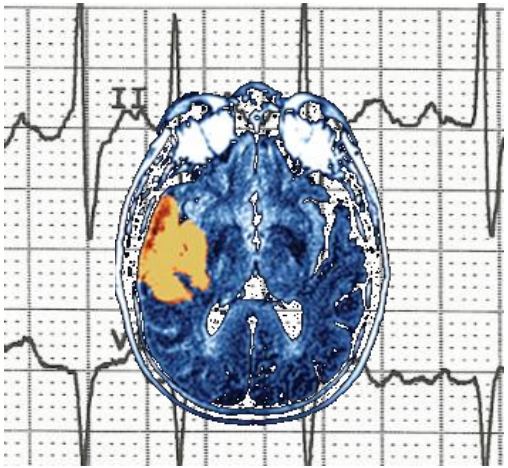
Supported by Bayer, Bristol-Myers Squibb and Pfizer Alliance, Boehringer Ingelheim, Daiichi Sankyo Europe GmbH and Medtronic in the form of educational grants. The scientific programme has not been influenced in any way by its sponsors.

ESC Heart & Brain Workshop



Novel Oral Anticoagulants Should Replace Warfarin in All Patients with Atrial Fibrillation: Pro

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BAYER

Boehringer Ingelheim

Daiichi-Sankyo

Bristol-Myers Squibb

Pfizer

Medtronic
Further, Together

Declaration of Interest

Chairman: ESC Guidelines on Atrial Fibrillation, 2010 and Update, 2012; ACC/AHA/ESC Guidelines on VAs and SCD; 2006; NICE Guidelines on ACS and NSTEMI, 2012; NICE Guidelines on Heart Failure, 2008; **Member:** NICE Guidelines on AF, 2006; ESC VA and SCD Guidelines, 2015; **Reviewer:** AHA/ACC/HRS Guidelines on AF, 2014; ACC/AHA/HRS SVT Guidelines, 2015; ESC AF Guidelines, 2016.

Steering Committees: multiple trials involving antiarrhythmic agents, heart failure drugs and novel anticoagulants.

DSMBs: multiple trials of devices and drugs.

Events Committees: one trial of novel oral anticoagulants and multiple trials of miscellaneous agents with CV adverse effects.

Editorial Role: Editor-in-Chief, European Heart Journal– Case Reports and Clinical Cardiology; Editor, European Textbook of Cardiology, European Heart Journal, Electrophysiology of the Heart, and Evidence Based Cardiology.

Consultant/Advisor/Speaker: Astellas, Astra Zeneca, ChanRX, Gilead, Laguna, Incarda, Merck, Menarini, Milestone, Otsuka, Sanofi, Servier, Xention, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Pfizer, Boston Scientific, Biotronik, Medtronic, Sorin, St. Jude Medical, Actelion, GlaxoSmithKline, InfoBionic, Incarda, Johnson and Johnson, Mitsubishi, Novartis, Takeda

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The Motion

Not just FXaIs and DTIs

Not now necessarily , but eventually

Novel Oral Anticoagulants Should Replace Warfarin in All Patients with Atrial Fibrillation

A gift to my opponent
a very high bar, but…..

