospital	242	4.0	2.6	0.56
Zhang et al. (2005)[216]	SoS	Repeat PCI in-hospital	242	0	0.9	0.48
Zhang et al. (2005)[216]	SoS	Repeat CABG In-hospital	242	1.6	0.9	1.00
Zhang et al. (2005)[216]	SoS	Cerebrovascular accident in hospital	242	0.8	0	1.00
Rodriguez et al. (2001)[213]	ERACI-II	Stroke at 30 days	450	0.9	0	NS
Morrison et al. (2001)[215]	AWESOME	Stroke at 30 days	454	1	1	Not reported

Long-term outcomes: PCI versus CABG

Refer to Table 5-10 for a summary of long-term outcomes for people randomised to PCI or CABG.

►Freedom from MACCE

After long term follow-up, two RCTs [214] [217] showed that CABG was associated with significantly lower rates of major adverse cardiac events. One cohort study showed significantly lower rates of death/MI/repeat revascularisation [218]. A propensity score matched cohort showed a non–significant difference between the two groups for death/MI/or stroke (HR 1.10 [0.75, 1.62]) [219].

Evidence level 1+ and 2+

►Death

Four RCTs [216] [214,217] [215]and two cohort studies [218,219] showed non–significant difference in death (or survival) between those who received CABG or PCI after long-term follow-up (1 to 5 years).

Level 1+ and 2+

►MI

After long-term follow-up, three RCTs [214] [217] [216] and one cohort study [218] showed a non–significant difference between those randomised to CABG or PCI for MI rates at one to five years.

Level 1+ and 2+

►Angina

Two RCTs showed a non–significant difference between CABG and PCI groups for anginal symptoms at five years [214] [215]

Level 1+

►Bleeding at 1 year

One RCT showed a non–significant difference between CABG and PCI for bleed rates after one year. [216]

Level 1+

►Repeat revascularisation

At long-term follow-up, three RCTs (ARTS [217], SoS [216], and ERACI-II [214]) showed significantly higher rates of repeat revascularisation in the PCI group compared with the CABG group. Similarly, a cohort study [219] showed that target vessel revascularisation at three years was significantly increased in those receiving PCI [HR 4.76 (2.80, 8.11)] compared with those randomised to CABG.

Level 1+ and 2+

Table 5-10. Summary of long-term outcomes: CABG versus PCI revascularisation strategies

Reference	RCT	Outcome	N	CABG (% events)	PCI (% events	P value
Rodriguez et al. (2005)[214]	ERACI-II	Freedom from MACE (death, Q-wave MI, stroke, or repeat revascularisation) – 5 years	450	76.4	65.3	0.019
De Feyter et al. (2002)[217]	ARTS	Freedom from MACCE (death, CVA, nonfatal MI, or repeat revascularisation by PCI or CABG) at 1 year	450	85.3	74.3	0.004
Zhang et al. (2005)[216]	SoS	Death at one year	242	1.6	2.6	0.63
De Feyter et al. (2002)[217]	ARTS	Death at one year	450	2.2	2.7	0.77
Rodriguez et al. (2005)[214]	ERACI-II	Death at five years	450	11.5	7.1	0.182
Morrison et al. (2001)[215]	AWESOME	Survival at five years	454	74	77	p>0.46 (Kaplan Meier curves)
Zhang et al. (2005)[216]	SoS	MI at one year	242	4.0	3.5	1.00
De Feyter et al. (2002)[217]	ARTS	MI at one year	450	5.8	5.8	0.98
Rodriguez et al. (2005)[214]	ERACI-II	Nonfatal MI at five years	450	6.2	2.8	0.128
Zhang et al. 2005)[216]	SoS	Bleeding at one year	242	4.0	2.6	0.56
Rodriguez et al. (2005)[214]	ERACI-II	Freedom from Angina at five years	450	82	86	0.916
Morrison et al. (2001)[215]	AWESOME	Survival free of UA at five years	454	60	55	p > 0.16 (Kaplan Meier curves)
Zhang et al. 2005)[216]	SoS	Repeat revascularisation by PCI at one year	242	4.8	10.3	0.10
De Feyter et al. (2002)[217]	ARTS	Repeat revascularisation by PCI at one year	450	2.7	10.6	0.002
De Feyter et al. (2002)[217]	ARTS	Repeat revascularisation by CABG at one year	450	0.9	6.2	<0.01
Zhang et al. 2005)[216]	SoS	Repeat revascularisation by CABG at one year	242	2.4	5.2	0.32
Zhang et al. 2005)[216]	SoS	Repeat revascularisation (by CABG or PCI) at one year	242	7.1	15.5	<0.001

Rodriguez et al. (2005)[214]	ERACI-II	Repeat revascularisations (either PTCA or CABG) at five years	450	7.2	28.4	0.0002
De Feyter et al. (2002)[217]	ARTS	Repeat revascularisation (by PCI or CABG) at one year	450	3.6	16.8	<0.01
Zhang et al. 2005)[216]	SoS	Adjusted improvement in SAQ at one year	242	35.1	34.1	0.74

5.2.4 HEALTH ECONOMIC METHODOLOGICAL INTRODUCTION

Two relevant cost-effectiveness studies were indentified both based on subgroup analyses of resource use and outcomes collected within RCTs[216,217].

Zhang et al.[216] reported a subgroup analysis of the SOS trial that analysed costs and outcomes for ACS and non-ACS people separately. The study compares within and between the ACS and non-ACS subgroups. Results are presented here for the ACS subgroup. Costs are calculated using UK prices but international resource use is used. The study was judged to be partially applicable (QALYs were not used and there is some uncertainty around the applicability of international resource use to the UK) with potentially serious limitations.

Zhang et al. reported a cost-consequence analysis from a UK NHS perspective based on 1 year effectiveness and resource use data for a subgroup of people with acute coronary syndrome from the SOS trial (n=242). People had multivessel disease eligible for both PCI and CABG. Bare metal stents were used. Patient level resource use collected during the trial was multiplied by unit costs to calculate the average costs per patient (2000 UK costs were used). This included the index hospitalisation costs and one year follow-up costs. Costs and outcomes were presented separately and not aggregated into a cost–effectiveness ratio. Outcomes reported were death, Q-wave MI, bleeding, cerebrovascular accident, repeat revascularisation, health status. No sensitivity analysis was performed.

Interpretation is inhibited as QALYs were not used and there is some uncertainty regarding the applicability of international resource use to the UK setting. The key limitations of the study include the short time horizon (1 year). Additionally, the analysis is based on a single trial that may not reflect the whole body of evidence in this area.

De Feyter et al. [217] reported a subgroup analysis of the ARTS trial that analysed costs and outcomes for stable angina and UA people separately. The country perspective of the economic evaluation is unspecified – costs are reported in US dollars, unit costs are from the Netherlands and the place of resources use collection is not reported. This study is judged to have very serious limitations but was included due to the limited evidence available. The study compares within and between the stable and unstable subgroups. Results are presented here for the unstable subgroup.

De Feyter et al.[217] reported a cost effectiveness analysis from an unspecified healthcare system perspective based on 1 year effectiveness and resource use data for a subgroup of people with UA from the ARTS trial (n=450). People had multivessel disease and were deemed equally treatable with either PCI or CABG. Bare metal stents were used. Patient level resource use collected during the trial was multiplied by unit costs to calculate the average costs per patient

(Netherlands costs were used expressed in 2002[19] US dollars – presented here converted to 2002 UK pounds using 2002 Purchasing Power Parities[138]). This included the initial procedure and hospitalisation, follow-up event diagnostic tests, rehospitalisation and medication. Cost effectiveness was measured in terms of cost per MACCE-free life year gained (MACCE = major adverse cardiac and cerebrovascular events and included death [all causes], cerebrovascular incident [stroke, TIA, reversible ischemic neurological deficits], non-fatal MI [spontaneous and peri-procedural], repeat revascularisation [PCI, CABG]). No sensitivity analysis was performed.

Key limitations of the study include the non-UK perspective, short time horizon (1 year), choice of outcome measure and unclear costing methods. Additionally, the analysis is based on a single trial that may not reflect the whole body of evidence in this area.

5.2.5 HEALTH ECONOMIC EVIDENCE STATEMENTS

Zhang et al.[216] (SoS trial) reported that costs with CABG compared to PCI were significantly higher in the index hospitalisation (£8248 versus £5015), significantly lower post-discharge to one year (£1832 versus £2998) and non–significantly higher overall (£10,080 versus £8014; difference = £2066, CI: -£690, £3487). Various health outcomes were presented disaggregated and were not combined with costs to give a cost–effectiveness ratio – there was significantly more repeat revascularisation with PCI compared to CABG and no significant difference in other outcomes. The key limitation of the study is the 1 year time horizon - if post-discharge costs continue to be lower each year with CABG this could impact conclusions.

De Feyter et al.[217] (ARTS trial) reported that CABG was associated with a cost of £20,701 per MACCE-free life year gained when compared with PCI with bare metal stents (95% CI: £8,403–£76,769). Without the use of QALYs this result is difficult to interpret. Examination of the breakdown of MACCE in the trial shows that the benefit of CABG is largely derived from the lower rates of repeat revascularisation compared with PCI. Costs were higher with CABG compared to PCI during the initial hospitalisation, lower in the follow up period and non–significantly higher overall (difference = £3267, p=NS). A key limitation of the study is the 1 year time horizon – if post-discharge costs continue to be lower each year the difference between CABG and PCI may diminish.

NHS reference costs for CABG and PCI

Due to the lack of relevant cost-effectiveness analyses, UK costs were sought for CABG and PCI to aid discussions regarding cost effectiveness. Below in

[19] The cost year was not stated and is assumed to be the same as the year of publication

Table **5-11** and Table 4-12 are costs extracted from the NHS reference costs [224].

Table 5-11. NHS reference costs

		Elective	Non-elective
EA14Z	Coronary Artery Bypass Graft (First Time)	£7976	£8800
EA15Z	Coronary Artery Bypass Graft (First Time) with Cardiac Catheterisation	£9421	£8617
EA16Z	Coronary Artery Bypass Graft (First Time) with Percutaneous Coronary Intervention, Pacing, EP or RFA +/- Catheterisation	£10,260	£10,456

Table 5-12. NHS reference costs

		Elective	Non-elective
EA31Z	Percutaneous Coronary Intervention (0-2 stents)	£2309	£2585
EA32Z	Percutaneous Coronary Intervention (0-2 stents) and Catheterisation	£2534	£2864
EA33Z	Percutaneous Coronary Intervention 3 with Stents	£3206	£3212
EA34Z	Percutaneous Coronary Intervention 3 with Stents and Catheterisation	£3169	£3759

5.2.6 EVIDENCE SUMMARY

Four randomised trials were identified in which people with UA or NSTEMI were randomised to PCI or CABG: ERACI-II[214], AWESOME[215], SoS[216], and ARTS[216].

- **ERACI-II** randomised 450 people with non-ST elevation acute coronary syndromes, classified by Braunwald's criteria[225].

- At 30 days those people undergoing CABG had significantly higher rates of death, acute MI and the composite endpoint of major adverse cardiac and cerebrovascular events (MACCE) than those in the PCI group. The mortality difference persisted to 33 months of follow-up, but after 30 days the number of additional deaths was the same in both groups. The difference became non–significant at 5 years. The 30 day mortality in the CABG group in this trial was 5.7% (compared to 0.9% in the PCI group), which the GDG felt to be much higher than would be expected in UK practice.
- Those undergoing PCI had a significantly higher rate of further revascularisation procedures at each point of the follow-up period, though most additional revascularisations in the PCI group took place within the first year.

- **AWESOME:** there was no difference in survival between the PCI (77%) and CABG (74%) groups , but significantly more people undergoing PCI required further revascularisation procedures during the 5 year follow-up period than those in the CABG group.
  - There was a high drop out rate by the end of the 5 year follow-up period, but this was comparable between groups.

- A subgroup analysis of the **SoS** trial described events in 242 people with ACS (defined as acute MI or UA) randomised to PCI or CABG. CCS IV angina was diagnosed in 62% of this cohort. There was no information on renal function, or LVEF, although 56% had a previous MI.
  - There was a non–significant difference in any outcome during the index hospitalisation for those randomised to PCI or CABG
  - After 1 year, there was a non–significant difference in death between the two trial arms (1.6% CABG versus 2.6% PCI) and repeat revascularisation was significantly higher in the PCI arm.

- A subgroup analysis of the **ARTS** trial compared PCI with CABG in 450 people with UA.
  - After 1 year, there was non significant difference in death between the two trial arms (2.2% CABG versus 2.7% PCI) and repeat revascularisation was significantly higher in the PCI arm.

The SOS and ARTS subgroup analyses described above also analysed resource use in the trial and estimated costs. They both found that costs in hospital were higher with CABG than PCI but that post-discharge to one-year costs were lower with CABG. The latter is attributable to the reduced rate of repeat revascularisation observed with CABG.

The ARTS study was judged on economic terms to have serious limitations; it was a non-UK perspective, had a short time horizon (1 year), did not estimate QALYs and was unclear in its costing methods. Differences in costs between the two treatment strategies were almost entirely due to the difference in frequency of repeat revascularisation procedures during the

follow-up period. Given that the study preceded the era when drug eluting stents became used (which might be expected to reduce this need for repeat procedures) the study was felt of limited applicability to current practice. The GDG discussed this paper but concluded that it did not allow robust conclusions about cost effectiveness to be drawn. The SoS trial was from a UK perspective with clearer methods but shared the other limitations noted above and so the GDG felt this also did not allow robust conclusions to be drawn.

5.2.7 EVIDENCE TO RECOMMENDATIONS

In its discussions the GDG particularly noted that of the four randomised trials identified:

- All recruited people with multivessel rather than single vessel coronary artery disease
- All excluded people with limited life expectancy due to advanced age or co-morbidity (average age 61-67 yrs across the four trials). Three (ERACI, ARTS, SoS) excluded people who had previously undergone CABG, and only AWESOME recorded including patients with severe left ventricular impairment (LVEF <0.35).
- All will have included troponin positive NSTEMI people but preceded the routine use of this biomarker so it is not possible to subdivide the recruited patient population into UA and NSTEMI
- One trial (AWESOME) had relatively low overall stent usage (55%), much lower than in current practice (used in 94.7% of all PCI procedures in the UK in 2007[178]), and had only 11% usage of GPIIbIIIa inhibitors.
- All preceded the use of drug eluting stents and therefore involved only bare metal stents, which are known to have a higher risk of re-stenosis. Given that the most significant difference between the outcome of people undergoing CABG compared to PCI is the increased requirement for further revascularisation procedures during follow up in the PCI group, this difference may be decreased with increasing use of drug eluting stents (55% of all stents inserted in the UK in 2007)[6].

In addition to the literature above, the GDG also reviewed the results of five cohort studies [218] [219] [220] [221].[222] but felt that few conclusions could be drawn from them because of the degree of selection inherent in their non-randomised nature, often incomplete details and lack of adjustment for confounding factors and other methodological issues. Nevertheless the findings from these registry data were felt compatible with the conclusions the GDG drew from the four randomised studies.

The two revascularisation strategies, CABG and PCI, have been employed in the management of people with UA and NSTEMI for nearly three decades, during which time surgical and PCI procedural techniques have advanced and adjunctive pharmacotherapy has changed. People most suitable for each therapy have been generally agreed (for example, CABG for diffuse triple vessel disease, PCI for single discrete lesions). However, the group of people regarded as potentially equally suitable for both treatment strategies has changed and continues to be the subject of randomised clinical trials, most notable of which recently was SYNTAX. [212] . Thus, any study comparing these two techniques is inevitably based on a subset of all people admitted

with UA/NSTEMI. As outlined above, even allowing for the inevitability of selection. The GDG noted that very few trials have actually specifically addressed people with UA or NSTEMI. Many trials have included these people (33-42% of people with UA/NSTEMI underwent CABG in FRISC II, TACTICS-TIMI 18, and RITA 3) but either not reported their outcome separately or have recruited too few of these people for a meaningful analysis to be undertaken.

Registry data specific to the UA/NSTEMI population has, on the whole, not been particularly useful in drawing conclusions about the applicability of each of these treatment strategies. Also, the definition of outcome events is not always clear between studies; for instance, some trials do not clearly separate those who had myocardial infarcts and those who died, sometimes recording deaths due to an MI simply as a death but not as an MI. The definition of MI is also unclear in some studies. The average age in the randomised trials ranged from 61 to 67 years, thus representing a cohort of people younger than many seen in current practice.

Trials comparing the use of CABG and PCI have generally required equivalent revascularisation; in other words, the cardiologist and cardiac surgeon have to agree that each coronary lesion can be equivalently revascularised by both techniques before randomisation can occur. More recently the potential use of PCI initially just for the perceived 'culprit lesion' (with the potential for subsequent further PCI – 'staged procedures') has been compared to initial complete PCI revascularisation[226]. Safety end points did not differ between groups. This practice may be appropriate when the risk of staged procedures is considered to be lower than one procedure at which full revascularisation is attempted (as might occur in people with renal impairment in whom a reduced single contrast load may be beneficial). Such practice introduces yet another potential variable when clinicians are considering the choice of most appropriate therapy.

The GDG concluded that the evidence supported the use of both revascularisation strategies, with their selection for individual people harmonizing with criteria already recommended in international guidelines, such as the extent and severity of their coronary disease, left ventricular function, the presence of co-morbidity, the estimated risk of each procedure, and patients' informed choice. There may be an early (<30 days) increase in MACCE for people undergoing CABG, as suggested in ERACI-II *(not seen in AWESOME)* but because of the later increased need for further revascularisations in the PCI group this difference became reversed after five years of follow-up. This is in keeping with the outcome of comparative trials in people with stable angina, where the difference between these two revascularisation techniques is mainly the higher need for repeat procedures in those initially undergoing PCI.

In many people clinical suitability dictates whether PCI or CABG should be undertaken but in a subgroup of people PCI or CABG are equally feasible and appropriate approaches and a relevant concern is which is cost–effective. PCI is a much less expensive procedure than CABG; however the group considered that longer term costs following CABG are likely to be lower than following PCI in particular due to the lower rates of repeat revascularisation as seen in the trials identified, but also potentially due to the greater pharmacological interventions associated with PCI to prevent restenosis. It was noted that a cost–effectiveness analysis in a broader PCI populations (that is, including stable people) has hinged upon whether in the long term a survival advantage accrues with CABG, with results favouring CABG if it does and PCI if it does not [227]. The GDG concluded that there was a lack of evidence regarding long term outcomes and as such great uncertainty as to which was most cost–effective. The group therefore agreed that a

research recommendation that addresses both the clinical and cost effectiveness of PCI versus CABG specifically in people with NSTEMI/UA would be useful to help inform the evidence base.

Patient representatives on the GDG stressed the importance of individuals being fully informed of the relative risks, benefits and differences between the two procedures so that they could make informed choice. Clinicians on the group agreed this was of fundamental importance and highlighted the need for appropriate consent processes[228,229], and the value of multi-disciplinary team (MDT) meetings in determining the most appropriate treatment strategy to recommend to people when both seem clinically appropriate[230].

5.2.8 RECOMMENDATIONS

R28 When advising patients about the choice of revascularisation strategy (PCI or CABG), take account of coronary angiographic findings, comorbidities, and the benefits and risks of each intervention.

R29 When the role of revascularisation or the revascularisation strategy is unclear, resolve this by discussion involving an interventional cardiologist, cardiac surgeon and other healthcare professionals relevant to the needs of the patient. Discuss the choice of revascularisation strategy with the patient.

5.2.9 RESEARCH RECOMMENDATION

What is the efficacy and cost effectiveness of CABG versus PCI in the management of patients with NSTEACS?

5.3 INTRA-AORTIC BALLOON COUNTERPULSATION

5.3.1 CLINICAL INTRODUCTION

Intra-aortic balloon counterpulsation (IABP) was first described in 1962[231] and was estimated in 1990 to have been used in over 70,000 cases annually in the USA[232]. It has been used as a means of supporting the circulation predominantly in those with failing left ventricles (particularly in cardiogenic shock), or as an adjunct to treatment by cardiac surgery or high risk coronary angioplasty[233].

The technique involves the insertion of a balloon catheter device, usually via a femoral artery, into the descending thoracic aorta, with the proximal end of the catheter attached to an external pumping device which inflates the intra-aortic balloon during diastole and deflates it just prior to the onset of systole. A full description of the haemodynamic effects of balloon pumping (more precisely termed intra-aortic balloon counterpulsation) is beyond the scope of this guideline, but its haemodynamic benefit arises from its potential to increase diastolic blood pressure (thereby improving coronary blood flow[234] , and reduce left ventricular afterload (increasing cardiac output, the amount of blood ejected by the heart). More recently, other percutaneously implanted, circulatory support devices have also been developed and show promise[235].

The technique require invasive intervention, the availability of sophisticated equipment, and staff who are familiar with its implementation and subsequent monitoring, and vascular complications can occur[236]. Also, patients with significant peripheral vascular disease may either be unsuitable for insertion of the counterpulsation balloon catheter, or may have ischaemic lower limb complications as a consequence of its insertion. Its use outside cardiac surgical centres has been limited in the past, although the British Cardiovascular Intervention Society reported 983 cases of IABP being used in the UK as an adjunct to coronary angioplasty (PCI) in 2007 (1.7% of all PCI cases), many of which were performed in non-cardiac surgical centres[177], and some of which will have been in patients with UA or NSTEMI.

The GDG therefore wished to review the evidence for its use in patients with UA or NSTEMI to determine whether there was evidence of improved patient outcome. The clinical question asked, and upon which the literature was searched was

> *'Does the use of Intra-Aortic Balloon Pump Counterpulsation affect the outcome of patients with non-ST elevation myocardial infarction or unstable angina?'*

5.3.2 CLINICAL METHODOLOGICAL INTRODUCTION

The literature was searched from 1995 to 2009 for systematic reviews, RCTs, comparative studies, and observational studies. There were no relevant studies identified specifically in people with UA or NSTEMI where IABP was used as a form of treatment in its own right to stabilise patients. Studies were excluded if IABP was electively used in stable cases to reduce procedural risk (during PCI or CABG). Studies were excluded if the population comprised mostly STEMI patients or if the population was unclear.

5.3.3 *HEALTH ECONOMIC METHODOLOGICAL INTRODUCTION*

No relevant economic studies were identified examining IABP in the population described above.

5.3.4 *GDG DEBATE*

Whilst IABP has a long track record as a therapeutic intervention in patients with ACS, (including UA and NSTEMI as well as ST elevation MI), its use has been reserved for those who are more severely ill and unstable. Examples of such patients would be those who have severe left ventricular failure, cardiogenic shock or who are haemodynamically unstable. Such patients will often be acutely unwell because of the severity of their myocardial ischaemia, and when unresponsive to medical therapy alone will be considered for IABP. Whilst such clinical scenarios are well described they occur in only a small minority of patients admitted with ACS and therefore a multi-centre study it be reasonable way forward. However there may be ethical issues given the severity of their condition and the relative failure of medical therapy, it may be inappropriate to withhold its use in the control group in those patients who deteriorate haemodynamically and hence equipoise would be difficult.

The GDG were therefore not surprised at the lack of data sufficient to allow a firm recommendation for the use of IABP to be made. However, they were persuaded of the potential for IABP to be beneficial for those patients with severe or recurrent ischaemia whose ischaemia cannot be managed adequately by medical therapy and/or coronary revascularisation alone. It is difficult to assess the size of the population of patients with UA or NSTEMI who may potentially be stabilised by, and may benefit from, the use of IABP but the GDG agreed that it was small (<5%). All cardiac centres undertaking coronary angioplasty (n=98 in 2007) are required, as part of best practice, to be capable of initiating IABP in their catheter laboratories[230]. These centres will already have the facility to undertake IABP if believed to be clinically appropriate, and therefore the GDG agreed that even if its use were to increase, the economic impact would be minimal.

Because of the infrequency with which IABP is used, particularly outside surgical or interventional centres, the GDG felt that clinicians should be encouraged to consider the option of IABP for those patients who remain clinically unstable due to recurrent myocardial ischaemia despite medical therapy or early revascularisation, and for those who are haemodynamically unstable prior to undergoing surgical or percutaneous revascularisation. Where IABP is unavailable in their own institution clinicians managing such 'refractory' patients should consider discussing the potential for its use in individual cases with a centre able to offer such intervention. The GDG could not, however, make a clear recommendation for its specific use due to a lack of robust evidence.

5.3.5 *RESEARCH RECOMMENDATION*

What is the efficacy and cost effectiveness of intra-aortic balloon counterpulsation (IABP) in the management of patients with non ST-segment elevation ACS?

5.4 TESTING FOR ISCHAEMIA

5.4.1 CLINICAL INTRODUCTION

In people with chronic stable coronary disease there is a strong association between the presence and severity of myocardial ischaemia and an adverse outcome. The ability to perform an exercise test and the exercise time are also predictive[237,238]. This adverse outcome can be improved by appropriate treatment whether, medical or revascularisation[239] and revascularisation provides better outcomes when inducible ischaemia involves more than 10% of the myocardium.

In people with unstable and acute coronary syndromes, once the initial unstable episode has stabilised, further spontaneous ischaemia is more frequent in people with NSTEMI than with STEMI and, if present, it increases subsequent mortality. People with NSTEMI also have higher reinfarction rates and mortality at one year than those with UA[240]. The INSPIRE trial showed that early ischaemia testing after myocardial infarction can identify a low risk group of people who may benefit from early discharge although approximately half of the study group had STEMI and so reliable conclusions could not be drawn about people with NSTEMI alone[20].

The majority of people with UA or NSTEMI will undergo angiography during their acute admission. The extent and severity of their coronary disease is thereby documented and, where appropriate, PCI or CABG can be offered to reduce future risk[241]. Later after hospital discharge when the acute episode has stabilised ischaemia testing can be helpful. The question therefore arises whether ischaemia testing may also be helpful before discharge in people where the coronary anatomy has not already been established by angiography.

The available provocative tests for ischaemia include stress electrocardiography (sECG), myocardial perfusion imaging by scintigraphy (MPS), magnetic resonance imaging (perfusion, viability and stress) and stress echocardiography (sEcho). Each of these has its strengths and weaknesses. MPS has been appraised by NICE and found to be clinically and cost effective for the diagnosis and management of people with angina and MI[242].

The clinical question posed was:

In patients with UA/NSTEMI who do not undergo angiography, does investigation prior to hospital discharge for myocardial ischaemia affect outcome?

5.4.2 METHODOLOGICAL INTRODUCTION

The literature was searched from 1995 to 2009 for systematic reviews, RCTs, comparative studies, and observational studies. There were no RCTs comparing ischaemia testing with no such testing before discharge, but two observational cohort studies were identified [243,244].

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[20] Mahmahrian JJ, Shaw LJ, Fillipchuk NG, et al. A multinational study to establish the value of early adenosine technetium-99m sestamibi myocardial perfusion imaging in identifying a low-risk group for early hospital discharge after acute myocardial infarction. J Am Coll Cardiol 2006; 48: 2448-57.

GUSTO IIb [243] (8011 people with non ST-segment elevation ACS) compared sECG against no sECG and reported death or non-fatal MI at 30 days, death at 30 days and one year, and MI at 30 days. There was no formal comparison between the relevant subgroups (sECG but no angiography, n=1061, and neither sECG nor angiography, n=2402). The NCC-CC therefore conducted a simple statistical analysis but we could not adjust for confounding variables.

The ACOS registry [244] included 5281 people with NSTEMI and compared sECG with no sECG before discharge and reported all cause mortality and revascularisation rates at one year. sECG was also compared with no sECG in 2872 people who did not undergo PCI in hospital.

The applicability of these studies was limited because a high proportion of people also received invasive procedures in both arms (44% angiography [243] or 77% angiography or PCI in the sECG cohorts [244], and 61% angiography [243] or 72% angiography or PCI [244] in the no sECG cohort).

5.4.3 CLINICAL EVIDENCE STATEMENTS

►Death at one year

Both studies showed a higher mortality in the no test groups than in the test groups (13.6% vs. 5.1% p<0.01 [244] and 11% versus 3.2% p<0.001 [243]). Undergoing sECG was associated independently with a lower mortality (adjusted HR 0.58, 95% CI 0.42 to 0.8) [243]. After exclusion of people with coronary angiography, MI, spontaneous ischaemia, congestive heart failure or death in the first 48 hours, one year mortality was significantly lower in those who had sECG (adjusted HR 0.61, 95% CI 0.43 – 0.87) [243].

Level 2+

Subgroup analysis

In people who did not undergo PCI in hospital, one year mortality was lower in the group with sECG than in those without sECG (6.9% vs. 18% p<0.01). [244]. Similarly, one year mortality (unadjusted OR 0.19 [95% CI 0.13 to 0.27]) was lower in people with sECG and no angiography than in those with neither sECG nor angiography [243].

Level 2+

►Death or MI

sECG was associated independently with a lower risk of 30 day death or MI (adjusted HR 0.56, 95% CI 0.38 to 0.83). Following exclusion of people with angiography, MI, recurrent spontaneous ischaemia, congestive heart failure or death in the first 48 hours, sECG was associated with a lower risk of death or MI at 30 days (adjusted HR 0.61, 95% CI 0.41to 0.90)[243].

Subgroup analysis

Six month death or MI (unadjusted OR 0.20, 95% CI 0.14 to 0.27) was lower in people with sECG but no angiography compared with those without either [243].

Level 2+

►Death / MI / Revascularization at six months

The composite end point of death, MI or revascularization at 6 months was not significantly different between both groups (adjusted HR 0.99, 95% CI 0.86 to 1.14).

Subgroup analysis

Six month death, MI, or revascularisation (unadjusted OR 0.50, 95% CI 0.41 to 0.60) was significantly lower in people with sECG but no angiography than in those without either [243].

Level 2+

►PCI at 1 year

There was no difference in PCI rate at one year for people with or without sECG (9.4% versus 9.1% p=0.75) [244]

Level 2+

►Coronary artery bypass surgery at 1 year

People with sECG had a lower rate of CABG at 1 year than those without sECG (7.3% versus 11%, p<0.01)[244]

Level 2+

5.4.4 HEALTH ECONOMIC METHODOLOGICAL INTRODUCTION

No economic analyses were identified that compared ischaemia testing and no such testing before discharge in UA/NSTEMI people who did not undergo angiography.

5.4.5 EVIDENCE SUMMARY

- Both cohort studies showed higher one year mortality in those who did not undergo ischaemia testing.

- In the GUSTO-IIb cohort[243] after exclusion of people who had MI, recurrent ischaemia, congestive heart failure, death or angiography within 48 hours of admission (those at highest risk), outcomes (30 day and one year mortality or MI) were significantly worse in people who had not undergone ischaemia testing.

- In the German Acute Coronary Syndrome Registry (ACOS)[244] when people who had undergone prior PCI were excluded, those without ischaemia testing had higher one year mortality.

A sub-group of the GUSTO-IIb people[243] did not undergo angiography during index hospital admission and this is the group most relevant to our question. In this subgroup those who had undergone ischaemia testing (n=1061) had a better outcome (mortality at six-months and one-year, or death/MI/revascularisation at six months) unadjusted for risk than those who had not (n=2404). However, the potential for confounding factors was considerable. People who did not undergo ischaemia testing were more likely to be older, female, have hypertension, diabetes or renal impairment, have previously identified coronary artery disease, and were less likely to be treated with aggressive secondary prevention measures. They were therefore at higher risk than those who underwent ischaemia testing and this may have led to their worse outcome.

5.4.6 EVIDENCE TO RECOMMENDATIONS

The lack of prospective randomisation and the high rate of angiography make these studies only partly relevant to the clinical question asked and therefore the GDG concluded that there was no data upon which they could recommend a routine policy of testing for myocardial ischaemia before hospital discharge in all people who do not undergo angiography during their index admission. Decisions on investigation must take account of individual circumstances and there will be people for whom ischaemia testing may or may not be clinically appropriate. Given this caveat the GDG noted:

- People with UA or NSTEMI with subsequent spontaneous or provocable ischaemia have worse outcomes.

- Myocardial revascularisation can improve outcome (see section 5.2), particularly in those at higher risk of a further ischaemic event.

- Those at higher risk can be identified by using risk scores (see section 0) and also by determining the extent and severity of coronary disease (see section 5.1) and/or the extent and severity of inducible myocardial ischaemia.

5.4.7 RECOMMENDATIONS

R30 To detect and quantify inducible ischaemia, consider ischaemia testing before discharge for patients whose condition has been managed conservatively and who have not had coronary angiography.

5.4.8 RESEARCH RECOMMENDATION

What is the role of ischaemia testing in people after an acute coronary syndrome and what is the comparative efficacy and cost effectiveness of the different non-invasive tests (for example, stress ECG, echocardiography, radionuclide scanning and magnetic resonance imaging)?

5.5 TESTING FOR LV FUNCTION

5.5.1 INTRODUCTION

Heart failure is a syndrome that develops when cardiac output is insufficient to meet the needs of the body. Impairment of left ventricular function secondary to ischaemic myocardial damage is its commonest cause and it is an important determinant of longer term outcome after an acute coronary syndrome[245]. NICE and others have published guidance on the detection and management of heart failure[246-248]. Medical therapy, myocardial revascularisation and devices such as implantable defibrillators and resynchronisation pacemakers can improve symptoms and outcome[249-251]. There is extensive literature on the association between the degree of left ventricular impairment and its effects on clinical outcome. However, much of this is in the setting of stable coronary disease and the findings may be less applicable early after ACS when the myocardium may be temporarily stunned, or before the onset of left ventricular remodelling or the effects of chronic medication. A further relevant question after ACS is the extent and transmurality of infarction, since the association between ST elevation during infarction and the amount of viable myocardium remaining in the infarct territory is poor. All of the commonly available imaging techniques are able to assess the extent and transmurality of infarction and the information is relevant in deciding whether revascularization of the infarct territory is important[252,253]. This aspect of investigation after ACS is not covered by this guideline.

The clinical questions asked, and upon which literature searching was undertaken, was:

> *"In people admitted with UA or NSTEMI, does unselected assessment of left ventricular function before discharge improve clinical outcome?"*

5.5.2 CLINICAL METHODOLOGICAL INTRODUCTION

The literature was searched from 1995 to 2009 for systematic reviews, RCTs, comparative studies, or observational studies. Studies were included if they reported outcomes after 30 days such as death, MI, stroke, bleeding, re-revascularisation and quality of life. Studies that assessed the predictive power of left ventricular function for future events, as opposed to the ability to affect outcome, were excluded.

5.5.3 CLINICAL EVIDENCE STATEMENT

No RCTs were found that assessed the effect of measuring left ventricular ejection function (LVEF) compared with not measuring (or delayed measuring) LVEF on outcomes in people with non ST-segment elevation ACS. Most studies were excluded because the populations comprised less than 60% UA or NSTEMI. Most studies were conducted in a more general acute infarction population with a high proportion of STEMI. Therefore, there was no evidence identified as being relevant to the question.

5.5.4 HEALTH ECONOMIC METHODOLOGICAL INTRODUCTION

No economic analyses were identified that compared measuring LVEF compared with not measuring (or delayed measuring) in people with UA/NSTEMI.

5.5.5 GDG DEBATE

UA, NSTEMI and STEMI are part of a continuous spectrum of pathology and people can move from one state to another. The influence of left ventricular dysfunction on outcome is likely to be independent of clinical presentation and whether the dysfunction arises from the index event or from previous events that may not have been clinically apparent.

During admission with an acute coronary syndrome, some people have echocardiography as part of their assessment, some have left ventriculography at the time of coronary angiography and some have radionuclide imaging for the assessment of myocardial ischaemia. All of these tests provide an assessment of left ventricular function and it is likely that only a minority of people with UA or NSTEMI do not have an opportunity for their left ventricular function to be recorded during their hospital admission or shortly thereafter.

In a previous clinical guideline on secondary prevention after MI (NSTEMI and STEMI) [4], it was recommended the assessment of left ventricular function in all people after MI. It would therefore be logical to assess left ventricular function in all people with UA and NSTEMI so that specific treatment for left ventricular dysfunction can be offered to improve symptoms and outcome. There is no evidence that assessment of left ventricular function in the subset of people with UA who have stabilised and who have not already had it assessed in the course of other investigations might improve outcome. It was felt that as this would be a very small number of people, a recommendation was justifiable in the interests of uniformity and simplicity.

Left ventricular function may improve after an acute ischaemic event with the resolution of myocardial stunning and the onset of healing. It may also deteriorate because of myocardial remodelling or progression of coronary disease[254]. It may therefore also be important to monitor left ventricular function during follow-up, because of this potential for change with time. The frequency of these assessments and the relative merits of the different techniques for assessing function are outside the scope of this guideline.

5.5.6 RECOMMENDATIONS

R31 Assessment of left ventricular function is recommended in all patients who have had an MI. (This recommendation is from 'MI: secondary prevention', NICE clinical guideline 48.)

R32 Consider assessing left ventricular function in all patients with unstable angina.

R33 Record measures of left ventricular function in the patient's care record and in correspondence with the primary healthcare team and the patient.

5.6 SPECIALIST CARE

5.6.1 CLINICAL INTRODUCTION

The management of ACS has become more complex with increased diagnostic and therapeutic options available to the clinician. Many of these options, for example continuous rhythm monitoring and the administration of specialist drugs, require staff with specialist knowledge and skills, and certain interventions now considered standard practice, such as coronary angiography, can only be delivered in specialist environments by specialist teams. However, many people, including the elderly, are admitted to general wards and managed by general medical or elderly care teams, with referrals to specialist care being dependent on local custom and practice. Specialist care impacts upon the accurate and timely assessment of risk including 12 lead ECG monitoring and early angiography, and interventions such as the use of certain drugs and resuscitation procedures which may be performed by staff with specialist training.

The clinical questions asked, and upon which literature searching was undertaken, was:

> *"Is there evidence that specialist cardiology care is more clinically and cost–effective than non-specialist care in an UA or NSTEMI population?"*

5.6.2 CLINICAL METHODOLOGICAL INTRODUCTION

The clinical question compared the care provided by specialist and non-specialist teams and not simply the involvement of one particular team member (such as a cardiologist) because the overall care of people requires a collaborative approach. The literature was searched from 1999 to 2009 for systematic reviews, RCTs, comparative studies, and observational studies comparing care of people with NSTE ACS by specialist cardiology teams versus non-specialist teams. The rationale for searching from January 1999 onwards was to reflect current practice, particularly the use of stents for revascularisation.

There were no RCTs that compared the care of people with UA/NSTEMI by specialist cardiology teams versus non-specialist teams. Observational studies were included if they reported outcomes including death, MI, bleeding, stroke, revascularisation, use of appropriate medication, uptake of angiography, uptake of cardiac rehabilitation, uptake of evidence-based practice. Studies were excluded if the NSTEMI/UA population comprised < 60% of the participants. Studies were excluded if the populations had undifferentiated chest pain, or if the population was unclear (such as 'acute MI' with no further detail on the proportion of the NSTEMI/UA population). Studies were excluded if the comparison was tertiary care hospitals versus community hospitals, or interventional centres (angiography) versus non-interventional centres because they did not address the specific question being asked, and because of the potentially different, non-randomised, populations.

The studies included focused on specialist care provided by a cardiologist.

A UK observational study (N total =83,599; N NSTEMI = 50,436; MINAP database) compared mortality, prescription of secondary prevention drugs, and angiography in people with acute MI who had received their initial care from a cardiologist or a non-cardiologist. Compared with people who were treated by non-cardiologists, people treated by cardiologists were younger,

more likely to be male, smoke, have ST elevation, and have lower co-morbidity. Effect sizes were adjusted for patient characteristics/history, and hospital cluster [255].

A US observational study (N non ST-segment elevation ACS= 55,994; CRUSADE database) compared mortality, re-infarction, prescription of secondary prevention drugs, and angiography in people admitted to tertiary hospitals with revascularisation capabilities who had received their initial care from a cardiologist or a non-cardiologist (defined as family practice/internal medicine/other). Compared with people who were treated by non-cardiologists, people treated by cardiologists were significantly younger, more likely to be male and had significantly lower co-morbidity. People cared for by cardiologists were significantly more likely to smoke, and had higher prevalence of a family history of CAD, hyperlipidaemia, prior MI, prior CHF, prior PCI, prior CABG, and significantly more likely to have ST depression. Effect sizes were adjusted for patient characteristics/history, and hospital, and geographic location [256].

5.6.3 CLINICAL EVIDENCE STATEMENTS

One observational study showed that factors most strongly associated with care by cardiologists were lower presenting heart rate, younger age, male sex, prior PCI, transient ST elevation, lack of renal insufficiency, lack of prior stroke, lack of diabetes, lack of CHF [256].

