Modern Management of AF

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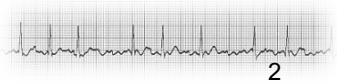
UK.PH.GM.XAR.2012.220m

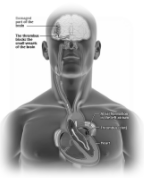
What is the prevalence of AF?

Prevalence: 1–2% of the general population, i.e. >6 million Europeans[1]

- Probably closer to 2% as AF may long remain undiagnosed (silent AF)
- 0.1–14% of the general population all over the world
- 3 to 6% of acute medical admissions have AF

1. Camm et al. Eur Heart J 2010;31:2369–429.
2. Lip et al. Chest 2012;e-published March 29, doi:10.1378/chest.11-2888.
3. Lip et al. Lancet 2012;379:648–61.





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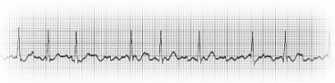
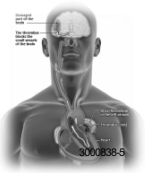
Non-Valvular Atrial Fibrillation
An EPIDEMIC?

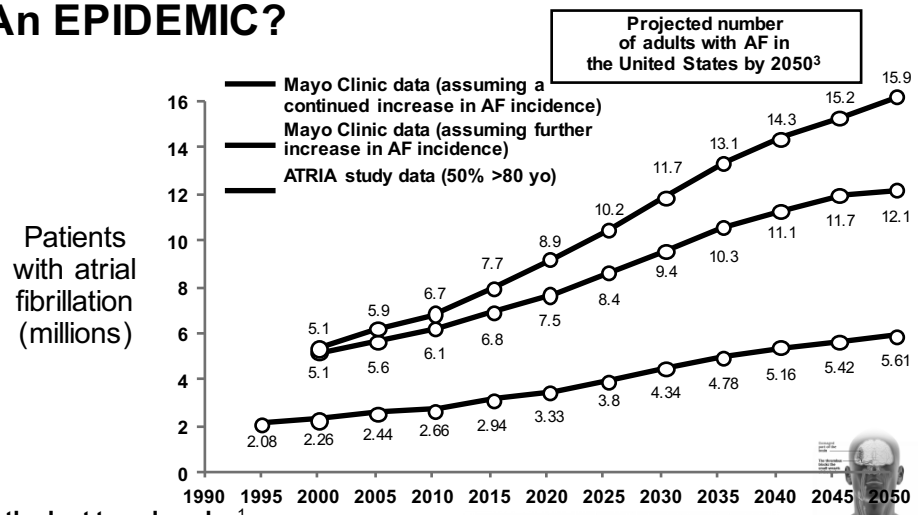
- Affects 1-1.5% of population in developed world
- Lifetime risk in men & women >40 is 1 in 4
- Prevalence
  - 0.5% age 0-59
  - 9.0% age >80
- Currently 2.5 million adults in U.S.

Savelieva: J Intern Med 250, 2001
Go: JAMA 285, 2001, Miyasaka: Circ 114, 2006



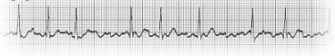


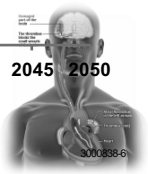
NVAF: Incidence of AF is predicted to rise
An EPIDEMIC?



13% in the last two decades[1]

Estimated **to at least double** in the next 50 years as the population ages[1,2]





AF, a high cost to society

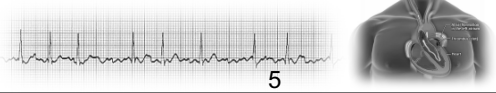
The presence of AF independently **increases the risk of mortality and morbidity** due to:

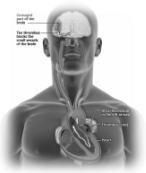
- Stroke and thromboembolism[1]
- Congestive heart failure[1]
- Impaired quality of life[2]

High health-care cost and public health burden[1]

Direct cost of AF represented 0.9–2.4% of the UK health-care budget in 2000 and had almost doubled over the previous 5 years.[3]

1. Lip et al. Lancet 2012;379:648–61.
2. Thrall et al. Am J Med 2006;119:448.e1–e19.
3. Wolowacz et al. Europace 2012;13:1375–85.





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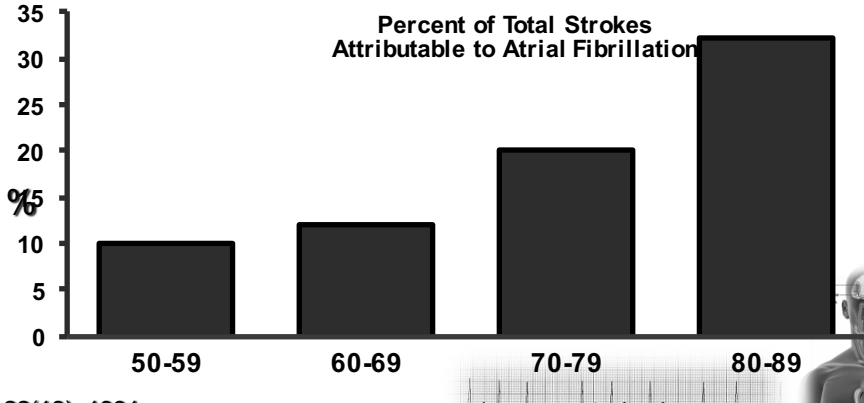
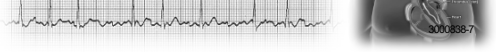
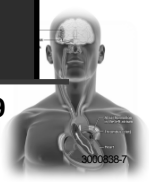
Non-Valvular Atrial Fibrillation

- 500,000 strokes/year in U.S.
- Up to 20% of ischemic strokes occur in patients with atrial fibrillation



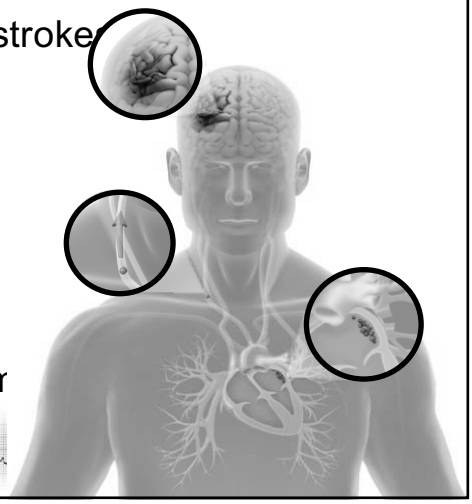
Stroke 22(18), 1991





AF confers an increased thromboembolic risk, notably in the brain

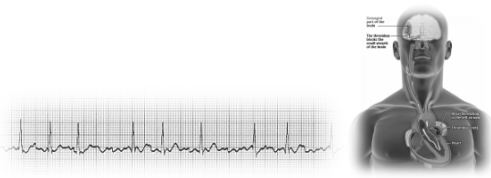
- AF confers a near 5-fold risk of stroke[1]
- It is estimated that 20% of all strokes are caused by AF[2]
- AF is often asymptomatic[3]
- The absence of symptoms eg palpitations, does not imply a lower risk of thromboembolism



1. Wolf et al. Stroke 1991;22:983–8.
2. Friedman et al. Circulation 1968;38:533–41.
3. Flaker et al. Am Heart J 2005;149:657–63.