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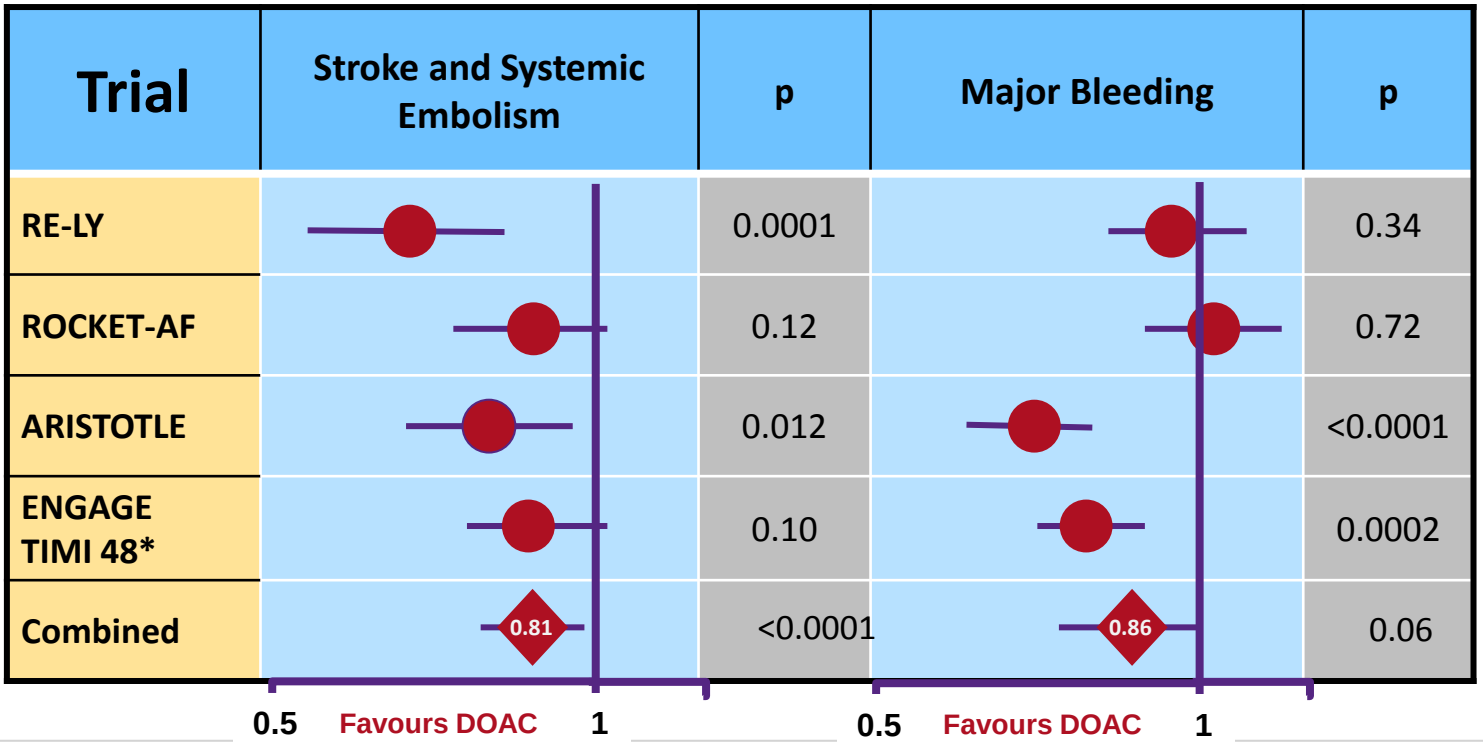
NOAC 4-trial Meta-analysis Full Dose

Pre-specified meta-analysis of all 71,683 patients



Ruff C, et al. Lancet 2013

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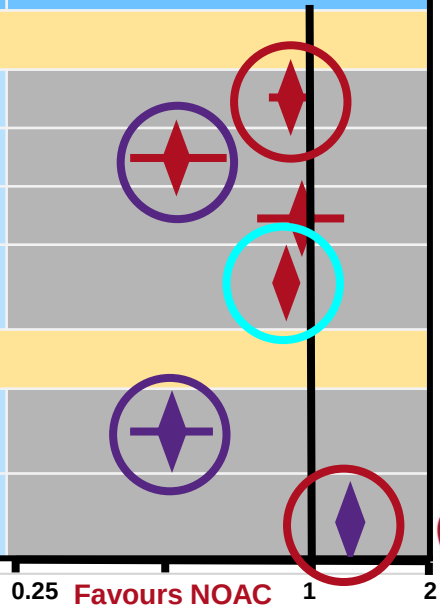
Efficacy vs Safety

NOAC 4-trial Meta-analysis Full Dose

Result	Pooled DOAC Events /Total	Pooled Warfarin Events /Total	Risk Ratio	95% CIs	p	Hazard Ratios
Efficacy						
Ischaemic Stroke	665/29292	724/29221	0.92	0.83-1.02	0.10	
Hemorrhagic stroke	130/29292	263/29221	0.49	0.38-0.64	<0.0001	
Myocardial Infarction	413/29292	432/29221	0.97	0.78-1.20	0.97	
All Cause mortality	2022/29292	2245/29221	0.90	0.851-0.95	0.0003	
Safety						
Intra-cranial hemorrhage	204/29287	425/29211	0.48	0.39-0.59	<0.0001	
Gastrointestinal bleeding	751/29287	591/29211	1.25	1.01-1.55	0.043	



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Ruff C, et al. Lancet 2014 Mar 15;383(9921):955-62.