Refer to Table 1-1 for a summary of outcomes in observational studies comparing care by cardiology versus non cardiology teams.

►Prescription of appropriate drugs at hospital discharge

One UK observational study showed a non–significant difference in the use of aspirin or ACE inhibitors for cardiology vs non-cardiology care [255].

By contrast a US observational study showed significantly higher odds of prescribing aspirin or ACE inhibitors when people received cardiology care compared with non-cardiology care [256].

Both studies showed significantly higher odds of prescribing beta blockers and statins (or other lipid lowering agents) when people received cardiology care compared with non-cardiology care [255] [256]

Level 3

►Death (in-hospital)

One study showed that cardiology care significantly decreased the risk of in-hospital death. However after further adjustment for differences in acute (<24 hour) medications, individual patient contraindications to acute medications, and the use of cardiac catheterisation within 48hours, this became non–significant [256].

Level 3

►Death at 90 days

One study suggested that treatment under a cardiologist was associated with a significant decrease in the risk of death at 90 days compared with a non-cardiologist [255].

Level 3

►Re-infarction (in-hospital)

One study suggested that people who received cardiology care were significantly less likely to have a re-infarction than those who received non-cardiology care [256].

Level 3

►Angiography

In non-interventional hospitals, people treated by a cardiologist were significantly more likely to undergo angiography than those treated by a non-cardiologist. In interventional hospitals, there was a non–significant difference in angiography for people treated by cardiologists versus non cardiologists [255].

People treated by cardiologists were significantly more likely to undergo catheterisation and early catheterisation (within 48hours) than those treated by non-cardiologists. [256].

Level 3

►Revascularisation

People treated by cardiologists were significantly more likely to undergo PCI and early PCI (within 48hours) than those treated by non-cardiologists. There was a non–significant differences between cardiology versus non-cardiology care for CABG procedures [256].

Level 3

There were no suitable studies evaluating the longer term outcomes of these people. Whether the early hazard related to early revascularisation was more than outweighed by longer-term benefits for this patient cohort could not be determined.

Table 4-1. Summary of outcomes for cardiology versus non-cardiology care.

Observational study	Outcome	N	Cardiology care (% events)	Non-cardiology care (% events)	Adjusted Effect size (95% CI)
CRUSADE[256]	ASA prescribed at hospital discharge	55994	92.5	87.5	OR 1.37 (1.27 to 1.48)
MINAP[255]	Non-prescription of ASA at hospital discharge	57508	5.5	7.6	RR 1.00 (0.86, 1.15)
CRUSADE[256]	Beta blocker prescribed at hospital discharge	55994	84.5	82.8	OR 1.13 (1.06 to 1.21)
MINAP[255]	Non-prescription of beta-blocker at hospital discharge	57508	21.4	28.6	RR 0.92 (0.87 to 0.97)
CRUSADE[256]	ACE inhibitor prescribed at hospital discharge	55994	61.0	60.0	OR 1.06 (1.01 to 1.12)
MINAP[255]	Non-prescription of ACE inhibitor at hospital discharge	57508	16.7	21.1	RR 0.98 (0.91 to 1.06)
CRUSADE[256]	Lipid lowering agents prescribed at hospital discharge	55994	82.1	77.9	OR 1.12 (1.03 to 1.22)
MINAP[255]	Non-prescription of statins at hospital discharge	57508	5.9	10.4	RR 0.83 (0.71 to 0.97)
CRUSADE[256]	Clopidogrel prescribed at hospital discharge	55994	61.3	47.2	OR 1.49 (1.40 to 1.59)
CRUSADE[256]	In-hospital death	55994	3.2	5.7	OR 0.80 (0.73 to 0.88)
MINAP[255]	Death (at 90 days)	76376	10.5	15.9	RR 0.86 (0.81 to 0.91)
CRUSADE[256]	Re-infarction (in-hospital)	55994	2.8	3.4	OR 0.74 (0.65to 0.84)
MINAP[255]	Angiography (non-interventional hospitals)	79374	36.9	26.5	RR 1.20 (1.07to 1.38)

MINAP[255]	Angiography (interventional hospitals)	79374	62.5	46.3	RR 1.10 (0.97 to 1.25)
CRUSADE[256]	Catheterisation	55994	81.4	57.8	OR 2.55 (2.32 to 2.80)
CRUSADE[256]	Catheterisation < 48 hours	55994	61.2	34.9	OR 2.25 (2.08 to 2.43)
CRUSADE[256]	PCI	55994	49.2	28.9	OR 1.86 (1.73 to 2.00)
CRUSADE[256]	PCI < 48 hours	55994	37.1	17.8	OR 2.06 (1.91 to 2.23)
CRUSADE[256]	CABG	55994	14.0	12.1	OR 1.13 (1.00 to 1.27)

5.6.4 HEALTH ECONOMIC METHODOLOGICAL INTRODUCTION

No economic analyses were identified that compared specialist cardiology care and non-specialist care in an UA or NSTEMI population.

5.6.5 EVIDENCE SUMMARY

Those initially seen by cardiologists in the **first registry (Myocardial Ischaemia National Audit Project; MINAP)** study were:

- *More likely to be younger, and less likely to have significant co-morbidity*.
    - This may be because more elderly people (who are those most likely to have co-morbidity) are admitted to hospital and managed by elderly care physicians, and perhaps because of the perception that those who are younger with acute coronary syndromes are somehow more appropriately managed by cardiologists. Given that the elderly are often those at highest risk of an adverse outcome this practice would be counter intuitive, assuming, of course, that specialist care may result in better patient outcome. If this were to be the case one might expect a higher proportion of elderly people being managed by cardiologists than that reported.
- *More likely to be male, and more likely to smoke*
    - One explanation for the apparent gender bias may be because female life expectancy is longer than for males and therefore a higher proportion of the elderly population will be female than in the younger cohort. Given that the

elderly are less likely to be managed by a cardiologist this may explain, at least in part, why they manage fewer women than non-cardiologists.

- It has been noted before that, contrary to expectation, current smokers may have better early outcomes following ST elevation MI than non-smokers, the so called 'smokers paradox'. One proposed explanation for this is that smokers present at an earlier age than non-smokers and that the benefit of relative youth counteracts the worsening prognosis associated with increasing age[257]. Therefore, it may be that the reason why more smokers are seen initially by cardiologists is a reflection of their younger age.

- *More likely to have ST elevation (STEMI) than non-ST elevation (NSTEMI) MI*
  - This may be due to a perception that NSTEMI is a more benign condition than STEMI and that therefore the threshold for referral for specialist cardiological care is higher. This is an erroneous perception because in modern day practice their outcomes are very similar[258].

- *More likely to be alive at 90 days*
  - Given that people initially seen by cardiologists were younger and had less co-morbidity, both major determinants of outcome, it is impossible to draw any conclusion regarding the effect of specialist care on 90-day outcome. Also, it is important to note that people who died during their hospital admission were excluded from analysis and so the 90-day mortality data relates only to those surviving to hospital discharge. A randomised trial is needed if this question concerning outcome, as it relates to system of care, is to be answered.

- *More likely to receive secondary prevention medication*
  - The uptake of aspirin and ACE inhibitors were not significantly different, but initial care under a cardiologist was associated with a higher prescription rate for statins and beta blockers. It is more difficult to explain this difference on reasons of age, gender, or co-morbidity, particularly with regards the statins (age and co-morbidity might influence beta blocker usage) and it may be that this reflects a true difference in adherence to best practice guidelines.

- *More likely to undergo coronary angiography*
  - This was reported for people admitted to hospitals without coronary intervention facilities on site, but there was no difference for people admitted to an interventional centre. There are a number of possible explanations for this, including heightened awareness of, and willingness to refer for, angiography amongst those non-cardiologists when services are on site and an appreciation of their use more directly experienced by the referring physician. Little can be concluded from this observation alone.

The second registry (CRUSADE database) reported on nearly 56,000 people from a US population and was different from the MINAP study because it involved only people admitted to hospitals where coronary revascularisation procedures (PCI and CABG) were available on-site (in UK terms a 'tertiary centre') whereas MINAP included people admitted to hospitals without revascularisation services. They compared people managed by cardiologists and non-cardiologists and made similar observations to MINAP; people under cardiologists were younger, had less co-morbidity and were more likely to be male, and to smoke. They were more likely to be prescribed secondary prevention medication, which in this study included being more likely to be prescribed aspirin. After various adjustments there was no difference in hospital mortality, but people under cardiological care had less in-hospital reinfarction, and were more likely to undergo coronary angiography, and PCI (but not CABG) than those under non-cardiologists.

5.6.6 EVIDENCE TO RECOMMENDATIONS

Only observational data is available and conclusions drawn from these must be made with caution because there is a potential for selection bias, and confounding factors, to influence observations. It is unclear if benefits gained reflect the overall care of people within a specialist cardiology service or are attributable to the cardiologist in isolation. The two registries (MINAP, CRUSADE) suggest that differences in practice may exist, particularly with respect to the uptake of secondary prevention therapies, and the use of angiography, and that there may be gender and age-related bias. These observations have also been reported elsewhere[259-262].

There is good evidence, reviewed elsewhere in this guideline, to support the use of various pharmacological agents, revascularisation procedures and cardiac rehabilitation, in the management of people with UA and NSTEMI. Adherence to best practice guidelines is known to vary between institutions[263], and types of healthcare services[264] , and have shown that better adherence can improve patient outcome[3-6]. Evidence also exists for the benefit of systematic implementation of quality assurance processes that encourage guideline implementation[265], and recent recommendations by the American College of Cardiology (ACC) and American Heart Association (AHA) have been made concerning the use of performance indicators which can be used to determine adherence to best practice guidelines[266].

The GDG concluded that while there was insufficient evidence to make any specific recommendations regarding the systems of multidisciplinary/specialist care in which people with UA or non ST-segment elevation ACS are managed, it felt that the assessment and management of such people by skilled staff in properly equipped settings is the preferred pathway of care. This was supported strongly by the patient representatives on the group.

In summary, the GDG concluded that:

- Adherence to best practice guidelines should be universally applied.
- Adherence to NICE guidelines and mortality should be the subject of regular internal and external process and metric audit.

- Audit results should be scrutinised at hospital and network/strategic health authority level to ensure equity of access and quality of care.

- Where a person's care involves more than one institution the whole of the person's in-patient pathway should be considered. Institutions should work together to ensure high performance. This should include the sharing of data and seamless clinical protocols.

5.6.7 RESEARCH RECOMMENDATION

What is the comparative efficacy and cost effectiveness of systems involving specialised care compared to non-specialised care?

5.7 REHABILITATION AND DISCHARGE PLANNING

5.7.1 CLINICAL INTRODUCTION

The World Health Organization has defined cardiac rehabilitation as 'the sum of activity and interventions required to ensure the best physical, mental, and social conditions so that people with chronic or post-acute cardiovascular disease may, by their own efforts, preserve or resume their proper place in society and lead an active life' (http://www.who.int/en/).

The National Service Framework for Coronary Heart Disease[267] identifies four phases of cardiac rehabilitation: phase 1 (before discharge from hospital); phase 2 and 3 (early post discharge phase); phase 4 (long term maintenance of changed behaviour). Please see Appendix D for further details regarding what comprises the four phases of rehabilitation.

Similarly, The British Association for Cardiac Rehabilitation (BACR) (2007) [268] identify standards and core components for the delivery of cardiac rehabilitation. The core components they identify are (1) lifestyle (physical activity and exercise, diet and weight management, smoking cessation), (2) education, (3) risk factor management, (4) psychosocial support, (5) cardioprotective drug therapy and implantable devices and (6) long-term management strategy. They recommend the core components should be based on a comprehensive assessment, appropriate referral and collaboration with the individual patient, family and carers.

The standard NHS contract for acute hospital services identifies healthcare obligations in relation to discharge communication. Information about this can be found at http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_081100?IdcService=GET_FILE&dID=158542&Rendition=Web

In addition, The Royal College of Physicians' Health Informatics Unity (HIU) has developed standards for record keeping. These can be accessed at: http://www.rcplondon.ac.uk/pubs/brochure.aspx?e=225.

Patient participation in cardiac rehabilitation following MI (whether an exercise-only programme[269], or a more comprehensive approach[270]) has been shown to reduce all-cause and cardiac mortality when compared to usual care. In 2000 the National Service Framework for Coronary Heart Disease[2] recommended that more than 85% of people discharged from hospital with a primary diagnosis of acute MI, or after coronary revascularisation, should be offered cardiac rehabilitation. However, less than a third of all people with a prior MI, or who have undergone coronary revascularisation, attend comprehensive cardiac rehabilitation. Uptake is particularly poor among certain groups including ethnic minorities, women, the elderly and those on low incomes or with physical or mental comorbidities[4].

In 2007 NICE published guidance on secondary prevention following MI [4]. See Appendix E for all recommendations. No distinction was made in the scope of the MI guideline between non-ST elevation MI and ST-elevation MI. As such, the literature review and recommendations from the MI guideline that pertain to rehabilitation, lifestyle advice and discharge planning are applicable to people with NSTEMI in this guideline.

Given the existing recommendations from the NICE MI Guideline[4] the GDG addressed the question of whether the psychosocial and educational interventions that constitute the early

part of the rehabilitation process should be initiated before hospital discharge, or whether such initiatives could be deferred until after the patient returns to community care.

The clinical question upon which the literature was searched was:

> *"Do early psychosocial and educational interventions, mobilisation and discharge planning (cardiac rehabilitation – Phase 1) improve emotional and physical wellbeing and long-term outcomes in people with unstable angina or NSTEMI compared to deferred cardiac rehabilitation (Phase 2)?"*

5.7.2 CLINICAL METHODOLOGICAL INTRODUCTION

The literature was searched from 1999 to 2009 for systematic reviews, RCTs, comparative and observational studies comparing early initation of cardiac rehabilitation with deferred cardiac rehabilitation in people with non ST segment elevation ACS . The rationale for searching from January 1999 onwards was to reflect current practice, particularly the use of stents for revascularisation.

The studies of Phase 1 cardiac rehabilitation provided little detail on the exact type of acute coronary syndrome to which they refer – only that the people had been admitted with MI. As a result, the requirement for a NSTEMI/UA population > 60% was relaxed. The key was that studies had to address early initation of cardiac rehabilitation in an ACS population. Studies were included therefore, if the population had ACS and if the intervention (education, counselling, early mobilisation, discharge planning) occurred in hospital prior to discharge. Outcomes of interest included 30 day and long-term survival, revascularisation, re-infarction, LV function, quality of Life, serious complications (e.g. stroke, GI bleed), therapy concordance, well-being, anxiety, depression, and risk factor profile.

One systematic review of 26 studies (16 controlled clinical trials CCT; 10 before and after studies) compared in-hospital intervention with no in-hospital intervention in people with ACS (STEMI, NSTEMI, or UA). The primary outcome was one year mortality, and secondary outcomes were re-admission rates, smoking cessation, and re-infarction [271]. This systematic review, while well-conducted, may be difficult to interpret. In order to be included, a trial had to have *at least* an in-hospital intervention that directly targeted the patient (such as education or counselling) However, trials could also be included if the intervention was an in-hospital healthcare provider intervention that tried to change attitudes/knowledge of healthcare providers such as improving physician's skills in counselling through an educational program or education/reminders on benefits of specific therapies. Trials could also be included if the intervention was an in-hospital system-level intervention that involved a global change in the organisation of care (such as critical pathways or facility outcome reporting). The systematic review therefore includes *at least* a patient-level intervention, with some interventions operating additionally at the provider and/or system levels. Interpretation of the results of this meta–analysis should be tempered by the fact that before and after studies are not randomised. In the before and after studies, outcomes following an intervention (implementation of an in-hospital rehabilitation program, for example) were compared with a control group of people who did not receive the intervention (a historical control cohort).

One open RCT (N=65; 3 months follow-up) randomised people hospitalised for a first-time MI to in-hospital psychological intervention plus standard MI educational material or to standard care involving cardiac rehabilitation nurse in-hospital visits plus standard MI educational material (control). The outcomes were patient perception of illness, angina pain post-discharge, and time to return to work. This study is limited by the small number of participants, short follow-up, and use of mail-in questionnaires [272].

One patient survey was conducted with 20 MI people within 72 hours of their intended discharge from the hospital. In a questionnaire format, people were asked to indicate the importance of 40 information needs. This study is limited by the small sample size, and is most relevant to English-speaking people with an uncomplicated MI [273].

5.7.3 CLINICAL EVIDENCE STATEMENTS

In-hospital intervention versus no in-hospital intervention

►Mortality (at one year)

One systematic review showed that in-hospital intervention significantly decreased the risk of mortality at one year (14 studies, N=37585; RR 0.79 [95% CI 0.69 to 0.92]). This effect was sensitive to the type of study: non–significant for studies that were controlled clinical trials (9 CCTs, N=1796; RR 0.96 [95% CI 0.64, 1.44]), whereas it was significant in before and after studies (5 before and after studies, N=35789; RR 0.77 [95% CI 0.66-0.90]) [271].

In studies that only had an in-hospital intervention at the patient level, there was a non–significant difference in the risk of one year mortality (11 studies; RR 0.93 [95% CI 0.63, 1.36]) [271].

In studies that used an in-hospital intervention designed to increase prescription of proven efficacious drugs, the in-hospital intervention significantly reduced the risk of one year mortality compared with no intervention (6 studies; RR 0.80 [95% CI 0.68-0.93]) [271].

Evidence Level: 1+

►Readmission Rate

One systematic review showed that in-hospital interventions significantly reduced the risk of re-admission to hospital (10 studies, N=34907; RR 0.84 [95% CI 0.73 to 0.98]). When only controlled clinical trials were analysed, there was a non–significant difference for readmission rates (5 CCTs, N=962; RR 0.96 [95% CI 0.79 to 1.17]) [271].

Evidence Level: 1+

►Re-infarction rate

One systematic review showed a non–significant difference between re-infarction rates for people receiving in-hospital interventions compared with no in-hospital intervention (5

studies, N=1428; RR 0.59 [95% CI 0.32 to 1.07]), however there was significant heterogeneity in this analysis (I^2 = 90%, p=0.04). When only controlled clinical trials were analysed, there was a non–significant difference for re-infarction rates (3 CCTs, N=673; RR 0.51 [95% CI 0.23, 1.13]) [271].

Evidence Level: 1+

►Smoking Cessation

In-hospital interventions significantly increased smoking cessation compared with no in-hospital intervention (12 studies, N=988; RR 1.29 (95% CI 1.02 to 1.63]), however there was significant heterogeneity in this analysis (I^2 =66%, p=0.001)[271].

Evidence Level: 1+

In-hospital psychological intervention versus standard in-hospital cardiac rehabilitation (control)

►Patient perceptions of MI

At hospital discharge, one RCT of 65 MI individuals [272] showed that people in the psychological intervention group had significantly:

- lower belief that their MI would have serious consequences (mean score 48.1% [control] versus 41.8% [intervention], p<0.05)
- lower belief that the consequences of their MI would last a long time/indefinitely (mean score 40.9% [control] versus 34.2% [intervention], p<0.05)
- lower distress about symptoms (mean score 43.2% [control] versus 32.2% [intervention], p<0.01)
- higher belief that their heart condition could be controlled (mean score 57.3% [control] versus 63.4% [intervention], p<0.01).

At 3 months follow-up, people in the psychological intervention group had significantly:

- lower belief that the consequences of their MI would last a long time/indefinitely (mean score 46.3% [control] versus 33.0% [intervention], p<0.001)
- higher belief that their heart condition could be controlled (mean score 56.8% [control] versus 62.4% [intervention], p<0.01).

Evidence Level: 1+

►Preparation for hospital discharge

Compared to the control group, people in the psychological intervention group had significantly higher satisfaction with the quality of information (mean score 5.47 [control] versus 6.27 [intervention] $p<0.05$), felt more prepared to leave hospital (mean score 4.91 [control] versus 5.63 [intervention] $p<0.05$), had a higher understanding of heart attack/condition (mean score 5.00 [control] versus 5.83 [intervention] $p<0.01$), and reported a greater likelihood of attending cardiac rehabilitation (mean score 5.72 [control] versus 6.67 [intervention] $p<0.01$) [272].

Evidence Level: 1+

►Attendance at cardiac rehabilitation (post-hospital discharge)

There was a non–significant difference in the percentage of people in the psychological intervention group (74.2%) attending cardiac rehab compared with control group (55.9%, $p<0.13$) [272].

Evidence Level: 1+

►Angina pain (post- hospital discharge)

At three months (N=56 total), significantly fewer people in the psychological intervention group (14.3%) reported angina pain than the control group (39.3%; $p<0.03$ between groups and adjusted for LDL levels and MI site) [272].

Evidence Level: 1+

►Information needs

One in-hospital patient survey (N=20)[273] showed that MI people rated receiving information about medication, complications, and symptoms of MI most highly and included the following themes:

- What to do if I have a reaction to a medication?
- When to stop taking each medication?
- How to recognise a complication?
- How to prevent a complication from occurring?
- Why I need to take each medication?
- How will my MI affect driving?

- Sources of support following my MI
- How will my MI affect employment?

Evidence Level: 3

5.7.4 HEALTH ECONOMIC METHODOLOGICAL INTRODUCTION

No economic analyses were identified that examined early psychosocial interventions (in-hospital counselling and patient education, phase 1 cardiac rehabilitation) in an UA or NSTEMI population.

5.7.5 EVIDENCE SUMMARY

An extensive literature search returned 1022 possible publications, though all but three were excluded. The most common reasons for exclusion were uncertainty regarding the patient population studied, lack of clarity regarding the time of initiating intervention or low quality of evidence. Of the three that were critically appraised all involved some form of intervention prior to hospital discharge, but none was a randomised comparison between timing of initiation and an initiation of the intervention after discharge from hospital.

In the meta–analysis of Auer et al[271] most of the studies reviewed were published before the widespread use of PCI, when hospital lengths of stay were much longer. It was also difficult to determine the proportion of people with NSTEMI versus STEMI, making its applicability to the present guideline uncertain. Also, to be included in the meta–analysis studies had to include some in-hospital intervention at a direct patient level, but there could also be interventions that could operate at a hospital level (changing physician practice, or hospital processes). With these caveats the systematic review did suggest that in-hospital intervention reduces the rate of readmission to hospital (but not reinfarction), and resulted in greater smoking cessation. However, when only controlled clinical trials were meta-analysed, there were non–significant differences between in-hospital intervention and no in-hospital intervention for mortality at one year, readmission rates, or re-infarction rates.

One RCT[272] compared formal and structured in-hospital psychological intervention in addition to standard educational input, with the latter alone. The study was limited by small number of people included (65 in total) but did show that people receiving psychological intervention felt better prepared for discharge from hospital, had a better understanding of the issues, and had more positive attitudes to the consequences of their myocardial infarct, both at discharge and at 3 month follow-up. They also had a lower frequency of angina at 3 months (14.3% for the psychological group versus 39.3% for the control group).

One survey of people's information needs before hospital discharge[273] demonstrated that people following MI rated receiving information about medication, potential complications, and relevance of symptoms most highly.

5.7.6 EVIDENCE TO RECOMMENDATIONS

The GDG acknowledged the limitations of the evidence that specifically looked at whether rehabilitation should be initiated early in hospital compared to deferred cardiac rehabilitation. However, an important assumption is made that rehabilitation is initiated after discharge, an assumption that is currently not justified given the patchy nature of rehabilitation services that exists across the country.

The GDG agreed that:

- Good evidence exists for the longer term benefits of a comprehensive rehabilitation process following MI. The post-MI guideline found rehabilitation to be cost effective and the GDG felt that this is good evidence that rehabilitation is cost effective in general.
- Recent NICE guidance [4] recommends that people with MI should receive formal rehabilitation and delivery of secondary prevention measures and they do not distinguish between people with NSTEMI and STEMI.
- Although no evidence exists specifically for people with UA, it is part of the same pathophysiological continuum as NSTEMI and so the recommendations would logically apply to both groups.
- It is vital that information and education is delivered in an appropriate format to people prior to discharge from hospital given the importance of establishing people on appropriate medication, and the value of people understanding the indications and actions of these medications, and the underlying nature of their cardiac condition and any effect of co-morbidity.
- Given the continuing importance of education, psychological support and a structured, graded exercise programme after discharge from hospital, systems must be in place to ensure that people are 'picked up' by the appropriate rehabilitation services on their return to the community, and that hospitals should work with their primary care colleagues to ensure continuity of care.
- With hospital lengths of stay tending to shorten the time available to deliver appropriate pre-discharge information, ensure adequate discharge planning, and ensure continuity of care in the community is very short. Systems need to be put in place to ensure that with the understandable emphasis on returning people home as quickly as possible, the elements of comprehensive rehabilitation that can, and should, be delivered in-hospital should not be overlooked.
- The patient representatives on the GDG stressed very strongly the importance of patient information and education before discharge from hospital, and the need for this to be comprehensive, yet in a form that is appropriate to the individual given ethnic, cultural, gender and psychological differences.
- "Rehabilitation", in its most general sense, actually starts from the moment of diagnosis because from this time onwards there is potential benefit to people from being well informed and psychologically supported, and therefore the distinction between in-hospital and post-discharge intervention is somewhat arbitrary. The overriding

consideration should be to ensure that the process is continuous and that responsibility for delivery of the components of rehabilitation (education, information, psychosocial support, structured exercise etc.) should be clearly attributed.

In conclusion, the GDG were unable to draw evidence-based conclusions specifically regarding the optimum time of delivery of educational and psychosocial intervention. However, the GDG agreed with the cardiac NSF which highlights that 'cardiac rehabilitation should begin as soon as possible after someone is admitted to hospital with CHD (Phase 1)' and as such made a consensus recommendation in support of this.

5.7.7 RECOMMENDATIONS

R34 Before discharge offer patients advice and information about:

- their diagnosis and arrangements for follow-up (in line with 'MI: secondary prevention', NICE clinical guideline 48)
- cardiac rehabilitation (in line with 'MI: secondary prevention', NICE clinical guideline 48)
- management of cardiovascular risk factors and drug therapy for secondary prevention (in line with 'MI: secondary prevention', NICE clinical guideline 48, and 'Lipid modification', NICE clinical guideline 67)
- lifestyle changes (in line with 'MI: secondary prevention', NICE clinical guideline 48).

R35 Cardiac rehabilitation should be equally accessible and relevant to all patients after an MI, particularly people from groups that are less likely to access this service. These include people from black and minority ethnic groups, older people, people from lower socioeconomic groups, women, people from rural communities and people with mental and physical health comorbidities. (This recommendation is from 'MI: secondary prevention', NICE clinical guideline 48.)

R36 All patients who smoke should be advised to quit and be offered support and advice, and referral to an intensive support service (for example, the NHS Stop Smoking Services) in line with 'Brief interventions and referral for smoking cessation in primary care and other settings' (NICE public health guidance 1). (This recommendation is adapted from 'MI: secondary prevention', NICE clinical guideline 48.)

6 APPENDIX A

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

SCOPE

1 Guideline title

Acute coronary syndromes: the management of unstable angina and non-ST segment elevation myocardial infarction

1.1 Short title

Acute coronary syndromes: unstable angina and NSTEMI

2 Background

- The National Institute for Health and Clinical Excellence ('NICE' or 'the Institute') has commissioned the National Collaborating Centre for Chronic Conditions to develop a clinical guideline on acute coronary syndromes (unstable angina and non-ST segment elevation myocardial infarction) for use in the NHS in England and Wales. This follows referral of the topic by the Department of Health (see appendix). The guideline will provide recommendations for good practice that are based on the best available evidence of clinical and cost effectiveness.
- The Institute's clinical guidelines will support the implementation of National Service Frameworks (NSFs) in those aspects of care where a Framework has been published. The statements in each NSF reflect the evidence that was used at the time the Framework was prepared. The clinical guidelines and technology appraisals published by the Institute after an NSF has been issued will have the effect of updating the Framework.
- NICE clinical guidelines support the role of healthcare professionals in providing care in partnership with patients, taking account of their individual needs and preferences, and ensuring that patients (and their carers and families, where appropriate) can make informed decisions about their care and treatment.

3 Clinical need for the guideline

The term 'acute coronary syndromes' encompasses a range of conditions from unstable angina to ST elevation myocardial infarction (STEMI), arising from thrombus formation on atheromatous plaque. This guideline will address unstable angina and non-ST elevation myocardial infarction. Untreated the prognosis is poor and mortality is high, particularly in people who have had myocardial damage. Appropriate triage and timely use of acute interventions, whether invasive or pharmacological, are vital and will be addressed in this

guideline. Timely assessment and classification of those presenting with undifferentiated chest pain are also important and is covered in the acute chest pain guideline being developed in parallel with this guideline see section 4.4.2.

4 The guideline

The guideline development process is described in detail in two publications that are available from the NICE website (see 'Further information'). 'The guideline development process: an overview for stakeholders, the public and the NHS' describes how organisations can become involved in the development of a guideline. 'The guidelines manual' provides advice on the technical aspects of guideline development.

This document is the scope. It defines exactly what this guideline will (and will not) examine, and what the guideline developers will consider. The scope is based on the referral from the Department of Health (see appendix).

The areas that will be addressed by the guideline are described in the following sections.

4.1 Population

4.1.1 Groups that will be covered

- Adults (18 years and older), with a diagnosis of unstable angina or non-ST elevation MI.

Recommendations will be made, as appropriate and based on the evidence, for specific groups:

- minority ethnic groups
- older people
- socio-economic groups
- women
- people with disabilities

4.1.2 Groups that will not be covered

a) People with ST segment elevation myocardial infarction

b) People with an ACS who have been discharged from hospital..

c) People with acute heart failure not due to non-ST segment elevation myocardial infarction.

d) People with undifferentiated chest pain.

4.2 Healthcare setting

The guideline will consider the care received in primary, secondary and tertiary healthcare centres, including care from ambulance teams and other paramedical staff before admission to hospital.

4.3 Clinical management

a) Risk stratification for triage and management purposes.

b) Percutaneous coronary intervention (PCI) or early coronary artery bypass grafting (CABG) .

c) Pharmacological therapies, for example antiplatelet drugs, anticoagulants, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors.

d) Information-giving and communication in the early stage of treatment.

The guideline development group will take reasonable steps to identify ineffective interventions and approaches to care. If robust and credible recommendations for re-positioning the intervention for optimal use, or changing the approach to care to make more efficient use of resources, can be made, they will be clearly stated. If the resources released are substantial, consideration will be given to listing such recommendations in the 'Key priorities for implementation' section of the guideline.

Note that guideline recommendations will normally fall within licensed indications; exceptionally, and only where clearly supported by evidence, use outside a licensed indication may be recommended. The guideline will assume that prescribers will use a drug's summary of product characteristics to inform their decisions for individual patients.

4.4 Status

4.4.1 Scope

This is the final scope.

4.5 Related guidance

The guideline being developed by the National Collaborating Centre for Primary Care 'Acute chest pain: assessment, investigation and management of acute chest pain of suspected cardiac origin' will address assessment and examination before diagnosis of the cause of the chest pain.

The following related NICE guidance will also be referred to as appropriate.

Published

- MI: secondary prevention. Secondary prevention in primary and secondary care for patients following a myocardial infarction. NICE clinical guideline 48 (2007). Available from: www.nice.org.uk/CG048

- Clopidogrel in the treatment of non-ST-segment-elevation acute coronary syndrome. NICE technology appraisal guidance 80 (2004). Available from: www.nice.org.uk/TA080 - **This TA is being updated by the guideline.**

- Myocardial perfusion scintigraphy for the diagnosis of angina and myocardial infarction. NICE technology appraisal guidance 73 (2003). Available from: www.nice.org.uk/TA073

- Guidance on the use of coronary artery stents. NICE technology appraisal guidance 71 (2003). Available from: www.nice.org.uk/TA071

- Guidance on the use of drugs for early thrombolysis in the treatment of acute myocardial infarction. NICE technology appraisal guidance 52 (2002). Available from: www.nice.org.uk/TA052

- Guidance on the use of glycoprotein IIb/IIIa inhibitors in the treatment of acute coronary syndromes. NICE technology appraisal guidance 47 (2002). Available from: www.nice.org.uk/TA047 - **This TA is being updated by the guideline.**

- Off-pump coronary artery bypass (OPCAB). NICE interventional procedure guidance 35 (2004). Available from: www.nice.org.uk/IPG035

In development

- Acute chest pain: assessment, investigation and management of acute chest pain of suspected cardiac origin. NICE clinical guideline (publication anticipated December 2009).

- Laser transmyocardial revascularisation for refractory angina pectoris. NICE interventional procedure guidance (publication date to be confirmed)

- Percutaneous laser revascularisation for refractory angina pectoris. NICE interventional procedure guidance (publication date to be confirmed)

4.5.1 Guideline

The development of the guideline recommendations will begin in April 2008.

5 Further information

Information on the guideline development process is provided in:

'The guideline development process: an overview for stakeholders, the public and the NHS'
'The guidelines manual'.

These booklets are available as PDF files from the NICE website (www.nice.org.uk/guidelinesmanual). Information on the progress of the guideline will also be available from the website.

Referral from the Department of Health

The Department of Health asked the Institute:

To prepare a clinical guideline on the assessment and management of unstable angina and non-ST elevation myocardial infarction.

7 APPENDIX B

The analysis of MINAP data for the cost–effectiveness analysis

Introduction

This document summarises the rationale and details relating to the analysis of MINAP data for input into the cost-effectiveness analysis. Analyses of the MINAP dataset were carried out by John Birkhead. The extrapolation analyses were carried out by the NCC–CC.

The cost-effectiveness model is reported in Appendix C.

Approach

The aim was to obtain contemporary UK event rate data for one of the treatment arms of the cost-effectiveness analysis. Other treatment arms would then be modelled by applying appropriate relative risks from clinical trials to the UK baseline event rates.

Management of UA and non-ST elevation myocardial infarction (UA/NSTEMI) is known to historically vary between countries and revascularisation rates have been lower in the UK than most other Western European countries[178]. Therefore baseline event rates from multinational RCTs undertaken to evaluate clinical effectiveness may not provide reliable estimates for UK practice. In addition randomised controlled trials are selective and therefore very high risk patients are often excluded. For these reasons UK specific baseline event rates for the cost-effectiveness model were sought.

The modelling undertaken for the NICE technology appraisal of glycoprotein IIb/IIIa inhibitors (GPIs) [210] used registry data from PRAIS UK (1998-1999) with six-month follow-up, supplemented by data from a PCI audit in Leeds 2000 for short-term modelling. Data from the Nottingham Heart attack registry with up to five years follow-up was used for longer term modelling. The GDG felt that obtaining contemporary baseline events from the UK Myocardial Ischaemia National Audit Project (MINAP)[40] dataset would capture changes in outcome over time due to changes in practice (including increased use of an invasive management strategy) and widespread use of clopidogrel. This includes improved outcomes for patients due to changes in management over time and potentially also an increase in bleeding. It also allowed detailed analysis based on patient risk scores to be undertaken.

The MINAP dataset

The Myocardial Ischaemia National Audit Project (MINAP)[40] collects information about the hospital management of acute coronary syndrome (ACS). Initially the project focussed on the hospital management of acute ST-elevation myocardial infarction (STEMI) but the dataset has been expanded to cover other ACS (including UA/NSTEMI). All hospitals in England and Wales that admit patients

with ACS contribute data. Linkage with the Office of National Statistics allows post-discharge mortality tracking. Examination of readmissions allows estimation of new MI events post-discharge.

The cohort used

A MINAP database for 2005-7 (download 19 Feb 2008) was used for these analyses, and was limited to English hospitals.

UA/NSTEMI patient selection:

The guideline addresses treatment of patients with UA/NSTEMI only and so records were selected if they fulfilled the following criteria:

- A final diagnosis code in MINAP of 'Myocardial infarction (non-ST elevation)' or 'ACS (trop+vs)' or 'ACS (trop (-ve)'
- 'Biomarker status' was available
- 'ECG appearances' was available (see below for how these were used)
- Direct admission to hospitals – no interhospital transfers were included.

Records having the following ECG appearances were included in the analyses:

- ST-segment depression (41%)
- Dynamic T wave changes (34%)
- Left bundle branch block where this was not considered to be new or masking changes of ST segment elevation (10%)
- Normal ECG where this was accompanied by elevated troponin (15%).

There were 75,627 records meeting these criteria. It was considered that all those included would be eligible for clopidogrel treatment and so were considered the appropriate population for the cost-effectiveness analysis. 88% of these had elevated biomarkers.

Selection of patients using certain drugs:

For the cost-effectiveness analysis the aim was to establish event rates for one arm of the model – a group receiving treatment with aspirin, clopidogrel, heparin (UFH or LMWH). On this basis a subgroup of patients receiving these agents in hospital was selected and used in all analyses. The dose and duration of treatment was unknown. Heparin (LMWH or UFH) use was universal and aspirin use also

close to 100%. Clopidogrel use was ~70%. Patients were excluded if they received a GPI except in the context of a coronary intervention (~5%).

MINAP does not record whether or not a GPI was used during a coronary intervention. 2005-2007 BCIS audit data indicated that GPI use during PCI for UA was 51%, 37% and 27% during 2005, 6, 7 respectively, and 54%, 52% and 39% in NSTEMI (although these figures will presumably include those that received a GPI upstream that was continued through PCI). This implies that mortality and MI event rates may be slightly lower and bleed rates slightly higher than in a cohort not receiving any GPIs. The impact of varying baseline event rates was investigated as a sensitivity analysis in the cost–effectiveness analysis.

The UA/NSTEMI cohort described above, with aspirin, clopidogrel and heparin use (without upstream GPI use) was used to inform the event rates for the aspirin, clopidogrel and heparin arm in the cost-effectiveness analysis. This includes 38,808 patients during 2005-2007 (24,199 for 2005-2006 only, on which mortality analyses were based). For PCI centres only this included 8299 patients.

Risk stratification

Each patient in the selected MINAP cohort was assigned a risk score based on the GRACE scoring system (the risk scoring methods are described below). This allowed patients to be grouped into risk groups to investigate how cost effectiveness varies with baseline risk.

The GRACE score uses 8 variables: age, systolic blood pressure, heart rate, cardiac arrest, bio-marker elevation, ST deviation, serum creatinine and Killip class. MINAP did not record serum creatinine throughout the period 2005-7 and Killip score is not included in the dataset. A mini-score, without these elements was created using the GRACE scoring system. The six-month risk scoring system was used inline with the other risk work undertaken for the guideline[21]. Patients were split into six risk groups based on their risk score: 1a (~12.5% of patients), 1b (~12.5%), 2a (~12.5%), 2b (~12.5%), 3 (~25%) and 4 (~25%). Group 1a is the lowest risk group and group 4 is highest risk score. See the Risk Chapter for more details about the GRACE scoring system used, the creation of the risk groups and interpretation in the wider guideline context.

36,299 patients receiving the drugs specified above also had sufficient data available to calculate a risk score 2005-2007 (20,021 for 2005-2006 only). For PCI centres this included 7,694 patients.

Acute management stratification

Outcomes were analysed by acute management strategy; that is whether patients underwent PCI, CABG, angiography only or no angiography or revascularisation during their acute UA/NSTEMI episode. This was because some of the clinical trial data being used in the cost–effectiveness model were in a specific subset of the population e.g. those undergoing PCI. As risks of events may vary by acute management strategy it was therefore appropriate to assess outcomes by management strategy. As the interventions being assessed by the model are all used during the acute phase, acute management strategy was determined as the appropriate stratification.

The MINAP record for angiography and revascularisation covers the acute episode including what happens in the admitting hospital and, where the admitting hospital does not have interventional facilities, the hospital they refer to for intervention. Patients were split into the following acute management strategy groups: 'PCI', 'CABG', 'Angio only', 'No angio', and 'Other'. The 'Other' group is not utilised in the cost-effectiveness analysis as management strategy is unknown.

Figure 1 MINAP data fields for coronary angiography and coronary intervention

4.13 Coronary angiography (performed or arranged, but not as part of the initial reperfusion strategy):

1. Protocol-driven investigation performed in this hospital
2. Symptom-driven investigation performed in this hospital
3. Protocol-driven investigation performed at another hospital
4. Symptom-driven investigation performed at another hospital
5. Planned after discharge
8. Not performed
9. Unknown

4.14 Coronary intervention (during this episode performed either in your hospital or by referral to another hospital)

1. Percutaneous intervention
2. CABG
4. PCI planned after discharge
5. CABG planned after discharge
8. Not performed or arranged
9. Unknown

The MINAP data fields for coronary angiography and coronary intervention are shown in Figure 1. Patients were first assigned as either 'yes' or 'no' to angiography. Yes = categories 1-5. No = category

8. Those where coronary angiography is unknown were excluded from the analysis. The ‘no’ category formed the ‘No angiography’ group.