AF : challenges

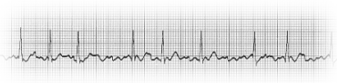
- How to recognise it
- How to treat rhythm
- How to prevent thromboembolism

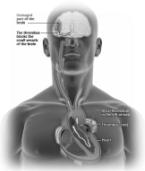


How to recognise/find AF

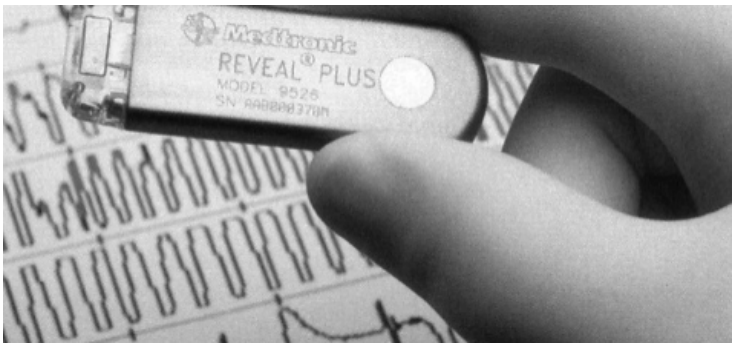
- Look particularly hard in patients with TIA/Stroke
- Symptoms that are sustained >few min, even if very intermittent/infrequent

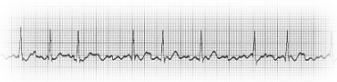
- 24h tape
- 7 day cardiac monitor (R test, Spider etc.)
- Implantable loop recorder – Reveal, Confirm
- Injectable implantable cardiac monitor
- Apps

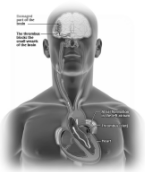




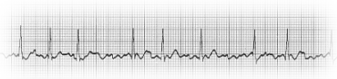
Implantable loop recorder (ILR)

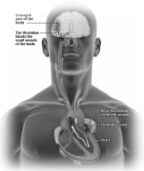




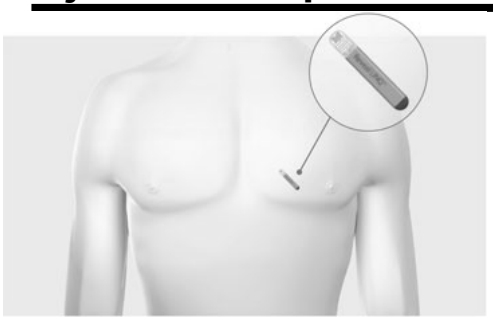


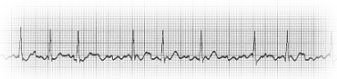
Implantable loop recorder - download

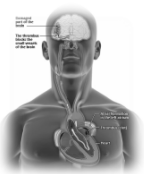




Injectable loop recorder



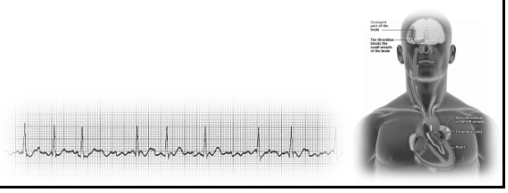




Alivecor

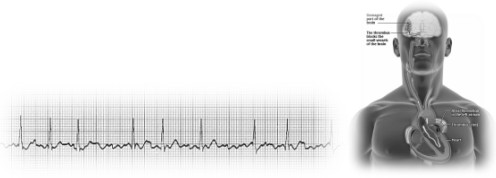
How to treat AF

- Thromboprophylaxis
- Rhythm/rate management
  - Rate vs. Rhythm



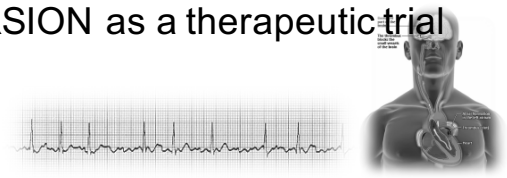
Rate vs. Rhythm control

- Aim for rhythm control in MAJORITY i.e. maintain SR
- Exceptions:
  - elderly asymptomatic, or
  - Asymptomatic esp. permanent AF with preserved LV function



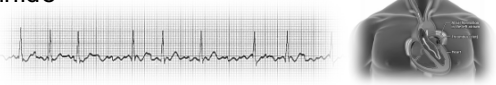
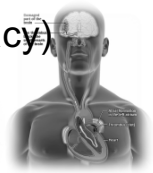
Rate vs. Rhythm control

- Aim for rhythm control in MAJORITY i.e. maintain SR
- Exceptions: accept rate control
  - Beta blockers: bisoprolol, atenolol / or Calcium channel blocker
  - Digoxin
- NB caution: many patients do not notice that they have gone into AF, but feel MUCH better when SR restored
- REMEMBER CARDIOVERSION as a therapeutic trial (NOT as a treatment)



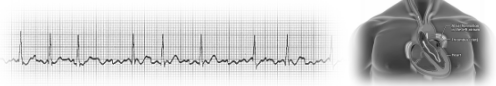
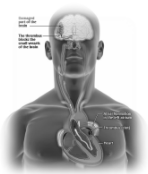
Rhythm control

- Frequency/duration of symptoms
  - ? Pill in the pocket
    - E.g. flecainide, bisoprolol
- Regular medication with top up.
  - E.g. bisoprolol (limited efficacy)
  - Add in/substitute with flecainide (better efficacy)
    - NB cautions with flecainide