Dabigatran: Favourable Benefit-Fisk Profile

FDA study of >134 000 Medicare patients

Dabigatran was associated with a lower risk of ischaemic stroke, intracranial haemorrhage and death than warfarin

	Incidence rate per 1000 person-years		Adjusted HR (95% CI)
	Dabigatran etexilate	Warfarin	
Ischaemic stroke	11.3	13.9	0.80 (0.67–0.96)
Intracranial haemorrhage	3.3	9.6	0.34 (0.26–0.46)
Major GI bleeding	34.2	26.5	1.28 (1.14–1.44)
Acute MI	15.7	16.9	0.92 (0.78–1.08)
Mortality	32.6	37.8	0.86 (0.77–0.96)

Comparison of matched new-user cohorts treated with dabigatran etexilate 150 mg or 75 mg* or warfarin for non-valvular AF based on 2010–2012 Medicare data *Primary findings are based on analysis of both doses (no stratification by dose)

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Graham DJ, et al. Circulation. 2014 Oct 30. pii: CIRCULATIONAHA.114.012061

Warfarin Drug Interactions

A total of **873 drugs** (5865 brand and generic names) are known to interact with warfarin.

- 214 major drug interactions (1010 brand and generic names)
- 454 moderate drug interactions (3475 brand and generic names)
- 205 minor drug interactions (1380 brand and generic names)

Show all medications in the database that may interact with warfarin.

Results of Cost-effectiveness Model Atrial Fibrillation

Estimated costs and outcomes	Warfarin (INR 2–3): mean (95% CI)	Apixaban (5 mg bd): mean (95% CI)	Dabigatran (150 mg bd): mean (95% CI)	Edoxaban (60 mg od): mean (95% CI)	Rivaroxaban (20 mg od): mean (95% CI)
Expected total costs (£)	24,418 (12,189 to 50,365)	23,340 (12,842 to 45,753)	23,064 (12,674 to 46,075)	23,985 (13,098 to 46,319)	24,841 (13,198 to 47,603)
Expected QALYs	5.166 (3.629 to 6.541)	5.488 (3.841 to 6.795)	5.416 (3.817 to 6.701)	5.405 (3.819 to 6.678)	5.451 (3.824 to 6.797)
Expected incremental total costs (£)	(– to –)	–1078 (–7626 to 2568)	–1354 (–8049 to 2273)	–433.4 (–6430 to 3619)	422.5 (–4730 to 5104)
Incremental expected QALYs	(– to –)	0.3227 (–0.0148 to 0.814)	0.2505 (–0.0803 to 0.702)	0.2389 (–0.112 to 0.684)	0.2851 (–0.0681 to 0.809)
Incremental expected net benefit (£20,000)	(– to –)	7533 (489.9 to 18,228)	6365 (–167.7 to 17,039)	5212 (–893.8 to 14,826)	5279 (–1097 to 15,180)