Patients who received coronary angiography were then categorised using the coronary intervention field. Patients were assigned to the ‘PCI’ group if they were recorded as ‘1) PCI’, and to the ‘CABG’ group if they were recorded as ‘2) CABG’. Patients who were recorded as ‘8) not performed or arranged’ were assigned to the ‘angio only’ group. Patients who were recorded as ‘9) Unknown’ were assigned to a group designated ‘Other’ (note that the data from this group is not used in the cost effectiveness model). Those recorded as ‘4) PCI planned after discharge’ and ‘5) CABG planned after discharge’ were a slightly complex group to assign. They were however also small in number – PCI planned after discharge = 2%, CABG planned after discharge – 0.5%. This was discussed with the health economic subgroup of the GDG and it was decided that for the purposes of analysing data for the cost-effectiveness analysis patients should be assigned based on what actually happened in the acute admission and so these patients were assigned to the ‘angio only’ group.

Analyses of the MINAP cohort

As described above, all analyses for the purposes of the cost-effectiveness model were restricted to UA/NSTEMI patients receiving aspirin, clopidogrel and heparin (UFH or LMWH) and not receiving an upstream GPI. All analyses were reported stratified by risk group (1a, 1b, 2a, 2b, 3, 4) and acute management strategy group (no angio, angio only, PCI, CABG, other) as far as possible (in some places this was not judged feasible due to low event numbers). This meant that only patients with the information required to assign to these groups were included in the analysis.

The population analysed included all non-interventional and interventional hospitals in England. The advantage of using the entire population is that this more accurately reflects national rates for mortality, but with a relative disadvantage that rates for intervention are understated. This arises because hospitals without interventional facilities may not know if or what intervention was performed after transfer, and may leave this information blank. Where appropriate, data from interventional hospitals only was used, or both were analysed.

Where one-year outcomes were required, the analysis was restricted to 2005/06 patients to ensure availability of one-year follow-up from the cohort.

Using the MINAP cohort described above the following events were analysed for the whole cohort and for each risk group, all split by acute management strategy:

- Mortality up to 1 year (section 0)
- Readmission up to 1 year (section 0)
- In-hospital re-infarction (section 0)
- In-hospital bleeding (section 0
- Non-fatal MI in those alive at 1 year (inhospital re-infarction or 1 year readmission) (section 0)

In addition data was analysed relating to the following:

- In-hospital management strategy (no angiography, angiography only, PCI or CABG) (section 0
- Length of stay (overall and with an in-hospital re-infarction or bleed) (section 0)
- Demographics: age/sex breakdown by risk group (section 0)

Details of these analyses follow. The results of the analyses from MINAP were graphed. Apparent anomalies in the data were reviewed to see if they might be accounted for by very low event numbers. Where this appeared to be the case this was discussed with the GDG. If judged likely to be attributable to low event numbers, risk groups were pooled for use in the cost-effectiveness analysis – details are provided below. Note that this mostly only occurred in the CABG group which is a small proportion of the total population.

Where results reported at different time points it is the one-year figures that are generally used in the cost-effectiveness analysis. The cost-effectiveness model report in Appendix C describes which data is used in the analysis in detail.

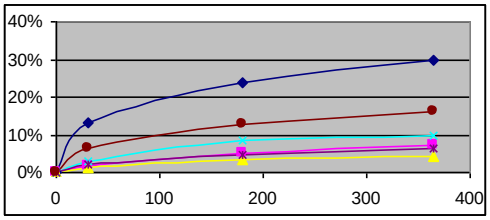
Mortality analyses

The census date for these analyses was Feb 19th 2008, using data available to ONS up to 31 Dec 2007. In order to have a complete 365 day follow-up interval, mortality analyses are based on the 2005-6 cohort. 17,280 patients were included in this analysis. The number of deaths at 30 days, 6 months and 1 year were reported.

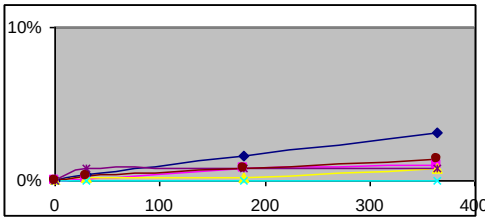
Results of analyses are presented in Figure 2 and Figure 3. Mortality increased by risk group, ranging from 1.4% at 1 year in risk group 1a to 44.4% in group 4. Anomalies were observed in the lower risk groups for CABG and PCI at one year. Event numbers in these groups were also observed to be very low: in the CABG group there were less than five events in groups 1a, 1b and 2a; in the PCI group there were less than five events in groups 1a and 1b. For these reasons in the cost-effectiveness model group 1a and 1b were pooled for CABG and for PCI, groups 2a and 2b were also pooled for CABG. See Figure 3 for pooled figures.

Figure 2 MINAP mortality analysis: trend over time by risk group

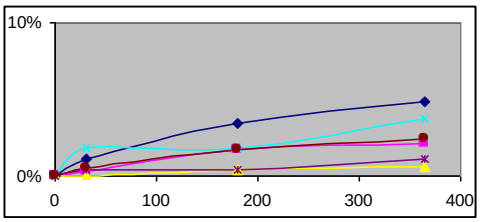
	Percentages					*Events (N = population, other data = events)*			
ALL	*0*	*30*	*180*	***365***	*days*	N	*30*	*180*	***365***
No angio	0	13.0%	23.8%	**29.8%**		7288	946	1734	**2174**
angio only	0	1.8%	4.9%	**7.0%**		5864	107	290	**412**
PCI	0	1.5%	3.3%	**4.4%**		2363	35	79	**103**
CABG	0	3.0%	8.3%	**9.9%**		372	11	31	**37**
Other	0	2.0%	4.6%	**6.4%**		1393	28	64	**89**
Total	0	6.5%	12.7%	**16.3%**		17280	1127	2198	**2815**



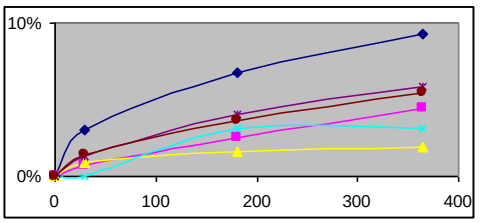
Group 1a	*0*	*30*	*180*	***365***	*days*	N	*30*	*180*	***365***
No angio	0	0.4%	1.6%	**3.1%**		486	2	8	**15**
angio only	0	0.1%	0.8%	**1.0%**		1035	1	8	**10**
PCI	0	0.2%	0.2%	**0.9%**		467	1	1	**4**
CABG	0	0.0%	0.0%	**0.0%**		45	0	0	**0**
Other	0	0.9%	0.9%	**0.9%**		233	2	2	**2**
Total	0	0.3%	0.8%	**1.4%**		2266	6	19	**31**



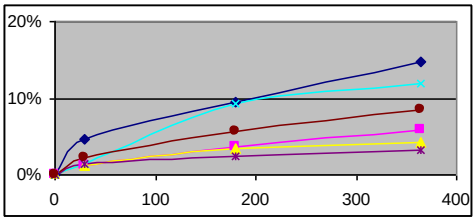
Group 1b	*0*	*30*	*180*	***365***	*days*	N	*30*	*180*	***365***
No angio	0	1.1%	3.4%	**4.9%**		617	7	21	**30**
angio only	0	0.3%	1.7%	**2.1%**		1119	3	19	**24**
PCI	0	0.0%	0.4%	**0.6%**		472	0	2	**3**
CABG	0	1.9%	1.9%	**3.7%**		54	1	1	**2**
Other	0	0.4%	0.4%	**1.1%**		263	1	1	**3**
Total	0	0.5%	1.7%	**2.5%**		2525	12	44	**62**



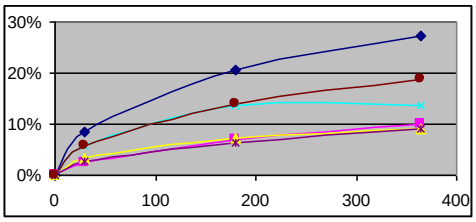
Group 2a	*0*	*30*	*180*	***365***	*days*	N	*30*	*180*	***365***
No angio	0	3.1%	6.7%	**9.3%**		654	20	44	**61**
angio only	0	0.7%	2.5%	**4.4%**		1036	7	26	**46**
PCI	0	0.9%	1.6%	**1.9%**		428	4	7	**8**
CABG	0	0.0%	3.2%	**3.2%**		63	0	2	**2**
Other	0	1.3%	4.0%	**5.8%**		223	3	9	**13**
Total	0	1.4%	3.7%	**5.4%**		2404	34	88	**130**



Group 2b	*0*	*30*	*180*	***365***	*days*	N	*30*	*180*	***365***
No angio	0	4.6%	9.6%	**14.7%**		740	34	71	**109**
angio only	0	1.1%	3.7%	**5.9%**		876	10	32	**52**
PCI	0	1.1%	3.4%	**4.2%**		357	4	12	**15**
CABG	0	1.3%	9.2%	**11.8%**		76	1	7	**9**
Other	0	1.4%	2.3%	**3.3%**		213	3	5	**7**
Total	0	2.3%	5.6%	**8.5%**		2262	52	127	**192**



Group 3	*0*	*30*	*180*	***365***	*days*	N	*30*	*180*	***365***
No angio	0	8.5%	20.5%	**27.2%**		2115	180	433	**576**
angio only	0	2.4%	6.9%	**10.1%**		1218	29	84	**123**
PCI	0	3.2%	7.3%	**9.1%**		439	14	32	**40**
CABG	0	5.7%	13.6%	**13.6%**		88	5	12	**12**
Other	0	2.6%	6.5%	**9.1%**		308	8	20	**28**
Total	0	5.7%	13.9%	**18.7%**		4168	236	581	**779**



Group 4	*0*	*30*	*180*	***365***	*days*	N	*30*	*180*	***365***
No angio	0	26.3%	43.2%	**51.7%**		2676	703	1157	**1383**
angio only	0	9.8%	20.9%	**27.1%**		580	57	121	**157**
PCI	0	6.0%	12.5%	**16.5%**		200	12	25	**33**
CABG	0	8.7%	19.6%	**26.1%**		46	4	9	**12**
Other	0	7.2%	17.6%	**23.5%**		153	11	27	**36**
Total	0	21.5%	36.6%	**44.4%**		3655	787	1339	**1621**

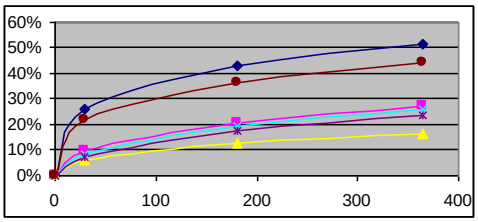
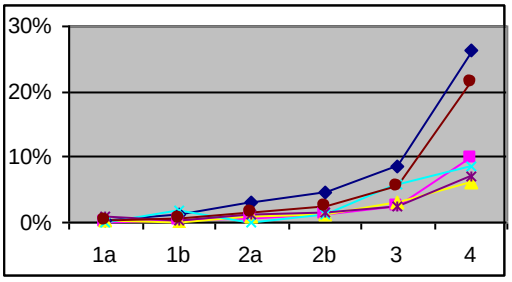
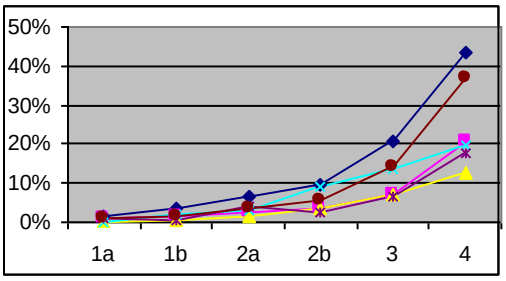


Figure 3 **MINAP mortality analysis: trend by risk group**

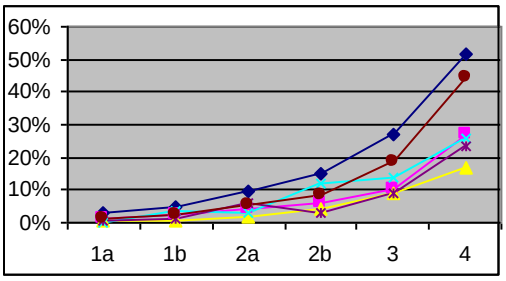
30 days	*1a*	*1b*	*2a*	*2b*	*3*	*4*
No angio	0.41%	1.13%	3.06%	4.59%	8.51%	26.27%
angio only	0.10%	0.27%	0.68%	1.14%	2.38%	9.83%
PCI	0.21%	0.00%	0.93%	1.12%	3.19%	6.00%
CABG	0.00%	1.85%	0.00%	1.32%	5.68%	8.70%
Other	0.86%	0.38%	1.35%	1.41%	2.60%	7.19%
Total	0.26%	0.48%	1.41%	2.30%	5.66%	21.53%



180 days	*1a*	*1b*	*2a*	*2b*	*3*	*4*
No angio	1.65%	3.40%	6.73%	9.59%	20.47%	43.24%
angio only	0.77%	1.70%	2.51%	3.65%	6.90%	20.86%
PCI	0.21%	0.42%	1.64%	3.36%	7.29%	12.50%
CABG	0.00%	1.85%	3.17%	9.21%	13.64%	19.57%
Other	0.86%	0.38%	4.04%	2.35%	6.49%	17.65%
Total	0.84%	1.74%	3.66%	5.61%	13.94%	36.63%

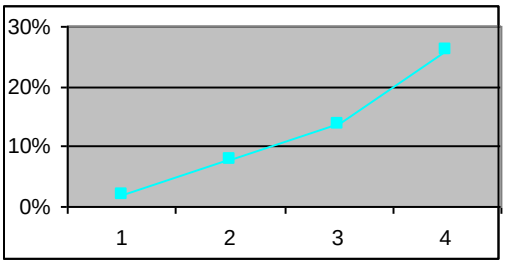


365 days	*1a*	*1b*	*2a*	*2b*	*3*	*4*
No angio	**3.09%**	**4.86%**	**9.33%**	**14.73%**	**27.23%**	**51.68%**
angio only	**0.97%**	**2.14%**	**4.44%**	**5.94%**	**10.10%**	**27.07%**
PCI	**0.86%**	**0.64%**	**1.87%**	**4.20%**	**9.11%**	**16.50%**
CABG	**0.00%**	**3.70%**	**3.17%**	**11.84%**	**13.64%**	**26.09%**
Other	**0.86%**	**1.14%**	**5.83%**	**3.29%**	**9.09%**	**23.53%**
Total	**1.37%**	**2.46%**	**5.41%**	**8.49%**	**18.69%**	**44.35%**

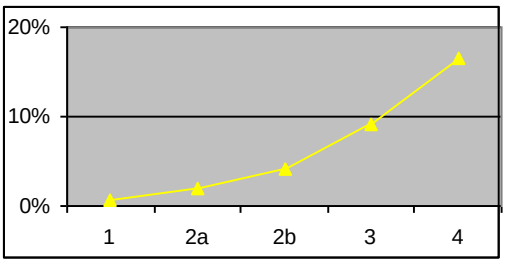


Data pooling for use in model:

365 days	*1*	*2*	*3*	***4***
CABG	**2.02%**	**7.91%**	**13.64%**	**26.09%**



365 days	*1*	*2a*	*2b*	*3*	***4***
PCI	**0.75%**	**1.87%**	**4.20%**	**9.11%**	**16.50%**



New MI events analyses

In-hospital re-infarction

In-hospital re-infarction is recorded by MINAP, and requires new cardiographic changes and new, or further elevation of cardiac markers in the context of new symptoms suggestive of cardiac ischaemia. Clinical trial definition of new MI generally includes all new MIs including those occurring in-hospital. Analyses in the literature have reported that experiencing a re-infarction is independently associated with increased hospital costs[38,274].

Analyses were based on first admissions. The quantity of missing data for re-infarction was noted.

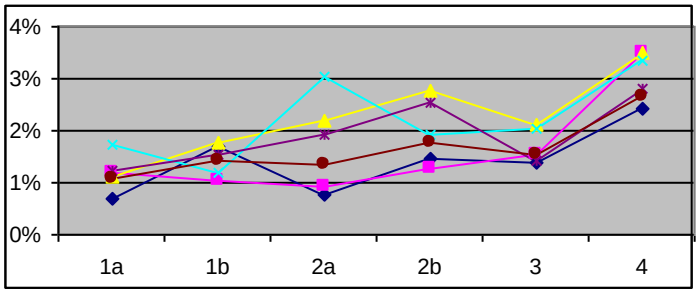
26,291 patients were included in this analysis. The number of re-infarctions in the acute episode were reported.

Results of analyses are presented in Figure 4. In-hospital re-infarction rates were fairly low but generally showed a trend for increasing with risk group in the overall population, ranging from 1.1% to 2.7%. Within acute management strategy groups the trend observed was more erratic. Event numbers in the CABG group were also very low and groups 1a and 1b, and 2a and 2b were pooled for use in the cost-effectiveness model – see Figure 4 for pooled figures.

Figure 4 **MINAP re-infarction analysis**

Percentages

	1a	*1b*	*2a*	*2b*	*3*	*4*	*All*
No angio	0.69%	1.71%	0.75%	1.45%	1.39%	2.43%	1.72%
angio only	1.18%	1.03%	0.94%	1.27%	1.55%	3.49%	1.45%
PCI	1.13%	1.77%	2.19%	2.76%	2.11%	3.50%	2.07%
CABG	1.72%	1.20%	3.03%	1.90%	2.04%	3.33%	2.17%
Other	1.24%	1.54%	1.91%	2.54%	1.44%	2.81%	1.80%
Total	1.08%	1.43%	1.34%	1.76%	1.53%	2.67%	1.71%

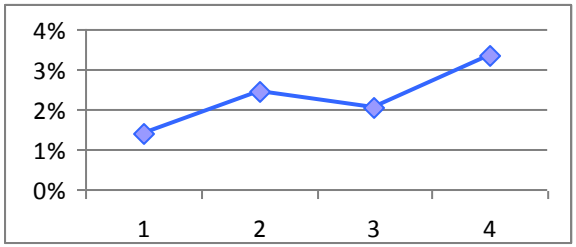


Events (n = population, r = events)

	1a		*1b*		*2a*		*2b*		*3*		*4*		*All*	
	n	*r*	*n*	*r*	*N*	*r*	*n*	*r*	*n*	*r*	*n*	*r*	*n*	*r*
No angio	723	5	878	15	928	7	1106	16	3308	46	4237	103	11180	192
angio only	1354	16	1450	15	1274	12	1184	15	1681	26	830	29	7773	113
PCI	800	9	790	14	732	16	616	17	760	16	314	11	4012	83
CABG	58	1	83	1	99	3	105	2	147	3	60	2	552	12
Other	483	6	518	8	470	9	393	10	625	9	285	8	2774	50
Total	3418	37	3719	53	3503	47	3404	60	6521	100	5726	153	26291	450

Data pooling for use in cost–effectiveness model:

	1	*2*	*3*	*4*
CABG	1.42%	2.45%	2.04%	3.33%



Readmission to hospital up to 1 year

Patients that experience a new ACS event following their acute admission who are readmitted to hospital will have a new MINAP record. This analysis is based on the presence of duplicate records having the same date of birth, patient case record number and hospital. From other MINAP analyses It is known that 85% readmissions after NSTEMI are for further infarction[275]. Readmission was analysed for admission during 2005/6 in order to have complete data for 1 year readmissions. 19,368 patients were included in this analysis. The number of readmissions at 30 days, 6 months and 1 year were reported.

Results of analyses are presented in Figure 5 and Figure 6. Event numbers in the CABG group were very low and in one risk group no events occurred at all. A pooled event rate across all risk groups was therefore used in the cost-effectiveness analysis for CABG – this was 2.3%.

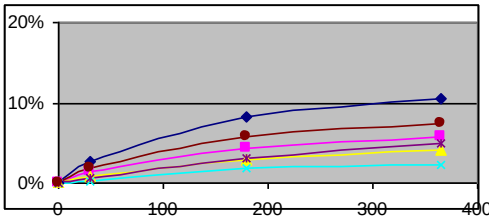
Figure 5 **MINAP readmission analysis: trend over time by risk group**

Percentages

ALL	*0*	*30*	*180*	***365***	*days*
No angio	0	2.7%	8.2%	**10.5%**	
angio only	0	1.4%	4.4%	**5.8%**	
PCI	0	0.8%	2.9%	**4.1%**	
CABG	0	0.3%	1.8%	**2.3%**	
Other	0	0.6%	3.2%	**5.0%**	
Total	0	1.8%	5.7%	**7.5%**	

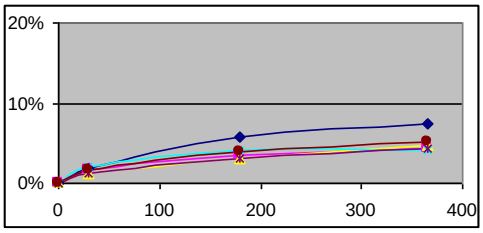
Events (n= population, other data = events)

N	*30*	*180*	***365***
8482	227	694	**891**
6446	93	281	**371**
2549	21	75	**104**
389	1	7	**9**
1502	9	48	**75**
19368	351	1105	**1450**



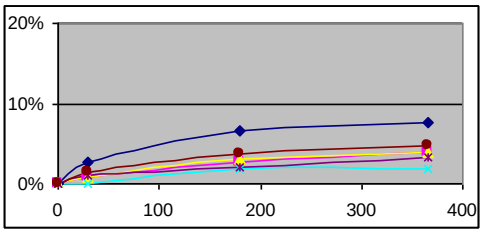
Group 1a	*0*	*30*	*180*	***365***	*days*
No angio	0	1.9%	5.8%	**7.4%**	
angio only	0	1.7%	3.5%	**4.3%**	
PCI	0	1.2%	3.1%	**4.8%**	
CABG	0	2.1%	4.2%	**4.2%**	
Other	0	1.2%	3.1%	**4.3%**	
Total	0	1.6%	3.9%	**5.1%**	

N	*30*	*180*	***365***
565	11	33	**42**
1126	19	39	**48**
516	6	16	**25**
48	1	2	**2**
256	3	8	**11**
2511	40	98	**128**



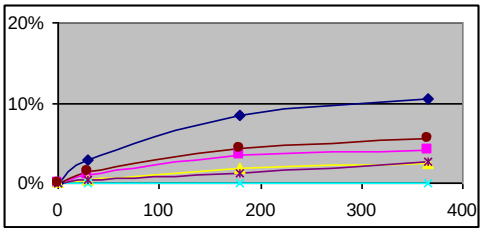
Group 1b	*0*	*30*	*180*	***365***	*days*
No angio	0	2.7%	6.7%	**7.5%**	
angio only	0	0.9%	2.8%	**3.8%**	
PCI	0	0.8%	3.2%	**3.9%**	
CABG	0	0.0%	1.8%	**1.8%**	
Other	0	1.1%	2.2%	**3.2%**	
Total	0	1.4%	3.8%	**4.7%**	

N	*30*	*180*	***365***
702	19	47	**53**
1196	11	33	**46**
507	4	16	**20**
56	0	1	**1**
278	3	6	**9**
2739	37	103	**129**



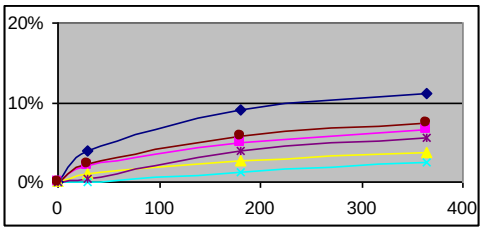
Group 2a	*0*	*30*	*180*	***365***	*days*
No angio	0	2.9%	8.5%	**10.6%**	
angio only	0	1.1%	3.6%	**4.2%**	
PCI	0	0.4%	1.8%	**2.4%**	
CABG	0	0.0%	0.0%	**0.0%**	
Other	0	0.4%	1.3%	**2.6%**	
Total	0	1.4%	4.4%	**5.5%**	

N	*30*	*180*	***365***
754	22	64	**80**
1121	12	40	**47**
453	2	8	**11**
66	0	0	**0**
232	1	3	**6**
2626	37	115	**144**



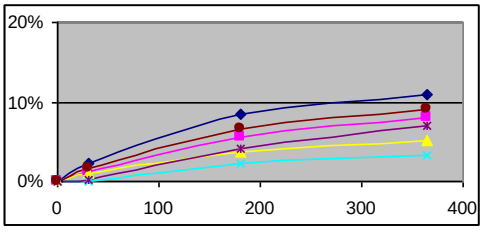
Group 2b	*0*	*30*	*180*	***365***	*days*
No angio	0	3.9%	9.0%	**11.1%**	
angio only	0	2.0%	5.0%	**6.6%**	
PCI	0	1.1%	2.6%	**3.7%**	
CABG	0	0.0%	1.3%	**2.6%**	
Other	0	0.4%	3.9%	**5.6%**	
Total	0	2.3%	5.8%	**7.5%**	

N	*30*	*180*	***365***
876	34	79	**97**
977	20	49	**64**
380	4	10	**14**
78	0	1	**2**
232	1	9	**13**
2543	59	148	**190**



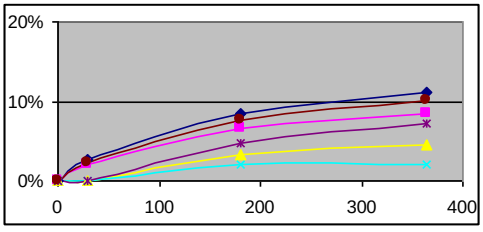
Group 3	*0*	*30*	*180*	***365***	*days*
No angio	0	2.3%	8.4%	**11.0%**	
angio only	0	1.2%	5.6%	**8.1%**	
PCI	0	1.1%	3.8%	**5.1%**	
CABG	0	0.0%	2.2%	**3.3%**	
Other	0	0.3%	4.1%	**7.1%**	
Total	0	1.7%	6.7%	**9.1%**	

N	*30*	*180*	***365***
2469	56	207	**271**
1373	17	77	**111**
475	5	18	**24**
92	0	2	**3**
338	1	14	**24**
4747	79	318	**433**



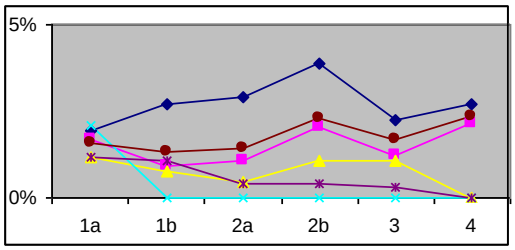
Group 4	*0*	*30*	*180*	***365***	*days*
No angio	0	2.7%	8.5%	**11.2%**	
angio only	0	2.1%	6.6%	**8.4%**	
PCI	0	0.0%	3.2%	**4.6%**	
CABG	0	0.0%	2.0%	**2.0%**	
Other	0	0.0%	4.8%	**7.2%**	
Total	0	2.4%	7.7%	**10.1%**	

N	*30*	*180*	***365***
3116	85	264	**348**
653	14	43	**55**
218	0	7	**10**
49	0	1	**1**
166	0	8	**12**
4202	99	323	**426**

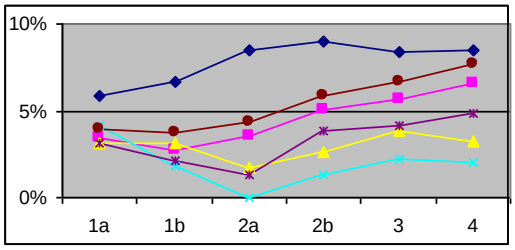


1 ***Figure 6*** **MINAP readmission analysis: trend by risk group**

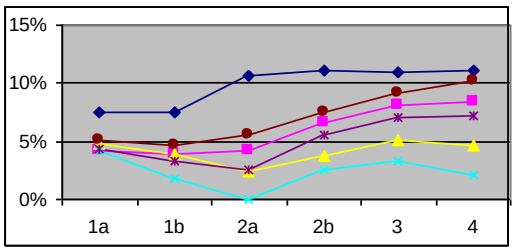
30 days	1a	1b	2a	2b	3	4
No angio	1.95%	2.71%	2.92%	3.88%	2.27%	2.73%
angio only	1.69%	0.92%	1.07%	2.05%	1.24%	2.14%
PCI	1.16%	0.79%	0.44%	1.05%	1.05%	0.00%
CABG	2.08%	0.00%	0.00%	0.00%	0.00%	0.00%
Other	1.17%	1.08%	0.43%	0.43%	0.30%	0.00%
Total	1.59%	1.35%	1.41%	2.32%	1.66%	2.36%



180 days	1a	1b	2a	2b	3	4
No angio	5.84%	6.70%	8.49%	9.02%	8.38%	8.47%
angio only	3.46%	2.76%	3.57%	5.02%	5.61%	6.58%
PCI	3.10%	3.16%	1.77%	2.63%	3.79%	3.21%
CABG	4.17%	1.79%	0.00%	1.28%	2.17%	2.04%
Other	3.13%	2.16%	1.29%	3.88%	4.14%	4.82%
Total	3.90%	3.76%	4.38%	5.82%	6.70%	7.69%



365 days	1a	1b	2a	2b	3	4
No angio	7.43%	7.55%	10.61%	11.07%	10.98%	11.17%
angio only	4.26%	3.85%	4.19%	6.55%	8.08%	8.42%
PCI	4.84%	3.94%	2.43%	3.68%	5.05%	4.59%
CABG	4.17%	1.79%	0.00%	2.56%	3.26%	2.04%
Other	4.30%	3.24%	2.59%	5.60%	7.10%	7.23%
Total	5.10%	4.71%	5.48%	7.47%	9.12%	10.14%



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3

Non-fatal MI at 1 year

This analysis is based on the patients who were alive at one year and had had either an in-hospital re-infarction or a new MINAP record (a readmission to hospital). Results were analysed for admissions during 2005/6 inline with the mortality and readmission analyses. 15,888 patients were included in this analysis.

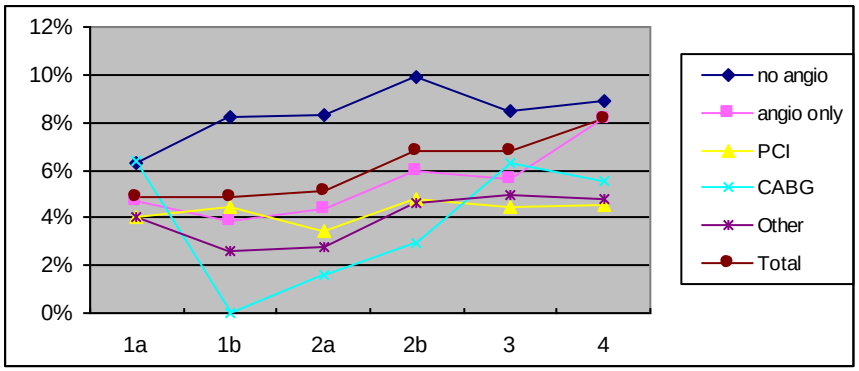
It is noted that using a new MINAP record and not specifically one for MI will slightly overestimate the number of people in the new MI group as it will include UA as well. 85% of readmission following NSTEMI are reported at being for MI[275].

Results of analyses are presented in Figure 7. Event numbers in the CABG group were very low and in one risk group no events occurred at all. Events were therefore pooled in group 1a and 1b, and 2a and 2b for use in the cost-effectiveness analysis – see Figure 7 for pooled figures.

Figure 7 **MINAP non-fatal MI at 1-year analysis**

Percentage of people alive with new non-fatal MI event (either in-hospital re-infarction or readmission)

	1a	1b	2a	2b	3	4	Total
no angio	6.3%	8.2%	8.3%	9.9%	8.4%	8.9%	8.5%
angio only	4.7%	3.8%	4.4%	5.9%	5.6%	8.1%	5.1%
PCI	4.0%	4.5%	3.4%	4.7%	4.5%	4.5%	4.2%
CABG	6.4%	0.0%	1.6%	2.9%	6.3%	5.6%	3.8%
Other	4.1%	2.6%	2.8%	4.6%	5.0%	4.8%	3.9%
Total	4.9%	4.8%	5.1%	6.8%	6.8%	8.1%	6.1%

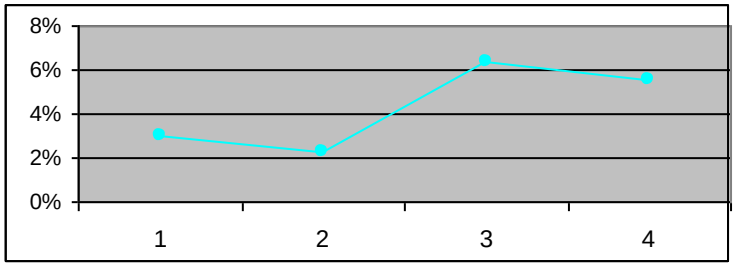


Events (r = number having had a new MI event, n = total number alive at 1 year)

	1a		1b		1		2a		2b		2		3		4		Total	
	r	n	r	n	r	N	r	n	r	n	r	n	r	n	r	n	r	n
no angio	33	523	54	659	87	1182	56	676	73	737	129	1413	151	1790	137	1539	504	5924
angio only	51	1086	44	1151	95	2237	46	1050	53	894	99	1944	67	1200	38	468	299	5849
PCI	20	500	22	494	42	994	15	436	17	358	32	794	19	426	8	178	101	2392
CABG	3	47	0	52	3	99	1	62	2	69	3	131	5	79	2	36	13	345
Other	10	246	7	268	17	514	6	218	10	218	16	436	15	303	6	125	54	1378
Total	117	2402	127	2624	244	5026	124	2442	155	2276	279	4718	257	3798	191	2346	971	15888

Data pooling for use in cost–effectiveness model:

	1	2	3	4
CABG	3.0%	2.3%	6.3%	5.6%



Bleeding analyses

Bleeding in relation to intervention can only safely be examined for those hospitals where interventional work is performed as this information is unlikely to be transmitted back to the referring hospital and then be recorded in MINAP. This limits the size of the cohort to those hospitals where intervention takes place. Note that surgery is not performed in all interventional hospitals and this may result in lower reported bleeding rates for CABG.

For the purposes of this analysis major bleeding was defined as the MINAP categories of: intracranial bleed; retroperitoneal bleed; blood loss > 5 G; and blood loss 3-5 G. Minor bleeding was defined as the MINAP category blood loss < 3 G. Patients with 'unknown' bleeding complications were excluded from the analysis.

Results could not be cross stratified by risk group and management group as event numbers were very low. Results were therefore presented stratified by each separately. 7123 patients were included in the analysis stratified by risk. 7233 were included in the analysis stratified by acute management strategy. (Note that numbers vary as only patients with sufficient information to allow the necessary stratification can be included in each analysis). Event numbers were also judged too low to split risk groups 1 and 2 into 1a and 1b, 2a and 2b.

Results of analyses are presented in Figure 8 and Figure 9. The number of in-hospital bleeding events was reported. Major bleeding increased by risk group, ranging from 0.2% in risk group 1 (1a and 1b combined) to 2.1% in group 4. Minor bleeding was fairly constant across groups 1-3 at around 1%, although increased in group 4 to 1.7%.

The GDG noted that bleed rates appeared lower than expected based on rates seen in randomised controlled trials. As trials for agents that potentially increase the risk of bleeding may well also exclude patients with high bleed risk, it might be thought that registries would have higher rates of bleed than that observed in clinical trials. It is noted that bleeding forms part of the MINAP validation process.

Management and risk could not be cross tabulated for bleed events as event numbers are very low but both a risk trend and variation by acute management strategy was observed (see Figure 8 and Figure 9). To account for this in the cost effectiveness analysis, a relative risk of a bleed event and confidence interval for each management strategy compared to 'total' was calculated. This could then be applied to the risk group rates to calculate a management strategy specific rate for each risk group. In addition, as risk group 1 and 2 could also not be split further into 1a and 1b, and 2a and 2b as event number were very low in the model the rates for 1 will be applied to both 1a and 1b, and the rate for 2 applied to 2a and 2b. The resulting event rates are included in the cost-effectiveness analysis report – see Appendix C.

Figure 8 **MINAP bleeding analysis: by acute management strategy**

	No angio	Angio only	PCI	CABG	Other	All
Major bleeding	25	19	20	6	2	72
	1.1%	*0.9%*	*0.9%*	*2.4%*	*0.7%*	*1.0%*
Minor bleeding	28	21	28	5	0	82
	1.2%	*1.0%*	*1.3%*	*2.0%*	*0.0%*	*1.1%*
Total patients	2348	2144	2227	245	269	7233

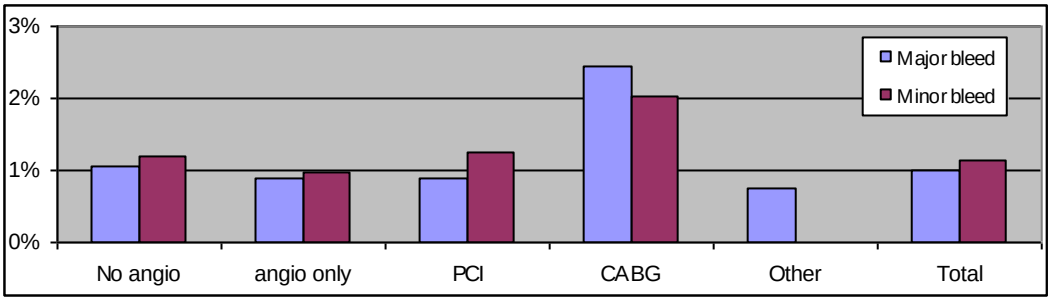
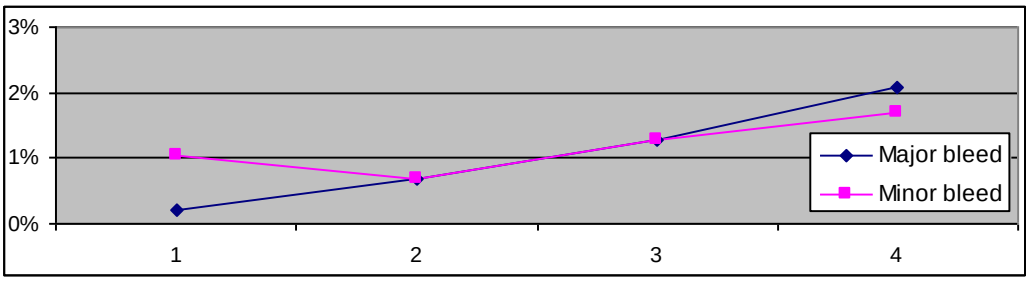


Figure 9 **MINAP bleeding analysis: by risk group**

	1a&1b	2a&2b	3	4	All
Major bleeding	4	13	22	32	71
	0.2%	*0.7%*	*1.3%*	*2.1%*	*1.0%*
Minor bleeding	20	13	22	26	81
	1.0%	*0.7%*	*1.3%*	*1.7%*	*1.1%*
Total patients	1934	1907	1738	1544	7123



Length of stay with complications analyses

Complications such as re-infarction and bleeding have been reported as independently associated with increased hospitalisation costs in patients with UA/NSTEMI[38,160,274,276]. On this basis, length of stay was analysed for patients experiencing these complications.

Length of stay overall and with an in-hospital re-infarction or bleed was analysed for 2007 patients only as analyses suggested that length of stay was falling over time. Length of stay with and without bleeding was analysed in interventional centres only for the reasons described above (Bleeding analyses section).

Results of analyses are presented in Figure 10 and Figure 11. Length of stay was greater in patients that experienced a re-infarction or a bleed complication compared to those that did not.

