Spontaneous Atrial Fibrillation and Noacs and Reversal agents

Laurent Lewkowiez, MD

Regional Service Chief, Hospital Cardiology CPMG

Cardiac Electrophysiology

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Educational Goals

- relationship between atrial fibrillation and stroke
- benefits and risks of NOACS versus warfarin
- factors that effect optimum selection of NOACS
- monitoring of anticoagulant effects of NOACS.
- reversal agents available and when to use.

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Atrial Fibrillation

- AF increases in prevalence with advancing age
- In the United States, the percentage of Medicare Fee-for-Service beneficiaries with AF in 2010 was reported as 2% for those <65 years of age and 9 % for those ≥65 years of age
- For individuals of European descent, the lifetime risk of developing AF after 40 years of age is 26% for men and 23% for women (Rotterdam Study)
- In African Americans, although risk factors for AF are more prevalent, the AF incidence appears to be lower

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Effect of Atrial Fibrillation on Patients

Event	Association with AF
Death	Increased mortality, especially cardiovascular mortality due to sudden death, heart failure or stroke.
Stroke	20–30% of all strokes are due to AF. A growing number of patients with stroke are diagnosed with 'silent', paroxysmal AF.
Hospitalizations	10–40% of AF patients are hospitalized every year.
Quality of life	Quality of life is impaired in AF patients independent of other cardiovascular conditions.
Left ventricular dysfunction and heart failure	Left ventricular dysfunction is found in 20–30% of all AF patients. AF causes or aggravates LV dysfunction in many AF patients, while others have completely preserved LV function despite long-standing AF.
Cognitive decline and vascular dementia	Cognitive decline and vascular dementia can develop even in anticoagulated AF patients. Brain white matter lesions are more common in AF patients than in patients without AF.

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AF and Age from the Rotterdam Study