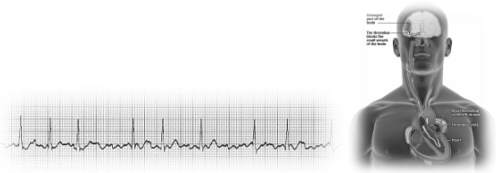
Whom to refer for AF ablation

- Anyone symptomatic with Paroxysmal AF
  - 1st or 2nd line treatment
- Anyone symptomatic with persistent AF despite good rate control (feels better in SR)
- Anyone with symptoms with persistent AF with impaired LV function

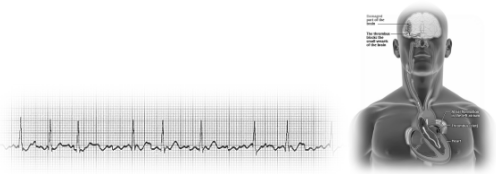
Benefits of AF ablation

- Restoration of SR
- Freedom from AAD
- Improvement in symptoms (vastly superior to AAD)
- Reduces the chance of progression to persistent AF
- Improves cardiac function and functional status in HF
- Reduces risk of stroke (large non-randomised studies)
- Reduces risk of dementia (large non-randomised studies)



Outcome of ablation

- Paroxysmal
  - 75% maintain SR at 1 year (PAF, off drugs)->90% on drugs
  - 60% maintain SR at 5 years
  - Repeat procedure SR 90% at 1 year
  - Repeat procedure SR 80% at 5 years
- Persistent
  - 60% maintain SR at 1 year (PAF, off drugs)->70% on drugs
  - 40% maintain SR at 5 years
  - Repeat procedure(s) SR 85% at 1 year
  - Repeat procedure(s) SR 80% at 5 years

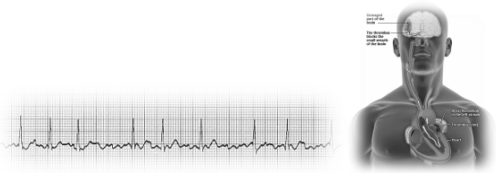


Risk of acceptance of AF

- Risks of AAD
- Risk of TTE/Stroke/Major bleeding
  - Remains despite thromboprophylaxis at 1-1.5% per annum
- Risk of progression to persistent arrhythmia

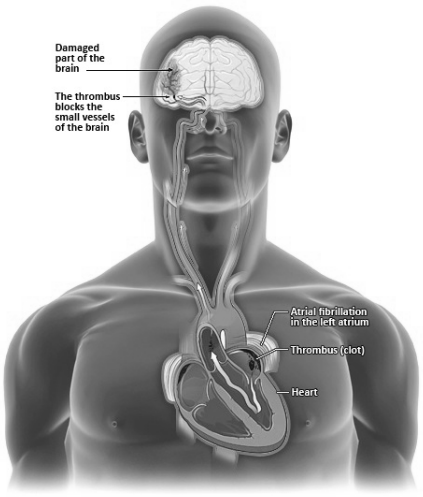
Risks

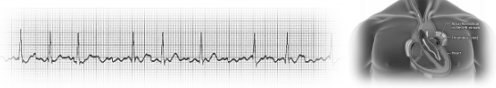
- Risks of procedure (mortality <0.1%, cardiac surgery 0.2%, Stroke/TIA 0.5%)
- Need for repeat procedures esp. with longer term follow up

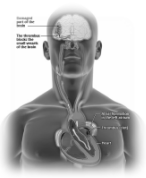


THROMBOPROPHYLAXIS OF STROKE

- Nothing
- Aspirin
- Warfarin/VKA
- NOAC
- LAA closure device



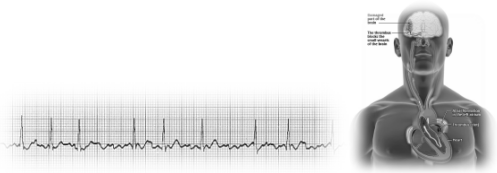




European Heart Journal (2012) **33**, 2719–2747
doi:10.1093/eurheartj/ehs253

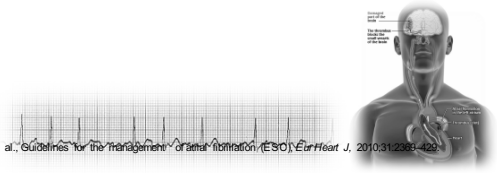
ESC GUIDELINES

2012 focused update of the ESC Guidelines for the management of atrial fibrillation



Refinement of stroke assessment in *relatively* low risk groups

$CHADS_2$		CHA_2DS_2-VASc	
Risk Factor	Points	Risk Factor	Points
CHF (C)	1	CHF/LV dysfunction (C)**	1
Hypertension (H)	1	Hypertension (H)**	1
Age ≥75 year (A)	1	Age ≥75 years (A)*	2
Diabetes (D)	1	Diabetes (D)**	1
Stroke/TIA/TE previously (S)	2	Stroke/TIA/TE previously (S)	2
		Vascular disease (V)**	1
		Age 65–74 years (A)**	1
		Female sex category (Sc)**	1



Camm AJ, Kirchhof P, Lip GY, et al., Guidelines for the management of atrial fibrillation (ESC), *Eur Heart J*, 2010;31:2369–429

Low $CHADS_2$ index is NOT benign

$CHADS_2$ criteria	Score
Congestive HF	1
Hypertension	1
Age ≥ 75 year	1
Diabetes	1
Stroke or TIA (previous history)	2

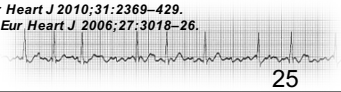
Sum

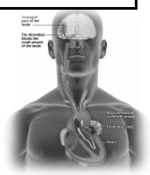
$CHADS_2$	Adjusted stroke rate* (95% CI)	Patients (%)[4]
6	18.2 (10.5–27.4)	~22%
5	12.5 (8.2–17.5)	
4	8.5 (6.3–11.1)	
3	5.9 (4.6–7.3)	
2	4.0 (3.1–5.1)	~27%
1	2.8 (2.0–3.8)	~33%
0	1.9 (1.2–3.0)	~18%

~50% with $CHADS_2$ 0 or 1

*Adjusted stroke rate = expected stroke rate per 100 patient-years from exponential survival model, assuming ASA not taken

1. Gage et al. JAMA 2001;285:2864–70.
2. Gage et al. Circulation 2004;110:2287–92.
3. Camm et al. Eur Heart J 2010;31:2369–429.
4. Nieuwlaat et al. Eur Heart J 2006;27:3018–26.