Figure 10 **MINAP analysis of length of stay with bleeding complications**

Bleeding complications	Mean	SD	Count
None	9	9	3069
Intracranial bleed*	13	9	8
Retroperitoneal bleed*	16	13	4
Blood loss > 5 G*	15	3	3
Blood loss 3-5 G*	15	12	11
Blood loss < 3 G	11	7	29
Total group	*9*	*9*	*3124*

* Classified as major bleed in analysis

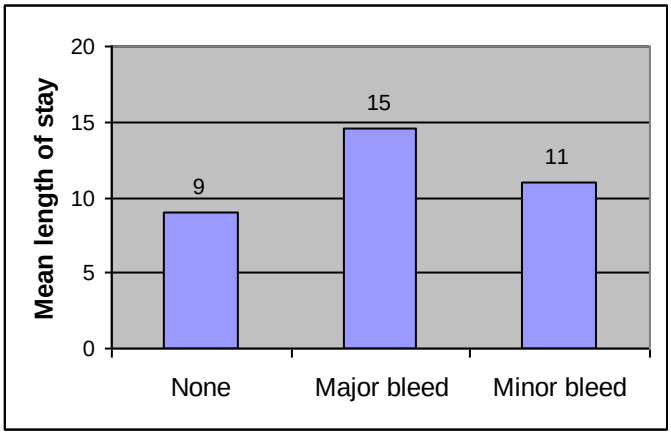
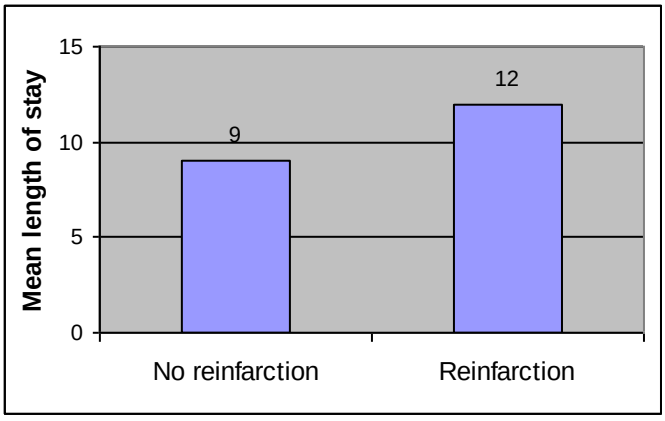


Figure 11 **MINAP analysis of length of stay with bleeding complications**

Re-infarction	Mean	SD	Count
No reinfarction	9	9	3069
Reinfarction	13	9	8
Total group	*9*	*9*	*3124*



Acute management split analyses

The relative percentages of patients undergoing an acute management strategy of no angio, angio only, PCI and CABG is most representative from PCI hospitals only. Intervention is under-represented when the relative percentage is based on all hospitals due to missing data. This arises because hospitals without PCI facilities may not know if or what intervention was performed after transfer, and are likely to leave this information blank.

The acute management split was analysed in both cohorts to verify this. The analyses include 8,299 patients for the PCI centres only and 38,808 patients for all centres. Based on interventional hospital data, 33% received no angiography or intervention, 28% received angiography only, 29% received PCI and 3% received CABG. In 7% the acute management strategy was unknown due to missing data. In comparison in all hospitals this figure rose to 20%.

Acute management strategy was also analysed by risk group. Results are shown in Table 1. Note that patients with missing data have been excluded from this table.

The GDG noted that the CABG rate appeared lower than expected based on BCIS audit data that suggested a 3:1 ratio of PCI to CABG in the UK. It is noted that this may be due a bias in the reporting whereby patients who are transferred for surgery are recorded as 'unknown'. Alternatively it may due to the fact that CABG patients are often discharged home and scheduled for CABG at a later date.

Table 1 **MINAP analysis of acute management strategy by risk group (interventional hospital only)**

	1a	1b	2a	2b	3	4	all
No angio	143	154	192	245	725	1074	2533
	15%	*15%*	*20%*	*26%*	*42%*	*68%*	*35%*
Angio only	348	378	341	313	497	296	2173
	37%	*38%*	*35%*	*33%*	*29%*	*19%*	*30%*
PCI	422	425	404	331	443	180	2205
	45%	*43%*	*41%*	*35%*	*26%*	*11%*	*31%*
CABG	27	37	46	49	67	23	249
	3%	*4%*	*5%*	*5%*	*4%*	*1%*	*3%*
Total patients	940	994	983	938	1732	1573	7160

Demographics

Demographics were reported for each risk group in terms of age breakdown in 10-year bands by gender. See Figure 12 and Table 2. These were used in the extrapolation analysis detailed below

Figure 12 **MINAP analysis age breakdown**

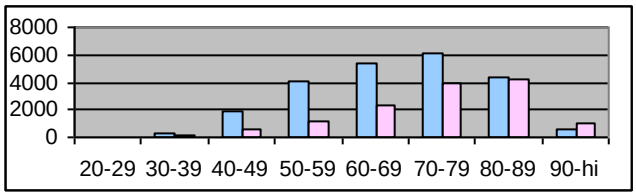
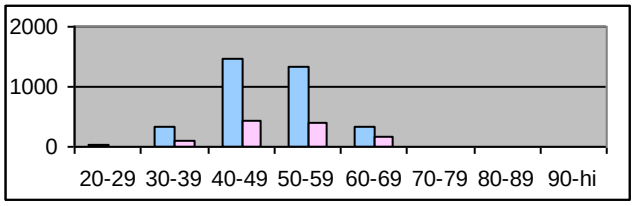
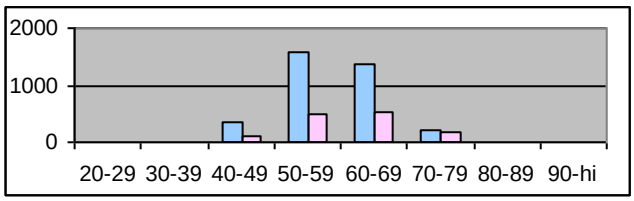
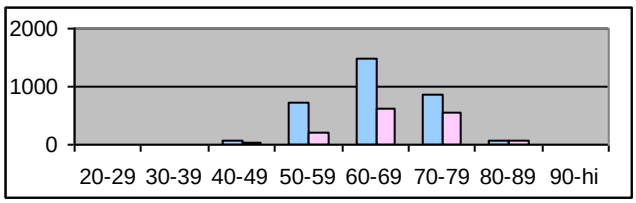
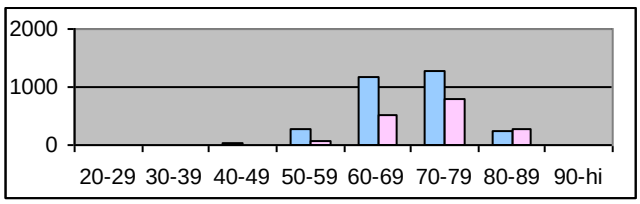
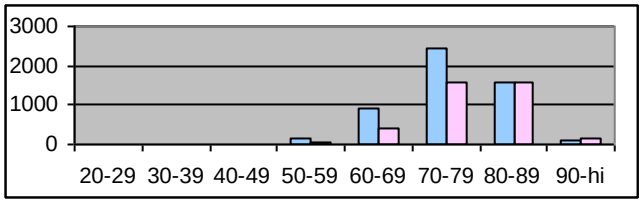
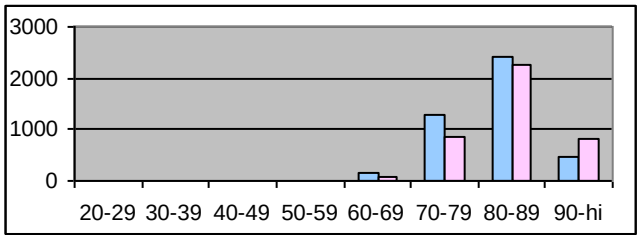
All	
Risk group 1a	
Risk group 1b	
Risk group 2a	
Risk group 2b	
Risk group 3	
Risk group 4	

Table 2 **MINAP analysis age breakdown**

All (mean age 70.6)

	20-29	30-39	40-49	50-59	60-69	70-79	80-89	90-hi	All	years
Male	18	351	1938	4041	5396	6145	4328	565	22782	Count
	25.6	36.6	46	55.6	65.1	75	84.2	92.5	68.3	Mean age
Female	7	109	570	1226	2318	3945	4216	981	13372	Count
	27.1	36.8	46	55.7	65.5	75.4	84.6	92.9	74.5	Mean age
									36154	Total count

Risk group 1a (mean age 49.6)

	20-29	30-39	40-49	50-59	60-69	70-79	80-89	90-hi	All	years
Male	17	338	1481	1321	323	13			3493	Count
	25.4	36.6	45.5	53.8	62.8	72.8			49.4	Mean age
Female	5	104	421	390	151	13			1084	Count
	27	36.7	45.6	54.1	62.8	72.5			50.5	Mean age
									4577	Total count

Risk group 1b (mean age 59.4

	20-29	30-39	40-49	50-59	60-69	70-79	80-89	90-hi	All	years
Male		10	350	1585	1352	206	5		3508	Count
		38	47.4	56.1	63.2	72.6	81.6		58.9	Mean age
Female	2	5	115	487	543	173	6		1331	Count
	27.1	38.6	47	56.1	63.8	72.7	82.1		60.6	Mean age
									4839	Total count

Risk group 2a (mean age 66.1)

	20-29	30-39	40-49	50-59	60-69	70-79	80-89	90-hi	All	years
Male		1	76	716	1491	878	68		3230	Count
		36.9	47.2	56.9	65.3	73.1	82.3		65.5	Mean age
Female			26	223	623	539	63		1474	Count
			47.2	57	65.4	73.4	82.8		67.5	Mean age
									4704	Total count

Risk group 2b (mean age 70.8)

	20-29	30-39	40-49	50-59	60-69	70-79	80-89	90-hi	All	years
Male	1	1	21	275	1167	1280	255	2	3002	Count
	29.1	34.1	46.9	57.5	66.2	73.8	82.5	90.9	69.9	Mean age
Female			5	85	503	780	279	3	1655	Count
			46.4	57.2	66.6	74.5	82.7	93.6	72.5	Mean age
									4657	Total count

Risk group 3 (mean age 77.3)

	20-29	30-39	40-49	50-59	60-69	70-79	80-89	90-hi	All	years
Male		1	9	132	911	2466	1599	84	5202	Count
	.	40	47.3	56.8	66.9	75.5	83.5	92.7	76.2	Mean age
Female			3	36	430	1600	1598	176	3843	Count
	.	.	48.1	56.6	67	76	83.9	93	78.8	Mean age
									9045	Total count

Risk group 4 (mean age 83.7)

	20-29	30-39	40-49	50-59	60-69	70-79	80-89	90-hi	All	years
Male			1	12	152	1302	2401	479	4347	Count
	.	.	48.2	58.2	67	76.8	84.9	92.5	82.6	Mean age
Female				5	68	840	2270	802	3985	Count
	.	.	.	57.5	67.6	77	85.4	92.9	84.8	Mean age
									8332	Total count

Estimation of life-years for the cost effectiveness model

In order to fully capture lifetime quality-adjusted life-years (QALYs) in the cost–effectiveness model an estimate of life expectancy beyond one year was required. The aim was to extrapolate from the MINAP data to attempt to reflect contemporary mortality rates.

Linear extrapolation estimation

It has been observed that following a UA/NSTEMI event mortality is high but that this rapidly declines over time. After possibly as little as one month and certainly by six months, the mortality rate is at a fairly low level[277,278]. In addition long-term studies plotting mortality over time suggest that after 3 months the survival curve is approximately linear[279,280]. On this basis it was planned to estimate life expectancy for patients alive at one year by linearly extrapolating the mortality rate between six months and one year from the MINAP cohort. A linear extrapolation implies an increasing mortality rate over time. Separate extrapolations were undertaken for each risk group as mean age varied considerably across risk groups.

The estimated life expectancy in the risk groups 1a and 1b was higher than that predicted using general population life expectancy estimates. This suggested that the linear extrapolation may not be plausible. This may be explained by the very different age profiles across the risk groups – risk group 1a has a mean age of 50 years, while risk group 4 has a mean age of 84 years. Looking at a survival curve for the general population it could be seen that while in older people a linear extrapolation may lead to a reasonable estimation of life expectancy, in younger people, a linear extrapolation may overestimate life expectancy. An alternative approach was therefore sought.

Standardised mortality ratio based estimation

As an alternative to the linear extrapolation, standardised mortality ratios (SMRs) for UA/NSTEMI patients were calculated based on the observed mortality in the MINAP UA/NSTEMI cohort between 6 months and 1 year, and mortality rates for the general population. Separate SMRs were calculated for each risk group.

Mortality rates for each risk group were calculated using the six-month to one-year rates from the MINAP cohort. Comparable mortality rates for the general population were estimated based on the demographic of the risk group in terms of age (in ten-year age bands) and gender, and mortality rates from 2005-2007 life tables for England and Wales[281]. An SMR was then calculated using this information. Formulae for these calculations are shown in Table 3.

Table 3 **Formulae for estimation of SMRs**

UA/NSTEMI annual mortality rate:

Calculated separately for those with MI at 6 months and those without for each risk group:

$$= - (\ln(1-P) / t$$

Where:
P = probability of death between 6 months and 1 year
t = time period (= 0.5 years)

Age and gender standardised annual mortality rate:

Calculated separately for each risk group:

$$= \frac{(M_a * N_a) + (M_b * N_b) \ldots + (M_p * N_p)}{(N_a + N_b \ldots + N_p)} = \frac{\sum_{x=a}^{p} (M_x * N_x)}{\sum_{x=a}^{p} N_x}$$

Where:
a-p = 10-year age bands by gender
males: a = 20-29 , b=30-39, c=40-49, d=50-59, e=60-69, f=70-79, g=80-89, h≥90;
females: i-p (same age bands)
M_x = mortality rate for England and Wales that corresponds to the mean age from the MINAP sample in a specified 10-year age band
N_x = number of people in a specified 10-year age band in the MINAP sample

Standardised mortality ratio (SMR):

Calculated separately for those with MI at 6 months and those without for each risk group:

$$= \frac{\text{UA/NSTEMI mortality rate}}{\text{Standardised mortality rate}}$$

Life expectancy for each risk group was then calculated using life tables, based on the gender split, mean age and the calculated SMR for the risk group. It was assumed that the SMR past six months is constant over time.

For the cost-effectiveness model we wished to obtain different estimates of life expectancy for people who are: 1) alive at one year and have had a new MI in the past year; and 2) alive at one year but have not had a new MI in the past year. This was in order to reflect the potential prognostic benefit of avoiding MI.

Additional data was obtained from the MINAP cohort in order to do this analysis. Patients who were alive at six months were split into two groups – those that had had a new MI event since their initial UA/NSTEMI event and those that had not. Mortality was then analysed at the one-year time point

(that is, 6 months later). Results of this analysis are shown in Table 4. As there were only two events in risk group 1a and none in 1b these events were pooled together and a single SMR calculated.

A new MI event was defined as an in-hospital re-infarction or a new MINAP record (readmission). It is noted that using a new MINAP record and not specifically one for MI will slightly overestimate the number of people in the new MI group as it will include UA as well. However, as 85% of readmission following NSTEMI is reported at being for MI this is considered a reasonable approximation[275]. The effect of this approximation is likely to be that the mortality rate in each group may be slightly reduced as patients with lower mortality are added to the MI group and patients while concurrently patients with a higher mortality are removed from the no MI group.

SMRs and estimates of life expectancy for those alive at one year are presented in Table 5.

Mortality was higher in the non-fatal MI group than the no event group in each risk group. This translated to a higher predicted life expectancy for those who did not have a new MI compared to those that did. Life expectancy in both UA/NSTEMI groups was lower than that estimated for a comparable group from the general population. These results were plausible and these methods were used to provide estimates of life expectancy for those alive at one year in the cost–effectiveness analysis

Table 4 **Mortality at one year in those alive at six months**

	1a	1b	2a	2b	3	4	Total
Alive without new MI at 6 months							
Population	2564	2793	2642	2511	4350	2964	17824
Deaths at 1 year	13	23	52	77	253	383	801
%	0.5%	0.8%	2.0%	3.1%	5.8%	12.9%	4.5%
Alive with new MI at 6 months							
Population	129	147	147	196	354	312	1285
Deaths at 1 year	2	0	7	14	49	75	147
%	1.6%	0.0%	4.8%	7.1%	13.8%	24.0%	11.4%

Table 5 **SMRs and estimates of life expectancy beyond one year by risk group**

	1a	1b	2a	2b	3	4	All
SMR							
With no new MI	1.9679		2.2213	2.0744	2.0106	2.6335	1.9720
With new MI	2.1225		5.4519	4.9358	4.9990	5.2331	5.2103
Estimated life expectancy for those alive at 1 year							
Mean age at initial UA/NSTEMI event	*49.6*	*59.4*	*66.1*	*70.8*	*77.3*	*83.7*	*70.6*
General population*	30.2	21.6	16.1	13.0	9.2	6.0	13.4
With no new MI	24.4	16.5	11.0	8.8	6.0	3.0	9.4
With new MI	23.7	16.0	6.6	5.1	3.1	1.7	5.2

*For comparison only – not used in model

8 APPENDIX C

A cost-effectiveness model comparing alternative combinations of antiplatelet and antithrombin agents in the treatment of unstable angina and non-ST elevation myocardial infarction (UA/NSTEMI)

Introduction

The GDG wished to evaluate the cost effectiveness of GPIs in combination with clopidogrel, taking into account contemporary management.

The analysis aimed to inform the following questions:

- In which patients should GPIs be used?
- Is bivalirudin a cost-effective alternative to using GPIs and heparin?
- Are the conclusions impacted if fondaparinux is being used instead of a heparin?

Comparators

The following combinations were considered in the model:

- Aspirin +clopidogrel +heparin (LMWH or UFH)
- Aspirin +clopidogrel +heparin +GPI selectively in those proceeding to PCI only
- Aspirin +clopidogrel +heparin +GPI routinely upstream of angiography
- Aspirin +clopidogrel +bivalirudin routinely upstream of angiography
- Asprin +clopidogrel +heparin +bivalirurin selectively in those proceeding to PCI only

In addition, the impact of fondaparinux being used instead of a heparin was considered and the following combinations were considered:

- Aspirin +clopidogrel +fondaparinux
- Aspirin +clopidogrel +fondaparinux +GPI selectively in those proceeding to PCI only
- Aspirin +clopidogrel +fondaparinux +GPI routinely upstream of angiography

Aspirin, clopidogrel and an antithrombin (a heparin – LMWH or UFH – or fondaparinux) are given early following admission to all patients. Patients going on to have coronary intervention (PCI) who initially have a heparin or fondaparinux will receive heparin during the procedure. GPIs can be used in different ways:

1) **GPI (PCI only):** selective use only in those patients who go on to have a PCI – administration of the agent is deferred until time of PCI (abciximab is the only agent licensed in the UK for this use).
2) **GPI (upstream):** routine early use as part of initial medical management (upstream) irrespective of any coronary intervention that may occur downstream (eptifibatide and tirofiban are agents licensed in the UK for this use).
3) **GPI not given** – note however, if patients go on to PCI, GPIs may still be used to treat complications during PCI if necessary (bailout).

Bivalirudin can be initiated upstream of angiography (in those planned for early angiography – as in the ACUITY study) or can alternatively be used selectively at the time of PCI (as in the REPLACE-2 study). In patients using bivalirudin, GPIs are not routinely used but may be used to treat complications during PCI if necessary (bailout use).

Population

The population of interest is people with an acute UA/NSTEMI event. In particular those eligible for clopidogrel, and so potentially inline to receive the combinations of treatments specified above. The analysis was further restricted to patients undergoing an early invasive management approach (all patients undergo angiography and a proportion proceeding to PCI and CABG), because trial results for GPIs and bivalirudin used in the analysis were not relevant to a population not undergoing angiography. This is discussed later in the report.

Cost effectiveness was analysed by risk subgroups. Six risk groups were defined as part of an analysis of MINAP data – a summary is provided in Table 1 below. The creation and interpretation of these risk groups is discussed in more detail in the Risk chapter of the guideline (Section 2) and the report of the analysis of MINAP data for the cost effectiveness analysis (Appendix B).

Table 1. Risk groups for analysis

Risk group	% population	Mini-GRACE risk score (range)	Risk of death
1a	~12.5%	0-70	Low ↓
1b	~12.5%	71-87	
2a	~12.5%	88-99	
2b	~12.5%	100-111	
3	~25%	112-133	
4	~25%	>134	High

Model overview

A cost-utility analysis was undertaken with costs and quality-adjusted life-years (QALYs) considered over patients' lifetime from a UK NHS perspective.

Despite these treatments being for short-term use during an acute episode, a lifetime horizon is most appropriate to capture the full impact of treatment. For example, if a treatment prevents a death and the patient then goes on to live out their full life expectancy, calculating effects at one year will underestimate the QALYs gained. People will also continue to consume healthcare resources during the time they are alive – it is appropriate to take these costs into account when calculating cost effectiveness.

Both costs and QALYs are discounted at a rate of 3.5% in line with NICE guidance[6].

Approach to modelling

The general approach taken was to obtain contemporary UK estimates of events for the aspirin, clopidogrel and heparin arm of the model from recent MINAP data. The effect of different treatment combinations is then modelled by applying relative risks from randomised controlled trials identified by the systematic review of the clinical literature for the guideline. By doing this we are assuming that while baseline event rates from international trials may not be transferable to the UK, relative risks of benefit or harms with treatments are. This is an approach employed in other analyses including the previous NICE technology appraisal of GPIs[210].

The model was built probabilistically in order to take account of the uncertainty around input parameter point estimates. A probability distribution is defined for each model input parameter. When the model is run a value for each input is randomly selected from each input distribution simultaneously and costs and QALYs are calculated using these values. The model is run repeatedly – in this case 10,000 times – and results are summarised. Probability distributions in the analysis were based on error estimates from data sources, for example confidence intervals around relative risk estimates. Various one-way and scenario sensitivity analyses, where one or more inputs were varied, were undertaken to test the robustness of model assumptions and data sources.

Model structure and QALYs

A decision tree was constructed to estimate the number of people at one year who:

- had died
- were alive but had had a new MI event and
- were alive but had not had a new MI event.

Each one-year state was attributed a number of life years. The total number of life years for the population was calculated by multiplying the number of people in each of the three states at one year by the estimated life years for each state and summing. QALYs were calculated by multiplying the number of life years with a quality of life weight. A depiction of the decision tree and this calculation is shown in Figure 1.

The decision tree has four initial branches representing the management strategy in the acute episode: no angiography, angiography only, PCI or CABG. Each initial management strategy is associated with a probability of being dead at one year, and, if alive, a probability of having had a new non-fatal MI event since the initial UA/NSTEMI event. The probability of death and non-fatal MI varies by acute management strategy. The probabilities of death and MI also vary by risk group. Note that the no angiography arm was not utilsied in the final analysis – this is discussed further later in the report.

For the aspirin, clopidogrel and heparin treatment combination, the probability of being dead at one year, and of, given that you are alive, having had a non-fatal MI event at one year are based on the analysis of MINAP data. The details of this analysis and any adjustments made to the original data are detailed in the separate report 'Analysis of MINAP data for the cost-effectiveness analysis' in Appendix B. The probabilities applied in the model are detailed in Table 2 below. These variables were assigned beta distributions for the probabilistic analysis.

Table 2. Baseline probabilities for death and non-fatal MI

Probability of death (1 yr)	1a	1b	2a	2b	3	4
No angio	3.1%	4.9%	9.3%	14.7%	27.2%	51.7%
Angiography only	1.0%	2.1%	4.4%	5.9%	10.1%	27.1%
PCI	0.7%	0.7%	1.9%	4.2%	9.1%	16.5%
CABG	2.0%	2.0%	7.9%	7.9%	13.6%	26.1%

Source: MINAP analysis Appendix B

Probability of non-fatal MI (1 yr)	1a	1b	2a	2b	3	4
No angio	5.4%	7.0%	7.0%	8.4%	7.2%	7.6%
Angiography only	4.0%	3.2%	3.7%	5.0%	4.7%	6.9%
PCI	3.4%	3.8%	2.9%	4.0%	3.8%	3.8%
CABG	2.6%	2.6%	1.9%	1.9%	5.4%	4.7%

Source: MINAP analysis Appendix B

The estimates of life years associated with each final state at one year are also based on the analysis of MINAP data. In brief, for those dead at one year, life years were estimated taking into account the observed timing of deaths over one year. The proportions of death occurring at each time point (30 days, 6 months and 1 year) were assigned a Dirichlet distribution for the probabilistic analysis. For those alive at one year, estimates of life years are calculated by an extrapolation analysis with different estimates for those who had a new non-fatal MI event and those that did not. The details of this analysis are provided in the separate report 'Analysis of MINAP data for the cost-effectiveness analysis' in Appendix B. The life-year parameter was not incorporated in the probabilistic analysis.

The values used in the model are detailed in Table 3 below – these are discounted at 3.5% per annum after one year as per NICE methodological guidance[6].

Table 3. Discounted life years associated with 1-year status

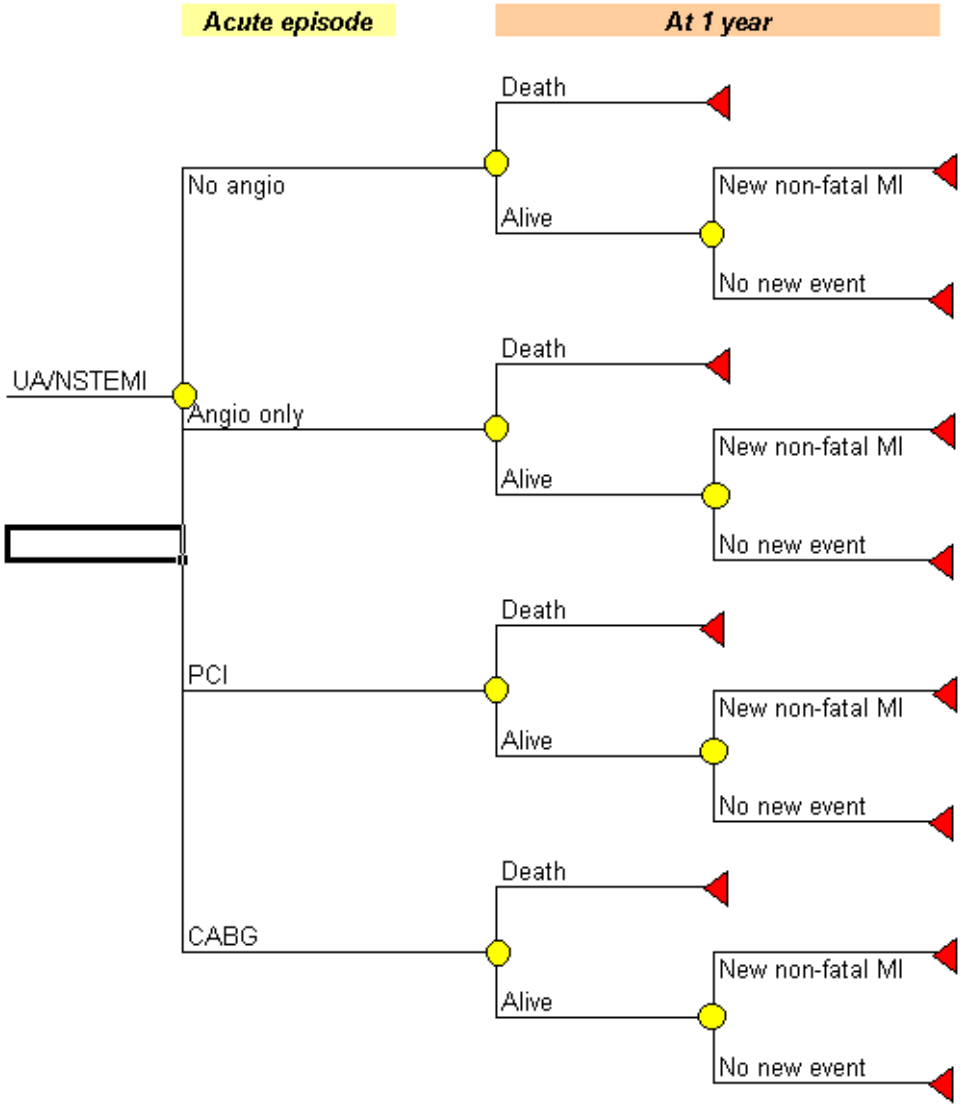
At 1 year	1a	1b	2a	2b	3.0	4.0
Dead	0.42	0.37	0.37	0.38	0.33	0.2
Alive without new MI	16.4	12.7	9.6	8.1	6.1	3.7
Alive with new MI	16.2	12.4	6.5	5.4	3.8	2.6

The probabilities of death and non-fatal MI will vary by treatment combination. As a result, the number of patients in each final state at one year will vary and so ultimately the QALYs associated with each treatment combination.

See below for details of the treatment effects used in the model.

A flat utility value (quality of life weight used to calculate QALYs) of 0.8 with a standard deviation of 0.09 was assumed. This is based on the estimate utilised in the cost-effectiveness model undertaken for the NICE technology appraisal of GPIs[210]. This variable was assigned a beta distribution for the probabilistic analysis.

Figure 1. **Illustration of decision tree and calculation of QALYs**



Patient #	Total life years	Utility	QALYs
a	Xyrs (dead yr1)	Q	a*X*Q
b	Yyrs (alive+MI yr1)	Q	b*Y*Q
c	Zyrs (alive no MI y1)	Q	c*Z*Q
d	Xyrs (dead yr1)	Q	d*X*Q
e	Yyrs (alive+MI yr1)	Q	e*Y*Q
f	Zyrs (alive no MI y1)	Q	f*Z*Q
g	Xyrs (dead yr1)	Q	g*X*Q
h	Yyrs (alive+MI yr1)	Q	h*Y*Q
i	Zyrs (alive no MI y1)	Q	i*Z*Q
j	Xyrs (dead yr1)	Q	j*X*Q
k	Yyrs (alive+MI yr1)	Q	k*Y*Q
l	Zyrs (alive no MI y1)	Q	l*Z*Q

Resource use and costs

First year resource use

Within the first year, resource use is based on the number of various events that occur. This includes: new MI events (in-hospital re-infarction and re-admission for MI), major and minor bleeding in hospital and revascularisation following the acute episode. The events incorporated are based on those with evidence that they are differentially impacted by treatment. All MI not just non-fatal MI are used for resource use purposes. Rates vary by acute management strategy and risk group. In addition the cost of secondary prevention medication is incorporated whilst patients remain alive.

For the aspirin, clopidogrel and heparin arm the event rates are based on the analysis of MINAP data except for revascularisation following the acute episode which was not available and is estimated from the literature.

The cost of the revascularisation during the acute episode is not incorporated as it is assumed that treatments do not differentially impact the acute management strategy (whether patients undergo angiography only, PCI, CABG). Trial results being used for this analysis do not provide evidence for an effect. This is judged likely to be a reasonable assumption for patients undergoing an early invasive strategy who routinely undergo angiography with revascularisation if indicated. This issue is discussed further later in the report.

Acute episode drug costs are discussed below.

MI and bleeding events

MI and bleed event rates used in the model for the aspirin, heparin and clopidogrel arm are summarised in Table 4 below. See the separate report on the analysis of MINAP data (Appendix B) for full details of the analyses and any adjustments made to the original data. These variables were assigned beta distributions for the probabilistic analysis.

Table 4. Baseline resource use rates (aspirin+clopidogrel+heparin arm)

New MI – readmission (1 yr)	1a	1b	2a	2b	3	4
No angiography	6.2%	7.2%	8.2%	9.5%	9.4%	9.4%
Angiography only	3.6%	3.3%	4.4%	5.8%	6.1%	7.4%
PCI	3.8%	4.6%	2.3%	2.8%	3.4%	4.0%
CABG	2.2%	2.2%	2.2%	2.2%	2.2%	2.2%

Source: MINAP analysis Appendix B

New MI - inhosp reinfarction	1a	1b	2a	2b	3	4
No angio	0.7%	1.7%	0.8%	1.4%	1.4%	2.4%
Angiography only	1.2%	1.0%	0.9%	1.3%	1.5%	3.5%
PCI	1.1%	1.8%	2.2%	2.8%	2.1%	3.5%
CABG	1.4%	1.4%	2.5%	2.5%	2.0%	3.3%

Source: MINAP analysis Appendix B

5. Major bleed (in-hospital)	1a	1b	2a	2b	3	4
No angio	0.2%	0.2%	0.7%	0.7%	1.4%	2.2%
Angiography only	0.2%	0.2%	0.6%	0.6%	1.1%	1.8%
PCI	0.2%	0.2%	0.6%	0.6%	1.1%	1.9%
CABG	0.5%	0.5%	1.7%	1.7%	3.1%	5.1%

Source: MINAP analysis Appendix B

6. Minor bleed (in-hospital)	1a	1b	2a	2b	3	4
No angiography	1.1%	1.1%	0.7%	0.7%	1.3%	1.8%

Angiography only	0.9%	0.9%	0.6%	0.6%	1.1%	1.5%
PCI	1.1%	1.1%	0.8%	0.8%	1.4%	1.9%
CABG	1.9%	1.9%	1.2%	1.2%	2.3%	3.0%

Source: MINAP analysis Appendix B

Revascularisation beyond the acute episode

Revascularisation beyond the acute episode could not be obtained from the MINAP analysis as only revascularisation prompted by an ACS event will be included in MINAP not all revascularisation.

Randomised controlled trials being used in the model were reviewed as a possible alternative source of rates. In addition studies of PCI versus CABG identified in the clinical literature search were reviewed and also the inputs used in the analysis undertaken as part of the NICE technology appraisal of GPIs[210]. The relevant data are shown in Table 5.

Table 5. **Revascularisation rate data**

Study	Population	Data	Notes
Studies being used in model for effectiveness data			

ISAR REACT 2 (RCT)[94]	UA/NSTEMI PCI population	• 16.2% target vessel revascularisation (TVR) at one year in aspirin, clopidogrel + heparin arm
		  ○ 90.2% PCI
		  ○ 9.8% CABG
			TVR would be expected to be lower than any revascularization

ACUITY (RCT)[111]	UA/NSTEMI early invasive population	• 8-9% unplanned revascularisation at one year across arms • In PCI subgroup 11-12% ○ The calculated rate in those not undergoing PCI is therefore ~5% (population = 11% CABG, 33% angiography only)	All arms either had GPI or bivalirudin use, therefore rate might be expected to be perhaps a little lower than in a aspirin, clopidogrel + heparin only group
OASIS 5 (RCT)[113]	UA/NSTEMI population	• Revascularisation not reported as an outcome	
Studies comparing PCI and CABG in UA/NSTEMI identified in systematic review			

ERACI-II (RCT)[214]	Mulitvessel CAD and UA	• CABG group
		  ○ Repeat revascularisations at five years = 7.2%
		• PCI group
		  ○ Repeat revascularisations at five years = 28.4%
		  ○ CABG at five years = 8.4% (30% of repeat revascs)
		• 66% of events occurred in first year in PCI arm
		  ○ PCI: 18.9% yr1; 5.5% yr2-5
		  ○ Assuming same % in yr1 in CABG arm: 4.8% yr1; 2.4% yr2-5	

AWESOME (RCT)[282]	Medically refractory UA	Not reported separately	
SOS –	Acute MI &	• CABG group	

ACS subgroup (RCT)[216]	UA (62% UA)	○ Repeat revasc = 7.1% ○ PCI at one year = 4.8% (67%) ○ Repeat CABG at one year = 2.4% (33%) • PCI group ○ Repeat revasc = 15.5% ○ Repeat PCI at one year = 10.3% (66%) ○ CABG at one year = 5.2% (34%)	
ARTS – UA subgroup (RCT)[217]	Multi vessel disease and LVEF ≥30% and UA	• CABG group ○ PCI at one year = 2.7% (75%) ○ Repeat CABG at one year = 0.9% (25%) • PCI group ○ Repeat PCI at one year = 10.6% (63%) ○ CABG at one year = 6.2% (37%)	
Palmerini (Italian cohort study)[218]	De novo ≥50% unprotected left main coronary stenosis; 63% UA/NSTEMI	Not reported separately	
Seung (Korean cohort study)[219]	Unprotected left main CAD; 57%UA, 11% NSTEMI	• CABG group ○ TVR at one year = 1.5% ▪ 100% PCI ○ TVR at two years = 2.4% (+0.9%) ○ TVR at three years = 2.6% (+0.2%) • PCI group ○ TVR at one year = 9% • 82.1% repeat PCI • 17.9% CABG ○ TVR at two years = 11.2% (+2.2%) ○ TVR at three years = 12.6% (+1.4%)	
GPI technology appraisal cost-effectiveness analysis[210]			
PRAIS-UK	UA/NSTEMI population	• Probability of repeat revascularization in six months in those that had an acute PCI = 4.8% (100% PCI) ○ Equates to 9.4% at one year assuming a constant rate • Probability of revascularization in six months in those that had no acute revascularization = 5% (48% PCI) ○ Equates to 9.8% at one year assuming a constant rate • No repeat revascularization incorporated for acute CABG patients	

It is noted that since many of the PCI vs CABG studies, drug eluting stent use will have reduced revascularisation rates following PCI[205]. Based on the data above and discussion with members of the GDG the rates of revascularisation as summarised in Table 6 were used in the model. These are considered likely to be fairly conservative. A flat rate is assumed across risk groups in the absence of other information. The impact of higher rates was explored in sensitivity analysis.

Table 6. Baseline revascularisation rates post-acute period

7. Non-acute revasc (1 yr)	1a	1b	2a	2b	3	4
No angiography	10.0%	10.0%	10.0%	10.0%	10.0%	10.0%
Angiography only	10.0%	10.0%	10.0%	10.0%	10.0%	10.0%
PCI	10.0%	10.0%	10.0%	10.0%	10.0%	10.0%
CABG	3.0%	3.0%	3.0%	3.0%	3.0%	3.0%

Source: assumption

The proportion of these revascularisations that were PCI vs CABG was also estimated as these have very different costs. Table 7 summarises the splits used. British Cardiovascular Intervention Society (BCIS) audit data suggests that overall the ratio of PCI to CABG is 3:1 (this includes revascularisation for other indications as well as UA/NSTEMI)[178]. For those that did not undergo a revascularisation in the acute period this ratio is applied in the absence of other data. Among patients who have a PCI as part of the acute episode, the split between PCI and CABG for repeat revascularisations is set equal to that observed in the aspirin, clopidogrel and heparin arm of the ISAR REACT-2 trial[94]. This was judged the most relevant data available (97% were stents, 49% with drug eluting stents, and all patients received clopidogrel during the acute episode). Among patients who have a CABG as part of the acute episode, the split between PCI and CABG is set equal to that observed in the ARTs trial[217] – this was the middle figure of the three available.

Table 7. **Proportion of non-acute revascularisation that are PCI/CABG**

	PCI	CABG
No angiography	75%	25%
Angiography only	75%	25%
PCI	90%	10%
CABG	75%	25%

These variables were not assigned distributions for the probabilistic analysis.

Secondary prevention medication

The cost of secondary prevention medication is applied to all patients throughout the model whilst they are alive. In the first year this is assumed to consist of aspirin, clopidogrel, an ACE inhibitor, a beta blocker and a statin based on what a typical patient would receive based on recommendations in the NICE Guideline for secondary prevention following an MI[283]. See Table 11 for details of drugs and dosing used.

Annual disease-related resource use beyond the first year

A flat annual cost is applied to all patients alive beyond one year. Resource use beyond one year was not available from the analysis of MINAP data. It was therefore estimated based on an assumed annual probability of having a new MI admission and a revascularisation as key cost drivers, plus the cost of secondary prevention medication. It is assumed the probability of having these events is constant over time. The figures used are summarised in Table 8.

An annual probability of having a new MI was estimated assuming that the rate of MI observed between six months and one year in the MINAP analysis overall cohort was constant. The annual probability of having a revascularisation was informed by the information identified to estimate revascularisation rates for the first year (as described earlier in the report). In the absence of other information the annual revascularisation rate post one-year was based on the rate observed in the ERACI-II study PCI arm.

Table 8. MI and revascularisation rates beyond first year

Event	Annual probability	Source
MI	4%	Estimate based on rate observed in MINAP overall cohort between six months and one year post UA/NSTEMI event
Revascularisation	2.5%	Estimate based on rate observed in ERACI-II study PCI arm years 2-5[214].

In terms of secondary prevention medication, patients were assumed to receive aspirin, an ACE inhibitor, a beta blocker and a statin post-one year based what a typical patient would receive based on recommendations in the NICE Guideline for secondary prevention following an MI[283].

Unit costs

Acute episode event costs

The cost of complications occurring in-hospital was based on differential length of stay data from the MINAP analysis (see MINAP analysis Appendix B) and the cost of an excess bed day for patients with suspected or actual MI from the 2006/2007 NHS reference costs[224]. These costs are summarised in Table 9. The additional length of stay and cost per day variables were assigned gamma distributions for the probabilistic analysis.

Table 9. Cost of complications

Complication	Additional length of stay	Cost per day	Total additional cost
Reinfarction	3 days	£182	£545
Major bleed	6 days		£1,006
Minor bleed	2 days		£363

Sources: MINAP analysis Appendix B, 2006/2007 NHS reference costs[224]

Post-acute episode event costs

The costs of post-acute episode events are summarised in Table 10. The cost of a readmission for MI is based on 2006/2007 NHS reference cost data incorporating the hospital stay, ambulance costs and A&E costs[224]. The GDG estimated that 85% of patients arrive at hospital by ambulance[284]. It is assumed that all patients incur an A&E cost. The cost of post-acute episode PCI and CABG is based on a weighted average of elective and non-elective 2006/2007 NHS reference cost data[224]. Cost variables were assigned gamma distributions for the probabilistic analysis.