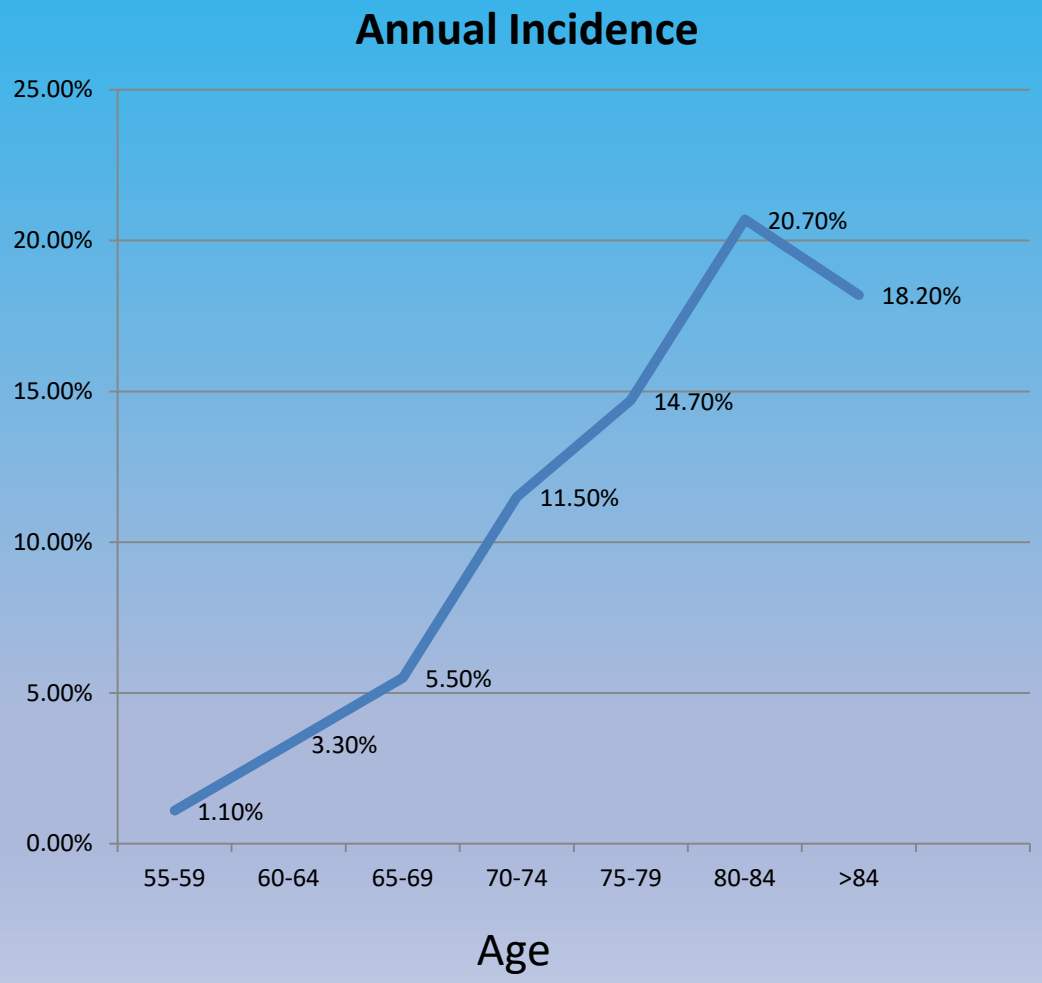

Table 5 Incidence rates of AF in three population-based studies

Age group	Framingham Study	Rotterdam Study	Cardiovascular Health Study
Men			
55–64	3.1	2.2	
65–74	~9.0	9.9	
65–69			12.3
70–74			22.8
75–84	~18	21.9	
75–79			34.8
≥80			58.7
≥85	38	25.4	
Women			
55–64	1.9	1.6	
65–74	~5.0	7.7	
65–69			10.9
70–74			9.1
75–84	~15	15.4	
65–69			23.1
≥80			25.1
≥85	31.4	16.2	

Rates are per 1000 person-years.

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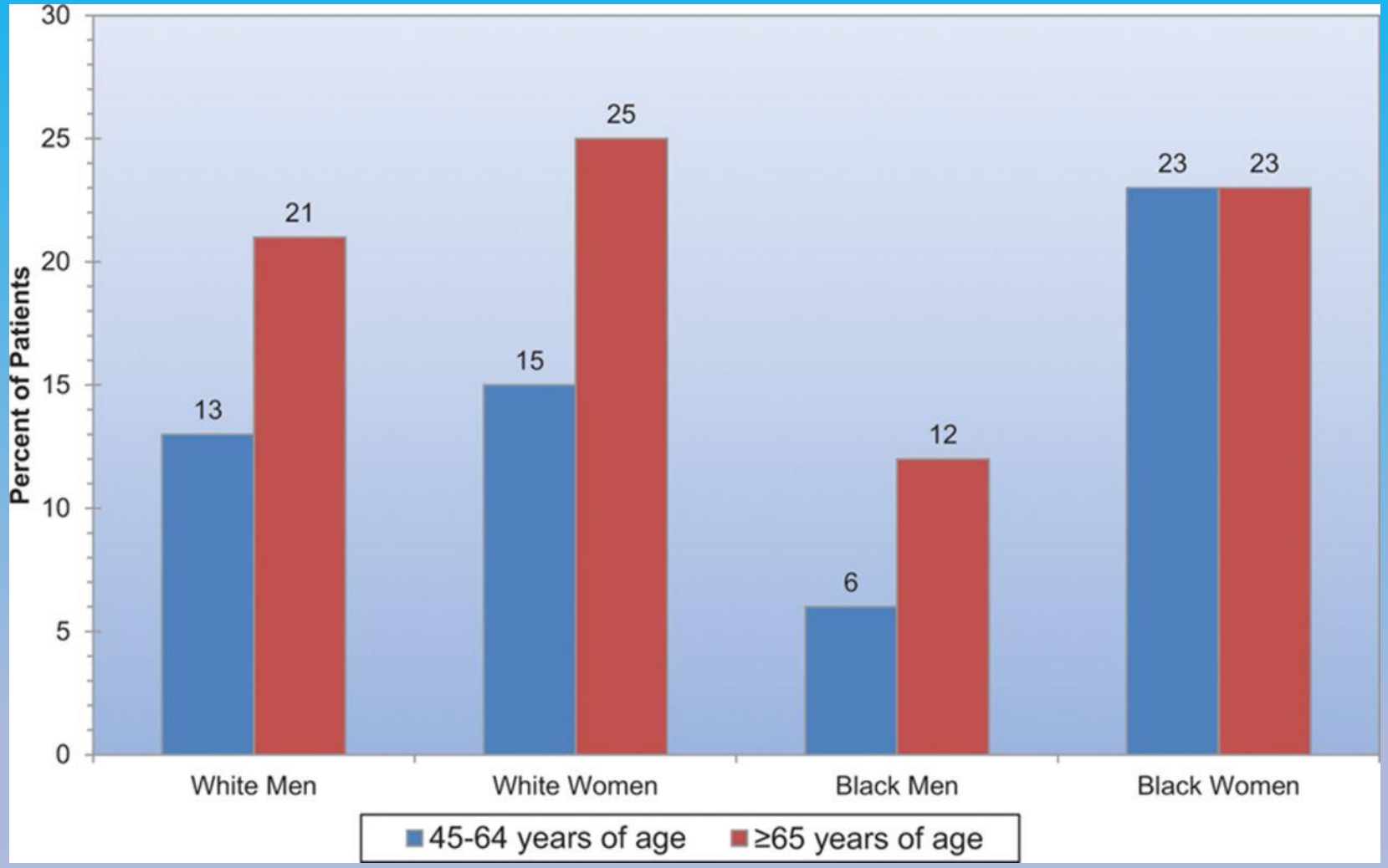
Heeringa et al. European Heart Journal (2006) 27, 949–953