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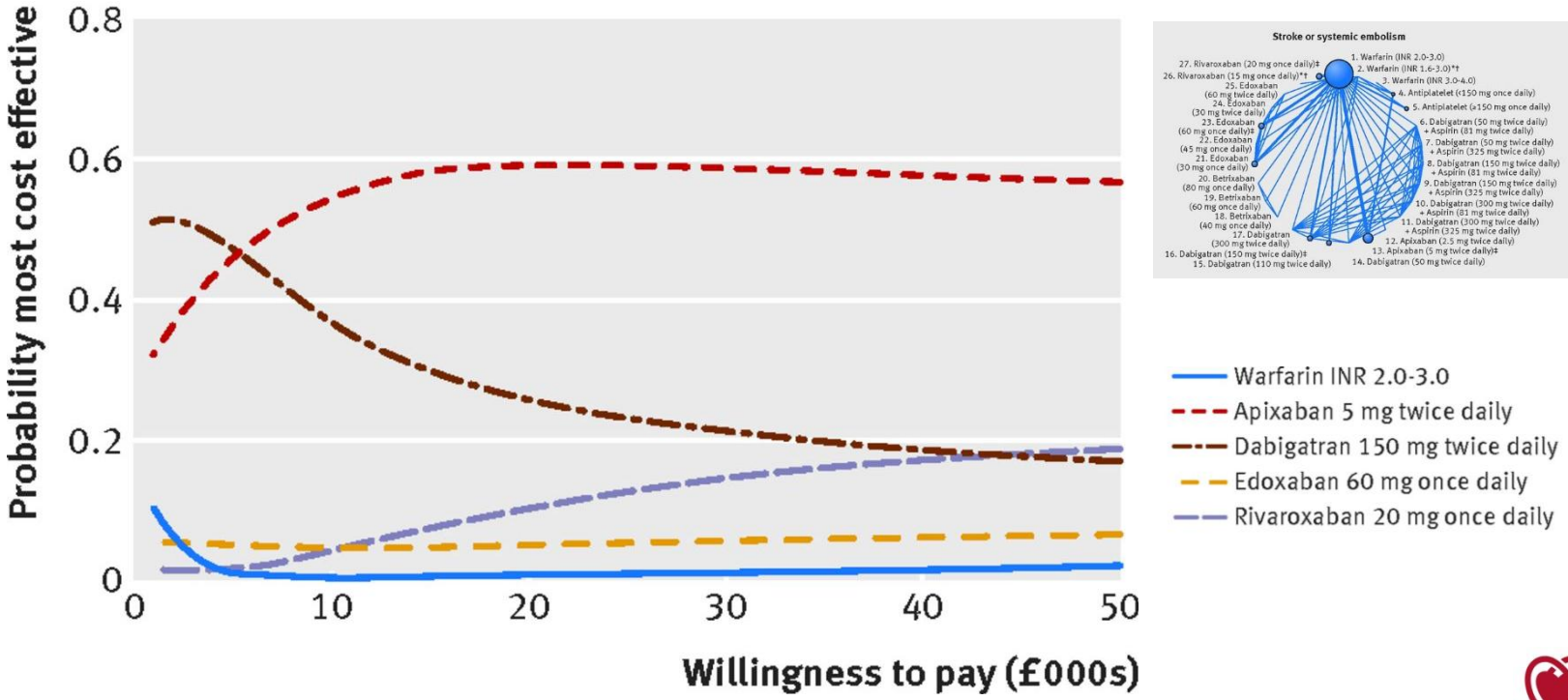
Sterne J, et al. Health Technology Assessment, No. 21.9 NIHR Journals Library; 2017 Mar

NOACs: Cost Effectiveness Acceptability Curves Network Meta-analysis



José A López-López et al. BMJ 2017;359:bmj.j5058

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INVICTUS Programme

INVestIgation of RheumatiC aTrial Fibrillation Treatment Using Vitamin K Antagonists, Rivaroxaban or Aspirin Studies

- **INVICTUS registry (17,000 patients)**
  - Registry of patients with RVHD
  - Continuation and expansion of the 3000 patient REMEDY registry[1,2]
- **INVICTUS non-inferiority randomized clinical trial (4500 patients)**
  - Rivaroxaban 20 mg (15 mg) vs vitamin K antagonist (VKA)
  - Patients with RVHD and AF (mitral stenosis or CHA2DS2-VASc ≥2) NCT02832544
- **INVICTUS superiority randomized clinical trial (2000 patients)**
  - Rivaroxaban 15 mg vs Aspirin
  - Patients with RVHD and AF but unsuitable for VKA therapy
  - OR patients with RVHD in sinus rhythm at high risk of stroke NCT02832531