***Table 10.* Cost of events post-acute episode**

Event	Cost per event
New MI readmission	£1,783
Revascularisation – PCI	£2,686
Revascularisation – CABG	£8,513

Source: 2006/2007 NHS reference costs[224]

Secondary prevention medication

Secondary prevention medication doses were based on dosing recommendations and discussion with the pharmacist on the GDG. Costs are from the BNF 58[139]. Doses and costs used are summarised in Table 11.

Table 11. Cost of secondary prevention drugs

Drug	Dose	Cost/year
Aspirin	75mg once daily	£6.97
Clopidogrel	75mg once daily (first 12 months only)	£442.26
ACE	Ramapril 5mg twice daily	£34.15
Beta blockers	Atenolol 25mg daily	£10.69
Statin	Simvastatin 80mg daily	£37.41
Total year 1		**£531**
Total year 2+		**£89**

Source: BNF 58[139]

Annual disease related costs post-one year

An annual disease related cost was estimated based on the event costs and event rates described above and incorporating the cost of secondary prevention medication. The average annual cost was estimated at £264 on this basis.

It is acknowledged that there was limited data to inform the estimate of disease-related costs post-one year. Comparison with long-term estimates of disease-related costs used in the cost-effectiveness analysis undertaken for the NICE technology appraisal of GPIs[210] suggested the figure of £264 was low. Annual costs of £1421, £3966, £1587 were associated with having no new event, the first year of having a new MI and subsequent years after having a new MI respectively. This was based on hospital resource use observed in the Nottingham Heart Registry Cohort (1998). Other sources of resource use/costs in the period post-one year in patients who had had a UA/NSTMI event were not identified in the literature – cost of illness papers were identified from the economic literature search. The impact of using a higher annual cost was explored in sensitivity analysis – a cost of £1600 was used.

Costs beyond one year were discounted at a rate of 3.5% per annum as per NICE methodological guidance.

Acute management split

The proportion of patients undergoing each acute management strategy was based on data from the MINAP analysis (Table 12) or the ACUITY trial[111], depending on the analysis. In the ACUITY trial where all patients underwent angiography, 32% received angiography only, 56% PCI and 11% CABG.

It is acknowledged that the data from MINAP may best represent the UK situation. However, conversely the treatment effects observed in the ACUITY timing trial (utilised for the comparison between selective GPI during PCI only use and routine upstream GPI use) may depend on the proportion of patients undergoing PCI to those who are not.

Table 12. MINAP acute episode management split

Basecase: MINAP management split						
	1a	**1b**	**2a**	**2b**	**3**	**4**
No angiography	15%	15%	20%	26%	42%	68%
Angiography only	37%	38%	35%	33%	29%	19%
PCI	45%	43%	41%	35%	26%	11%
CABG	3%	4%	5%	5%	4%	1%

Sources: MINAP analysis Appendix

B

Note that the proportion of patients in the MINAP 'no angiography' group will not impact the results as treatment effects are not applied in these patients for GPIs and bivalirudin as the trials weren't relevant to this population. The ratio of patients receiving no angiography, PCI and CABG may impact results as these patient groups have different baseline event risks and treatment costs. This is discussed further later in the report.

Treatment effect data

As described above baseline event rates for the aspirin, clopidogrel plus heparin arm of the model were obtained from an analysis of MINAP data, and additional sources where necessary. The impact of alternative treatment combinations were then modelled by applying relevant relative risks from randomised controlled trials to these baseline event rates.

Studies

Relative risks were sought from the studies identified in the systematic evidence reviews undertaken for the guideline and for the NICE GPI technology appraisal (TA47). Studies relating to use of GPIs, bivalirudin and fondaparinux were identified. In order to best represent effects on a background of clopidogrel and aspirin, effectiveness data were used from trials where there was 50% or more clopidogrel use (all trials had close to 100% aspirin use).

In addition, in the clinical review for the guideline studies were only included if the population was at least 60% UA/NSTEMI, and so this cut-off was also used when checking studies identified in the GPI technology appraisal for relevance. Additionally, trials were checked to ensure stents were used in PCIs in order to reflect contemporary practice.

Table 13 below summarises the studies identified in the systematic review for the guideline and the GPI technology appraisal, and whether they meet the criteria for inclusion in the cost-effectiveness analysis.

Table 13. **Studies from systematic literature review**
Selective deferred PCI GPI vs no GPI

Study	Search	Clopidogrel[u]	UA/NSTEMI[v]	Included?
CAPTURE[285]	TA47	×	✓	No
Chen[286]	TA47	×	✓	No
EPIC[287-289]	TA47	×	×	No
EPILOG[290,291]	TA47	×	×	No
EPISTENT[292]	TA47	×	×	No
ERASER[293]	TA47	×	✓	No
ESPRIT[96,294]	TA47	✓	×	No
Galassi[295]	TA47	×	✓	No
Harrington[296]	TA47	×	×	No
IMPACT II[297]	TA47	×	×	No
RESTORE[298]	TA47	×	✓	No

[u] ✓ If clopidogrel use ≥50%; × If clopidogrel use <50%

[v] ✓ If UA/NSTEMI ≥60%; × If UA/NSTEMI <60%

ELISA-2[97]	Guideline	✓	✓	No*
ISAR-REACT 2[91,94]	Guideline	✓	✓	**Yes**

*Different clopidogrel doses in each arm

Upstream non-selective GPI use vs no GPI

Study	Search	Clopidogrel[u]	UA/NSTEMI[v]	Included?
GUSTO IV[299]	TA47	×	✓	No
PARAGON A[300]	TA47	×	✓	No
PARAGON B[301]	TA47	×	✓	No
PRISM[302]	TA47	×	✓	No
PRISM-PLUS[303]	TA47	×	✓	No
PURSUIT[304]	TA47	×	✓	No
Canadian lamifiban study[305]	TA47	×	✓	No

Selective deferred PCI GPI vs upstream non-selective GPI

Study	Search	Clopidogrel[u]	UA/NSTEMI[v]	Included?
ACUITY timing (unpublished heparin background only subgroup)[99,109]	Guideline	✓	✓	**Yes**
Early ACS[100]	Guideline	✓	✓	**No***

* The Early ACS trial was published late in the guideline development process. Early ACS only reports 30-day outcomes whereas the model had been developed with 1-year rates and effectiveness data. Meta analysis undertaken for the guideline reported similar results to the ACUITY study alone. On this basis Early ACS was not incorporated into the cost-effectiveness analysis base case. Sensitivity analyses were undertaken to examine the possible impact.

Bivalirudin vs heparin (LMWH or UFH) + GPI

Study	Search	Clopidogrel[u]	UA/NSTEMI[v]	Include?
ACUITY[110,111] (bivalirudin initiated upstream of angiography)	Guideline	✓	✓	**Yes**
REPLACE 2 ACS subgroup[112] (bivalirudin initiated at PCI)	Guideline	✓	✓	**Yes**

Fondaparinux versus heparin

Study	Source	Clopidogrel[u]	UA/NSTEMI[v]	Include?
OASIS-5[113]	Guideline	✓	✓	**Yes**

Key studies were therefore:

- ISAR REACT 2
    - GPI (abciximab) use during PCI versus no GPI use
    - UA/NSTEMI patients undergoing PCI population
    - Background drugs: 100% aspirin, 100% clopidogrel, 100% heparin (UFH)
    - 30-day and 1-year follow-up

- ACUITY timing (heparin background and clopidogrel before angiography or before PCI subgroup)[w]
    - Routine upstream GPI (eptifibatide or tirofiban) use versus selective deferred GPI use during PCI (abciximab or eptifibatide[x])
    - UA/NSTEMI patients treated with an early invasive strategy (that is routine angiography within 72hrs with revascularisation if indicated)
    - 99% angiography: 56% PCI, 11% CABG, 33% and medically managed (angiography only)
    - Background drugs: 98% aspirin, 100% clopidogrel, 100% heparin(UFH or LMWH)
    - 30-day and 1-year follow-up
- ACUITY (clopidogrel before angiography or before PCI subgroup)
    - Bivalirudin (routine use upstream of angiography) vs heparin (routine upstream LMWH or UFH) + GPI (50% routine upstream eptifibatide or tirofiban/50% selective abciximab or eptifibatide deferred to PCI)[y]
    - UA/NSTEMI patients treated with an early invasive strategy (that is routine angiography within 72hrs with revascularisation if indicated)
    - 99% angiography: 56% PCI, 11% CABG, 33% medically managed (angiography only)
    - Background drugs: 98% aspirin, 100% clopidogrel
    - 30-day and 1-year follow-up
- REPLACE 2 (ACS subgroup)
    - Bivalirudin use during PCI (bailout GPI use only) versus heparin (UFH) + planned GPI (eptifibatide or abciximab) use
    - ACS patients undergoing PCI population
    - Background drugs: 100% aspirin, 85% clopidogrel
    - 30-day (all endpoints), 6-months (death, MI and revascularisation) and 1-year (death only) follow-up
- Oasis 5
    - Fondaparinux vs enoxaparin (LMWH)
    - General UA/NSTEMI population (angiography or revascularisation neither mandated nor discouraged)
    - 66% angiography: 34% PCI, 9% CABG (in hospital)
    - Background drugs: 98% aspirin, 67% clopidogrel
    - 9-day, 30-day and 6-month follow-up

Reconciling the MINAP population and the trial populations

Patients with UA/NSTEMI can be treated in a number of ways. Some patients will undergo angiography and revascularisation (PCI or CABG) if indicated. It is recommended practice in many patients for this to occur routinely and early (this guideline has recommended angiography within 96

[w] Note that ACUITY and ACUITY timing are different analyses of the same study. Note that the clopidogrel subgroup was used for all ACUITY data for the cost-effectiveness model to maintain consistency in the clinical effects.

[x] Eptifibatide is not licensed for this use in the UK – by using the results from this trial we are assuming a class efficacy effect.

[y] Note that the ACUITY study also include a bivalirudin + GPI (50% upstream/50% deferred selective use during PCI) – this combination is not incorporated in the model as it did not demonstrate benefits over heparin + GPI and is more expensive.

hours of admission). In other patients a conservative strategy will be taken whereby patients receive medical therapy and are only referred for angiography if ischemia persists. In patients who undergo angiography (at any time point) around a third will not require revascularisation.

MINAP, being a registry, represents the real current UK situation and as such contains a mixture of management strategies with patients treated optimally and treated less than optimally. This is both the strength and weakness of using it. In interventional centres in the UK the median time from admission to PCI was 3.2 days in 2007[178]. Across all types of centres, average time to PCI has been unofficially estimated at 7-8 days.

Trials however are in specified international populations that may vary to the UK real-world population. Of the trials utilised in this analysis, the ISAR REACT 2 trial has a PCI population where the recommended strategy was early PCI with stenting within six hours from establishment of ACS. The ACUITY trial is an early angiography population with a median time from admission to angiography of 20hrs.

This makes interpreting trials in a UK context difficult. One approach would be not to attempt to use UK specific data and undertake an analysis purely based on the clinical trial data. However, while this would be neat and internally consistent it would not necessarily be very useful in the context of UK decision-making.

Therefore in this analysis we have aimed to combine UK specific data with the available trial evidence. This does however introduce uncertainties into the analysis. We have tried to address these, where feasible, through sensitivity analysis.

For these reasons the following were performed:

- MINAP data was used as a source of event rates for the analysis
- MINAP data was analysed by acute management strategy defined as ‘no angiography’, ‘angiography only’, ‘PCI’ and ‘CABG’.
    - It was considered that splitting the no angiography and angiography only patients into two groups was more flexible in terms of the analysis.
    - Patients who have undergone angiography and deemed not to require revascularisation are potentially quite different to those that do not undergo angiography.
    - The latter may include low risk patients whose symptoms settled down with medical management but also patients deemed too high risk to undergo an invasive procedure.
    - The ‘angiography only’, ‘PCI’ and ‘CABG’ groups will more closely represent an early angiography population.
- Treatment effects were not applied to the ‘no angiography’ group.
    - While there is evidence for use of GPIs in medically managed populations who do not undergo angiography, the trials being used for this analysis (that is where clopidogrel is also used) simply did not cover this population.
    - MI and death rates in the ‘no angiography’ arm were generally higher than in the other arms
    - The ACUITY study reports amalgamated results for the whole early angiography population (i.e. including patients who underwent only angiography with medical treatment, those who underwent PCI and those who underwent CABG). The comparison between routine use of upstream GPIs and selective use in PCI patients only may therefore be dependent upon the relative proportions of these groups (for example, if no patients undergoes PCI you would not expect the benefits to be the same as observed when 56% of patients underwent PCI).

- It was assumed that treatment choice did not differentially impact the acute management strategy (whether patients undergo PCI, CABG, angiography only or no angiography or revascularisation)
    - This was judged a reasonable assumption for patients undergoing an early invasive strategy who will routinely receive angiography with revascularisation performed if indicated)
    - In addition the studies being used do not provide evidence of an impact on acute management strategy – the ACUITY revascularisation endpoint is specifically unplanned revascularisation for ischemia following the initial planned acute management strategy.

It is acknowledged that this approach has strengths and weaknesses but it is judged to be a reasonable and pragmatic approach to assessing cost effectiveness based on the available data.

Relative risks

Relative risks and confidence intervals at one-year are used as reported in published studies where available. Where relative risks were not reported these were calculated using RevMan5. Relative risks specifically for non-fatal MI were not reported. Where a 'death or MI' composite was reported non-fatal MI event numbers were calculating by subtracting death events, and the relative risk calculated using RevMan5. Where a 'death or MI' composite was not reported the MI relative risk was used.

For consistency, relative risks based on in-hospital TIMI bleeding were used where available. If not, the closest time point available and/or the trial bleeding definition was used.

Unpublished one-year data are used from the ACUITY study for the relative outcomes for patients treated with bivalirudin upstream of angiography, heparin + routine GPI use upstream of angiography, and heparin + selective GPI use during PCI only[109]. For the bivalirudin comparisons a clopidogrel subgroup is most appropriate in line with licensing and so in the model all outcomes are used from this group although it is noted that GPI use is not dependant on clopidogrel use unlike bivalirudin. This is judged appropriate to maintain consistency in the relative risks between all these groups and because one of the aims of the analysis was to look at GPI use in combination with clopidogrel.

Relative risks were applied in the following cumulative manner to generate an estimate of event numbers for each treatment arm in the model. This preserves the relative treatment effects observed between comparators in trials. Relative risks are only applied to the population to whom they rela. Baseline probabilities = those for the aspirin+clopidogrel+heparin arm

- ASPIRIN+CLOPIDOGREL+HEPARIN+GPIduringpci arm: Relative risks from the ISAR-REACT trial were applied to the baseline event rates for the PCI patients only. This generates a new set of event rates which only varies from the baseline rates in the PCI patients.
- ASPIRIN+CLOPIDOGREL+HEPARIN+GPIupstream arm: Relative risks from the ACUITY timing study (heparin background subgroup) were then applied to the ASPIRIN+CLOPIDOGREL+HEPARIN+GPIduringpci event rates in 'angiography only', 'PCI' and 'CABG' patients.
- ASPIRIN+CLOPIDOGREL+BIVALIRUDIN arm: Relative risks based on the ACUITY study bivalirudin monotherapy arm and the heparin+upstream GPI arm were then applied to the ASPIRIN+CLOPIDOGREL+HEPARIN+GPIupstream event rates in 'angiography only', 'PCI' and 'CABG' patients.
- ASPIRIN+CLOPIDOGREL+HEPARIN+BIVALIRUDINduringPCI arm: Relative risks from the REPLACE-2 ACS subgroup were applied to the event rates in the ASPIRIN+CLOPIDOGREL+HEPARIN+GPIduringpci arm for the PCI patients only. This generates a new set of event rates which only varies in the PCI patients.

The impact of having a starting point of fondaparinux rather than a heparin was modelled by first applying the relative risks from OASIS 5 trial to the baseline probabilities for the aspirin+clopidogrel+heparin arm to generate NEW baseline probabilities. The GPI comparisons are then reapplied to the new baseline rates – this assumes that the effect of GPIs is independent of whether heparin or fondaparinux is used. Fondaparinux is not incorporated into the bivalirudin arms at all, as currently there is no experience using these agents together and so it was judged inappropriate to do so.

Figure 2 below illustrates this cumulative application of relative risks. Table 14 summarises the relative risks used in the model. Relative risks are assumed to be constant across risk groups. Relative risks were assigned lognormal distributions for the probabilistic analysis.

Figure 2. **Illustration of cumulative application of relative risks in model**

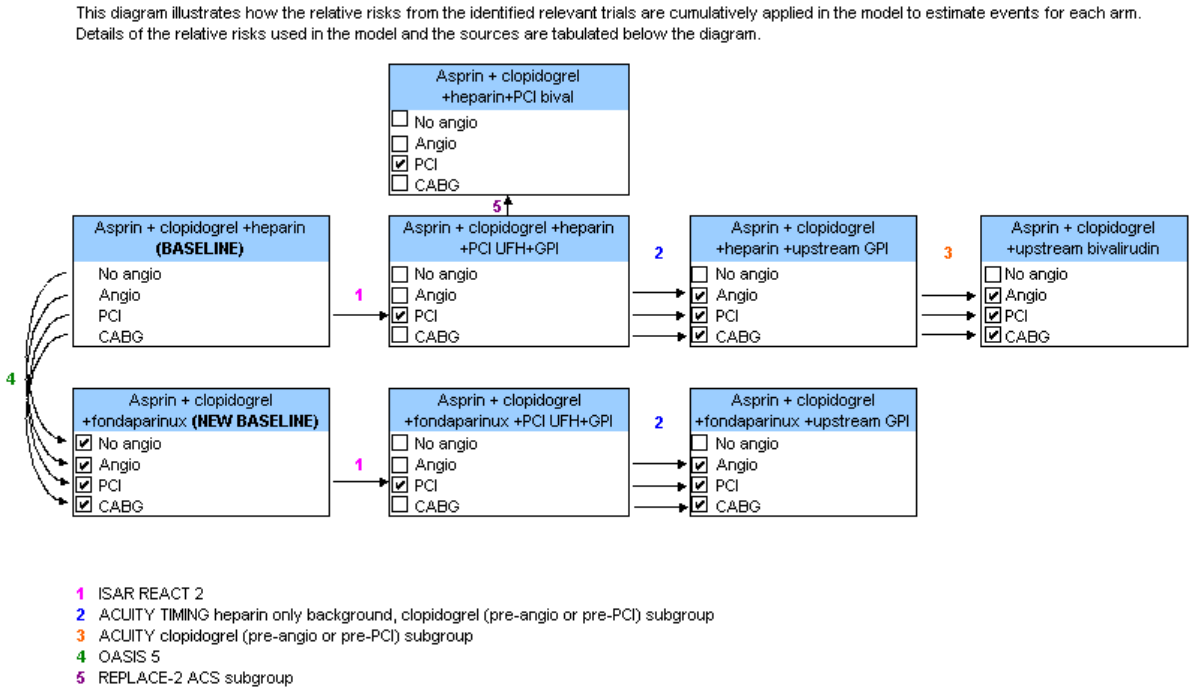


Table 14. **Relative risks used in model**

Mortality (1 year)				
	RR	***LCI***	***UCI***	**SOURCE**
1	0.91	0.61	1.24	*ISAR REACT 2 1 year results*
2	1.03	0.71	1.49	*Unpublished ACUITY data (pre-angio/pre-PCI clop subgroup). Upstream GPI vs deferred GPI (hep background only) at 1 year.*
3	0.89	0.64	1.24	*Unpublished ACUITY data (pre-angio/pre-PCI clop subgroup). Bival monotherapy vs upstream GPI (hep background only) at 1 year.*
4	0.89	0.80	1.00	*OASIS-5 6 months results - assume RR maintained at 1 year*
5	0.85	0.37	1.95	*REPLACE-2 1 year result*
MI (1 year) - applied to inhospital reinfarction and readmissions for MI				
	RR	***LCI***	***UCI***	**SOURCE**
1	0.76	0.58	1.00	*ISAR REACT 2 1 year results*
2	0.90	0.68	1.18	*Unpublished ACUITY data (pre-angio/pre-PCI clop subgroup). Upstream GPI vs deferred GPI (hep background only) at 1 year.*

3	1.09	0.85	1.39	*Unpublished ACUITY data (pre-angio/pre-PCI clop subgroup). Bival monotherapy vs upstream GPI (hep background only) at 1 year.*
4	0.95	0.85	1.06	*OASIS-5 6 months results - assume RR maintained at 1 year*
5	1.06	0.73	1.53	*REPLACE-2 6 months results (outcome not recorded at 1 year) - assume RR maintained at 1 year*
Non-fatal MI (1 year)				
	RR	***LCI***	***UCI***	**SOURCE**
1	0.68	0.51	0.91	*ISAR REACT 2 1 year results - calculated from Death/MI events minus death events*
2	0.93	0.69	1.24	*Unpublished ACUITY data (pre-angio/pre-PCI clop subgroup). Upstream GPI vs deferred GPI (hep background only) at 1 year. calculated from Death/MI events minus death events*
3	1.08	0.83	1.39	*Unpublished ACUITY data (pre-angio/pre-PCI clop subgroup). Bival monotherapy vs upstream GPI (hep background only) at 1 year. calculated from Death/MI events minus death events*
4	0.96	0.85	1.09	*OASIS-5 6 months results - calculated from Death/MI events minus death events - assume RR maintained at 1 year*
5	1.13	0.77	1.65	*REPLACE-2 6 months results (outcome not recorded at 1 year) - calculated from Death/MI events minus death events - assume RR maintained at 1 year*
Repeat revascularisation (1 year)				
	RR	***LCI***	***UCI***	**SOURCE**
1	0.83	0.67	1.02	*ISAR REACT 2 1 year results for target vessel revascularisation - assumed the relative benefits for all revasc would be the same*
2	1.04	0.83	1.30	*Unpublished ACUITY data (pre-angio/pre-PCI clop subgroup). Upstream GPI vs deferred GPI (hep background only.*
3	1.08	0.83	1.39	*Unpublished ACUITY data (pre-angio/pre-PCI clop subgroup). Bival monotherapy vs upstream GPI (hep background only) at 1 year.*
4	1	-	-	*Not reported. Assume no effect.*
5	1.40	1.01	1.93	*REPLACE-2 6 months results (outcome not recorded at 1 year) - assume RR maintained at 1 year*
Major bleed (inhospital)				
	RR	***LCI***	***UCI***	**SOURCE**
1	1.00	0.50	2.08	*ISAR REACT 2 inhosptial rates, TIMI definition*
2	1.05	0.61	1.78	*Unpublished ACUITY data (pre-angio/pre-PCI clop subgroup). Upstream GPI vs deferred GPI (hep background only. 30day RR (inhospital not reported), TIMI definition*
3	0.41	0.24	0.72	*Unpublished ACUITY data (pre-angio/pre-PCI clop subgroup). Bival monotherapy vs upstream GPI (hep background only). 30 days (inhospital not reported, TIMI definition.*
4	0.55	0.41	0.74	*OASIS 5 9 day results, TIMI definition*
5	0.59	0.33	1.05	*REPLACE-2 30 day results (inhospital not reported), trial definition*
Minor bleed (inhospital)				
	RR	***LCI***	***UCI***	**SOURCE**
1	1.27	0.81	1.99	*ISAR REACT 2 inhosptial rates, TIMI definition*
2	1.29	0.96	1.73	*Unpublished ACUITY data (pre-angio/pre-PCI clop subgroup). Upstream GPI vs deferred GPI (hep background only. 30day RR (inhospital not reported), TIMI definition*
3	0.54	0.41	0.71	*Unpublished ACUITY data (pre-angio/pre-PCI clop subgroup). Bival monotherapy vs upstream GPI (hep background only). 30 days (inhospital not reported, TIMI definition.*
4	0.34	0.27	0.42	*OASIS 5 9 day results, trial definition (TIMI minor bleeding not reported)*
5	0.48	0.38	0.60	*REPLACE-2 30 day results (inhospital not reported), trial definition*

2 *Unpublished ACUITY data (pre-angio/pre-PCI clop subgroup). Upstream GPI vs deferred GPI (hep background only) at 1 year provided by The Medicines Company*

3 *Unpublished ACUITY data (pre-angio/pre-PCI clop subgroup). Bival monotherapy vs upstream GPI (hep background only). 30 days (inhospital not reported, TIMI definition provided by The Medicines Company*

Treatment costs

Treatment costs were estimated for each of the treatment options being compared in the model. Costing assumptions were agreed in discussion with GDG members.

Note that the cost of aspirin and clopidogrel will not vary between treatment arms in the acute episode as all patients receive these drugs in the model – they are therefore not included in the costing below. Note however that they are included in the ongoing secondary prevention drug costs that are applied whilst patients remain alive.

Two approaches to costing were used to estimate treatment costs for the treatment options in the model:

1) Treatment costs based on vial usage from trials
    - This is most consistent with the clinical effectiveness data used in the model
    - The ACUITY trial provided data comparing three of the five treatment options in the model) – median time from admission to angiography was 20hrs in this trial[110]; median time from study randomization to angiography was 4hrs (mean 10hrs)
    - It is considered that in UK practice this time from admission to angiography is short and so may the trial may not reflect current UK practice and therefore drug costs
2) Treatment costs built up from dosing and duration assumptions to explore a longer treatment duration scenario
    - This allowed us to explore scenarios that may be more reflective of drug costs in the UK
    - Median time from admission to PCI in centres with PCI facilities is 3.2 days (NSTEMI/UA/convalescent STEMI)[178], in those without it is likely to be longer
    - A pre-angiography treatment period of 72hrs was used in this costing
    - It is acknowledged however that as the clinical evidence is not adjusted in the model to take account of different treatment durations this introduces inconsistency between the costs and effects and a potential bias against the upstream treatment whose costs will be increased but effects remain the same.

Unit costs were taken from the BNF 58[139]; these are summarised in Table 15 below.

Table 15. **Drug unit costs used in costings**

Drug	Unit cost	Preparation
Abciximab	£250.24	Abciximab, ReoPro® (Lilly),injection, 2mg/ml, 5ml vial
Eptifibatide	£13.89 £43.65	Eptifibatide, Integrilin® (GSK), injection, 2mg/ml, 10ml vial Eptifibatide, Integrilin® (GSK), infusion, 750micrograms/ml, 100ml vial
Tirofiban	£146.11	Tirofiban, Aggrastat® (MSD), concentrate for iv infusion, 250micrograms/ml, 50ml vial
Enoxaparin	£3.03, £4.04, £4.57, £5.19, 6.43; £21.33	Enoxparin, Clexane® (Rhône-Poulenc Rorer), injection, 100mg/ml, 0.2ml, 0.4ml, 0.6ml, 0.8ml, 1ml pre-filled syringe; 3ml multidose vial
Fondaparinux	£6.66	Fondaparinux, Arixtra® (GSK), injection, 5mg/ml, 0.5ml pre-filled syringe
Bivalirudin	£310.00	Bivalirudin, Angiox® (Nycomed), injection, powder for reconstitution, 250mg vial
UFH	£0.37, £0.93, £1.60, £2.63	Heparin sodium, injection, 1000 units/ml, 1ml, 5ml, 10ml, 20ml ampoule

Source: BNF 58[139]

1. Treatment costs based on vial usage from trials

Vial usage used for all arms in the model is summarised in Table 16 below. Costs applied in the model for this costing scenario are summarised in Table 17 below.

Vial use reported from the ACUITY trial was used for the heparin + upstream GPI arm, heparin + PCI GPI arm, and the bivalirudin initiated pre-angiography arm[109,161]. In the ACUITY study, time from randomisation to angiography was a median of 4hrs (mean 10hrs) and so vial usage of agents initiated upstream of angiography will reflect this.

GPI and bivalirudin vial use was reported from the pre-angiography/pre-PCI clopidogrel subgroup that is used for the efficacy data[109]. The reported average vial use was calculated by estimating the number of vials required for each patient receiving the drug in the trial and taking the average. Part vials were rounded up where appropriate during this calculation to account for vial wastage. No further rounding is therefore required when calculating costs to account for vial wastage and the unit cost per vial is multiplied by the average vial cost. Enoxaparin vial use was reported across the heparin arms combined assuming use of the multidose vial formulation (which does not require part vials to be discarded)[161].

LMWH or UFH use was allowed in the ACUITY trial. In these costings LMWH costs are assumed for all patients. Drug costs of LMWH are slightly more than UFH but other studies have suggested that the additional monitoring costs of UFH may offset this difference and so this assumption is considered unlikely to impact results[134]. Some patients that received LMWH also received UFH – these costs are not incorporated in this costing; this is also considered unlikely to impact results.

Tirofiban and eptifibatide could be used upstream of angiography in the ACUITY trial and both are licensed for this use in the UK. In this costing a weighted average cost is therefore used based on the relative usage of the two agents in the ACUITY trial[109]. Tirofiban use was 40% and eptifibatide 60%.

In the ACUITY study abciximab or eptifibatide could be used when GPI was initiated at PCI but in the UK only abciximab is licensed for this use. Abciximab is therefore used in this costing. In the heparin + GPI during PCI arm of the model, all patients that undergo PCI receive a GPI. In the bivalirudin upstream of angiography arm of the model bailout use during PCI was based on GPI use observed in the bivalirudin arm of ACUITY.

In the heparin alone arm of the model (not included in the ACUITY study), heparin use was assumed to be the same as in the heparin +GPI arms described above.

In the heparin + selective bivalirudin use during PCI arm of the model (not included in the ACUITY study), heparin use was also assumed to be the same as in the heparin +GPI arms described above. Bivalirudin vial use in this scenario was based on data from the REPLACE-2 study overall population[163].

It is assumed that bailout use of GPIs will be the same in the heparin alone arm, the bivalirudin upstream of angiography arm and the bivalirudin during PCI arm of the model. The bailout GPI used is assumed to be abciximab to reflect UK licensing. Vial usage is based on abciximab usage in the ACUITY trial. The percentage of PCIs requiring GPI bailout use was assumed to be the same as in the bivalirudin monotherapy arm of ACUITY at 9%.

In the analysis where heparin is replaced by fondaparinux in the heparin alone, heparin + upstream GPIs and heparin + PCI GPI arms, one dose of fondaparinux is assumed. This is on the basis that the mean time randomisation to angiography was 10hrs in the ACUITY study and one dose of fondaparinux is required per day. It is not a weight adjusted dose.

In the model patients are stratified into angiography only, PCI, and CABG. Vial use from ACUITY are the average across all patients who receive the drug. Due to this the cost applied across management strategies is the same for agents initiated before angiography, such as upstream GPIs, although they may well vary between management strategies. This is not an issue when the management split used in the model is as per the ACUITY study where these vial uses come from (as is applied when this costing scenario is used).

Table 16. **Summary of vial usage**

	Vial usage/ patient using drug	**Cost/ vial**	**Cost/ patient using drug**	**Vial use source**	**Use in early angio population (all patients receive angiography then triaged to PCI, CABG or medical management)**
Heparin alone					
Enoxaparin 300mg multidose vial	0.759	£21.33	£16.19	Assumption	All patients
Abciximab 10 mg vial	3.29	£250.24	£823.29	Assumption	Bailout use in 9% of patients who undergo PCI
Heparin + GPI during PCI only					
Enoxaparin 300mg multidose vial	0.759	£21.33	£16.19	ACUITY	All patients
Abciximab 10 mg vial	3.25	£250.24	£813.28	ACUITY	Only patients who undergo PCI
Heparin + GPI (started upstream of angiography in all patients)					
Enoxaparin 300mg multidose vial	0.759	£21.33	£16.19	ACUITY	All patients
Tirofiban 12.5 mg vial	1.49	£146.11	£217.70	ACUITY	All patients; 40% tirofiban, 60% eptifibatide
Eptifibatide bolus 20 mg vial	1.08	£13.89	£15.00	ACUITY	
Eptifibatide infusion 75 mg vial	3.12	£43.65	£136.19	ACUITY	
Aspirin + clopidogrel + bivalirudin (started upstream of angiography in all patients)					
Bivalirudin 250 mg vial	2.22	£310.00	£688.20	ACUITY	All patients
Abciximab 10 mg vial	3.29	£250.24	£823.29	ACUITY	Bailout use in 9% of patients who undergo PCI
Heparin + Bivalirudin during PCI only					
Enoxaparin 300mg multidose vial	0.759	£21.33	£16.19	Assumption	100%
Bivalirudin 250 mg vial	1.35	£310.00	£418.50	REPLACE-2	Only patients who undergo PCI
Abciximab 10 mg vial	3.37	£250.24	£843.31	Assumption	Bailout use in 9% of patients who undergo PCI
Fondaparinux alone					
Fondaparinux 2.5mg pre-filled syringe	1	£6.41	£6.41	Assumption	100%
Abciximab 10 mg vial	3.29	£250.24	£823.29	Assumption	Bailout use in 9% of patients who undergo PCI

Table 17. **Drug costs applied in model; trial vial use costing scenario (pre-angiography treatment duration median 4hrs/mean 10hrs)**

	Angio	***PCI***	***CABG***
GPI during PCI only	£0	£813.28	£0

GPI initiated upstream of angiography	£177.80	£177.80	£177.80
Bailout GPI use (when GPIs not routinely used)*	£0	£74.82	£0
Heparin	£16.19	£16.19	£16.19
Fondaparinux	£6.41	£6.41	£6.41
Bivalirudin initiated upstream of angiography	£688.20	£688.20	£688.20
Bivalirudin during PCI only	£0	£434.69	£0

*Based on 9% bailout GPI use

2. Treatment costs built up from dosing and duration assumptions to explore alternative treatment duration scenarios

In order to estimate costs for a scenario where there was a longer pre-angiography treatment period, a costing simulation was set up. Treatment costs for the agents being compared were estimated based on recommended licensed dosing from summaries of product characteristics, costs from the BNF, assumptions regarding treatment durations and a distribution of patient weights. The dosing used are summarised in Table 18 below. The costs applied in the model for this costing scenario are summarised in Table 19 below.

The pre-angiography treatment duration for agents initiated upstream of angiography was 72hrs in this costing based on the expert opinion of the GDG. The duration of PCI was assumed to be 1hr based on the expert opinion of the GDG. It was assumed that any part vial wastage is discarded (and so part vial usage was rounded up). Upstream GPI use costs were based on an average of costs for tirofiban and eptifibatide with treatment duration assumed to be the same.

Costs were calculated using a simulation where weight was varied with a normal distribution with a mean of 83kg and a standard deviation of 16.3. These parameters were estimated based on the ACUITY trial that reported a median weight of 83kg and an interquartile range of 73-95, assuming a normal distribution. It was considered whether this might be too high for a UK population, however an analysis of the ACUITY trial data reported that using a European subgroup made little difference to costs[161] – on this basis this was assumed to be reasonable. The simulation was run 1000 times. Each time a weight was randomly selected from within the distribution. Vials required to fulfil each drug for a patient undergoing angiography only, PCI and CABG was calculated, and from this costs were calculated. Enoxaparin pre-filled syringes were used in this costing. The mean cost was then calculated for each drug for a patient undergoing angiography alone, PCI and CABG in each treatment arm of the model. By using a simulation with a distribution of weight it means the natural variability in the population is taken into account and drug costs are not unfairly inflated if using the mean weight means that the vial usage for a particular agent is only just above the nearest whole vial.

It was considered most appropriate to assume that the treatment duration pre-angiography would be the same for GPIs and bivalirudin when initiated upstream of angiography in this costing. Treatment durations for upstream GPIs are similar to those used in the 2005 Technology Appraisal of GPIs. Duration was 48hr/72hr for tirofiban/eptifibatide in upstream use. Differences are considered to represent current practice.

Costing assumptions were agreed based on discussion with GDG members in light of data from relevant trials and other sources, and licensing recommendations. Note that in the model all patients receive angiography; a proportion will proceed to PCI and others will either undergo CABG or medical management only as indicated. In the model all patients are attributed the full acute drug cost.

Drug costs are calculated based on the following assumptions:

- Heparin alone:
    - All patients receive enoxaparin pre-angiography

    - Patients that proceed to PCI receive UFH during the procedure
    - Patients who proceed to CABG receive enoxaparin up until the procedure and UFH during the procedure*
    - Patients who are triaged to medical management only, receive no further heparin post-angio
- Heparin + GPI use upstream of angiography:
    - All patients receive heparin as in the heparin alone arm*
    - All patients also receive a GPI (eptifibatide or tirofiban) pre-angiography
    - Patients who proceed to PCI continue the infusion for a further 12 hours (covering the procedure and a period afterwards)
    - Patients who proceed to CABG or are triaged to medical management only have the GPI infusion stopped following angiography
- Heparin + GPI use only during PCI:
    - All patients receive heparin as in the heparin alone arm*
    - Only patients who proceed to PCI receive a GPI – abciximab for 12 hours (covering the procedure and a period afterwards)
- Bivalirudin use upstream of angiography:
    - All patients receive bivalirudin pre-angiography
    - Patients who proceed to PCI continue bivalirudin during the procedure
    - Patients who proceed to CABG have the bivalirudin infusion stopped following angiography and then receive enoxaparin up until the procedure and UFH during the procedure*
    - Patients who are triaged to medical management only have the bivalirudin infusion stopped following angiography
- Heparin + bivalirudin use only during PCI
    - All patients receive enoxaparin pre-angiography
    - Only patients who proceed to PCI receive bivalirudin during the procedure
    - Patients who proceed to CABG receive enoxaparin up until the procedure and UFH during the procedure*
    - Patients who are triaged to medical management only receive no further heparin post-angio

*As patients in all arms of the model triaged to CABG following angiography are assumed to receive the same treatment (that is, enoxaparin or fondaparinux up to surgery with UFH during surgery) this cost is not incorporated into the costing for simplicity.

Table 18. **Dosing used for costing purposes**

Drug	**Dose**	**Source**
GPI PCI: abciximab	0.25mg/kg initial bolus 0.125µg/kg/min infusion over 12hrs	Product licence[306]
GPI upstream: eptifibatide	180microgram/kg initial bolus 2.0µg/kg/min infusion	Product licence[307]
GPI upstream: tirofiban	400ng/kg/min for initial 30min 100ng/kg/min infusion	Product licence[308]
Enoxaparin	1mg/kg every 12hrs	Product licence[26]
Fondaparinux	2.5mg per day	Product licence[309]
Bivalirudin – initiated pre-angiography	***Pre-angio*** 0.1mg/kg initial bolus 0.25mg/kg/hr up ***In those who proceed to PCI:***	Product licence[310]

	0.5mg/kg additional bolus at PCI 1.75mg/kg/h during PCI	
Bivalirudin in PCI only – initiated post-angiography, pre-PCI	0.75mg/kg initial bolus 1.75mg/kg/hr during PCI	Product licence[310]
UFH during PCI	5000 units iv bolus injection, 18 units/kg/hr	Annals Internal Medicine 1993;119:874-81[311]

Table 19. Drug costs used in model – 72hr pre-angiography treatment period costing scenario

	Angio	***PCI***	***CABG***
GPI during PCI only	£0	£833.55	£0
GPI initiated upstream of angiography*	£474.78	£543.59	£474.78
Bailout GPI use (when GPIs not routinely used)**	£0	£75.75	£0
Heparin (including UFH during PCI)	£37.48	£39.08	£37.48
Fondaparinux (including UFH during PCI)	£19.23	£20.83	£19.23
Bivalirudin initiated upstream of angiography	£2,008.18	£2,236.96	£2,008.18
PCI bivalirudin during only	£0	£396.15	£0

* Average of tirofiban and eptifibatide costs (angio/CABG: eptifibatide £449.87, tirofiban £499.70; PCI: eptifibatide £519.84, tirofiban £567.35)

**Based on 9% bailout GPI use

Results

The widely used cost-effectiveness metric is the incremental cost-effectiveness ratio (ICER). This is calculated by dividing the difference in costs associated with two alternatives by the difference in QALYs. The decision rule then applied is that if the ICER falls below a given threshold the result is considered to be cost effective. If both costs are lower and QALYs are higher the option is said to dominate and an ICER is not calculated.

- ICER = $(Costs_B – Costs_A) \div (QALYs_B – QALYs_A)$
- Cost effective if: ICER < Threshold

When there are more than two comparators, as in this analysis, options must be ranked in order of increasing cost then options ruled out by dominance or extended dominance before calculating ICERs excluding these options.

However, for a particular cost-effectiveness threshold, it is possible to re-express cost effectiveness in term of incremental net benefit (INB). This is calculated by multiplying the difference in QALYs for a comparison of two alternatives by the threshold cost per QALY value (for example, £20,000) and then subtracting the difference in costs. The decision rule then applied is that if the INB is greater than 0 the result is considered to be cost effective at the specified threshold.