Proportion of patients with recurrent stroke within 5 years after first stroke (Framingham Heart Study)



Go A S et al. Circulation. 2014;129:e28-e292

American Heart Association.

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Risk Factors for Developing Atrial fibrillation

Table 8 Cardiovascular and other conditions independently associated with atrial fibrillation

Characteristic/comorbidity	Association with AF
Genetic predisposition (based on multiple common gene variants associated with AF)[64]	HR range 0.4–3.2
Older age[19] 50–59 years 60–69 years 70–79 years 80–89 years	HR: 1.00 (reference) 4.98 (95% CI 3.49–7.10) 7.35 (95% CI 5.28–10.2) 9.33 (95% CI 6.68–13.0)
Hypertension (treated) vs. none[19]	HR 1.32 (95% CI 1.08–1.60)
Heart failure vs. none[19]	HR 1.43 (95% CI 0.85–2.40)
Valvular heart disease vs. none[205]	RR 2.42 (95% CI 1.62–3.60)
Myocardial infarction vs. none[19]	HR 1.46 (95% CI 1.07–1.98)
Thyroid dysfunction[206,207] Hypothyroidism Subclinical hyperthyroidism Overt hyperthyroidism	(reference: euthyroid) HR 1.23 (95% CI 0.77–1.97) RR 1.31 (95% CI 1.19–1.44) RR 1.42 (95% CI 1.22–1.63)
Obesity[19,208] None (BMI <25 kg/m²) Overweight (BMI 25–30 kg/m²) Obese (BMI ≥31 kg/m²)	HR: 1.00 (reference) 1.13 (95% CI 0.87–1.46) 1.37 (95% CI 1.05–1.78)
Diabetes mellitus vs. none[19]	HR 1.25 (95% CI 0.98–1.60)
Chronic obstructive pulmonary disease[209] FEV1 ≥80% FEV1 60–80% FEV1 <60%	RR: 1.00 (reference) 1.28 (95% CI 0.79–2.06) 2.53 (95% CI 1.45–4.42)
Obstructive sleep apnoea vs. none[210]	HR 2.18 (95% CI 1.34–3.54)
Chronic kidney disease[211] None Stage 1 or 2 Stage 3 Stage 4 or 5	OR: 1.00 (reference) 2.67 (95% CI 2.04–3.48) 1.68 (95% CI 1.26–2.24) 3.52 (95% CI 1.73–7.15)
Smoking[212] Never Former Current	HR: 1.00 (reference) 1.32 (95% CI 1.10–1.57) 2.05 (95% CI 1.71–2.47)
Alcohol consumption[213] None 1–6 drinks/week 7–14 drinks/week 15–21 drinks/week >21 drinks/week	RR: 1.00 (reference) 1.01 (95% CI 0.94–1.09) 1.07 (95% CI 0.98–1.17) 1.14 (95% CI 1.01–1.28) 1.39 (95% CI 1.22–1.58)
Habitual vigorous exercise[214] Non-exercisers <1 day/week 1–2 days/week 3–4 days/week 5–7 days/week	RR: 1.00 (reference) 0.90 (95% CI 0.68–1.20) 1.09 (95% CI 0.95–1.26) 1.04 (95% CI 0.91–1.19) 1.20 (95% CI 1.02–1.41)