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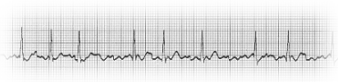
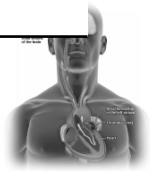
CHA_2DS_2 - VASc Risk Scoring for AF patients and Thromboprophylaxis Guidelines (ESC)[1]

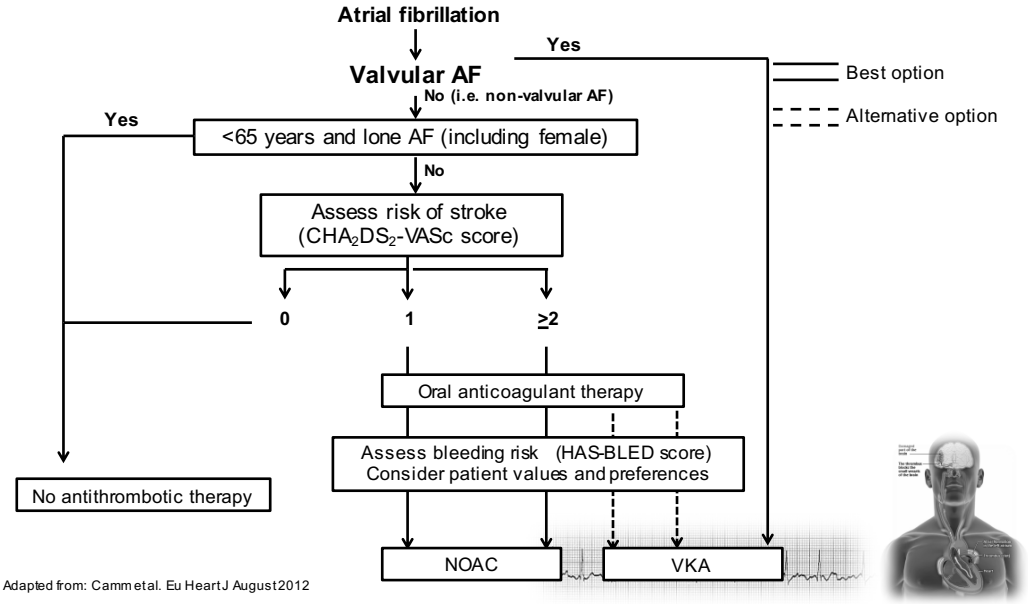
Score	Risk	Considerations
0	Low	Aspirin daily or no antithrombotic therapy
1	Moderate	**Preferred: No antithrombotic therapy** Oral anticoagulant or Aspirin daily **Preferred: Oral anticoagulant therapy**
2 or more	Moderate / High	**Oral anticoagulant therapy**

1. Camm *et al*, 2010





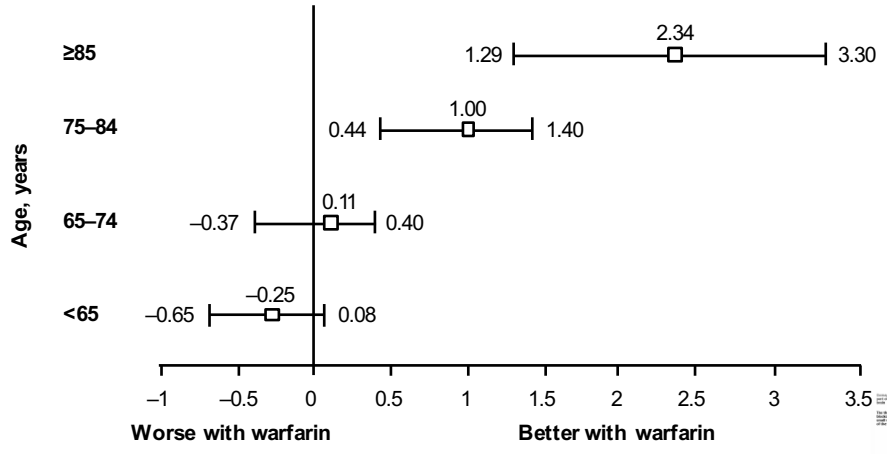
Choice of anticoagulant in AF: ESC Guidelines 2012



Adapted from: Camm et al. Eu Heart J August 2012

Oral anti-coagulation: benefit–risk improves with increasing age

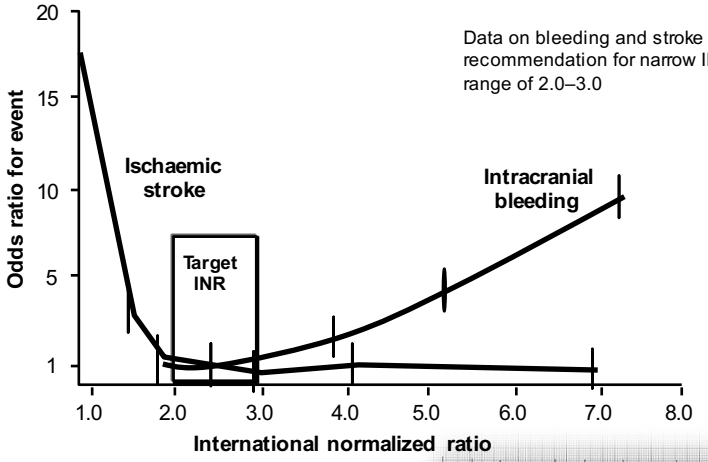
Net clinical benefit: events prevented per 100 person-years[1]



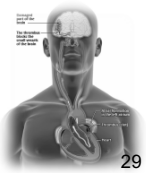
Singer DE *et al. Ann Intern Med* 2009;151:297–305

VKAs have a narrow therapeutic window

Adjusted odds ratios for ischaemic stroke and intracranial bleeding in relation to intensity of anticoagulation



Data on bleeding and stroke risk support recommendation for narrow INR target range of 2.0–3.0