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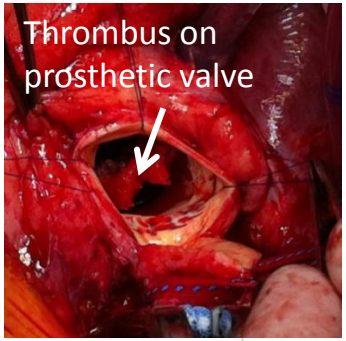
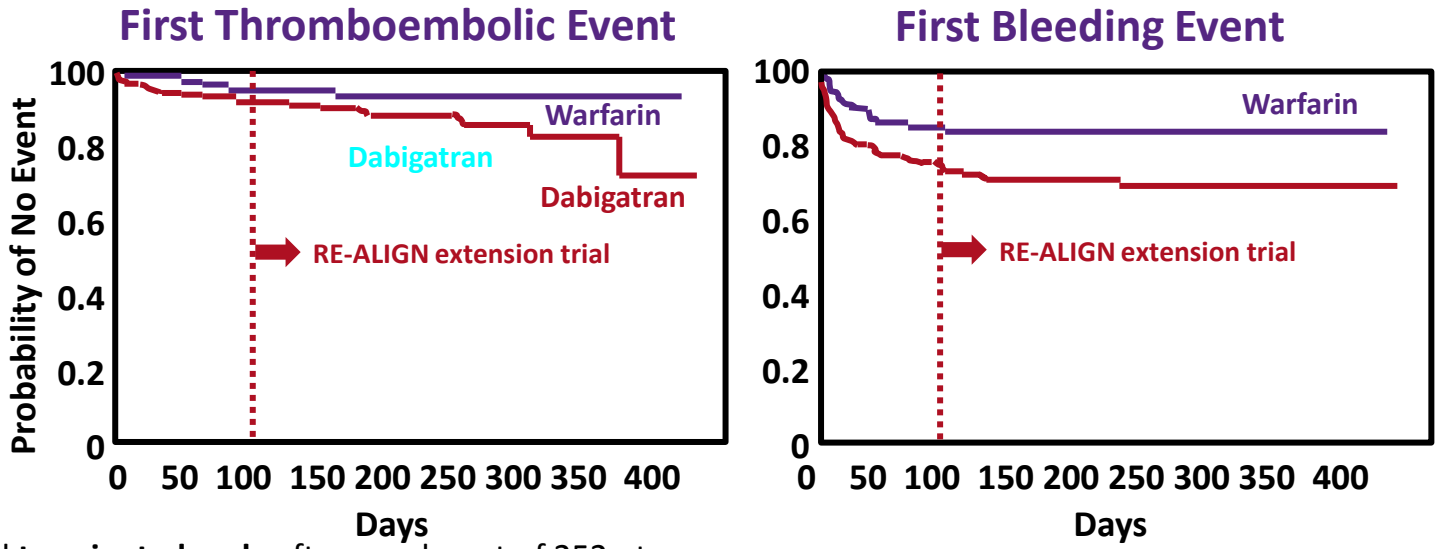
1. Karthikeyan G et al. *Am Heart J.* 2012;163:535-40. 2. Zühlke L et al. *Eur Heart J.* 2015;36:1115-22.

RE-ALIGN

Warfarin vs. Dabigatran with Mechanical Heart Valves



RE-ALIGN - ph2 dose-finding trial of dabigatran in pts with mechanical valves, 150-330 mg bid, adjusted based on renal function and results of **Hemoclot**