- INB = (Incremental QALYs x Threshold) – incremental costs
- cost effective if: INB > 0

When there are multiple treatment options the one with the highest mean INB is the option that provides the highest QALY gain at an acceptable cost.

For ease of computation mean INB is used to identify the optimal treatment option when running the model and so is presented in the results tables. The highest INB is highlighted to indicate the preferred strategy at a threshold of £20,000/QALY and £30,000/QALY.

Also presented is the percentage of simulations where each strategy was the most cost effective (had the highest INB). This gives an indication of the strength of evidence in favour of that strategy being cost effective. However, this is less useful than the mean INB, since it can give spurious results if for example the treatment effects of some of the strategies are correlated.

Detailed results are presented over the next few pages. Results are from the probabilistic analysis unless otherwise specified. Results are presents for two analyses:

5. Trial aligned analysis (shorter upstream treatment duration costing – based on trial vial usage where pre-angiography treatment period median 4hrs/mean 10hrs; ACUITY management split) – see Table 20, Figure 3, Table 21
    - Costing based on trial vial usage; ACUITY management split (see methods above for details)
    - The ACUITY trial which includes 3 of the 5 comparators had a median treatment period pre-angiography of 4hrs (mean 10hrs)
    - This analysis is most aligned with the available trial data
6. Adjusted analysis (longer upstream treatment duration costing – based on 72hr pre-angiography treatment period; MINAP management split) – see Table 22, Figure 4, Table 23
    - Costing based on a simulation assuming 72hr pre-angiography treatment duration and a 1hr PCI treatment duration; MINAP management split

- This analysis makes some adjustments to costing and management split that may be more typical for the UK
- Note that this analysis potentially biases against upstream treatments as costs are increased but efficacy remains the same and so should be interpreted carefully with this in mind.

Two sets of results are presented for each risk group for each of the above analyses; one where heparin is the baseline antithrombin and one where it is fondaparinux. As described in the methods, results relate to a population undergoing early invasive management. Results are also depicted graphically on the cost-effectiveness plane where mean incremental costs and mean incremental QALYs are presented compared to aspirin+clopidogrel+heparin(or fondaparinux). Comparisons not ruled out by dominance or extended dominance are joined by a line where the slope represents the ICER. Breakdowns by risk group for each comparator in terms of patient status at one year, number of resource use events, and costs (split into treatment costs, year one resource use costs and year two plus resource use costs) are also presented.

Following the details results tables and graphs is a section summarising the results and the interpretation.

1. Trial aligned analysis (pre-angiography treatment period median 4hrs/mean 10hrs; ACUITY management split)

Table 20. **Results summary (probabilistic analysis): costs, QALYs and INB (trial aligned analysis)**

	QALYs*	Incr v baseline	Cost*	Incr v baseline	INB (20K)	% CE (20K)	INB (30K)	% CE (30K)
Risk group 1a					*highlighted cells indicate optimal strategy*			
A+C+H (baseline)	13.026	0	£5,040	£0	**£0**	31%	**£0**	22%
A+C+H+GPIpci	13.031	0.0055	£5,418	£378	-£268	1%	-£213	2%
A+C+H+GPIup	13.026	0.0005	£5,145	£105	-£95	32%	-£90	26%
A+C+B	13.038	0.0120	£5,714	£674	-£433	7%	-£312	15%
A+C+H+Bpci	13.034	0.0082	£5,304	£263	-£98	30%	-£16	35%
A+C+F (baseline)	13.039	0	£5,028	£0	**£0**	42%	**£0**	30%
A+C+F+GPIpci	13.044	0.0048	£5,405	£377	-£281	1%	-£233	4%
A+C+F+GPIup	13.040	0.0005	£5,131	£103	-£93	40%	-£88	39%
A+C+B	13.038	-0.0016	£5,714	£686	-£717	6%	-£733	13%
A+C+H+Bpci	13.034	-0.0054	£5,304	£276	-£383	11%	-£437	14%
Risk group 1b								
A+C+H (baseline)	10.025	0	£4,054	£0	**£0**	35%	**£0**	24%
A+C+H+GPIpci	10.029	0.0048	£4,433	£379	-£283	0%	-£235	1%
A+C+H+GPIup	10.024	-0.0012	£4,160	£106	-£129	33%	-£141	27%
A+C+B	10.036	0.0116	£4,728	£674	-£442	9%	-£326	19%
A+C+H+Bpci	10.032	0.0071	£4,318	£264	-£122	23%	-£51	29%
A+C+F (baseline)	10.039	0	£4,042	£0	**£0**	46%	**£0**	35%
A+C+F+GPIpci	10.043	0.0042	£4,421	£379	-£294	0%	-£252	2%
A+C+F+GPIup	10.039	-0.0005	£4,148	£106	-£116	41%	-£122	41%
A+C+B	10.036	-0.0030	£4,728	£686	-£746	7%	-£776	14%
A+C+H+Bpci	10.032	-0.0075	£4,318	£276	-£426	5%	-£501	8%
Risk group 2a								
A+C+H (baseline)	7.316	0	£3,140	£0	£0	11%	£0	7%
A+C+H+GPIpci	7.334	0.0181	£3,526	£386	-£24	5%	£158	8%
A+C+H+GPIup	7.327	0.0115	£3,254	£114	£116	28%	£231	23%
A+C+B	7.346	0.0306	£3,821	£681	-£68	25%	£238	32%
A+C+H+Bpci	7.335	0.0194	£3,410	£270	**£118**	31%	**£312**	31%
A+C+F (baseline)	7.345	0	£3,133	£0	£0	16%	£0	9%
A+C+F+GPIpci	7.362	0.0171	£3,519	£386	-£44	10%	£128	16%
A+C+F+GPIup	7.356	0.0113	£3,246	£113	**£112**	47%	**£225**	43%
A+C+B	7.346	0.0015	£3,821	£689	-£659	18%	-£645	23%
A+C+H+Bpci	7.335	-0.0098	£3,410	£278	-£473	9%	-£571	9%

A = aspirin
C = clopidogrel
H = heparin (LMWH or UFH)
F = fondaparinux
GPIpci = GPI used only in PCI patients
GPIup = routine GPI use upstream of angiography
B = bivalirudin initiated upstream of angiography
Bpci = bivalirudin used only in PCI patients

QALYs	Average QALYs for treatment arm.
Incr v baseline	Difference in QALYs between this treatment arm and baseline treatment arm.
Costs	Average costs for treatment arm.
Incr v baseline	Difference in costs between this treatment option and baseline treatment arm.
INB (20K)	The incremental net benefit for this treatment option compared to the baseline treatment arm at a £20,000 per QALY cost-effectiveness threshold. The option with the highest INB is the most cost effective at this threshold – this is highlighted in dark green with bold text.
% CE (20K)	The percentage of times this treatment option was the most cost effective at this threshold (the model is run 10,000 times for the probabilistic analysis).
INB (30K)	The incremental net benefit for this treatment arm compared to the baseline treatment arm at a £30,000 per QALY cost-effectiveness threshold. The option with the highest INB is the optimal strategy at this threshold – this is highlighted in dark green with bold text.
% CE (30K)	The percentage of times this treatment option was the most cost effective at this threshold (the model is run 10,000 times for the probabilistic analysis).

Risk group 2b

A+C+H (baseline)	6.098	0	£2,753	£0	£0	8%	£0	5%
A+C+H+GPIpci	6.124	0.0259	£3,139	£386	£132	7%	£391	9%
A+C+H+GPIup	6.114	0.0157	£2,864	£111	£204	22%	£362	17%
A+C+B	6.140	0.0423	£3,437	£684	£161	27%	£584	33%
A+C+H+Bpci	6.129	0.0306	£3,025	£272	**£340**	37%	**£646**	36%
A+C+F (baseline)	6.136	0	£2,748	£0	£0	9%	£0	6%
A+C+F+GPIpci	6.160	0.0239	£3,133	£385	£93	13%	£332	16%
A+C+F+GPIup	6.152	0.0164	£2,857	£109	**£219**	41%	**£382**	38%
A+C+B	6.140	0.0047	£3,437	£689	-£595	21%	-£549	24%
A+C+H+Bpci	6.129	-0.0070	£3,025	£277	-£416	16%	-£486	16%

Risk group 3

A+C+H (baseline)	4.360	0	£2,193	£0	£0	8%	£0	7%
A+C+H+GPIpci	4.389	0.0288	£2,579	£386	£191	7%	£480	8%
A+C+H+GPIup	4.373	0.0131	£2,301	£108	£153	15%	£284	12%
A+C+B	4.413	0.0521	£2,873	£681	£362	31%	£883	35%
A+C+H+Bpci	4.400	0.0399	£2,465	£272	**£527**	39%	**£926**	38%
A+C+F (baseline)	4.412	0	£2,187	£0	£0	8%	£0	6%
A+C+F+GPIpci	4.438	0.0261	£2,572	£385	£138	14%	**£400**	15%
A+C+F+GPIup	4.425	0.0132	£2,293	£106	**£157**	35%	£289	33%
A+C+B	4.413	0.0008	£2,873	£686	-£670	23%	-£662	26%
A+C+H+Bpci	4.400	-0.0114	£2,465	£278	-£505	20%	-£619	20%

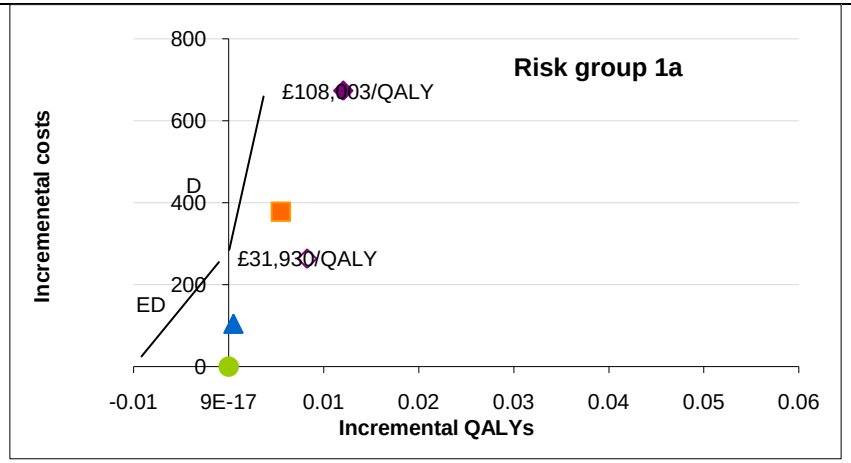
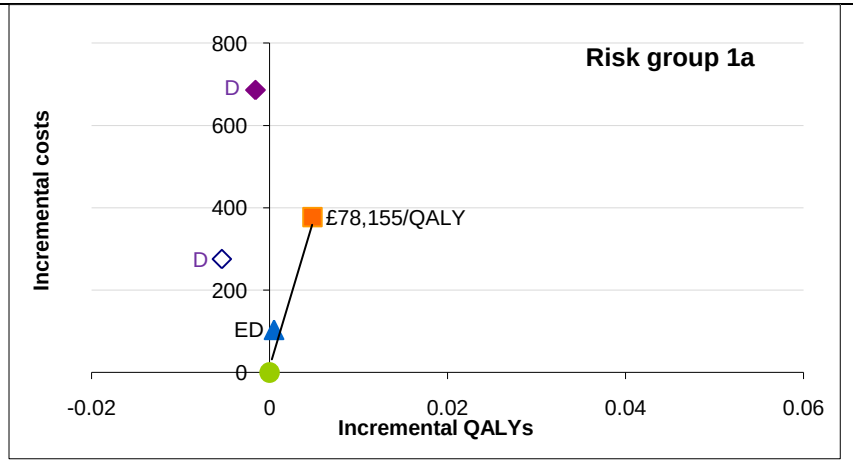
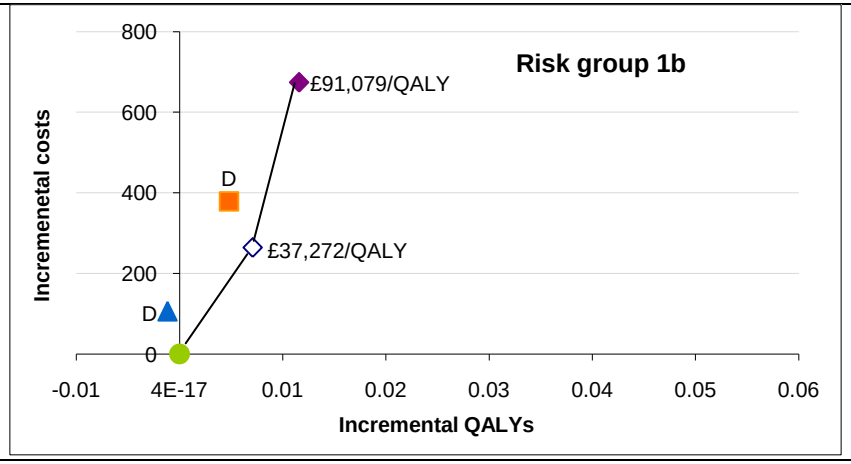
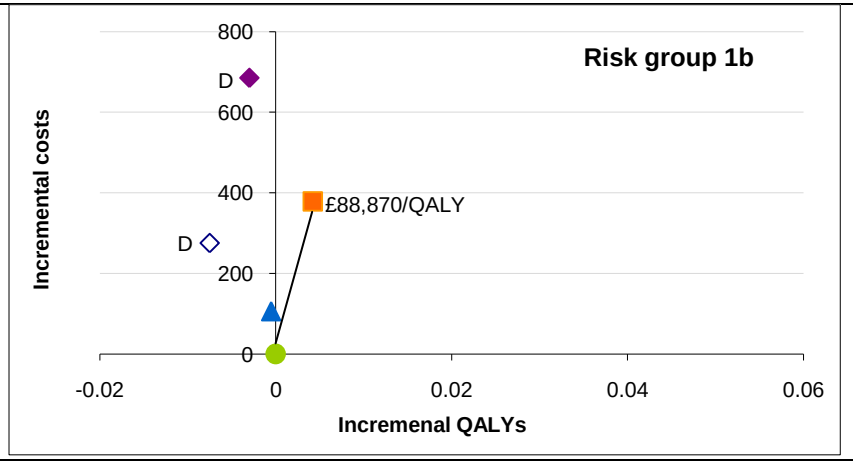
Risk group 4

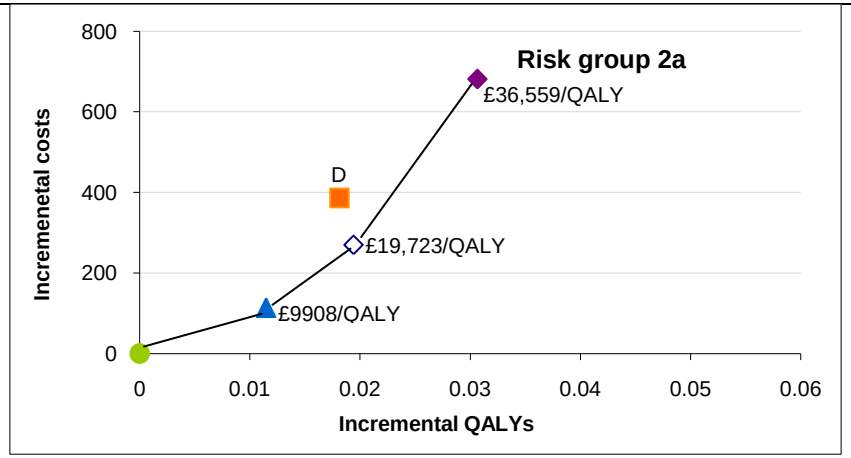
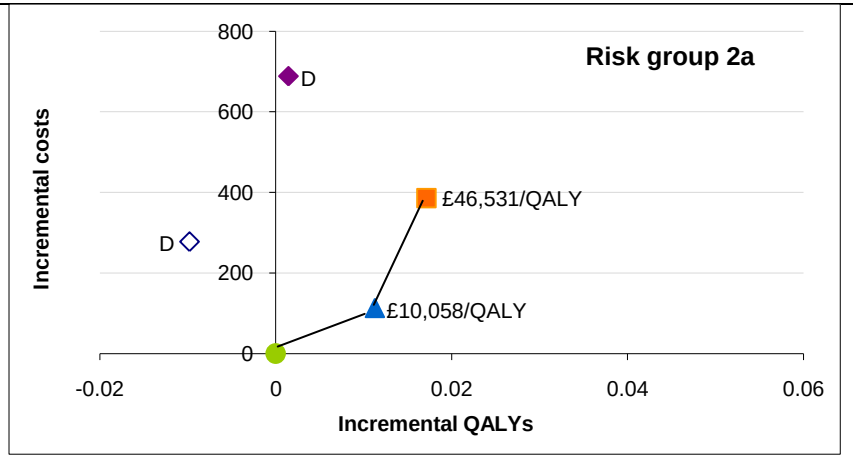
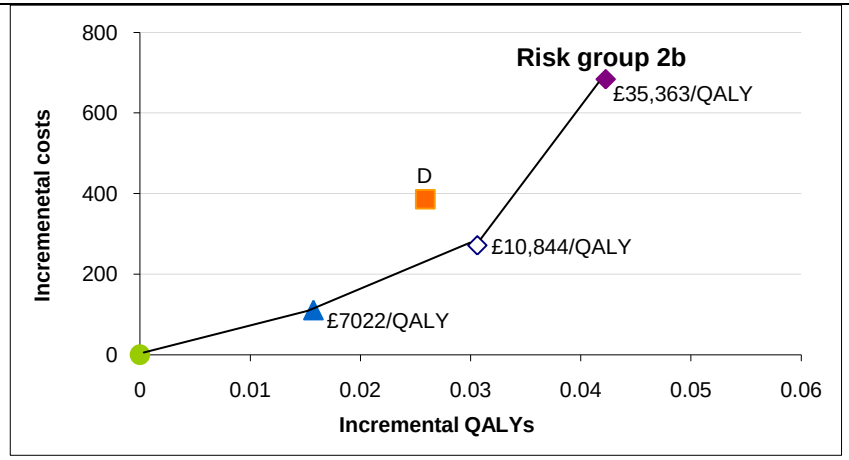
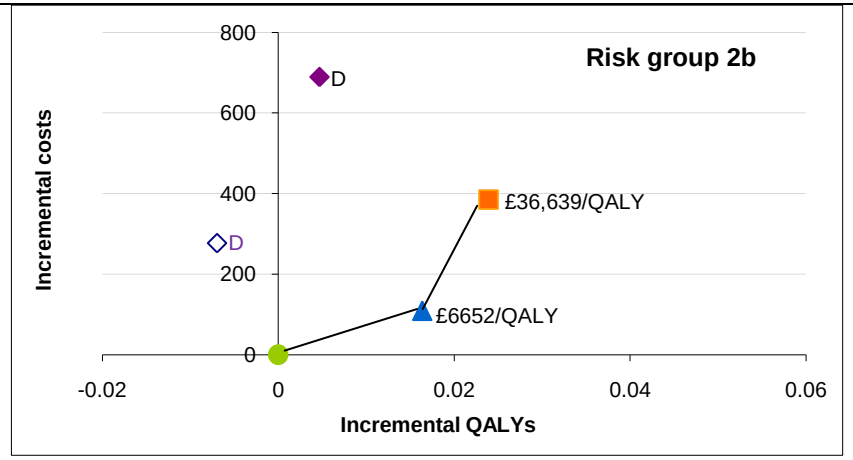
A+C+H (baseline)	2.353	0	£1,527	£0	£0	8%	£0	7%
A+C+H+GPIpci	2.377	0.0244	£1,913	£386	£102	6%	£346	7%
A+C+H+GPIup	2.354	0.0006	£1,632	£105	-£93	13%	-£88	11%
A+C+B	2.407	0.0535	£2,206	£679	£390	36%	**£925**	39%
A+C+H+Bpci	2.391	0.0376	£1,798	£271	**£481**	37%	£857	36%
A+C+F (baseline)	2.416	0	£1,523	£0	£0	10%	£0	8%
A+C+F+GPIpci	2.438	0.0216	£1,907	£384	**£48**	13%	**£264**	14%
A+C+F+GPIup	2.419	0.0023	£1,626	£103	-£57	34%	-£35	32%
A+C+B	2.407	-0.0099	£2,206	£683	-£880	26%	-£979	28%
A+C+H+Bpci	2.391	-0.0257	£1,798	£275	-£789	17%	-£1,046	17%

* Average for 'angio only', 'pci' and 'cabg' patients only

See Figure 3 for incremental costs and QALYs graphically displayed with appropriate incremental cost-effectiveness ratios (costs per QALY gained).

Figure 3. **Results summary (probabilistic analysis): on the cost-effectiveness plane (trial aligned analysis)**

Heparin baseline	Fondaparinux baseline
Incremental costs and QALYs are versus baseline. Comparisons not ruled out by dominance (D) or extended dominance (ED) are joined by a line where the slope equals the 'cost per QALY gained's	
● Aspirin+clopidogrel+heparin (baseline) ■ Aspirin+clopidogrel+heparin+GPI(pcionly) ▲ Aspirin+clopidogrel+heparin+GPI ◆ Aspirin+clopidogrel+bivalirudin ◇Aspirin+clopidogrel+heparin+bivalirudin(pcionly)	● Aspirin+clopidogrel+fondaparinux (baseline) ■ Aspirin+clop+ fonda+GPI(pcionly) ▲ Aspirin+clopidogrel+ fondaparinux+GPI ◆ Aspirin+clopidogrel+bivalirudin ◇Aspirin+clopidogrel+heparin+bivalirudin(pcionly)
	
	

Heparin baseline	Fondaparinux baseline
Incremental costs and QALYs are versus baseline. Comparisons not ruled out by dominance (D) or extended dominance (ED) are joined by a line where the slope equals the 'cost per QALY gained'	
● Aspirin+clopidogrel+heparin (baseline) ■ Aspirin+clopidogrel+heparin+GPI(pcionly) ▲ Aspirin+clopidogrel+heparin+GPI ◆ Aspirin+clopidogrel+bivalirudin ◇Aspirin+clopidogrel+heparin+bivalirudin(pcionly)	● Aspirin+clopidogrel+fondaparinux (baseline) ■ Aspirin+clop+ fonda+GPI(pcionly) ▲ Aspirin+clopidogrel+ fondaparinux+GPI ◆ Aspirin+clopidogrel+bivalirudin ◇Aspirin+clopidogrel+heparin+bivalirudin(pcionly)
	
	

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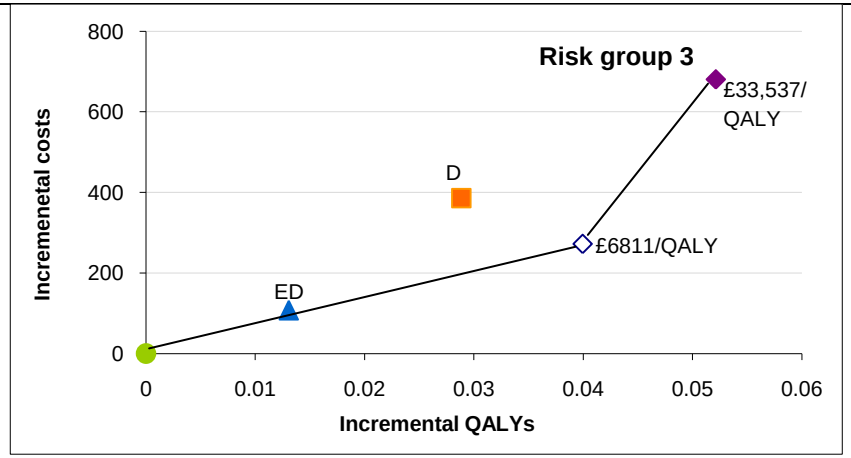
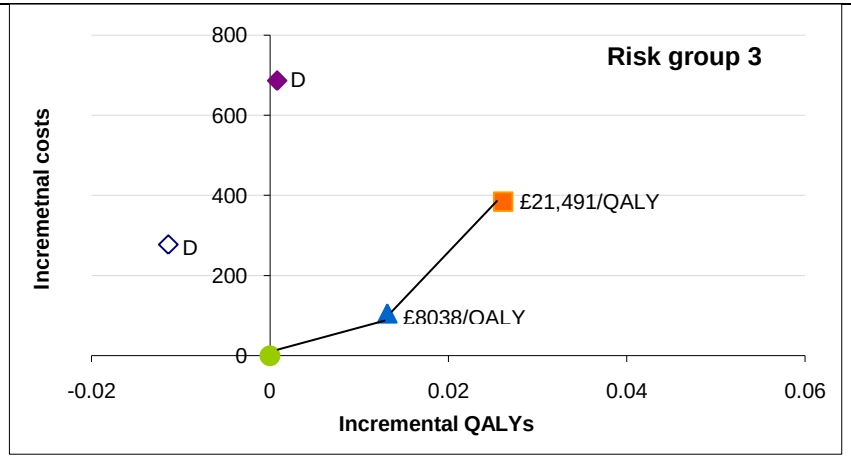
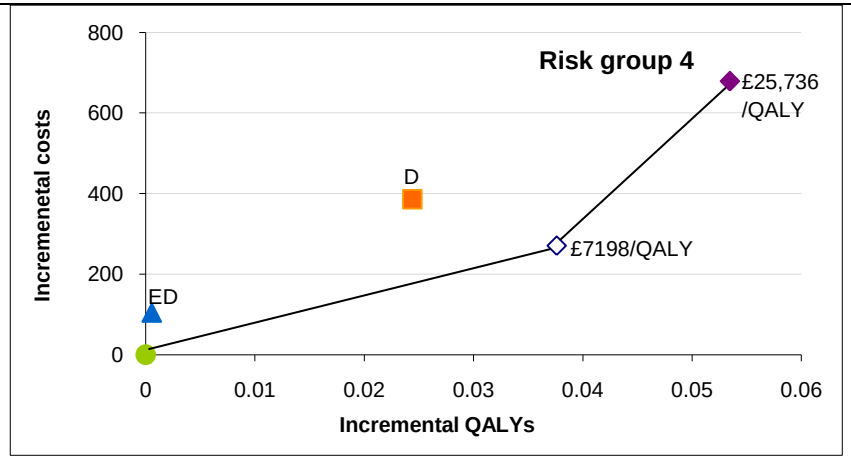
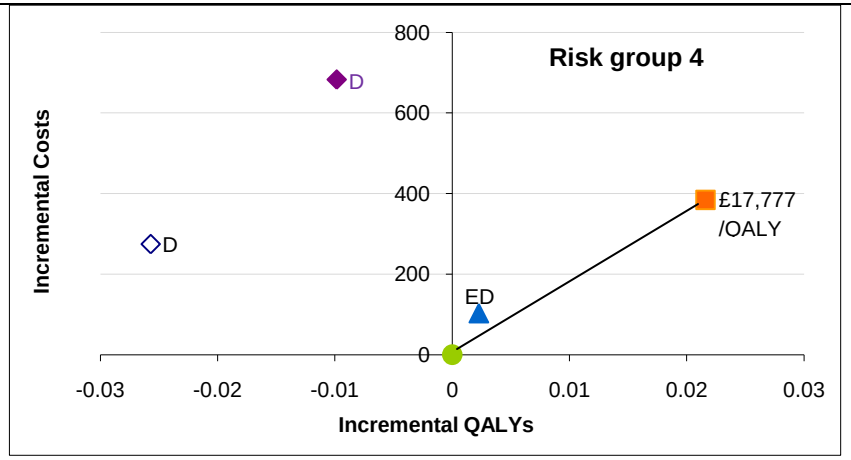
Heparin baseline	Fondaparinux baseline
Incremental costs and QALYs are versus baseline. Comparisons not ruled out by dominance (D) or extended dominance (ED) are joined by a line where the slope equals the 'cost per QALY gained'	
● Aspirin+clopidogrel+heparin (baseline) ■ Aspirin+clopidogrel+heparin+GPI(pcionly) ▲ Aspirin+clopidogrel+heparin+GPI ◆ Aspirin+clopidogrel+bivalirudin ◇Aspirin+clopidogrel+heparin+bivalirudin(pcionly)	● Aspirin+clopidogrel+fondaparinux (baseline) ■ Aspirin+clop+ fonda+GPI(pcionly) ▲ Aspirin+clopidogrel+ fondaparinux+GPI ◆ Aspirin+clopidogrel+bivalirudin ◇Aspirin+clopidogrel+heparin+bivalirudin(pcionly)
	
	

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£11,445/QALY

1 ***Table 21.*** **Results summary (probabilistic analysis): breakdown of events and costs (trial aligned analysis)**

	Patient status at 1 year (per 1000)*			Resource use events at 1 year (per 1000)*					Discounted cost breakdown* (average per patient)		
	These numbers drive the QALY estimates as each one year status is associated with a different number of life-years.			Acute episode			Post acute episode				
				These numbers impact the 1-year cost estimates.							
Risk group 1a	**Dead**	**Alive w/ new MI**	**Alive no new MI**	**Reinf-arction**	**Maj bleed**	**Min bleed**	**Readm MI**	**Revasc**	**Treatment**	**Year 1**	**Year 2+**
A+C+H	10	35	956	12	2	12	37	92	£58	£413	£4,569
A+C+H+GPIpci	9	29	962	10	2	14	32	83	£475	£373	£4,571
A+C+H+GPIup	10	27	963	9	3	18	29	87	£194	£382	£4,569
A+C+B	9	29	962	10	1	10	32	94	£730	£410	£4,573
A+C+Bpci	9	31	960	11	2	9	33	103	£294	£437	£4,572
A+C+F	9	34	958	11	1	4	36	92	£49	£405	£4,574
A+C+F+GPIpci	8	28	964	10	1	5	30	83	£465	£365	£4,576
A+C+F+GPIup	9	26	965	9	1	6	27	86	£184	£373	£4,574
A+C+B	9	29	962	10	1	10	32	94	£730	£410	£4,573
A+C+Bpci	9	31	960	11	2	9	33	103	£294	£437	£4,572
Risk group 1b											
A+C+H	13	34	952	15	2	12	32	92	£58	£405	£3,590
A+C+H+GPIpci	13	28	959	13	2	14	27	83	£475	£366	£3,592
A+C+H+GPIup	14	26	960	11	3	18	25	87	£194	£376	£3,590
A+C+B	12	28	959	12	1	10	27	94	£730	£403	£3,594
A+C+Bpci	13	30	957	13	2	9	29	103	£294	£431	£3,593
A+C+F	12	33	955	14	1	4	30	92	£49	£398	£3,595
A+C+F+GPIpci	12	27	962	12	1	5	26	83	£465	£359	£3,597
A+C+F+GPIup	12	25	963	11	1	6	24	87	£184	£369	£3,595
A+C+B	12	28	959	12	1	10	27	94	£730	£403	£3,594
A+C+Bpci	13	30	957	13	2	9	29	103	£294	£431	£3,593
Risk group 2a											
A+C+H	34	30	936	18	8	8	26	92	£58	£399	£2,683
A+C+H+GPIpci	33	25	942	15	8	9	23	83	£475	£362	£2,689
A+C+H+GPIup	34	23	942	14	9	12	21	87	£194	£373	£2,687
A+C+B	31	25	944	15	4	7	23	94	£730	£397	£2,694
A+C+Bpci	32	27	941	16	6	6	24	103	£294	£426	£2,690
A+C+F	30	29	941	17	4	3	24	92	£49	£391	£2,693
A+C+F+GPIpci	29	24	947	14	4	3	22	83	£465	£355	£2,699
A+C+F+GPIup	31	22	947	13	5	4	20	87	£184	£365	£2,697
A+C+B	31	25	944	15	4	7	23	94	£730	£397	£2,694

A+C+Bpci	32	27	941	16	6	6	24	103	£294	£426	£2,690
Risk group 2b											
A+C+H	52	39	909	22	8	8	38	92	£58	£423	£2,271
A+C+H+GPIpci	50	33	917	19	8	9	34	83	£475	£384	£2,280
A+C+H+GPIup	52	30	917	17	9	12	31	87	£194	£393	£2,277
A+C+B	47	33	920	19	4	7	34	94	£730	£420	£2,286
A+C+Bpci	48	35	917	20	6	6	35	103	£294	£449	£2,282
A+C+F	46	38	916	21	4	3	36	92	£49	£414	£2,285
A+C+F+GPIpci	45	31	924	18	4	3	32	83	£465	£375	£2,293
A+C+F+GPIup	47	29	924	16	5	4	29	86	£184	£382	£2,290
A+C+B	47	33	920	19	4	7	34	94	£730	£420	£2,286
A+C+Bpci	48	35	917	20	6	6	35	103	£294	£449	£2,282
Risk group 3											
A+C+H	99	39	862	19	14	15	49	92	£58	£449	£1,685
A+C+H+GPIpci	95	33	872	16	15	17	43	83	£475	£408	£1,695
A+C+H+GPIup	100	30	870	15	16	22	39	87	£194	£417	£1,690
A+C+B	90	33	877	16	7	12	43	94	£730	£439	£1,704
A+C+Bpci	92	35	873	17	12	12	45	103	£294	£471	£1,700
A+C+F	89	38	874	18	8	5	46	92	£49	£435	£1,704
A+C+F+GPIpci	85	32	883	16	8	6	41	83	£465	£394	£1,713
A+C+F+GPIup	89	30	881	14	9	8	37	86	£184	£401	£1,708
A+C+B	90	33	877	16	7	12	43	94	£730	£439	£1,704
A+C+Bpci	92	35	873	17	12	12	45	103	£294	£471	£1,700
Risk group 4											
A+C+H	210	38	752	35	23	19	48	92	£58	£467	£1,002
A+C+H+GPIpci	203	33	764	30	24	23	42	83	£475	£427	£1,012
A+C+H+GPIup	212	30	758	27	26	29	38	87	£194	£436	£1,002
A+C+B	192	34	774	30	11	16	42	94	£730	£452	£1,023
A+C+Bpci	197	35	768	31	19	15	44	102	£294	£487	£1,017
A+C+F	187	38	775	33	13	7	45	92	£49	£447	£1,028
A+C+F+GPIpci	181	33	786	29	13	8	40	83	£465	£406	£1,036
A+C+F+GPIup	189	30	781	26	14	10	37	87	£184	£414	£1,028
A+C+B	192	34	774	30	11	16	42	94	£730	£452	£1,023
A+C+Bpci	197	35	768	31	19	15	44	102	£294	£487	£1,017

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2. Adjusted analysis (costing assuming 72hr pre-angiography treatment period; MINAP management split)

Table 22. **Results summary (probabilistic analysis): costs, QALYs and INB (adjusted analysis)**

	QALYs*	Incr v baseline	Cost*	Incr v baseline	INB (20K)	% CE (20K)	INB (30K)	% CE (30K)
Risk group 1a					*highlighted cells indicate optimal strategy*			
A+C+H (baseline)	13.037	0	£5,079	£0	**£0**	44%	£0	30%
A+C+H+GPIpci	13.042	0.0050	£5,445	£366	-£265	1%	-£215	3%
A+C+H+GPIup	13.037	0.0004	£5,522	£443	-£436	10%	-£433	16%
A+C+B	13.048	0.0111	£7,178	£2,099	-£1,876	0%	-£1,765	0%
A+C+Bpci	13.045	0.0081	£5,294	£215	-£53	46%	**£28**	50%
A+C+F (baseline)	13.050	0	£5,058	£0	**£0**	67%	**£0**	50%
A+C+F+GPIpci	13.054	0.0046	£5,423	£365	-£273	2%	-£227	6%
A+C+F+GPIup	13.050	0.0006	£5,500	£443	-£430	12%	-£424	20%
A+C+B	13.048	-0.0015	£7,178	£2,120	-£2,150	0%	-£2,166	0%
A+C+Bpci	13.045	-0.0046	£5,294	£236	-£327	19%	-£373	24%
Risk group 1b								
A+C+H (baseline)	10.037	0	£4,093	£0	**£0**	49%	**£0**	33%
A+C+H+GPIpci	10.042	0.0041	£4,443	£350	-£267	0%	-£226	2%
A+C+H+GPIup	10.035	-0.0021	£4,540	£447	-£488	15%	-£509	22%
A+C+B	10.049	0.0116	£6,190	£2,097	-£1,866	0%	-£1,750	0%
A+C+Bpci	10.044	0.0061	£4,300	£206	-£85	36%	-£24	44%
A+C+F (baseline)	10.053	0	£4,074	£0	**£0**	76%	**£0**	60%
A+C+F+GPIpci	10.057	0.0038	£4,423	£350	-£274	1%	-£237	4%
A+C+F+GPIup	10.052	-0.0015	£4,520	£446	-£475	15%	-£490	25%
A+C+B	10.049	-0.0041	£6,190	£2,116	-£2,198	0%	-£2,239	0%
A+C+Bpci	10.044	-0.0095	£4,300	£226	-£417	8%	-£512	10%
Risk group 2a								
A+C+H (baseline)	7.323	0	£3,185	£0	£0	17%	£0	10%
A+C+H+GPIpci	7.339	0.0164	£3,545	£360	-£31	8%	£133	12%
A+C+H+GPIup	7.332	0.0097	£3,638	£453	-£259	29%	-£162	30%
A+C+B	7.351	0.0281	£5,287	£2,102	-£1,540	1%	-£1,259	5%
A+C+Bpci	7.340	0.0172	£3,397	£212	**£131**	45%	**£303**	43%
A+C+F (baseline)	7.352	0	£3,169	£0	**£0**	32%	£0	16%
A+C+F+GPIpci	7.367	0.0154	£3,529	£359	-£51	18%	**£104**	26%
A+C+F+GPIup	7.362	0.0100	£3,622	£452	-£252	36%	-£152	39%
A+C+B	7.351	-0.0012	£5,287	£2,118	-£2,141	1%	-£2,153	5%
A+C+Bpci	7.340	-0.0121	£3,397	£228	-£470	13%	-£591	13%

A = aspirin
C = clopidogrel
H = heparin (LMWH or UFH)
F = fondaparinux
GPIup = routine GPI use upstream of angiography
B = bivalirudin initiated upstream of angiography
Bpci = bivalirudin used only in PCI patients

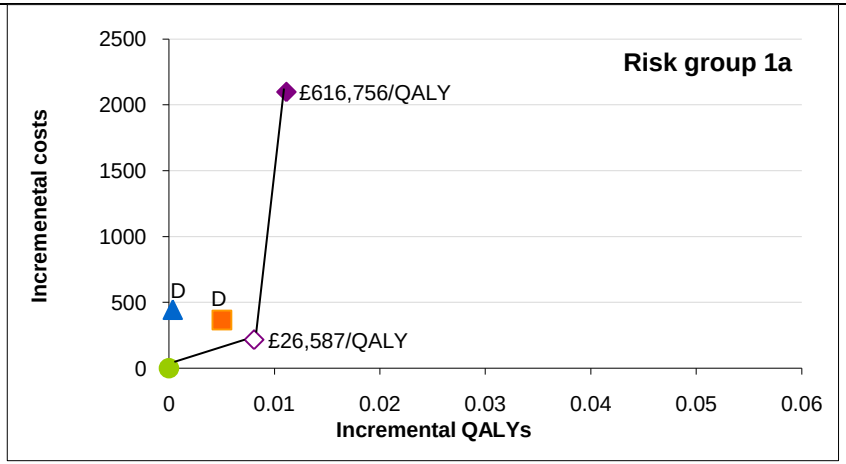
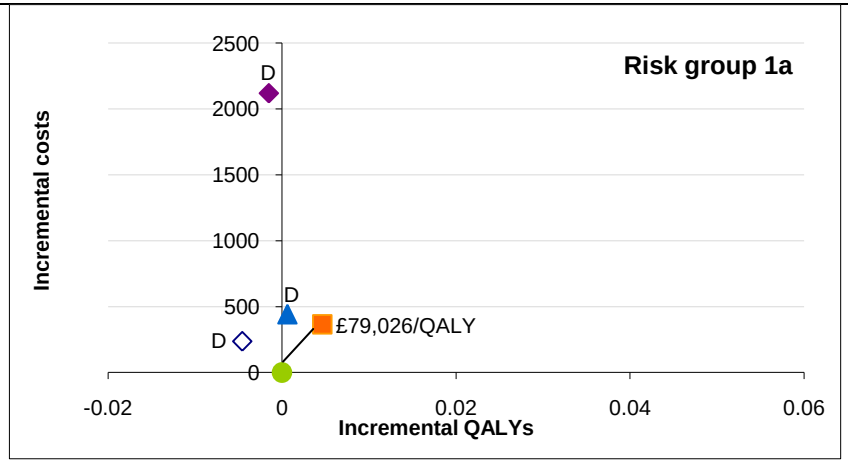
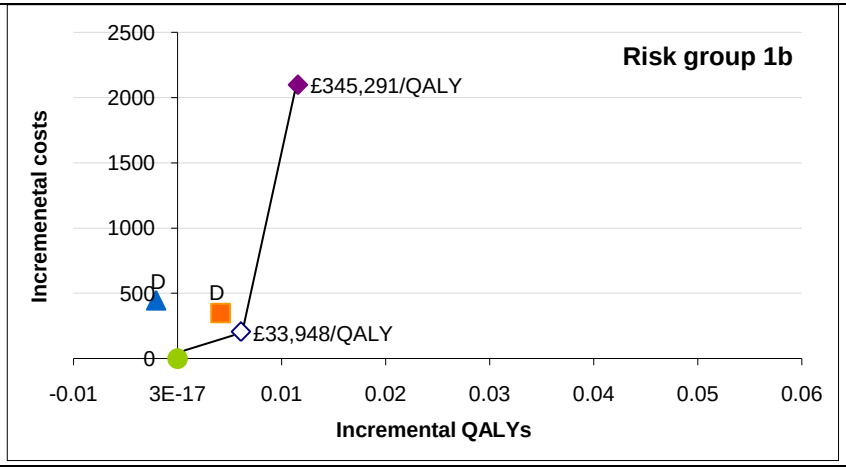
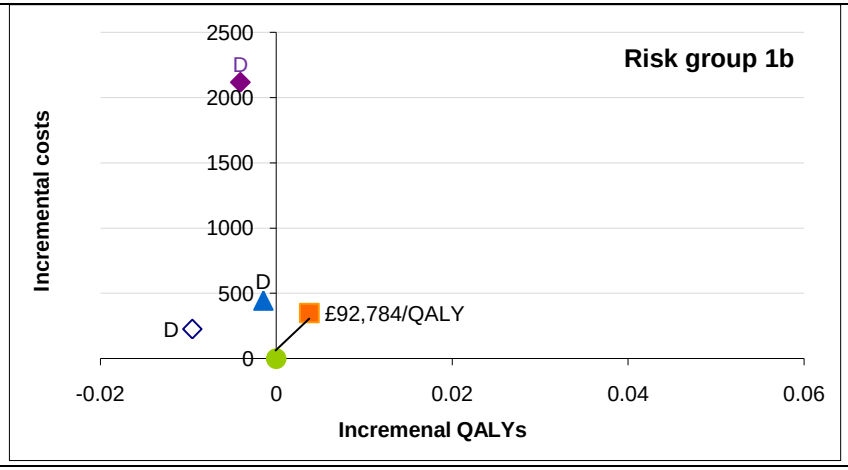
QALYs	Average QALYs for treatment arm.
Incr v baseline	Difference in QALYs between this treatment arm and baseline treatment arm.
Costs	Average costs for treatment arm.
Incr v baseline	Difference in costs between this treatment option and baseline treatment arm.
INB (20K)	The incremental net benefit for this treatment option compared to the baseline treatment arm at a £20,000 per QALY cost-effectiveness threshold. The option with the highest INB is the most cost effective at this threshold – this is highlighted in dark green with bold text.
% CE (20K)	The percentage of times this treatment option was the most cost effective at this threshold (the model is run 1000 times for the probabilistic analysis).
INB (30K)	The incremental net benefit for this treatment arm compared to the baseline treatment arm at a £30,000 per QALY cost-effectiveness threshold. The option with the highest INB is the optimal strategy at this threshold – this is highlighted in dark green with bold text.
% CE (30K)	The percentage of times this treatment option was the most cost effective at this threshold (the model is run 1000 times for the probabilistic analysis).