Adapted from Wann et al. Circulation 2011;123;e269-e367

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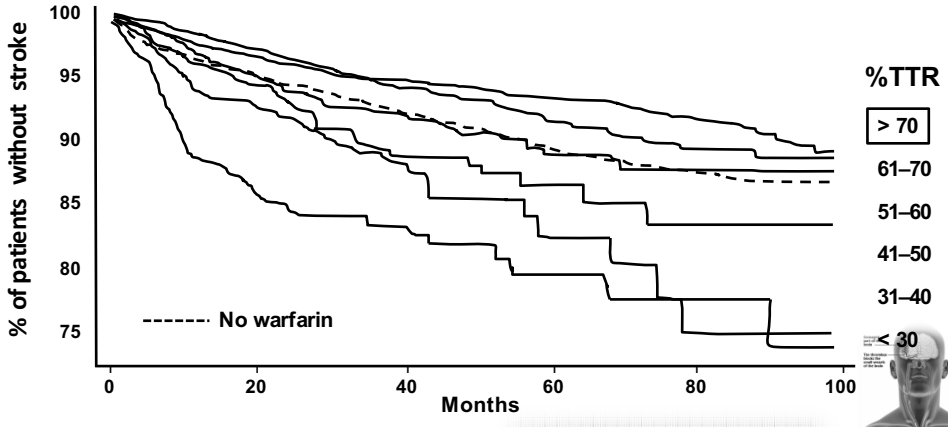
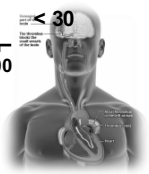
Poor INR control increases the risk of stroke in real-world practice

Stroke survival in 37,907 AF patients – UK General Practice Research Database (27,458 warfarin users and 10,449 not treated with an antithrombotic)





Adapted from Gallagher et al. Thromb Haemost 2011;106:968–77.

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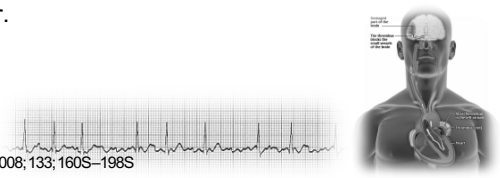
Drug and food interactions with warfarin

Traditional anticoagulants: drawbacks

- Oral VKAs[2]
  - Narrow therapeutic window
  - Many patients have reduced time in therapeutic range (TTR)
  - Slow onset of action
  - Interaction with food and drugs
  - Frequent monitoring and dose adjustment required
- Novel oral anticoagulants (NOAC) developed to overcome these limitations:
  - Rivaroxaban, Apixaban and Dabigatran are orally active antithrombotic agents.
  - Rivaroxaban and Apixaban are oral direct factor Xa inhibitors.
  - Dabigatran is a direct thrombin inhibitor.

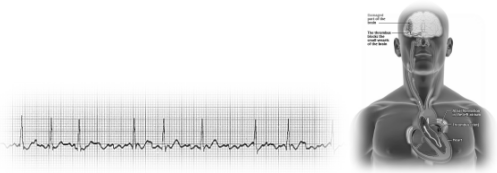


1. Hirsh J et al. Chest 2008;133;141S–159S
2. Ansell J et al. Chest 2008;133;160S–198S

1. Hirsh J *et al. Chest* 2008;133;141S–159S; 2. Ansell J *et al. Chest* 2008;133;160S–198S

Novel Oral Anticoagulants (NOACs)

EVIDENCE BASE



Comparisons: 3 NOACs licensed for NVAF

DABIGATRAN

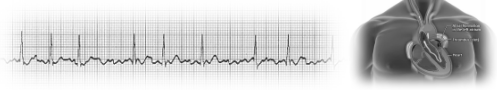
- **NICE issued a Technology Appraisal (TA 249) March 2012.**
- Dabigatran recommended as an option for the prevention of stroke and systemic embolism in NVAF with one or more of the following risk factors:
- previous stroke, TIA or systemic embolism
- LVEF below 40%
- symptomatic heart failure NYHA class 2 or above
- age 75 years or older
- age 65 years or older with one of the following: diabetes mellitus, coronary artery disease or hypertension.

RIVAROXABAN

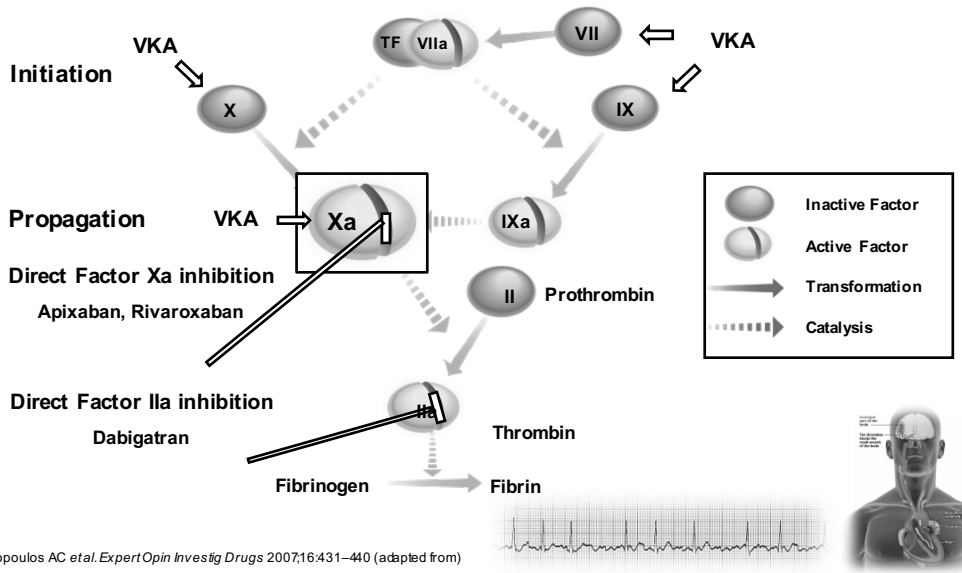
- **NICE issued a Technology Appraisal (TA 256) May 2012.**
- Rivaroxaban recommended as an option for the prevention of stroke and systemic embolism in NVAF with one or more risk factors such as:
- Congestive heart failure
- Hypertension
- Age 75 years or older
- Diabetes mellitus,
- Prior stroke or TIA

APIXABAN

- **NICE issued a Technology Appraisal (TA 275) Feb 2013.**
- Apixaban recommended for the prevention of stroke and systemic embolism in NVAF, with one or more risk factors, such as
  - Prior stroke or TIA
  - Age ≥75 years
  - Hypertension
  - Diabetes mellitus
  - Symptomatic heart failure (NYHA Class ≥II)



Coagulation pathway



Spyropoulos AC *et al. Expert Opin Investig Drugs* 2007;16:431–440 (adapted from)

NOAC: Comparing properties with Warfarin in SPAF

Rapid onset 2-4h

	Once daily	No Food Interactions	Predictable response	No routine coagulation monitoring	Fixed dosing	Wide therapeutic window	Easily Adaptable for compliance aids
OPTIMAL[1]	✓	✓	✓	✓	✓	✓	✓
Warfarin[1,2]	✓						
NOAC[3]	X1 or x2	✓ Taken with food	✓	✓	✓	✓	✓