Trial **terminated early** after enrolment of 252 pts

Eikelboom JW, et al. N Engl J Med 2013;369:1206-1214

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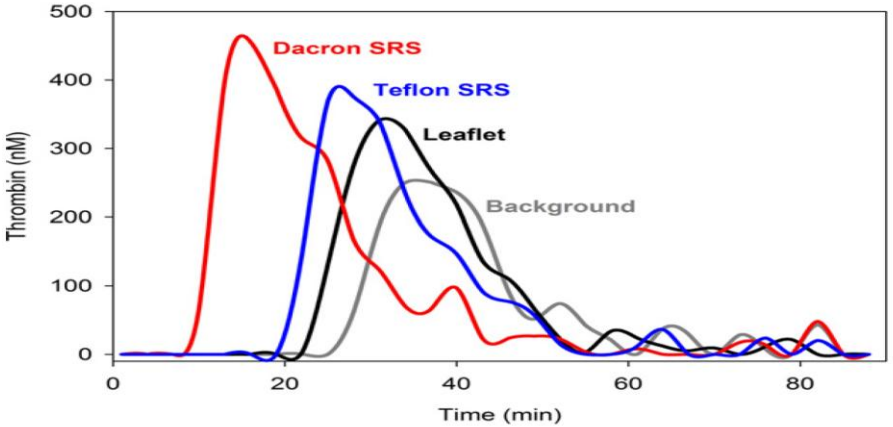
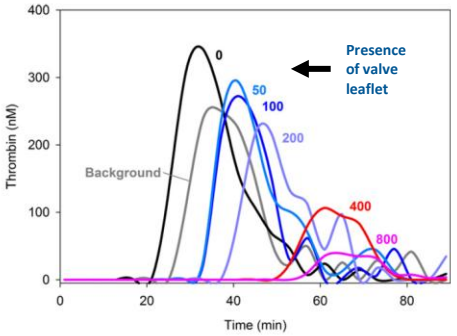
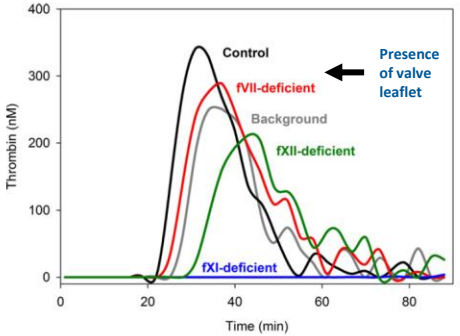
Heart Valves, Dabigatran and Warfarin

Attenuating Mechanical Heart Valve-Induced Thrombin Generation







- ***Thrombin generated via contact pathway overwhelms safe dabigatran concentration (50 ng/ml)***
- ***Dabigatran concentration of 260 ng/ml needed***
- ***? Need to give 3m anticoagulation for bioprostheses***