age

HTN

HF

Valvular dz

MI

Thyroid

obesity

Diabetes

copd

OSA

CKD

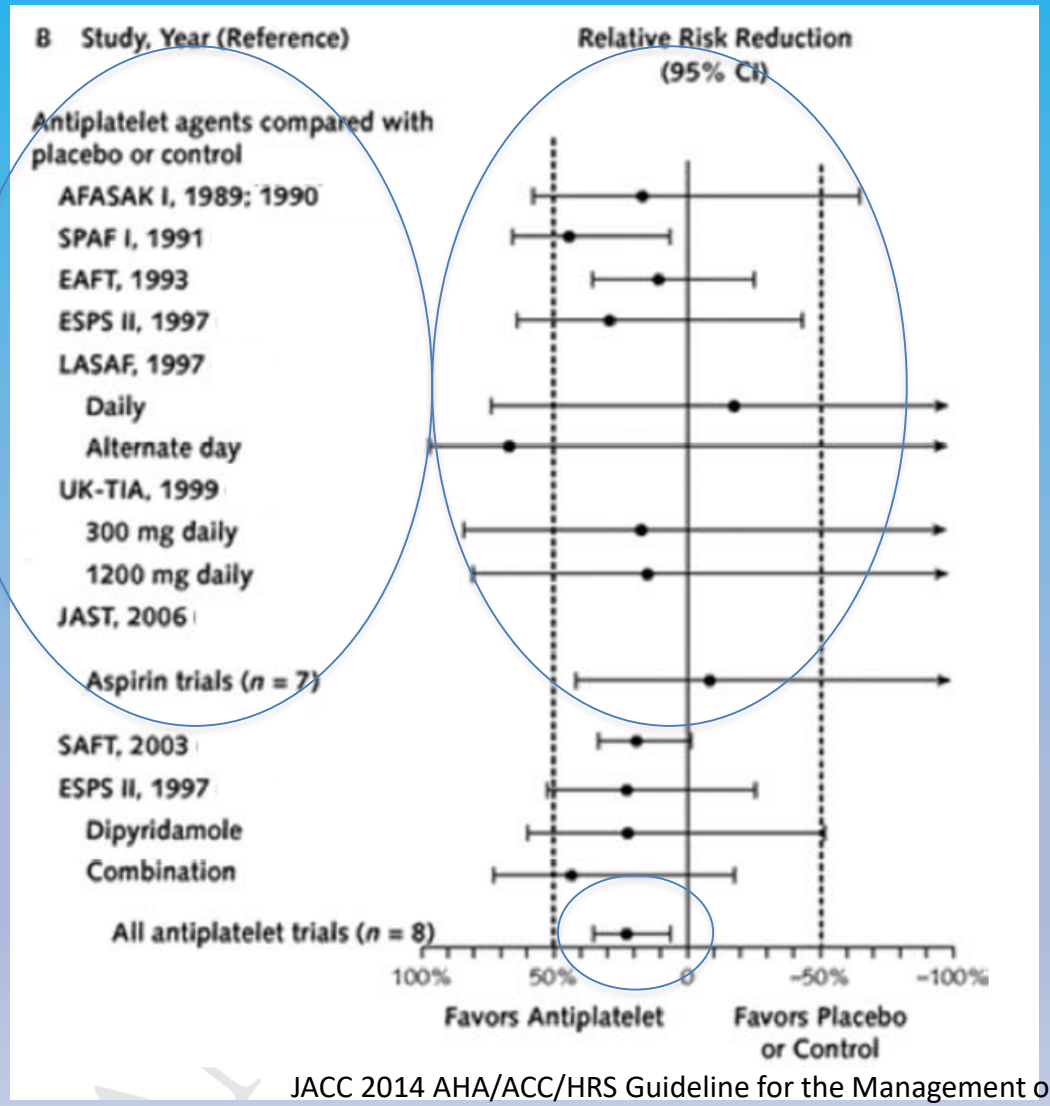
smoking

ETOH

Exercise – dose dependent

Aizer A, Gaziano JM, Cook NR, Manson JE, Buring JE, Albert CM. Relation of vigorous exercise to risk of atrial fibrillation. *Am J Cardiol* 2009;**103**:1572–1577.

Antiplatelets for stroke prevention in patients with AF



JACC 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation

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Anticoagulation Guidelines

Risk Factor	Score
Congestive heart failure/LV dysfunksjon	1