Clinical pharmacology of various novel oral anticoagulants

	Apixaban[1,2]	Rivaroxaban[1,3]	Dabigatran[1,4]
Mechanism of action	Direct factor Xa inhibitor	Direct factor Xa inhibitor	Direct thrombin inhibitor
Oral bioavailability	~50%	80–100%	~6.5%
Pro-drug	No	No	Yes
Food effect	No	Yes (20 mg and 15 mg doses taken with food)	No
Renal clearance	~27%	~33 % *	85%
Dialysis	Not recommended	Not dialysable	Dialysable
Mean half-life ($t_{1/2}$)	~12 h	5–13 h	12–14 h (patients
T_{max}	3–4 h	2–4 h	0.5–2 h

direct renal excretion as uncharged active substance

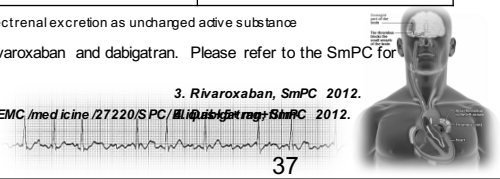
The information in this table is based on the SmPC for apixaban, rivaroxaban and dabigatran. Please refer to the SmPC for further information.

1. Ansell J. Hematology Am Soc Hematol Educ Program 2010:221–8.

2. Apixaban SPC December 2012. Available at http://www.medicines.org.uk/EMC/medicine/27220/SPC/Eliquis+2.5mg+film-coated+tablets/ .

3. Rivaroxaban, SmPC 2012.

4. Dabigatran, SmPC 2012.



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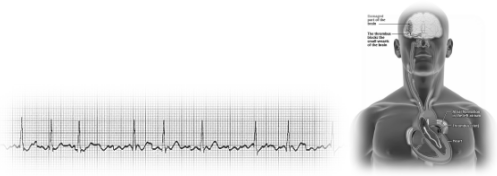
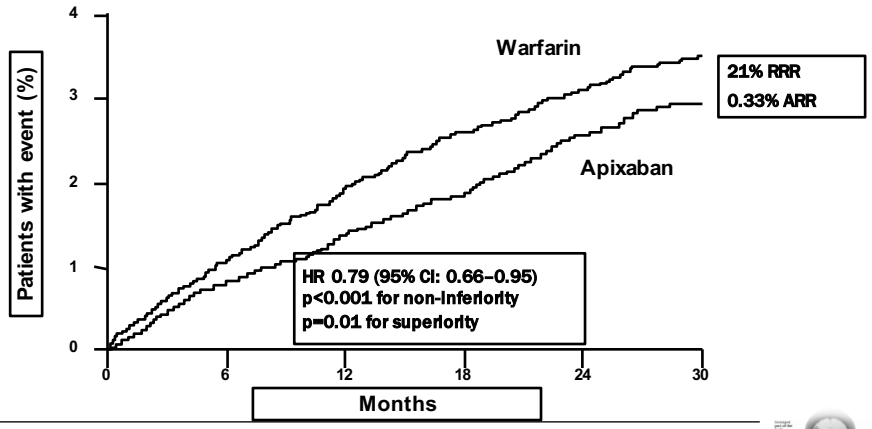
Clinical Trials of NOACs in prevention of stroke and systemic embolism in NVAF

- **Rivaroxaban - ROCKET AF**
- **Dabigatran - RE-LY**
- **Apixaban - ARISTOTLE**

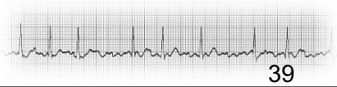


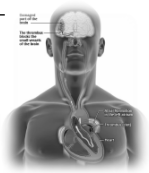
ARISTOTLE: Primary efficacy outcome - apixaban was superior to warfarin in preventing stroke or systemic embolism



No. at risk						
Apixaban	9,120	8,726	8,440	6,051	3,464	1,754
Warfarin	9,081	8,620	8,301	5,972	3,405	1,768

Adapted from Granger et al. N Engl J Med 2011;365:981–92.





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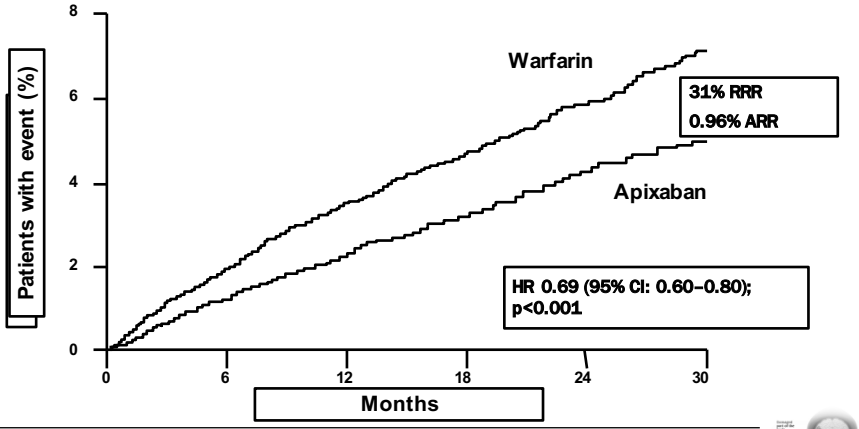
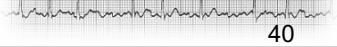
ARISTOTLE primary safety outcome: apixaban significantly reduced the risk of major bleeding* vs. warfarin

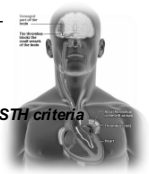


No. at risk						
Apixaban	9,088	8,103	7,564	5,365	3,048	1,515
Warfarin	9,052	7,910	7,335	5,196	2,956	1,491

Adapted from Granger et al. N Engl J Med 2011;365:981–92.