Jaffer I, et al. J Am Heart Assoc. 2015;4:e002322 doi: 10.1161/JAHA.115.002322

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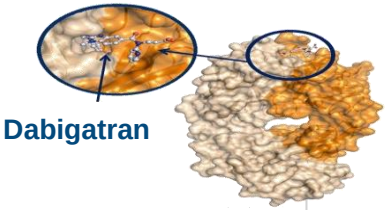
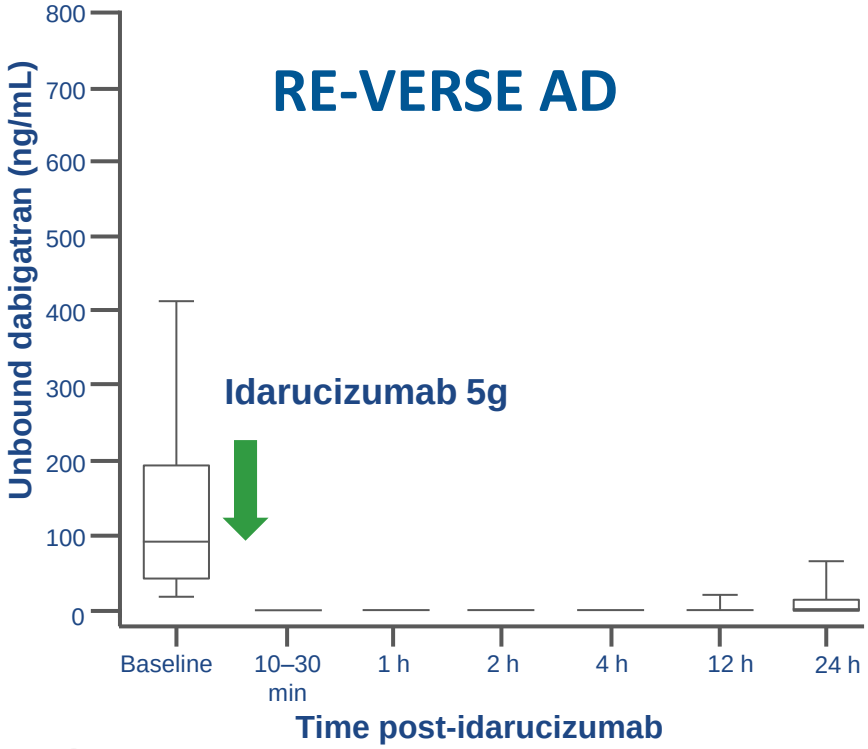
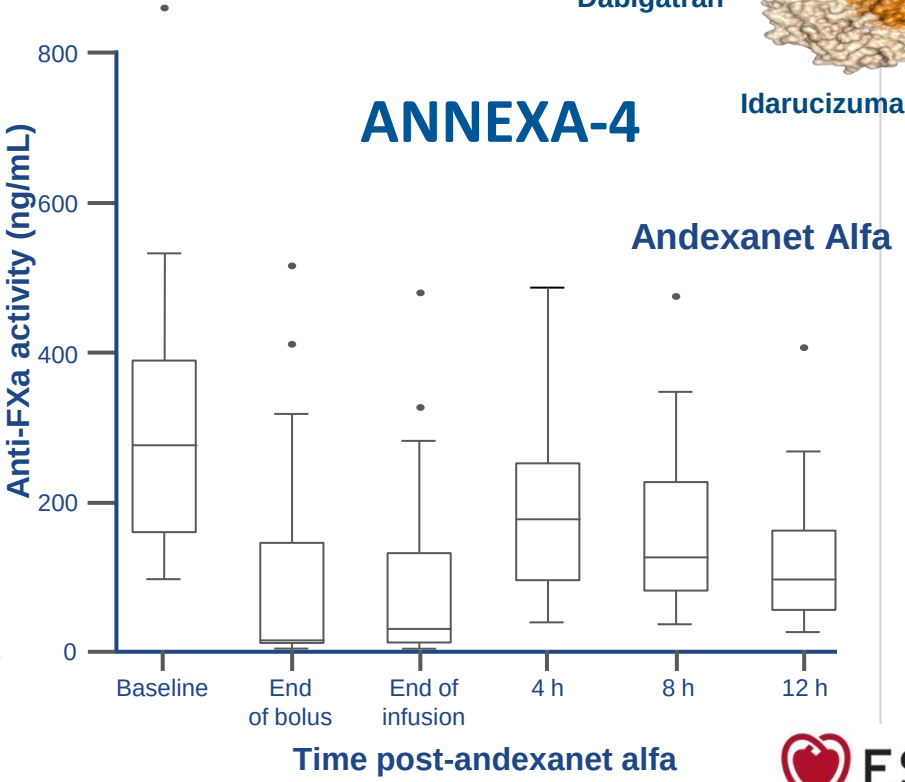
NOACs and Reversal Agents







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Pollack et al. N Engl J Med 2017

Connolly et al. N Engl J Med 2016

ESC 2016 AF Guidelines
Stroke Prevention in Patients with AF

Recommendations	Class	Level
When oral anticoagulation is initiated in a patient with AF who is eligible for a NOAC (apixaban, dabigatran, edoxaban, or rivaroxaban), **a NOAC is recommended in preference to a Vitamin K antagonist**.	I	A
AF patients already **on treatment with a vitamin K antagonist may be considered for NOAC treatment** if TTR is not well controlled despite good adherence, or if **patient preference** without contra-indications to NOAC (e.g. prosthetic valve).	IIb	A

Kirchhof P et al. Eur Heart J 2016 Aug 27. pii: ehw210

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In summary

- NOACs do not require anticoagulation status monitoring (but can be measured)
- NOACs are associated with less strokes and far less intra-cranial haemorrhage
- NOACs are associated with a better quality of life
- NOACs reduce mortality when compared to warfarin
- NOACs have no food-drug interactions and few drug-drug interactions
- NOACs are cost-effective and in many situations cheaper than warfarin
- NOACs are not now recommended in moderate/severe mitral stenosis, but ….
- NOACs are not now recommended for metallic valves, but new NOACs will be
- NOACs can be easily reversed
- NOACs are recommended over warfarin in ESC AF guidelines
- NOACs are preferred by physicians – warfarin will disappear