Hypertensjon	1
Age ≥ 75 y	2
Diabetes mellitus	1
Stroke/TIA/TE	2
Vascular disease (prior myocardial infarction, peripheral artery disease, or aortic plaque)	1
Age 65-74 y	1
Sex **C**ategory (ie female gender)	1

LV = left ventricular; TE=thromboembolism.

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CHADS2 vasc score and stroke risk

chads 2 score	stroke risk
0	1.9%
1	2.8%
2	4%
3	5.9%
4	8.5%
5	12.5%
6	18.2%

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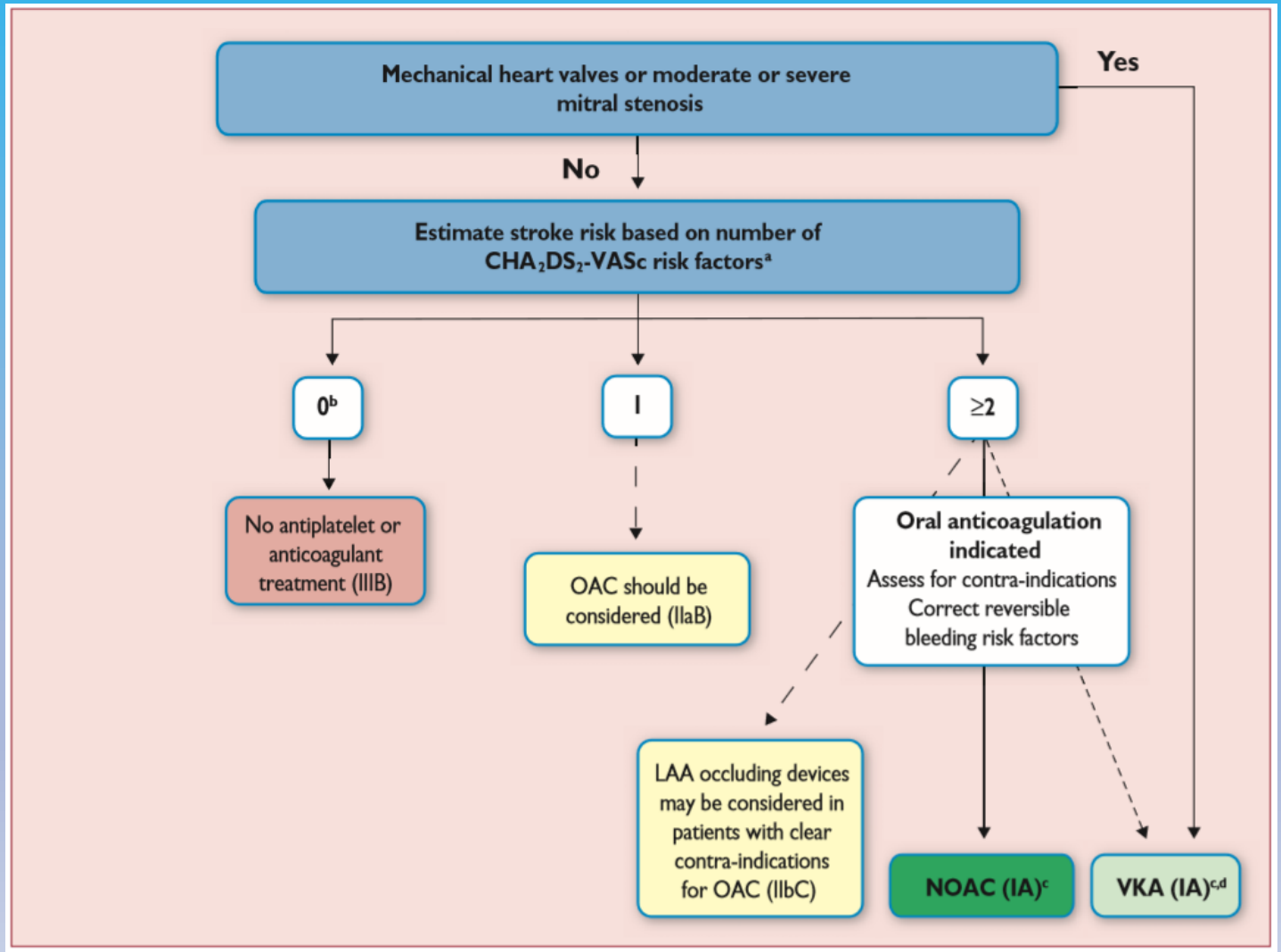
Recommendation for Anticoagulation ESC