** Major bleeding was defined according to ISTH criteria*





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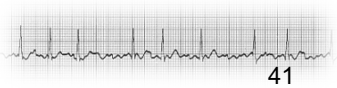
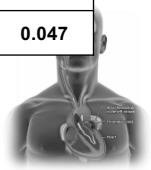
ARISTOTLE: main efficacy outcomes

Outcome	Apixaban (n=9,120) Event rate (%/yr)	Warfarin (n=9,081) Event rate (%/yr)	HR (95% CI)	P value
Primary efficacy outcome: stroke or systemic embolism	1.27	1.60	**0.79** (0.66–0.95)	**0.01**
Stroke	1.19	1.51	**0.79** (0.65–0.95)	**0.01**
Ischaemic or uncertain	0.97	1.05	0.92 (0.74–1.13)	0.42
Haemorrhagic	0.24	0.47	**0.51** (0.35–0.75)	**<0.001**
Systemic embolism	0.09	0.10	0.87 (0.44–1.75)	0.70
Myocardial infarction	0.53	0.61	0.88 (0.66–1.17)	0.37
Death from any cause	3.52	3.94	**0.89** (0.80–0.998)	**0.047**

Adapted from Granger et al. N Engl J Med 2011;365:981–92.





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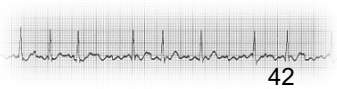
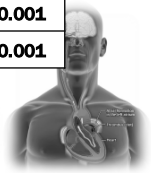
ARISTOTLE: apixaban significantly reduced the rate of MAJOR bleeding irrespective of the bleeding definition used

Outcome	Apixaban (n=9,088) Event rate (%/yr)	Warfarin (n=9,052) Event rate (%/yr)	HR (95% CI)	P value
Primary safety outcome: ISTH major bleeding	**2.13**	**3.09**	**0.69** (0.60–0.80)	**<0.001**
Intracranial	**0.33**	**0.80**	**0.42** (0.30–0.58)	**<0.001**
Other location	**1.79**	**2.27**	**0.79** (0.68–0.93)	**0.004**
Gastrointestinal	**0.76**	**0.86**	0.89 (0.70–1.15)	0.37
Major or clinically relevant non-major bleeding	**4.07**	**6.01**	**0.68** (0.61–0.75)	**<0.001**
GUSTO severe bleeding	**0.52**	**1.13**	**0.46** (0.35–0.60)	**<0.001**
TIMI major bleeding	**0.96**	**1.69**	**0.57** (0.46–0.70)	**<0.001**
Any bleeding	**18.1**	**25.8**	**0.71** (0.68–0.75)	**<0.001**

Adapted from Granger et al. N Engl J Med 2011;365:981–92..





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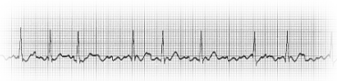
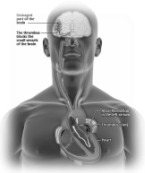
ROCKET AF

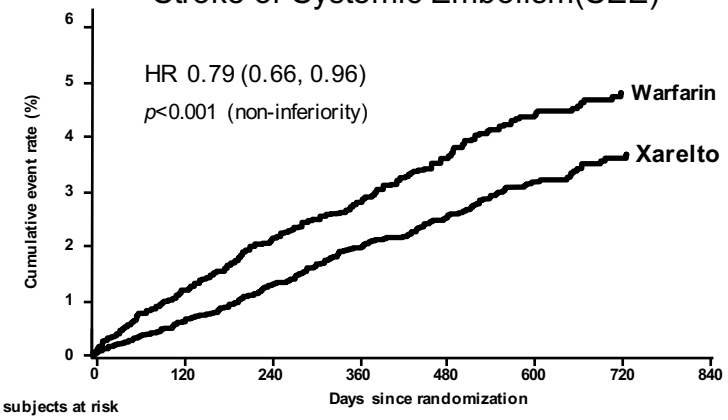
Rivaroxaban Once-daily oral direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation





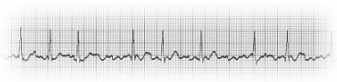
ROCKET AF- Xarelto is effective in the prevention of stroke and SE, with comparable efficacy vs. warfarin

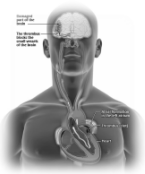
Stroke or Systemic Embolism(SEE)



Number of subjects at risk								
Rivaroxaban	6958	6211	5786	5468	4406	3407	2472	1496
Warfarin	7004	6327	5911	5542	4461	3478	2539	1538

Per-protocol population – as treated population



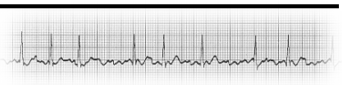


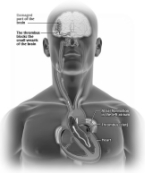
Adapted from Patel MR et al. NEJM 2011;365:883-891

ROCKET AF: Significantly fewer haemorrhagic strokes with Xarelto vs. warfarin

Event Rates are per 100 patient-years Based on Intention-to-Treat Population	Xarelto Event Rate	Warfarin Event Rate	HR (95% CI)	P-value
Vascular Death, Stroke, Embolism	4.51	4.81	0.94 (0.84, 1.05)	0.265
Stroke Type				
Hemorrhagic	0.26	0.44	0.58 (0.38, 0.89)	**0.012**
Ischemic	1.02	1.04	0.99 (0.82, 1.20	0.916
Unknown Type	0.15	0.14	1.05 (0.55, 2.01)	0.871
Non-CNS Embolism	0.16	0.21	0.74 (0.42, 1.32	0.308
Myocardial Infarction	1.02	1.11	0.91 (0.72, 1.16)	0.464
All Cause Mortality	4.52	4.91	0.92 (0.82, 1.03)	0.152
Vascular	2.91	3.11	0.94 (0.81, 1.08)	0.350
Non-vascular	1.15	1.22	0.94 (0.75, 1.18)	0.611
Unknown Cause	0.46	0.57	0.80 (0.57, 1.12)	0.195

Data on file: ROCKET



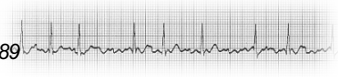


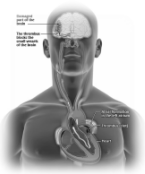
Net clinical benefit: ESC guidelines conclusions

- Because of the relatively low risk of IC bleeding, NOAC may confer net clinical benefit in even lower CHA_2DS_2VASc categories
- "When the risk of bleeding and stroke are both high, all three new drugs appear to have a greater net clinical benefit compared to warfarin"

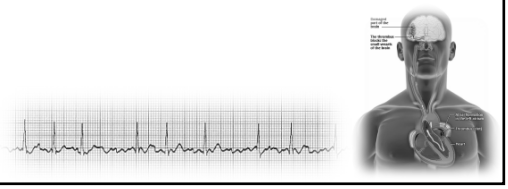
The risk of ICH is significantly lower with all the NOACs than with VKA