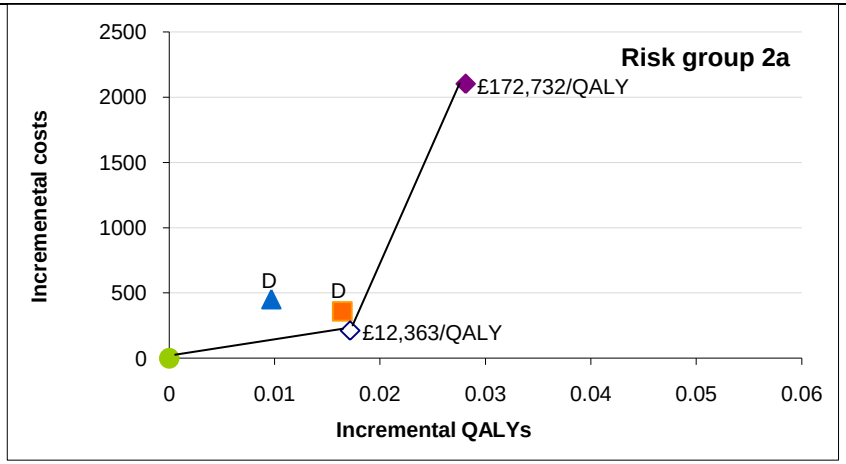
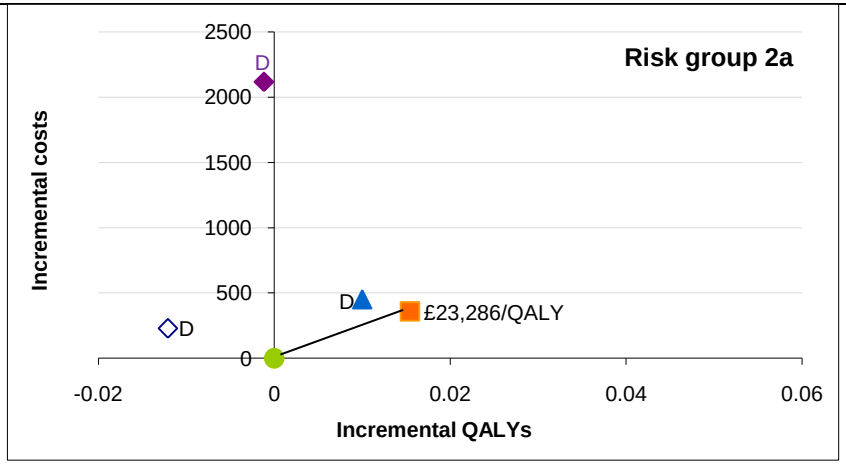
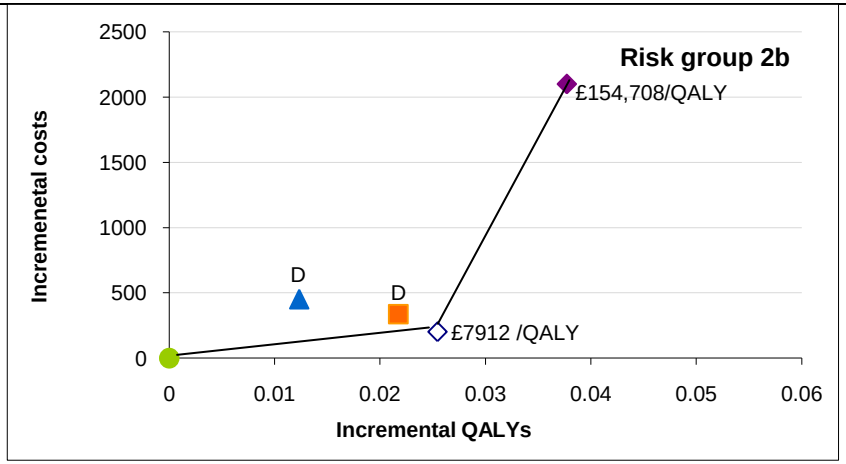
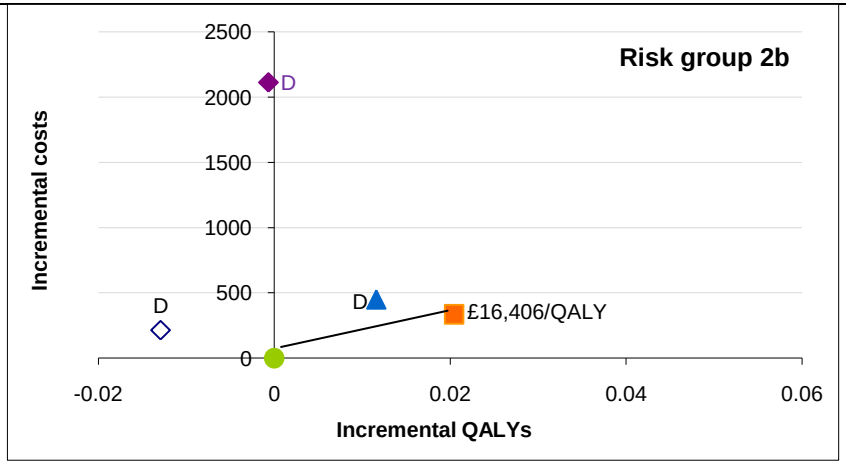
Risk group 2b								
A+C+H (baseline)	6.096	0	£2,795	£0	£0	12%	£0	8%
A+C+H+GPIpci	6.118	0.0217	£3,131	£336	£98	11%	£316	13%
A+C+H+GPIup	6.108	0.0123	£3,246	£451	-£205	26%	-£82	24%
A+C+B	6.134	0.0377	£4,894	£2,099	-£1,344	3%	-£967	10%
A+C+Bpci	6.122	0.0254	£2,996	£201	**£308**	48%	**£562**	45%
A+C+F (baseline)	6.134	0	£2,781	£0	£0	18%	£0	11%
A+C+F+GPIpci	6.155	0.0205	£3,117	£336	**£74**	25%	**£278**	27%
A+C+F+GPIup	6.146	0.0116	£3,231	£450	-£218	34%	-£102	36%
A+C+B	6.134	-0.0006	£4,894	£2,112	-£2,125	3%	-£2,132	9%
A+C+Bpci	6.122	-0.0129	£2,996	£215	-£473	20%	-£602	17%
Risk group 3								
A+C+H (baseline)	4.351	0	£2,235	£0	£0	11%	£0	8%
A+C+H+GPIpci	4.374	0.0226	£2,545	£310	£141	11%	£367	11%
A+C+H+GPIup	4.358	0.0070	£2,686	£450	-£310	22%	-£239	19%
A+C+B	4.396	0.0455	£4,326	£2,091	-£1,181	9%	-£726	18%
A+C+Bpci	4.382	0.0308	£2,420	£185	**£432**	48%	**£740**	44%
A+C+F (baseline)	4.403	0	£2,222	£0	£0	15%	£0	10%
A+C+F+GPIpci	4.424	0.0210	£2,531	£309	**£111**	24%	**£320**	24%
A+C+F+GPIup	4.410	0.0070	£2,671	£449	-£310	33%	-£240	33%
A+C+B	4.396	-0.0064	£4,326	£2,105	-£2,233	7%	-£2,297	14%
A+C+Bpci	4.382	-0.0211	£2,420	£198	-£620	21%	-£831	19%
Risk group 4								
A+C+H (baseline)	2.289	0	£1,559	£0	£0	11%	£0	8%
A+C+H+GPIpci	2.304	0.0150	£1,812	£253	£47	9%	£198	9%
A+C+H+GPIup	2.280	-0.0088	£2,011	£451	-£628	20%	-£717	16%
A+C+B	2.340	0.0513	£3,640	£2,080	-£1,055	19%	-£542	29%
A+C+Bpci	2.314	0.0250	£1,710	£151	**£349**	42%	**£599**	37%
A+C+F (baseline)	2.358	0	£1,550	£0	£0	19%	£0	13%
A+C+F+GPIpci	2.372	0.0139	£1,802	£252	**£26**	23%	**£165**	23%
A+C+F+GPIup	2.349	-0.0087	£1,999	£449	-£622	33%	-£709	33%
A+C+B	2.340	-0.0178	£3,640	£2,090	-£2,446	14%	-£2,624	21%
A+C+Bpci	2.314	-0.0441	£1,710	£161	-£1,043	10%	-£1,484	9%

* Average for 'angio only', 'pci' and 'CABG' patients only

See Figure 4 for incremental costs and QALYs graphically displayed with appropriate incremental cost-effectiveness ratios (costs per QALY gained).

Figure 4. **Results summary (probabilistic analysis): on the cost-effectiveness plane (adjusted analysis)**

Heparin baseline	Fondaparinux baseline
Incremental costs and QALYs are versus baseline. Comparisons not ruled out by dominance (D) or extended dominance (ED) are joined by a line where the slope equals the 'cost per QALY gained'	
● Aspirin+clopidogrel+heparin (baseline) ■ Aspirin+clopidogrel+heparin+GPI(pcionly) ▲ Aspirin+clopidogrel+heparin+GPI ◆ Aspirin+clopidogrel+bivalirudin ◇Aspirin+clopidogrel+heparin+bivalirudin(pcionly)	● Aspirin+clopidogrel+fondaparinux (baseline) ■ Aspirin+clop+ fonda+GPI(pcionly) ▲ Aspirin+clopidogrel+ fondaparinux+GPI ◆ Aspirin+clopidogrel+bivalirudin ◇Aspirin+clopidogrel+heparin+bivalirudin(pcionly)
	
	

Heparin baseline	Fondaparinux baseline
Incremental costs and QALYs are versus baseline. Comparisons not ruled out by dominance (D) or extended dominance (ED) are joined by a line where the slope equals the 'cost per QALY gained'	
● Aspirin+clopidogrel+heparin (baseline) ■ Aspirin+clopidogrel+heparin+GPI(pcionly) ▲ Aspirin+clopidogrel+heparin+GPI ◆ Aspirin+clopidogrel+bivalirudin ◇Aspirin+clopidogrel+heparin+bivalirudin(pcionly)	● Aspirin+clopidogrel+fondaparinux (baseline) ■ Aspirin+clop+ fonda+GPI(pcionly) ▲ Aspirin+clopidogrel+ fondaparinux+GPI ◆ Aspirin+clopidogrel+bivalirudin ◇Aspirin+clopidogrel+heparin+bivalirudin(pcionly)
	
	

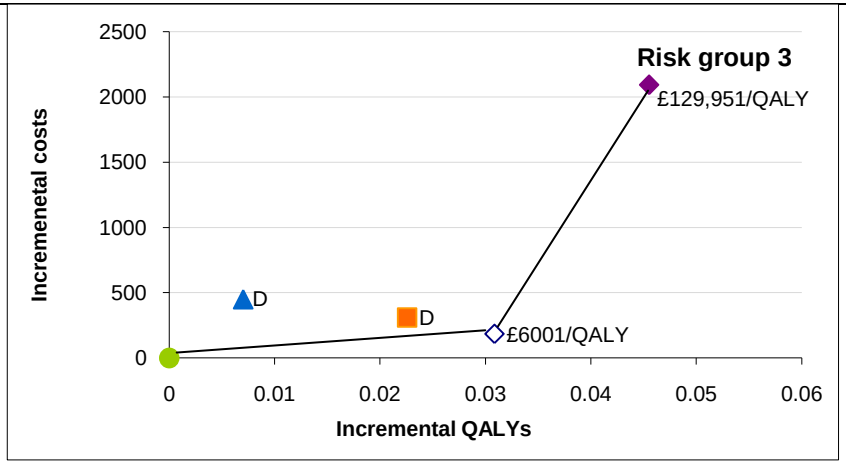
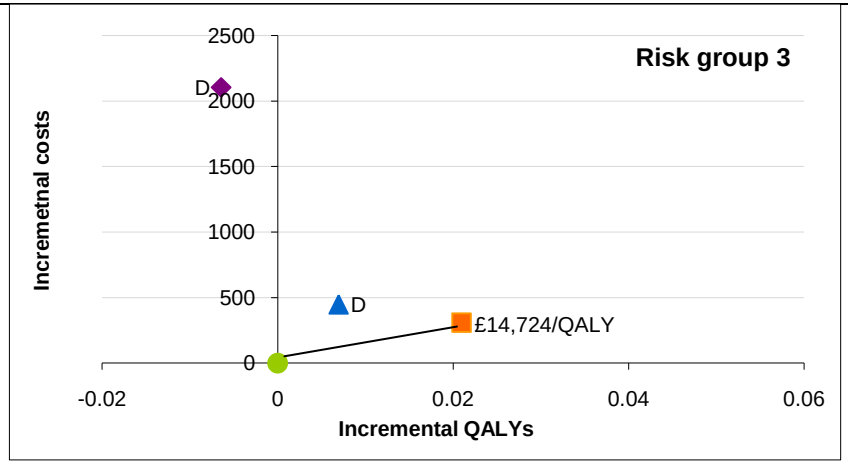
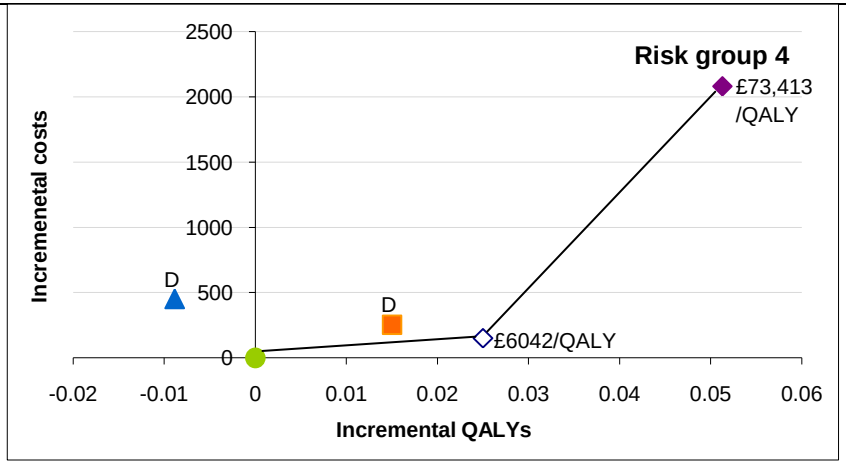
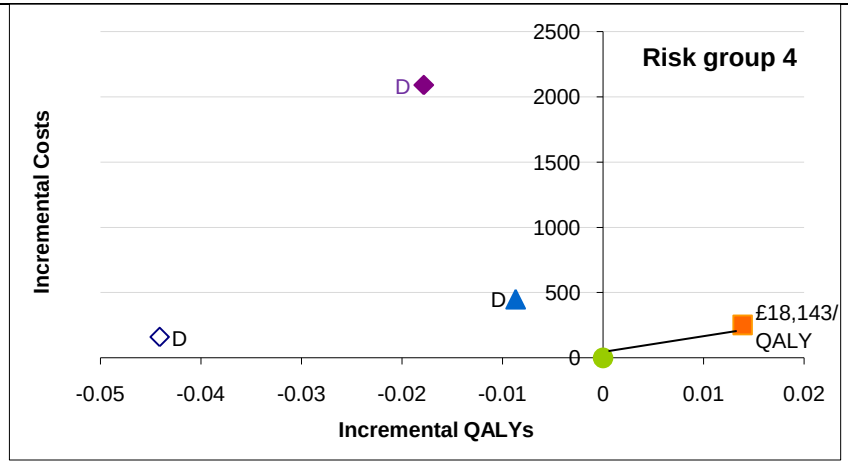
Heparin baseline	Fondaparinux baseline
Incremental costs and QALYs are versus baseline. Comparisons not ruled out by dominance (D) or extended dominance (ED) are joined by a line where the slope equals the 'cost per QALY gained'	
● Aspirin+clopidogrel+heparin (baseline) ■ Aspirin+clopidogrel+heparin+GPI(pcionly) ▲ Aspirin+clopidogrel+heparin+GPI ◆ Aspirin+clopidogrel+bivalirudin ◇Aspirin+clopidogrel+heparin+bivalirudin(pcionly)	● Aspirin+clopidogrel+fondaparinux (baseline) ■ Aspirin+clop+ fonda+GPI(pcionly) ▲ Aspirin+clopidogrel+ fondaparinux+GPI ◆ Aspirin+clopidogrel+bivalirudin ◇Aspirin+clopidogrel+heparin+bivalirudin(pcionly)
	
	

Table 23. **Results summary (probabilistic analysis): breakdown of events and costs (adjusted analysis)**

	Patient status at 1 year (per 1000)*			Resource use events at 1 year (per 1000)*					Discounted cost breakdown* (average per patient)		
	These numbers drive the QALY estimates as each one year status is associated with a different number of life-years.			Acute episode			Post acute episode		These numbers impact the 1-year cost estimates.		
Risk group 1a	**Dead**	**Alive w/ new MI**	**Alive no new MI**	**Reinf-arction**	**Maj bleed**	**Min bleed**	**Readm MI**	**Revasc**	**Treatment**	**Year 1**	**Year 2+**
A+C+H	9	36	955	12	2	11	38	98	£78	£437	£4,563
A+C+H+GPIpci	9	31	961	10	2	13	33	89	£480	£400	£4,565
A+C+H+GPIup	9	28	963	9	2	17	30	93	£550	£409	£4,563
A+C+B	8	31	961	10	1	9	33	101	£2,169	£441	£4,567
A+C+Bpci	8	32	959	11	2	9	35	107	£268	£460	£4,566
A+C+F	8	35	957	11	1	4	37	98	£60	£430	£4,568
A+C+F+GPIpci	8	29	963	10	1	4	32	89	£462	£392	£4,569
A+C+F+GPIup	8	27	965	9	1	6	29	93	£531	£401	£4,568
A+C+B	8	31	961	10	1	9	33	101	£2,169	£441	£4,567
A+C+Bpci	8	32	959	11	2	9	35	107	£268	£460	£4,566
Risk group 1b											
A+C+H	14	35	951	14	2	11	33	97	£77	£431	£3,585
A+C+H+GPIpci	14	29	957	12	2	13	29	89	£460	£396	£3,587
A+C+H+GPIup	15	27	958	11	2	17	26	93	£548	£407	£3,585
A+C+B	13	29	958	12	1	9	28	101	£2,162	£438	£3,589
A+C+Bpci	14	31	956	13	2	9	30	106	£257	£455	£3,588
A+C+F	13	33	954	14	1	4	31	97	£58	£424	£3,591
A+C+F+GPIpci	13	28	960	12	1	4	27	89	£442	£389	£3,592
A+C+F+GPIup	13	26	961	10	1	6	25	93	£530	£400	£3,590
A+C+B	13	29	958	12	1	9	28	101	£2,162	£438	£3,589
A+C+Bpci	14	31	956	13	2	9	30	106	£257	£455	£3,588
Risk group 2a											
A+C+H	33	31	936	17	7	7	27	96	£77	£420	£2,688
A+C+H+GPIpci	32	27	941	14	7	9	25	87	£464	£388	£2,693
A+C+H+GPIup	34	25	941	13	8	11	22	91	£548	£399	£2,691
A+C+B	31	27	942	14	3	6	25	99	£2,164	£426	£2,697
A+C+Bpci	32	28	940	15	6	6	25	105	£259	£445	£2,694
A+C+F	30	30	940	16	4	3	26	96	£59	£413	£2,698
A+C+F+GPIpci	29	26	945	13	4	3	23	87	£446	£380	£2,703
A+C+F+GPIup	30	24	946	12	4	4	21	91	£530	£391	£2,701
A+C+B	31	27	942	14	3	6	25	99	£2,164	£426	£2,697

A+C+Bpci	32	28	940	15	6	6	25	105	£259	£445	£2,694
Risk group 2b											
A+C+H	53	41	906	21	7	7	42	95	£74	£449	£2,272
A+C+H+GPIpci	51	36	913	18	7	9	38	87	£436	£416	£2,279
A+C+H+GPIup	53	33	913	16	8	11	35	91	£546	£424	£2,276
A+C+B	48	36	915	18	3	6	38	99	£2,154	£455	£2,285
A+C+Bpci	50	38	913	18	6	6	39	104	£245	£470	£2,281
A+C+F	47	40	913	20	4	3	40	95	£56	£439	£2,286
A+C+F+GPIpci	45	34	920	17	4	3	36	87	£418	£406	£2,293
A+C+F+GPIup	48	32	920	15	4	4	33	91	£528	£414	£2,289
A+C+B	48	36	915	18	3	6	38	99	£2,154	£455	£2,285
A+C+Bpci	50	38	913	18	6	6	39	104	£245	£470	£2,281
Risk group 3											
A+C+H	99	39	862	18	13	14	54	95	£72	£480	£1,684
A+C+H+GPIpci	96	35	869	16	13	15	50	88	£405	£448	£1,692
A+C+H+GPIup	100	32	867	15	15	20	45	92	£543	£456	£1,686
A+C+B	91	35	874	16	6	11	49	100	£2,142	£484	£1,700
A+C+Bpci	94	36	870	17	11	11	51	103	£229	£497	£1,695
A+C+F	88	38	873	17	7	5	52	95	£53	£466	£1,703
A+C+F+GPIpci	85	34	881	15	7	5	48	88	£387	£434	£1,710
A+C+F+GPIup	89	32	879	14	8	7	43	92	£525	£441	£1,705
A+C+B	91	35	874	16	6	11	49	100	£2,142	£484	£1,700
A+C+Bpci	94	36	870	17	11	11	51	103	£229	£497	£1,695
Risk group 4											
A+C+H	232	43	725	35	21	17	58	97	£65	£518	£976
A+C+H+GPIpci	228	40	733	32	21	19	54	91	£338	£493	£981
A+C+H+GPIup	237	37	726	29	23	25	49	95	£538	£501	£972
A+C+B	214	41	745	32	10	14	54	103	£2,118	£526	£996
A+C+Bpci	224	41	735	33	18	15	55	103	£194	£531	£986
A+C+F	207	43	750	33	12	6	55	97	£47	£499	£1,004
A+C+F+GPIpci	203	39	757	30	12	7	52	91	£320	£473	£1,009
A+C+F+GPIup	212	36	751	28	13	9	47	95	£519	£480	£1,000
A+C+B	214	41	745	32	10	14	54	103	£2,118	£526	£996
A+C+Bpci	224	41	735	33	18	15	55	103	£194	£531	£986

Results summary

The table above are fairly complex due to the number of risk groups, different analyses, and the uncertainty in the results. Summary tables were constructed to give a snap shot of the results. The tables below summarise, for each analysis, the highest mean incremental net benefit (INB) from the probabilistic analysis. While this metric is the most appropriate indicator of the single optimal strategy (that is the most cost effective at the specified threshold), the percentage of the 10,000 simulations that each strategy is the optimal strategy provides some indication of the uncertainty in the analysis. For this reason, the table also includes two columns summarising this information. Finally the table also includes the deterministic INB (in the deterministic analysis results are calculated using parameter point estimates) for comparison with the probabilistic mean INB. Again, the highest mean INB from the probabilistic analysis is the most appropriate indicator of the expected optimal strategy rather than from the deterministic; however, where these differs it is a further indication of the impact of uncertainty in the analysis. A threshold of £20,000 per QALY gained is used.

Fondaparinux baseline

See Table 24 and Table 25. The analysis incorporating a fondaparinux baseline (that is fondaparinux replaces heparin in the aspirin+clopidogrel+heparin, aspirin+clopidogrel+heparin+GPI during PCI, aspirin+clopidogrel+heparin+GPIupstream arms of the model),was considered most relevant to clinical decision making in the majority of cases. Fondaparinux has been found to be cost-effective compared to heparin as shown in the published literature[114]. Fondaparinux is cheaper than enoxaparin and is associated with clinical benefits. In the model Aspirin+clopidogrel+fondaparinux dominated Aspirin+clopidogrel+heparin in all of our analyses (although this comparison was a secondary objective of the analysis).

In the trial aligned analysis (reflective of a short time to angiography) routine addition of upstream GPIs seems to be most cost-effective for patients in risk groups 2 and 3, with selective PCI GPI use most cost-effective in risk group 4. This is based on these options having the highest mean INB at a £20,000 per QALY threshold. In the adjusted analysis (with treatment costs estimated using a 72hr pre-angiography treatment duration and the MINAP management split employed) selective use of GPIs at PCI was found to be the most cost-effective strategy; however, this analysis was considered likely to bias against upstream use of GPIs as treatment costs are increased but efficacy is not adjusted.

There was considerable uncertainty in the results. This is evidenced by differences between the deterministic optimal strategy and probabilistic optimal strategy especially in Groups 1a and 4. Also, there is a wide spread of the probability of cost-effectiveness across different strategies. In places the optimal strategy as based on mean INB is not the one with the highest probability of being cost-effective as based on the highest proportion of simulations. In addition there is uncertainty regarding applicability as the trial aligned analysis may not represent typical treatment durations in the UK; whereas the longer term analysis is limited by the lack of effectiveness data. It was also noted that from a clincal perspective, the longer the wait for angiography the more likely a patient would need a GPI prior to angiography and deferring use until PCI is undertaken may not be a clinically acceptable option.

Interpretation of results is complicated by the uncertainty in the analysis. Additional clinical considerations should be employed in interpretation and it was considered that it may be reasonable to recommend more than one option to reflect this uncertainty. Risk group 1 is considered least likely to benefit from additional treatment over and above aspirin+clopidogrel+fondaparinux. Dependent on appropriate clinical interpretation, due to the uncertainty it was considered that use of either GPI use upstream of angiography or selective GPI use in PCI might be considered likely to be cost-effective in higher risk groups. This is due to the fact that different options were found to be most cost-effective in

the trial aligned and adjusted analysis but limitations in the analysis mean that a definitive conclusion is not possible based on these model results alone.

Note that the fondaparinux baseline analysis is dependent on the assumption that the relative effect of GPIs will not be impacted by whether heparin or fondaparinux is used as the baseline antithrombin – there were no studies that assessed GPIs against no GPIs in a population using fondaparinux. The OASIS-5 trial addresses this issue somewhat by examining 30-day outcomes for fondaparinux versus enoxaparin in subgroups of patients receiving clopidogrel and GPIs[115]. This analysis suggested that the benefits of fondaparinux are maintained in patients receiving clopidogrel or GPIs.

Note that the discussion section below examines the uncertainties and limitations of the analysis in more detail.

Key:
A+C+F = Aspirin+clopidogrel+fondaparinux
GPIpci = GPI given selectively from time of PCI
GPIup = GPI given routinely upstream of angiography
Bpci = Bivalirudin given selectively from time of PCI
B = Bivalirudin given routinely upstream of angiography (instead of heparin or fondaparinux)

Table 24. **Optimal strategies (£20k per QALY) – fondaparinux background – trial aligned analysis**

Decision rule Risk group	Highest mean INB	Highest mean INB or INB highest in >30% simulations	Highest mean INB or INB highest in >20% simulations	Highest deterministic INB
1a	A+C+F	A+C+F A+C+F+GPIup	A+C+F A+C+F+GPIup	A+C+F
1b	A+C+F	A+C+F A+C+F+GPIup	A+C+F A+C+F+GPIup	A+C+F
2a	A+C+F+GPIup	A+C+F+GPIup	A+C+F+GPIup	A+C+F+GPIup
2b	A+C+F+GPIup	A+C+F+GPIup	A+C+F+GPIup A+C+B	A+C+F+GPIup
3	A+C+F+GPIup	A+C+F+GPIup	A+C+F+GPIup A+C+B	A+C+F+GPIup
4	A+C+F+GPIpci	A+C+F+GPIup A+C+F+GPIpci	A+C+F+GPIup A+C+B A+C+F+GPIpci	A+C+F+GPIup

Table 25. **Optimal strategies (£20k per QALY) – fondaparinux background – adjusted analysis***

Decision rule Risk group	Highest mean INB	Highest mean INB or INB highest in >30% simulations	Highest mean INB or INB highest in >20% simulations	Highest deterministic INB
1a	A+C+F	A+C+F	A+C+F	A+C+F
1b	A+C+F	A+C+F	A+C+F	A+C+F
2a	A+C+F	A+C+F A+C+F+GPIup	A+C+F A+C+F+GPIup	A+C+F
2b	A+C+F+GPIpci	A+C+F+GPIup A+C+F+GPIpci	A+C+F+GPIup A+C+F+GPIpci	A+C+F+GPIpci
3	A+C+F+GPIpci	A+C+F+GPIup A+C+F+GPIpci	A+C+F+GPIup A+C+F+GPIpci	A+C+F+GPIpci
4	A+C+F+GPIpci	A+C+F+GPIup A+C+F+GPIpci	A+C+F+GPIup A+C+F+GPIpci	A+C+F+GPIpci

* This model potentially biases against GPIup and Bup because although it estimates the increased cost associated with the longer duration (compared with the trials) it does not account for any increased effects.

Heparin baseline

See Table 26 and Table 27. If fondaparinux is not an appropriate option, then the analysis with a heparin baseline is most appropriate to review. In this analysis, risk group one is least likely to benefit from additional treatment over and above aspirin+clopidogrel+heparin. Heparin use with selective bivalirudin during PCI seems to be most cost-effective in risk groups 2-4. This is based on the mean INB from the heparin baseline analyses in both the trial aligned analysis (reflective of a short time to angiography) and the adjusted analysis (with treatment costs estimated using a 72hr pre-angiography treatment duration and the MINAP management split employed). Bivalirudin use pre-angiography was associated with more QALYs than selective bivalirudin use but also additional costs and based on the mean INB this use was not cost effective at a £20,000 per QALY threshold.

As in the fondaparinux baseline analysis there was considerable uncertainty in the heparin-baseline analysis. In the trial aligned analysis (reflective of a short time to angiography) bivalirudin PCI was considered the most cost-effective treatment based on mean INB, bivalirudin use upstream of angiography, and upstream GPI use generally also had a high level of simulations where they were optimal. As risk increased the likelihood of bivalirudin initiated upstream of angiography being cost effective increased. It was also raised that there will sometime be a clinical need to give additional treatment upstream of angiography, for example if the patient is actively unstable. Interpretation of results is complicated by the uncertainty in the analysis. Additional clinical rationale should be employed in interpretation and it was considered that it may be reasonable to recommend more than one option to reflect this uncertainty. Dependent on appropriate clinical interpretation, due to the uncertainty it was considered that use of the following might be considered likely to be cost effective: bivalirudin used selectively during PCI; upstream bivalirudin; heparin plus upstream GPIs.

In the adjusted analysis (where costing was based on a 72hr pre-angiography treatment duration) PCI bivalirudin was also most cost effective, as would be expected as the upstream treatments will have higher costs in the model but the effectiveness was not adjusted. In addition, this analysis was considered the least clinically relevant because if patients were not going for angiography relatively quickly they would be most likely to be considered suitable for fondaparinux.

Note that the discussion section below examines the uncertainties and limitations of the analysis in more detail.

Key

A+C+H = Aspirin+clopidogrel+heparin
GPIpci = GPI given selectively from time of PCI
GPIup = GPI given routinely upstream of angiography
Bpci = Bivalirudin given selectively from time of PCI
B = Bivalirudin given routinely upstream of angiography (instead of heparin or fondaparinux)

Table 26. **Optimal strategies (£20k per QALY) – heparin background – trial aligned analysis**

Decision rule Risk group	Highest mean INB	Highest mean INB or INB highest in >30% simulations	Highest mean INB or INB highest in >20% simulations	Highest deterministic INB
1a	A+C+H	A+C+H A+C+H+GPIup	A+C+H A+C+H+GPIup A+C+Bpci	A+C+Bpci
1b	A+C+H	A+C+H A+C+H+GPIup	A+C+H A+C+H+GPIup A+C+Bpci	A+C+H
2a	A+C+H+GPIup A+C+Bpci*	A+C+H+GPIup A+C+Bpci	A+C+H+GPIup A+C+Bpci	A+C+Bpci

			A+C+B	
2b	A+C+Bpci	A+C+Bpci	A+C+H+GPIup A+C+B A+C+Bpci	A+C+Bpci
3	A+C+Bpci	A+C+B A+C+Bpci	A+C+B A+C+Bpci	A+C+Bpci
4	A+C+Bpci	A+C+B A+C+Bpci	A+C+B A+C+Bpci	A+C+Bpci

* A+C+H+GPIup had a INB only £2 less than A+C+Bpci and so has been included here as well.

Table 27. **Optimal strategies (£20k per QALY) – heparin background – adjusted analysis***

Decision rule **Risk group**	**Highest mean INB**	**Highest mean INB or INB highest in >30% simulations**	**Highest mean INB or INB highest in >20% simulations**	**Highest deterministic INB**
1a	A+C+H	A+C+H A+C+Bpci	A+C+H A+C+Bpci	A+C+Bpci
1b	A+C+H	A+C+H A+C+Bpci	A+C+H A+C+Bpci	A+C+H
2a	A+C+Bpci	A+C+Bpci	A+C+H+GPIup A+C+Bpci	A+C+Bpci
2b	A+C+Bpci	A+C+H+GPIup A+C+Bpci	A+C+H+GPIup A+C+Bpci	A+C+Bpci
3	A+C+Bpci	A+C+Bpci	A+C+H+GPIup A+C+Bpci	A+C+Bpci
4	A+C+Bpci	A+C+Bpci	A+C+Bpci	A+C+Bpci

* This model potentially biases against GPIup and B because although it estimates the increased cost associated with the longer duration (compared with the trials) it does not account for any increased effects.

Sensitivity analyses

Sensitivity analysis can be used to investigate whether changing assumptions or data used in the model changes the conclusions drawn from the analysis. Sensitivity analyses were based on the probabilistic analysis with 5000 simulations.

A series of different scenarios were examined in sensitivity analysis. Each of the following was examined for each base case with both a heparin and fondaparinux baseline.

0. Base case
    a. Trial aligned analysis (trial vial usage where pre-angiography treatment period median 4hrs/mean 10hrs; ACUITY management split)
    b. Adjusted analysis (costing assuming 72hr pre-angiography treatment period; MINAP management split)
1. Acute episode management split was changed from that based on the MINAP analysis to that based on that applied in the ACUITY study or vice versa.
2. Doubled post-acute revascularisation rates to address concerns that estimated rates may be low (for details of issue see methods section).
3. Increased baseline major and minor bleeding rates to address concerns that MINAP rates appeared low (300% and 800% increase respectively).
4. Relative risks of major and minor bleeding for upstream GPIs vs deferred PCI GPIs taken from pooled ACUITY timing and Early ACS data (instead of ACUITY timing alone).
5. A higher post-year one disease related cost (£1600) was used to address concerns that the basecase estimate was low (for details of issue see methods section).

6. Reduced mortality and MI baseline rates plus shorter treatment duration to mimic an improved management situation where patients are treated quicker and event rates are lower.
7. Reduced mortality and MI baseline rates, increased bleeding rates, increased post-acute episode revascularisation to combine various scenarios above.

See Table 28 and Table 29 for results of sensitivity analyses. These are presented in terms of the optimal strategy for each risk group based on mean INB. Also presented is summary information regarding the simulation results as presented in the summary tables above.

Fondaparinux baseline analyses

In the fondaparinux baseline analyses, sensitivity analyses mostly did not impact on what was found to be the optimal strategy based on mean INB. Where the optimal strategy changed these are described below.

In the shorter term analysis, where treatment costs were based on trial vial usage and the ACUITY management split was used, in three analyses in risk group 3 PCI use of GPIs became more cost-effective than upstream use of GPIs. This was in the analyses where MINAP management split was used, when the non-acute revascularisation rate was doubled and when the relative risk for bleeding for upstream GPIs versus PCI GPIs was based on the meta analysis of the ACUITY trial and the Early ACS trial instead of that from just the ACUITY trial. In two analyses in risk group 4, fondaparinux alone became the preferred strategy instead of upstream GPIs. This was in the two analyses where baseline mortality and MI rates were reduced by 30%, in one of these the baseline bleed rate was also increased.

In the longer term analysis, where costs were based on a 72hr pre-angiography treatment duration and the MINAP management split was used, in two analyses in risk groups 2b, 3 and 4 fondaparinux alone became the optimal strategy instead of fondaparinux and PCI GPI use. This was in the two analyses where baseline mortality and MI rates were reduced by 30%, in one of these the baseline bleed rate was also increased. This results was also reflected when looking at the simulation summary where the likelihood of fondaparinux +GPIpci being the preferred strategy was reduced and the likelihood fondaparinux alone was the preferred strategy was increased.

Heparin baseline analyses

In the heparin baseline analyses, sensitivity analyses generally did not change the optimal strategy based on mean INB.