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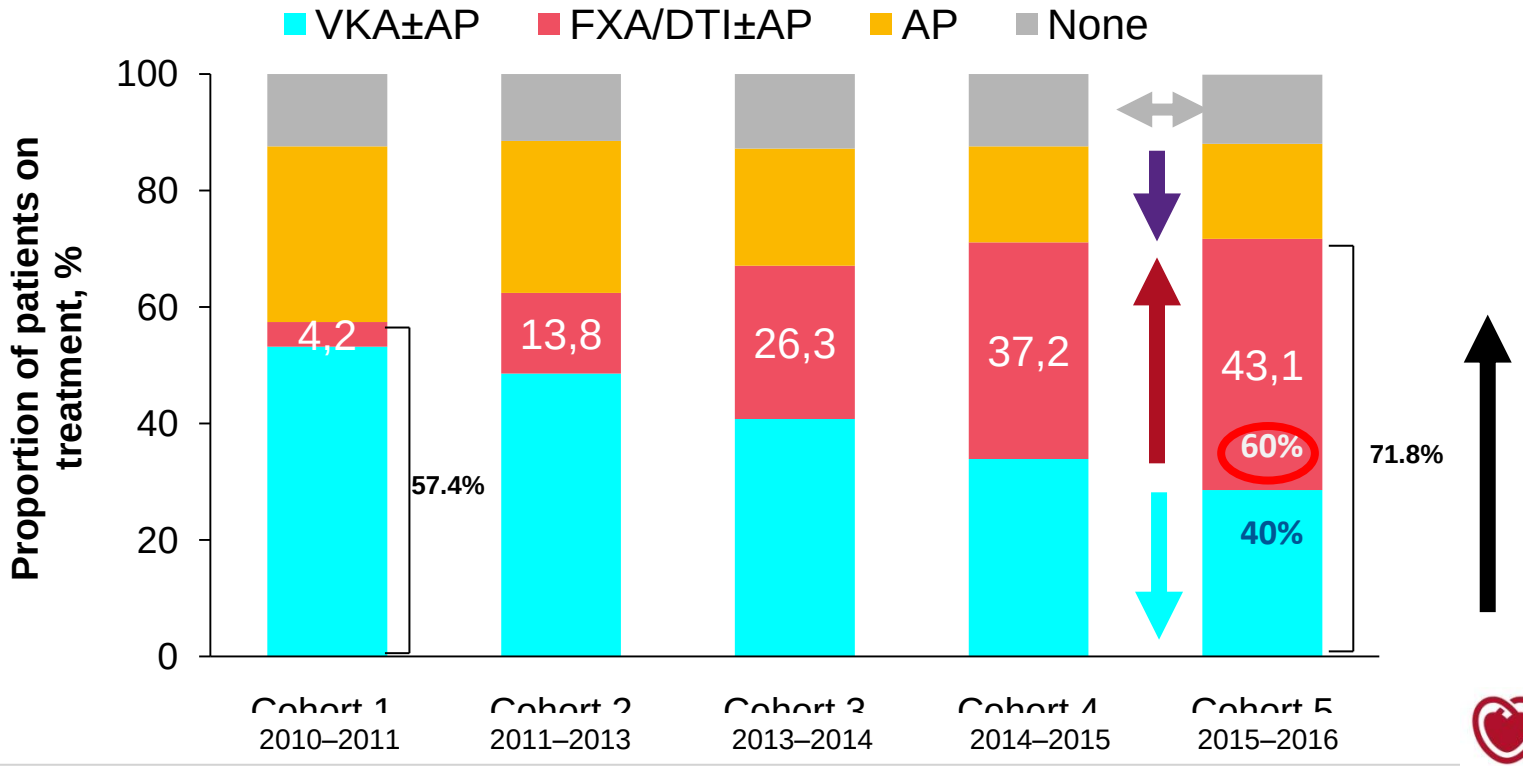
Evolution in Baseline Treatment for Patients Enrolled in GARFIELD-AF



Camm AJ, et al. BMJ 2016

Cohorts 1–5, N=51,270

AF Garfield global anticoagulant registry in the field

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In view of all of this, I think that we should all agree that:

Novel Oral Anticoagulants Should Replace Warfarin in All Patients with Atrial Fibrillation

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