Banerjee & Lip. Thromb Haemost 2012; 107: 584–589





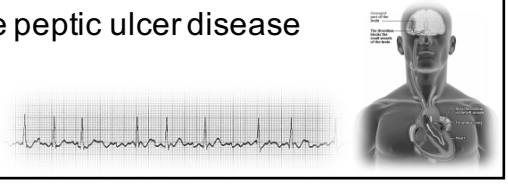
- ALL NOACs reduce the risk of ICH compared to warfarin
- Major bleeding similar to VKA, perhaps lower with low dose dabigtran and
- ALL cost effective
- None require monitoring



NOACs vs. VKA

- **Warfarin remains a suitable first-line oral anticoagulant**
  - **Mainly because it is cheap**
  - **If patients are well established on VKA**

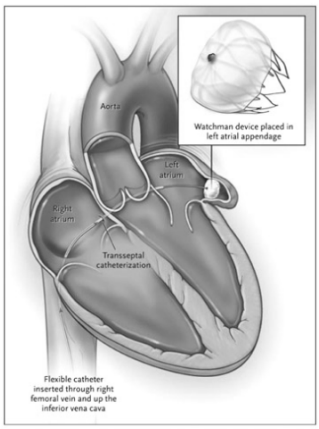
- **Warfarin should be the preferred option in patients:**
- with eGFR < 30
- (NB Patients with a baseline eGFR of 30-40 are at risk or progressive/acute renal dysfunction and the potential risks of bleeding with NOACs should be weighed on an individual basis)
- with a history of significant active peptic ulcer disease

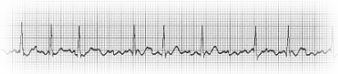


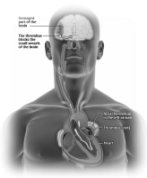
Bleeding on NOACs

Rivaroxaban	Dabigatran	Apixaban
Ensure diuresis	Ensure diuresis	Ensure diuresis
Highly protein bound so not dialysable	Dialysis can remove drug effectively as not highly protein bound	Highly protein bound so not dialysable
Prothrombin complex concentrates eg Octaplex can reverse the coagulation tests but no data on clinical efficacy. Suggested dose 50u/kg	Activated PP eg FEIBA may be considered but only evidence is from animal model. Consider F VIIa 90 mcg/kg after haematological advice	Administration of recombinant factor VIIa (rFVIIa) may be considered
		Activated charcoal may be useful in the management of overdose

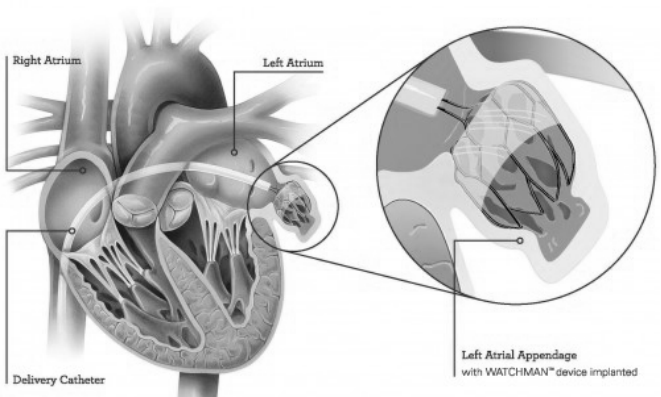
What if patient cannot have long term anticoagulation?



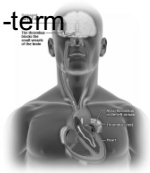




Left atrial appendage closure device



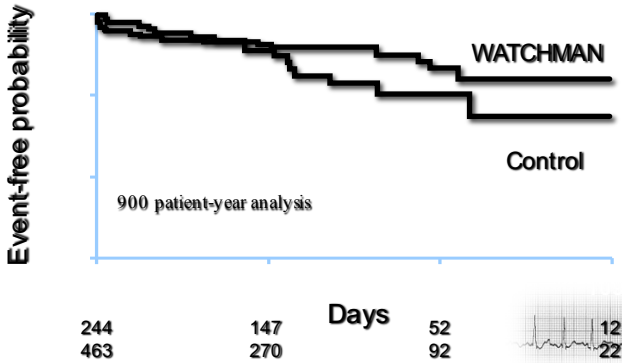
- Prospective, randomized study of WATCHMAN LAA Device vs long-term warfarin therapy
- 800 patients enrolled from Feb 2005 to Jun 2008
- 59 enrolling centers (U.S. & Europe)



Intent-to-Treat

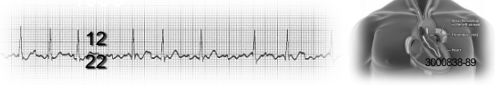
Primary Efficacy Results

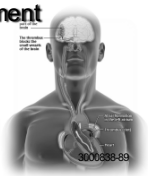
	Device			Control				Posterior probabilities	
Cohort	Events (no.)	Total pt-yr	Rate (95% CI)	Events (no.)	Total pt-yr	Rate (95% CI)	RR (95% CI)	Non-inferiority	Superiority
600 pt-yr	18	409.3	4.4 (2.6, 6.7)	13	223.6	5.8 (3.0, 9.1)	0.76 (0.39, 1.67)	0.992	0.734
900 pt-yr	20	582.3	3.4 (2.1, 5.2)	16	318.0	5.0 (2.8, 7.6)	0.68 (0.37, 1.41)	0.998	0.837



Randomization allocation (2 device:1 control)

ITT cohort: patients analyzed based on their randomly assigned group (regardless of treatment received)

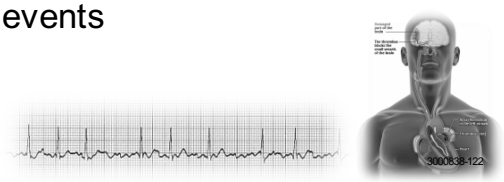




Risk/Benefit Analysis

Per-protocol analysis

- Superiority for the primary efficacy event rate
- Approximately 86% of patients in the device group were able to be successfully implanted and discontinue warfarin therapy
- Study demonstrates the role of the left atrial appendage in the pathogenesis of stroke due to AF
- Based on average age, patients will experience a 56% reduction in safety events



Summary

- Discussed the epidemiology, prevalence and increasing incidence of AF
- Discussed how to diagnose AF
- Discussed rate versus rhythm control
- Options for rhythm control
- Thromboprophylaxis treatment guidelines from ESC
- VKA vs. NOACs
- Risks vs. benefits of NOACs
- LAA closure