Table 28. **Sensitivity analyses:** Trial aligned analysis (trial vial usage where pre-angiography treatment period median 4hrs/mean 10hrs; ACUITY management split)

	***0* Base case**	***1***	***2***	***3***	***4***	***5***	***6***	***7***
Treatment duration	trial	trial	trial	trial	trial	trial	trial	trial
Management split	ACUITY	MINAP	ACUITY	ACUITY	ACUITY	ACUITY	ACUITY	ACUITY
Mortality rate adjustment	0%	0%	0%	0%	0%	0%	-30%	-30%
MI readmission adjustment	0%	0%	0%	0%	0%	0%	-30%	-30%
Reinfarction adjustment	0%	0%	0%	0%	0%	0%	-30%	-30%
Major bleed adjustment	0%	0%	0%	300%	0%	0%	0%	300%
Minor bleed adjustment	0%	0%	0%	800%	0%	0%	0%	800%
Non-acute revasc adjustment	0%	0%	100%	0%	0%	0%	0%	0%
Long term costs	Base	Base	Base	Base	Base	Higher	Base	Base
Alternative GPI up vs pci RRs	None	None	None	None	Bleed	None	None	None

Max mean INB:

1a	H	H	H	H	H	H	H	H
1b	H	H	H	H	H	H	H	H
2a	H+Bpci H+Gup*	H+Bpci	H+Gup	H+Bpci	H+Bpci	H+Bpci	H+Gup	H+Gup
2b	H+Bpci	H+Bpci	H+Bpci	H+Bpci	H+Bpci	H+Bpci	H+Bpci	H+Bpci
3	H+Bpci	H+Bpci	H+Bpci	H+Bpci	H+Bpci	H+Bpci	H+Bpci	H+Bpci
4	H+Bpci	H+Bpci	H+Bpci	H+Bpci	H+Bpci	H+Bpci	H+Bpci	H+Bpci

***** A+C+H+Gup had a INB only £2 less than A+C+Bpci and so has been included for the basecase as well; for other scenarios only the maximum INB is displayed

Max mean INB or >30% (>20%) simulations where max INB:

1a	H; H+Gup; (H+Bpci)	H; H+Gup; H+Bpci	H; H+Gup; (H+Bpci)	H; H+Gup; H+Bpci	H; H+Gup; H+Bpci	H; H+Gup; (H+Bpci)	H; H+Gup; (H+Bpci)	H; H+Gup; (H+Bpci)
1b	H; H+Gup; (H+Bpci)	H; H+Gup; (H+Bpci)	H; H+Gup;	H; H+Gup; (H+Bpci)	H; H+Gup; (H+Bpci)	H; H+Gup; (H+Bpci)	H; H+Gup;	H; H+Gup;
2a	H+Gup; (B); H+Bpci	(H+Gup); (B); H+Bpci	H+Gup; (B); (H+Bpci)	(H+Gup); (B); H+Bpci	(H+Gup); (B); H+Bpci	(H+Gup); (B); H+Bpci	H+Gup; (H+Bpci)	H+Gup; (H+Bpci)
2b	(H+Gup); (B); H+Bpci	(H+Gup); (B); H+Bpci	(H+Gup); (B); H+Bpci	(H+Gup); (B); H+Bpci	(H+Gup); (B); H+Bpci	(H+Gup); (B); H+Bpci	(H+Gup); (B); H+Bpci	(H+Gup); (B); H+Bpci
3	B; H+Bpci	B; H+Bpci	B; H+Bpci	B; H+Bpci	B; H+Bpci	(B); H+Bpci	(B); H+Bpci	(B); H+Bpci
4	B; H+Bpci	B; H+Bpci	B; H+Bpci	B; H+Bpci	B; H+Bpci	B; H+Bpci	B; H+Bpci	B; H+Bpci

Max mean INB:

1a	F	F	F	F	F	F	F	F
1b	F	F	F	F	F	F	F	F
2a	F+Gup	F+Gup	F+Gup	F+Gup	F+Gup	F+Gup	F+Gup	F+Gup
2b	F+Gup	F+Gup	F+Gup	F+Gup	F+Gup	F+Gup	F+Gup	F+Gup
3	F+Gup	F+Gpci	F+Gpci	F+Gup	F+Gpci	F+Gup	F+Gup	F+Gup
4	F+Gpci	F+Gpci	F+Gpci	F+Gpci	F+Gpci	F+Gpci	F	F

Max mean INB or >30% (>20%) simulations where max INB:

1a	F; F+Gup;	F; F+Gup;	F; F+Gup;	F; F+Gup;	F; F+Gup;	F; F+Gup;	F; F+Gup;	F; F+Gup;
1b	F; F+Gup;	F; F+Gup;	F; F+Gup;	F; F+Gup;	F; F+Gup;	F; F+Gup;	F; F+Gup;	F; F+Gup;
2a	F+Gup;	F+Gup;	F+Gup;	F+Gup;	F+Gup;	F+Gup;	(F); F+Gup;	(F); F+Gup;
2b	F+Gup; (B);	F+Gup; (B);	F+Gup; (B);	F+Gup; (B);	F+Gup;	F+Gup;	F+Gup;	F+Gup;
3	F+Gup; (B); (H+Bpci)	F+Gpci; F+Gup; (B);	F+Gpci; F+Gup; (B);	F+Gup; (B); (H+Bpci)	F+Gpci; F+Gup; (B); (H+Bpci)	F+Gup; (B); (H+Bpci)	F+Gup; (B); (H+Bpci)	F+Gup;
4	F+Gpci; F+Gup; (B);	F+Gpci; F+Gup; (B);	F+Gpci; F+Gup; (B);	F+Gpci; F+Gup; (B);	F+Gpci; F+Gup; (B);	F+Gpci; F+Gup; (B);	F; F+Gup; (B);	F; F+Gup; (B);

Table 29. **Sensitivity analyses: Adjusted analysis (costing assuming 72hr pre-angiography treatment period; MINAP management split)**

	0 **Base case**	***1***	***2***	***3***	***4***	***5***	***6***	***7***
Treatment duration	72hrs	72hrs	72hrs	72hrs	72hrs	72hrs	72hrs	72hrs
Management split	MINAP	ACUITY	MINAP	MINAP	MINAP	MINAP	MINAP	MINAP
Mortality rate adjustment	0%	0%	0%	0%	0%	0%	-30%	-30%
MI readmission adjustment	0%	0%	0%	0%	0%	0%	-30%	-30%
Reinfarction adjustment	0%	0%	0%	0%	0%	0%	-30%	-30%
Major bleed adjustment	0%	0%	0%	300%	0%	0%	0%	300%
Minor bleed adjustment	0%	0%	0%	800%	0%	0%	0%	800%
Non-acute revasc adjustment	0%	0%	100%	0%	0%	0%	0%	0%
Long term costs	Base	Base	Base	Base	Base	Higher	Base	Base
Alternative GPI up vs pci RRs	None	None	None	None	Bleed	None	None	None
Max mean INB:								
1a	H	H	H	H	H	H	H	H
1b	H	H	H	H	H	H	H	H
2a	H+Bpci	H+Bpci	H+Bpci	H+Bpci	H+Bpci	H+Bpci	H+Bpci	H+Bpci
2b	H+Bpci	H+Bpci	H+Bpci	H+Bpci	H+Bpci	H+Bpci	H+Bpci	H+Bpci
3	H+Bpci	H+Bpci	H+Bpci	H+Bpci	H+Bpci	H+Bpci	H+Bpci	H+Bpci
4	H+Bpci	H+Bpci	H+Bpci	H+Bpci	H+Bpci	H+Bpci	H+Bpci	H+Bpci
Max mean INB or >30% (>20%) simulations where max INB:								
1a	H; H+Bpci	H; H+Bpci	H; H+Bpci	H; H+Bpci	H; H+Bpci	H; H+Bpci	H; H+Bpci	H; H+Bpci
1b	H; H+Bpci	H; H+Bpci	H; H+Bpci	H; H+Bpci	H; H+Bpci	H; H+Bpci	H; (H+Bpci)	H; (H+Bpci)
2a	(H+Gup); H+Bpci	(H+Gup); H+Bpci	(H+Gup); H+Bpci	(H+Gup); H+Bpci	(H+Gup); H+Bpci	(H+Gup); H+Bpci	(H); (H+Gup); H+Bpci	(H); (H+Gup); H+Bpci
2b	(H+Gup); H+Bpci	(H+Gup); H+Bpci	(H+Gup); H+Bpci	(H+Gup); H+Bpci	(H+Gup); H+Bpci	(H+Gup); H+Bpci	(H+Gup); H+Bpci	(H+Gup); H+Bpci
3	(H+Gup); H+Bpci	(H+Gup); H+Bpci	(H+Gup); H+Bpci	(H+Gup); H+Bpci	(H+Gup); H+Bpci	(H+Gup); H+Bpci	(H+Gup); H+Bpci	(H+Gup); H+Bpci
4	(H+Gup); H+Bpci	H+Bpci	H+Bpci	H+Bpci	H+Bpci	(H+Gup); H+Bpci	(H+Gup); H+Bpci	(H+Gup); H+Bpci
Max mean INB:								
1a	F	F	F	F	F	F	F	F
1b	F	F	F	F	F	F	F	F
2a	F	F	F	F	F	F	F	F
2b	F+Gpci	F+Gpci	F+Gpci	F+Gpci	F+Gpci	F+Gpci	F	F
3	F+Gpci	F+Gpci	F+Gpci	F+Gpci	F+Gpci	F+Gpci	F	F
4	F+Gpci	F+Gpci	F+Gpci	F+Gpci	F+Gpci	F+Gpci	F	F
Max mean INB or >30% (>20%) simulations where max INB:								
1a	F;	F;	F;	F;	F;	F;	F;	F;
1b	F;	F;	F;	F;	F;	F;	F;	F;
2a	F; F+Gup;	F; F+Gup;	F; (F+Gpci); F+Gup;	F; F+Gup;	F; F+Gup;	F; F+Gup;	F; (F+Gup);	F; (F+Gup);
2b	F+Gpci; F+Gup; (H+Bpci)	F+Gpci; F+Gup; (H+Bpci)	F+Gpci; F+Gup;	F+Gpci; F+Gup; (H+Bpci)	F+Gpci; F+Gup; (H+Bpci)	F+Gpci; F+Gup; (H+Bpci)	F; F+Gup; (H+Bpci)	F; F+Gup; (H+Bpci)
3	F+Gpci; F+Gup; (H+Bpci)	F+Gpci; F+Gup; (H+Bpci)	F+Gpci; F+Gup; (H+Bpci)	F+Gpci; F+Gup; (H+Bpci)	F+Gpci; F+Gup; (H+Bpci)	F+Gpci; F+Gup; (H+Bpci)	F; (F+Gpci); F+Gup; (H+Bpci)	F; (F+Gpci); F+Gup; (H+Bpci)
4	F+Gpci; F+Gup;	F+Gpci; F+Gup; (H+Bpci)	F+Gpci; F+Gup;	F+Gpci; F+Gup;	F+Gpci; F+Gup;	F+Gpci; F+Gup;	F; (F+Gpci); F+Gup;	F; (F+Gpci); F+Gup;

Discussion

Summary

This analysis aimed to examine the cost effectiveness of GPIs in the current context of widespread clopidogrel use, an increase in invasive management and the availability of new therapies. It compared the following strategies in an early invasive management situation:

- no planned GPI use (aspirin, clopidogrel, heparin or fondaparinux)
- GPI use only during PCI (aspirin, clopidogrel, heparin or fondaparinux, GPIpci)
- GPI use routinely upstream of angiography (aspirin, clopidogrel, heparin or fondaparinux, GPIupstream)
- bivalirudin use routinely upstream of angiography instead of heparin or fondaparinux, and instead of planned GPI use (aspirin, clopidogrel, bivalirudin).
- Bivalirudin use only during PCI (asprin, clopidogrel, heparin, bivalirudinpci)

Fondaparinux baseline analysis:

The analysis incorporating a fondaparinux baseline (that is fondaparinux replaces heparin in the aspirin+clopidogrel+heparin, aspirin+clopidogrel+heparin+GPI during PCI, aspirin+clopidogrel+heparin+GPIupstream arms of the model),was considered most relevant to clinical decision making in the majority of cases. Fondaparinux has been found to be cost-effective compared to heparin as shown in the published literature[114]. Fondaparinux is cheaper than enoxaparin and is associated with clinical benefits. In the model Aspirin+clopidogrel+fondaparinux dominated Aspirin+clopidogrel+heparin in all of our analyses (although this comparison was a secondary objective of the analysis).

In the trial aligned analysis (when trial vial usage was used for costings and the ACUITY management split employed) routine addition of upstream GPIs seems to be most cost-effective for patients in risk groups 2 and 3, with selective PCI GPI use the most cost-effective in risk group 4. This is based on these options having the highest mean INB at a £20,000 per QALY threshold. In the adjusted analysis (with treatment costs estimated using a 72hr pre-angiography treatment duration and the MINAP management split employed) selective use of GPIs at PCI was found to be most cost-effective strategy; however, this analysis was considered likely to bias against upstream use of GPIs as treatment costs are increased but efficacy is not adjusted.

There was considerable uncertainty in the results. This is evidenced by differences between the deterministic optimal strategy and probabilistic optimal strategy especially in Groups 1a and 4. Also, there is a wide spread of the probability of cost-effectiveness across different strategies. In places the optimal strategy as based on mean INB is not the one with the highest probability of being cost-effective as based on the highest proportion of simulations. In addition there is uncertainty regarding applicability as the trial aligned analysis may not represent typical treatment durations in the UK; whereas the longer term analysis is limited by the lack of effectiveness data. It was also noted that from a clincal perspective, the longer the wait for angiography the more likely a patient would need a GPI prior to angiography and deferring use until PCI is undertaken may not be a clinically acceptable option.

Interpretation of results is complicated by the uncertainty in the analysis. Additional clinical considerations should be employed in interpretation and it was considered that it may be reasonable to recommend more than one option to reflect this uncertainty. Risk group 1 is considered least likely to benefit from additional treatment over and above aspirin+clopidogrel+fondaparinux. Dependent on appropriate clinical interpretation, due to the uncertainty it was considered that either GPI use upstream of angiography or selective GPI use in PCI might be considered likely to be cost-effective in higher risk groups. This is due to the fact that different options were found to be most cost-effective in the trial aligned and

adjusted analysis but limitations in the analysis mean that a definitive conclusion is not possible based on these model results alone.

Note that the fondaparinux baseline analysis is dependent on the assumption that the relative effect of GPIs will not be impacted by whether heparin or fondaparinux is used as the baseline antithrombin – there were no studies that assessed GPIs against no GPIs in a population using fondaparinux. The OASIS-5 trial addresses this issue somewhat by examining 30-day outcomes for fondaparinux versus enoxaparin in subgroups of patients receiving clopidogrel and GPIs[115]. This analysis suggested that the benefits of fondaparinux are maintained in patients receiving clopidogrel or GPIs.

Heparin baseline analysis:
If fondaparinux is not an appropriate option, then the analysis with a heparin baseline is most appropriate to review. In this analysis, risk group one is least likely to benefit from additional treatment over and above aspirin+clopidogrel+heparin. Heparin use with selective bivalirudin during PCI seems to be most cost-effective in risk groups 2-4. This is based on the mean INB from the heparin baseline analyses in both the trial aligned analysis (reflective of a short time to angiography) and the adjusted analysis (with treatment costs estimated using a 72hr pre-angiography treatment duration and the MINAP management split employed). Bivalirudin use pre-angiography was associated with more QALYs than the selective bivalirudin use but also additional costs and based on the mean INB this use was not cost effective at a £20,000 per QALY threshold.

As in the fondaparinux baseline analysis there was considerable uncertainty in the heparin-baseline analysis. In the trial aligned analysis (reflective of a short time to angiography) bivalirudin PCI was considered the most cost-effective treatment based on mean INB, bivalirudin use upstream of angiography, and upstream GPI use generally also had a high level of simulations where they were optimal. As risk increased the likelihood of bivalirudin initiated upstream of angiography being cost effective increased. It was also raised that there will sometime be a clinical need to give additional treatment upstream of angiography, for example if the patient is actively unstable. Interpretation of results is complicated by the uncertainty in the analysis. Additional clinical rationale should be employed in interpretation and it was considered that it may be reasonable to recommend more than one option to reflect this uncertainty. Dependent on appropriate clinical interpretation, due to the uncertainty it was considered that use of the following might be considered likely to be cost effective: bivalirudin used selectively during PCI; upstream bivalirudin; heparin plus upstream GPIs.

In the adjusted analysis (where costing was based on a 72hr pre-angiography treatment duration) PCI bivalirudin was also most cost effective, as would be expected as the upstream treatments will have higher costs in the model but the effectiveness was not adjusted. In addition, this analysis was considered the least clinically relevant because if patients were not going for angiography relatively quickly they would be most likely to be considered suitable for fondaparinux.

Comparison with the literature
No comparable analyses comparing all these treatment options were available in the literature.

The 2002 NICE technology appraisal of GPIs examined the cost effectiveness of different GPI strategies[37,210]. It found that use of upstream GPIs in moderate to high risk patients was cost effective but not in lower risk patients (risk as defined in the TA rather than by risk score). The analysis undertaken for this guideline takes a similar approach but uses different data. As

well as utilising evidence for GPIs specifically on a background of clopidogrel use to reflect current practice, it incorporates head-to-head evidence comparing upstream GPI use with PCI GPI use, and evidence relating to the new agent bivalirudin, as an alternative to heparin plus a GPI. It also incorporates fondaparinux. The use of invasive management has increased considerably and risk assessment in UA/NSTEMI has also progressed since this previous analyses and this is also addressed.

Economic evaluations of bivalirudin in the literature have suggested that it is a cost-effective option compared to heparin + GPI when used as per the clinical trials. This analysis also found that bivalirudin use may be cost-effective in the same circumstances. However, when fondaparinux was substituted as the baseline antithrombin the bivalirudin options became much less favourable.

Selective GPIs during PCI versus non-selective upstream

Use of upstream GPIs as opposed to PCI GPIs appeared to confer benefits in terms of reduced MI events based on the meta analysis of 30-day results undertaken for the guideline However, bleeding was significantly increased. This potentially implies a trade-off between ischemic benefits with bleeding risk. The death endpoint will incorporate deaths from ischemic and bleed complications and so this will reflect both effects. The relative risk for mortality was close to one and not-significantly different, although with a slight numerical trend to favouring PCI GPIs.

In the model we deal with incorporating different outcomes by converting to QALYs. Death up to one year will capture the impact of bleeding and ischemic events. The analysis also models a benefit of avoiding MI on the basis that avoiding an MI is an important clinical outcome in its own right and that it has a prognostic benefit. In the model people that have experienced a new MI in the first year are attributed a lower life expectancy than those that do not. The difference in QALYs with upstream GPI use compared with PCI use comes from a combination of death and MI based on the non-significant relative risks from ACUITY timing data (heparin only background, clopidogrel subgroup). The model is built probabilistically so it takes account of the uncertainty around the point estimates of relative risk (i.e. the fact that they aren't significant).

The base case analysis does not incorporate the Early ACS trial data. The Early ACS trial was published late in the guideline development process. Early ACS only reports 30-day outcomes whereas the model had been developed with one-year baseline event rates and effectiveness data. Meta-analysis undertaken for the guideline reported similar results to the ACUITY study alone. On this basis Early ACS was not incorporated into the cost-effectiveness analysis base case. Sensitivity analyses were undertaken to examine the possible impact. The pooled bleed rates from ACUITY timing and EARLY ACS from the meta analysis were used in one sensitivity analysis. This did not have a significant impact.

Uncertainty in the analysis

Why are upstream GPIs cost-effective in risk groups 2 and 3 but PCI GPIs in risk group 4?

Closer examination was given to the effects observed in the fondaparinux baseline analysis where upstream GPIs were found to be the most cost-effective option in risk groups 2 and 3, but PCI GPIs in risk group 4 (in the trial aligned analysis with short upstream treatment based costing). In general, upstream GPI QALYs were impacted by the following in the model:

- The relative risk of non-fatal MI favouring upstream over PCI GPIs (0.93) but the relative risk of death slightly favouring PCI GPIs (1.03) – these effects work in opposite directions in terms of QALYs
- The relative baseline rates of death and MI in the different risk groups.

    - Mortality consistently increases by risk group (in group 4 the death rate is about double that in group 3)
    - In risk groups 2, 3 and 4 new non-fatal MIs is fairly similar
- The relative benefits of avoiding MI or death in the different risk groups, in terms of life years gained
    - The benefit of avoiding death consistently decreases by risk group (as life expectancy decreases by risk group)
    - The benefit of avoiding MI peaks in the middle risk groups and diminishes at either end
- Uncertainty around the relative risk point estimates
    - Relative risks are non-significant and so cross 1
    - If the model is run deterministically upstream GPIs always have more QALYs than heparin alone, but when the model is run probabilistically, taking into account uncertainty, at times QALYs with upstream GPIs are less than with heparin alone.

In terms of the different result in risk group 3 (where upstream GPIs were the most cost-effective option) and risk group 4 (where PCI GPI were), in these risk groups the risk of non-fatal MI is fairly similar but the risk of death is doubled. As we apply constant relative risks this means that there is more death relative to MI in risk group 4 than 3. This will mean that for upstream GPIs the decrease in QALYs will be higher (from additional deaths) but the increase in QALYs will be about the same (as MIs are about the same). This means that in risk group 4 the incremental QALYs compared to baseline are lower than in risk group 3.

Why are there less QALYs with upstream GPIs than no GPIs in some risk groups?
The QALYs with upstream GPIs relative to no GPIs are dependent on the relative risks for upstream GPIs versus PCI GPIs, and also the relative risks for PCI GPIs versus no GPIs. QALYs are dependent on both the rates of death and the rates of non-fatal MI. MI is reduced with PCI GPIs versus no GPIs and also with upstream GPIs versus PCI GPIs. However, while death is reduced with upstream GPIs versus no GPIs, death is (slightly) increased with upstream GPIs versus PCI GPIs. This means that if the death effect with upstream GPIs outweighs the MI effect there could be less QALYs with upstream GPIs than PCI GPIs (as can be seen in the analyses). Also, as relative risks fro PCI GPIs versus no GPIs are only applied in the PCI population but relative risks for upstream GPIs versus PCI GPIs are applied across the whole early angiography population (in line with the trial populations), a small effect in the latter can outweigh a bigger effect in the former. In the deterministic analysis, using the point estimates, QALYs are higher with upstream GPIs than no GPIs and are higher with PCI GPIs than upstream GPIs. However, when inputs are varied probabilistically, to reflect the uncertainty around the point estimates, this can result in QALYs with upstream GPIs sometimes being lower than with no GPIs. This occurs for example if the relative risk for death with upstream GPIs versus PCI GPIs is less favourable i.e. greater than 1.03. It can also occur if the relative risk for death with PCI GPIs versus no GPIs is less favourable i.e. greater than 0.96. Due to the uncertainty in the model when the analysis is run probabilistically, on average QALYs sometimes result in being less with upstream GPIs than with no GPIs. However, in contrast to this mean result, when this occurs the proportion of simulations in which upstream GPIs is the most cost-effective is still high – in some cases the highest. This is a further indicator of uncertainty in the model.

Subgroup analysis
Extensive subgroup analysis based on risk assessment was incorporated into the analysis. The aim of this was to allow discrimination based on patient risk as those at higher risk can often be expected to gain more absolute benefit than those at lower risk and so treatment

may be more cost effective. However, the assumption of the analysis is that relative benefits and harms of treatment are constant across risk groups. No evidence was available from trials to suggest otherwise. However, this assumption has a noticeable impact in the analysis. As described above, in one analysis PCI GPIs is cost effective in risk group 4, but upstream GPIs in risk groups 2 and 3. The reason for this is due to the assumption of constant relative benefits and harms applied to baseline rates of death and MI that increase at different rates between risk groups. Death is doubled in risk group 4 over risk group 3 but MI is similar. The assumption of constant relative risk means that the small increase in death (RR 1.03) with upstream GPIs over PCI GPIs is magnified and the reduction in MI is increased to the same relative amount to counteract this effect. Whether this represents a real life effect is unknown.

Other relevant clinical issues not captured by the model

Some clinical issues were raised related to the use of upstream agents that are not incorporated into the analysis; one being that practically, irrespective of risk stratification, some patients will be clinically unstable in the period prior to angiography and it may be necessary to attempt to stabilise them with additional treatment. In this situation deferring treatment only to those who subsequently undergo PCI is not an appropriate strategy and there may be a clinical imperative to treat. In these patients it was considered that their propensity to benefit from additional treatment may be higher than the population as a whole and that therefore this 'targeted' use of upstream agents may be cost effective.

The trade off between bleeding and ischemic events

It is noted that in a number of comparisons in the analysis there appears to be a possible trade off between reducing ischemic events such as MI and revascularisation and increasing bleeding events, or vice versa. Understanding of the impact of bleeding is a developing area. Recent analyses suggest that both bleeding and ischemic events contribute to the risk of death[312]. Mortality estimates in trials will therefore take into account the impact of both effects. In this analysis a prognostic impact of MI is incorporated. It is unclear whether a similar longer term implication of bleeding would be appropriate and so it is not incorporated into the model.

It is assumed in the model that relative risks of benefit and harm are constant across risk groups. Given the lack of clear evidence of a difference in effect this assumption was considered reasonable. For example, analyses of ACUITY timing by TIMI risk group did not find a significant interaction effect[99]. In addition the higher risk patients may well have been excluded from studies. However, it is imaginable that relative propensity for benefit and harm may vary by risk group and will certainly vary in individuals, for example depending on their risk of bleeding. It may be that the trade-off between ischaemic complications and bleeding is different in different risk groups or different individuals and this may impact on all-cause mortality and cost effectiveness. It would therefore be reasonable to not apply a strategy based on these population results to specific individual clinical situations, for example where bleeding risk is known to be high. While the sensitivity analysis of increased baseline bleeding rates in this analysis addresses the cost of bleeding it does not account for any increased relative risk of bleeding with treatment. Nor does it account for the potential for increased mortality with increased bleeding risk.

Applicability

As described in the methods section, reconciling the available clinical evidence with UK specific data has some challenges. The analysis is primarily relevant to a population undergoing an early invasive strategy as the trial evidence used is not in a population being medically managed who do not undergo angiography. As such, treatment effects in the model were only applied to baseline rates from MINAP for patients who received an invasive investigation/treatment. This MINAP data is however from any patients managed invasively

and not just those who underwent this 'early'. In the MINAP population of those who did not undergo angiography or revascularisation, death and MI event rates were higher. There is uncertainty regarding cost effectiveness in these patients and it is difficult to extrapolate from this analysis.

The applicability of international trials to the UK setting is also an uncertainty. The ACUITY trial may not represent typical UK management. For example, patients may wait longer for angiography in the UK and as such receive upstream GPIs for longer. This may in turn impact the relative effectiveness of upstream GPIs compared to downstream. While this analysis attempted partially to reflect this by using longer treatment durations to estimate costs and using UK specific rates of PCI and CABG, efficacy could not be adjusted.

Limitations

There are a number of issues that inhibit interpretation of the clinical data in the UK setting and these therefore also impact the cost effectiveness analysis. In many trials eptifibatide can be utilised for deferred PCI, but this use is not licensed in UK. In addition, trials have varying rates of angiography, PCI, CABG and varying times to angiography/PCI management. In the trials utilised in this analysis, time to angiography/PCI is generally shorter than that reported in the UK (around three days in interventional centres[178]).

As described throughout the report there are a number of limitations in the data that was available to undertake the analysis. A trial including all the interventions in the model was not available and so indirect comparisons were undertaken. In addition, some studies or some endpoints within studies did not have a one-year follow-up period and 6-month relative risks were assumed to hold at one year. This was the case for the death and MI outcomes for the fondaparinux versus enoxaparin comparison from the OASIS-5 trial and the MI and revascularisation endpoints for the bivalirudin during PCI versus GPI during PCI comparison from the REPLACE-2 study. Follow-up available from MINAP was limited for this analysis to one-year; longer-term data may improve the estimation of life expectancy used in the model. It is noted that longer-term follow-up could potentially be obtained from MINAP. However, for the purposes of this analysis an available cohort was used that had already been mortality checked as this is a time consuming and expensive exercise. In addition, to obtain longer follow up would mean starting with an older cohort and one of the reasons for using MINAP data was to reflect modern clinical management and therefore outcomes for patients that have occurred over recent years. There was a lack of data available to inform post-acute episode revascularisation rates. Rates have been estimated using information from the literature and discussion with the GDG as described in the methods section. An attempt was made to obtain rates for the MINAP cohort through linkage with the interventional and surgical procedures audit databases. However, complexities in the analysis and time constraints meant this was not possible to complete.

While these factors certainly do represent difficulties in interpreting the available data and understanding the implications of the analysis, we have attempted to make a reasonable estimate of cost effectiveness to inform decision making in the UK context and we have explored areas of uncertainty. Many of these issues in reality affect clinical decision making throughout this area and are no less of an issue in this analysis. All conclusions should therefore bear this in mind.

9 APPENDIX D

The National Service Framework for Coronary Heart Disease (department of health 2000)

Before discharge from hospital (Phase 1)

To be offered as soon as is practical as an integral part of the acute care of someone admitted (or planned to be admitted) to hospital with CHD:

- Assessment of physical, psychological and social needs for cardiac rehabilitation
- Negotiation of a written individual plan for meeting these identified needs (copies should be given to the patient and the general practitioner)
- Initial advice on lifestyle e.g. smoking cessation, physical activity (including sexual activity),diet, alcohol consumption and employment
- Prescription of effective medication and education about its use, benefits and harms
- Involvement of relevant informal carer(s)
- Provision of information about cardiac support groups
- Provision of locally relevant written information about cardiac rehabilitation

Early post-discharge period (Phase 2)

- Comprehensive assessment of cardiac risk, including physical, psychological and social needs for cardiac rehabilitation; and a review of the initial plan for meeting these needs
- Provision of lifestyle advice and psychological interventions according to the agreed plan from relevant trained therapists who have access to support from a cardiologist
- Maintain involvement of relevant informal carer(s)
- Review involvement with cardiac support groups
- Offer resuscitation training for family members

Phase 3: as Phase 2 plus

- Structured exercise sessions to meet the assessed needs of individual patients

- Maintain access to relevant advice and support from people trained to offer advice about
- Exercise, relaxation, psychological interventions, health promotion and vocational advice

Long-term maintenance of changed behaviour (Phase 4)

- Long term follow-up in primary care (see chapter 2)
- Offer involvement with local cardiac support groups
- Referral to specialist cardiac, behavioural (e.g. exercise, smoking cessation) or psychological services as clinically indicated.

10 APPENDIX E

NICE MI: Secondary prevention clinical guideline cardiac rehabilitation recommendations

Comprehensive cardiac rehabilitation

All patients (regardless of their age) should be given advice about and offered a cardiac rehabilitation programme with an exercise component.

Cardiac rehabilitation programmes should provide a range of options, and patients should be encouraged to attend all those appropriate to their clinical needs. Patients should not be excluded from the entire programme if they choose not to attend certain components.

If a patient has cardiac or other clinical conditions that may worsen during exercise, these should be treated if possible before the patient is offered the exercise component of cardiac rehabilitation. For some patients, the exercise component may be adapted by an appropriately qualified healthcare professional.

Patients with left ventricular dysfunction who are stable can safely be offered the exercise component of cardiac rehabilitation.

1.2.2 Patient engagement

Cardiac rehabilitation should be equally accessible and relevant to all patients after an MI, particularly people from groups that are less likely to access this service. These include people from black and minority ethnic groups, older people, people from lower socioeconomic groups, women, people from rural communities and people with mental and physical health comorbidities.

Healthcare professionals should take into account patients' wider health and social needs, which may involve identifying and addressing economic, welfare rights, housing or social support issues. This may be a particular issue for people in more deprived circumstances, and rehabilitation services should assess the likely scale of these needs when planning how their services meet the needs of the local population.

Cardiac rehabilitation programmes should be culturally sensitive. Employing bilingual peer educators or cardiac rehabilitation assistants who reflect the diversity of the local population should be considered.

Cardiac rehabilitation programmes should include an exercise component designed to meet the needs of older patients or patients with significant comorbidity. Any transport problems should be addressed.

Healthcare professionals should ask patients whether they would prefer single-sex classes or mixed classes.

Healthcare professionals should establish patients' health beliefs and level of health literacy before offering appropriate lifestyle advice.

Healthcare professionals, including senior medical staff involved in providing care for patients after an MI, should actively promote cardiac rehabilitation.

Reminders such as:

- telephone calls
- telephone calls in combination with direct contact from a healthcare
- professional motivational letters should be used to improve uptake of cardiac rehabilitation.

1.2.3 Health education and information

Comprehensive cardiac rehabilitation programmes should include health education and stress management components.

A home based programme validated for patients who have had an MI (such as 'The Edinburgh heart manual'; see www.cardiacrehabilitation.org.uk/heart_manual/heartmanual.htm) that incorporates education, exercise and stress management components with follow-ups by a trained facilitator may be used to provide comprehensive cardiac rehabilitation.

Most patients who have had an MI can return to work. Any advice should take into account the physical and psychological status of the patient, the nature of the work and the work environment.

Healthcare professionals should be up to date with the latest Driver and Vehicle Licensing Agency guidelines. Regular updates are published on the agency's website (www.dvla.gov.uk).

After an MI without complications, patients can usually travel by air within 2–3 weeks. Patients who have had a complicated MI need expert individual advice.

Patients who hold a pilot's licence should seek advice from the Civil Aviation Authority.

Most patients can return to normal activities of daily living. Any advice about the

timing of this should take into account the patient's physical and psychological status, as well as the type of activity planned.

An estimate of the physical demand of a particular activity, and a comparison between activities, can be made using tables of metabolic equivalents (METS) of different activities (for further information please refer to www.cdc.gov/nccdphp/dnpa/physical/measuring/met.htm). Patient should also be advised how to use a perceived exertion scale to help monitor physiological demand. Patients who have had a complicated MI may need expert advice.

Advice on competitive sport may need expert assessment of function and risk, and is dependent on what sport is being discussed and the level of competitiveness.

1.2.4 Psychological and social support

Stress management should be offered in the context of comprehensive cardiac rehabilitation.

Complex psychological interventions such as cognitive behavioural therapy should not be offered routinely.

There should be provision to involve partners or carers in the cardiac rehabilitation programme if the patient wishes.

For recommendations on the management of patients with clinical anxiety and/or depression, refer to 'Anxiety' (NICE clinical guideline 22) and 'Depression' (NICE clinical guideline 23).

1.2.5 Sexual activity

Patients should be reassured that after recovery from an MI, sexual activity presents no greater risk of triggering a subsequent MI than if they had never had an MI.

Patients who have made an uncomplicated recovery after their MI can resume sexual activity when they feel comfortable to do so, usually after about 4 weeks.

The subject of sexual activity should be raised with patients within the context of cardiac rehabilitation and aftercare.

When treating erectile dysfunction, treatment with a PDE5 (phosphodiesterase type 5) inhibitor may be considered in patients who had an MI more than 6 months earlier and who are now stable.

PDE5 inhibitors must be avoided in patients treated with nitrates and/or nicorandil because this can lead to dangerously low blood pressure.

11 APPENDIX F

Question ID	Section number	Question wording	Study Type Filters used	Databases and Years
RISK	**3**	**Which tables, equations, engines or scoring systems for patient-risk stratification are most predictive of death, re-infarction or other vascular events in patients with UA/NSTEMI?**	**Systematic Reviews, RCTs, Comparative Studies and Observational Studies**	**Medline 1999-2009** **Embase 1999-2009** **Cochrane 1999-2009** **Cinahl 1999-2009**
ASA	**4**	**What is the efficacy and safety of aspirin therapy in the medical management of patients with UA or NSTEMI compared to placebo?**	**None**	**Cochrane 1995-**
CLOP1	**4**	**What is the efficacy and safety of clopidogrel in the medical management of patients with UA or NSTEMI compared to other antiplatelets or placebo?**	**Systematic Reviews and RCTs**	**Medline 2003-2009** **Embase 2003-2009** **Cochrane 2003-2009** **Cinahl 2003-2009**
LMWH	**4**	**What is the efficacy and safety of adding a LMWH compound to aspirin (with or without clopidogrel) in the medical management of patients with UA or NSTEMI compared to the combination of unfractionated heparin and aspirin (with or without clopidogrel)?**	**Systematic Reviews and RCTs**	**Medline 1999-2009** **Embase 1999-2009** **Cochrane 1999-2009** **Cinahl 1999-2009**
GLYCO1	**4**	**What is the efficacy and safety of adding a GPI (tirofiban, eptifibatide and abcixmab) to aspirin and heparin therapy in the medical management of patients with UA or NSTEMI compared to the combination of aspirin and**	**Systematic Reviews and RCTs**	**Medline 2002-2009** **Embase 2002-2009** **Cochrane 2002-2009** **Cinahl 2002-2009**

		LMWH?		
GLYCO 2	**4**	**What is the efficacy and safety of adding a GPI (tirofiban, eptifibatide and abcixmab) to aspirin and heparin therapy as adjunct therapy to patients with UA/ NSTEMI undergoing PCI compared to the combination of aspirin and LMWH?**	**Systematic Reviews and RCTs**	**Medline 2002-2009** **Embase 2002-2009** **Cochrane 2002-2009** **Cinahl 2002-2009**
THROMB1	**5**	**What is the efficacy and safety of adding a Thrombin inhibitor (Bivalirudin) to the combination of aspirin, with or without a GPI, in the medical management of patients with UA or NSTEMI compared to the combination of LMWH/UFH, aspirin, with or without a GPI?**	**Systematic Reviews and RCTs**	**Medline 1999-2009** **Embase 1999-2009** **Cochrane 1999-2009** **Cinahl 1999-2009**
THROMB2	**5**	**What is the efficacy and safety of adding a Thrombin inhibitor (Hirudin and Bivalirudin) to the combination of aspirin and a GPI as adjunct therapy to patients with UA/ NSTEMI undergoing PCI compared to the combination of LMWH/UFH, aspirin, and a GPI?**	**Systematic Reviews and RCTs**	**Medline 1999-2009** **Embase 1999-2009** **Cochrane 1999-2009** **Cinahl 1999-2009**
PENTA1	**5**	**What is the efficacy and safety of adding a factor Xa inhibitor (fondaparinux) to aspirin in the medical management of patients with UA or NSTEMI compared to the combination of LMWH/ UFH and aspirin therapy?**	**Systematic Reviews and RCTs**	**Medline 1999-2009** **Embase 1999-2009** **Cochrane 1999-2009** **Cinahl 1999-2009**
PENTA2	**5**	**What is the efficacy and safety of adding a synthetic pentasaccharide (fondaparinux and enoxaparin) to aspirin as**	**Systematic Reviews and RCTs**	**Medline 1999-2009** **Embase 1999-2009**

		adjunct therapy to patients with UA/ NSTEMI undergoing PCI compared to the combination of LMWH/UFH and aspirin therapy?		**Cochrane 1999-2009** **Cinahl 1999-2009**
IABP	**6**	**Does the use of Intra-Aortic Balloon Pump Counterpulsation affect the outcome of patients with non-ST elevation myocardial infarction or unstable angina**	**Systematic Reviews, RCTs, Comparative Studies and Observational Studies**	**Medline 1995-2009** **Embase 1995-2009** **Cochrane 1995-2009** **Cinahl 1995-2009**
ANGIO	**7**	**In adults with UA or non-ST elevation MI does early invasive investigation (i.e. angiography) with intent to assess for (and in those patients deemed suitable, to perform) revascularization improve outcomes in comparison with initial conservative treatment, with or without later angiography?**	**Systematic Reviews, RCTs, Comparative Studies and Observational Studies**	**Medline 1995-2009** **Embase 1995-2009** **Cochrane 1995-2009** **Cinahl 1995-2009**
RISK2B	**7**	**In patients with UA/NSTEMI who do not undergo angiography, does investigation prior to hospital discharge for myocardial ischaemia affect outcome?**	**Systematic Reviews, RCTs, Comparative Studies and Observational Studies**	**Medline 1995-2009** **Embase 1995-2009** **Cochrane 1995-2009** **Cinahl 1995-2009**
RISK2A	**7**	**Does pre-discharge assessment of left ventricular function predict future risk in patients with UA/NSTEMI**	**Systematic Reviews, RCTs, Comparative Studies and Observational Studies**	**Medline 1995-2009** **Embase 1995-2009** **Cochrane 1995-2009** **Cinahl 1995-2009**
PCI-CABG	**7**	**In adults with UA or non-ST elevation MI does CABG improve**	**Systematic Reviews, RCTs,**	**Medline 1995-2009**

		outcomes in comparison with PCI?		**Embase 1995-2009** **Cochrane 1995-2009** **Cinahl 1995-2009**
SPEC	**8**	**Does management of inpatient care for people with unstable angina or NSTEMI by a specialist cardiology team vs non specialist team improve clinical outcomes?**	**Systematic Reviews, RCTs, Comparative Studies and Observational Studies**	**Medline 1999-2009** **Embase 1999-2009** **Cochrane 1999-2009** **Cinahl 1999-2009**
PSYCH1	**9**	**Do early psychosocial and educational interventions, mobilisation and discharge planning (cardiac rehabilitation – Phase 1) improve emotional and physical wellbeing and long-term outcomes in people with unstable angina or NSTEMI compared to deferred (cardiac rehabilitation Phase 2)?**	**Systematic Reviews, RCTs, Comparative Studies and Observational Studies**	**Medline 1999-2009** **Embase 1999-2009** **Cochrane 1999-2009** **Cinahl 1999-2009**

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