Treatment with OAC as Secondary Prevention in atrial fibrillation

Recommendations for secondary stroke prevention

Recommendations	Class[a]	Level[b]	Ref[c]
Anticoagulation with heparin or LMWH immediately after an ischaemic stroke is not recommended in AF patients.	III (harm)	A	477
In patients who suffer a TIA or stroke while on anticoagulation, adherence to therapy should be assessed and optimized.	IIa	C	
In patients who suffer a moderate-to-severe ischaemic stroke while on anticoagulation, anticoagulation should be interrupted for 3–12 days based on a multidisciplinary assessment of acute stroke and bleeding risk.	IIa	C	
In AF patients who suffer a stroke, aspirin should be considered for prevention of secondary stroke until the initiation or resumption of oral anticoagulation.	IIa	B	485
Systemic thrombolysis with rtPA is not recommended if the INR is above 1.7 (or, for patients on dabigatran, if aPTT is outside normal range).	III (harm)	C	472, 474
NOACs are recommended in preference to VKAs or aspirin in AF patients with a previous stroke.	I	B	363,482
After TIA or stroke, combination therapy of OAC and an antiplatelet is not recommended.	III (harm)	B	486
After intracranial haemorrhage, oral anticoagulation in patients with AF may be reinitiated after 4–8 weeks provided the cause of bleeding or the relevant risk factor has been treated or controlled.	IIb	B	483, 484, 487

AF = atrial fibrillation; INR = international normalized ratio; LMWH = Low Molecular Weight Heparin; NOAC = non-vitamin K antagonist oral anticoagulant; OAC = oral anticoagulation; TIA = transient ischaemic attack; VKA = vitamin K antagonist.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

NOACs recommended as OAC of choice over VKA in secondary prevention patients with A fib

Class I recommendation ESC.

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Ntaios G, Papavasileiou V, Diener HC, Makaritsis K, Michel P. Nonvitamin-K-antagonist oral anticoagulants in patients with atrial fibrillation and previous stroke or transient ischemic attack: a systematic review and meta-analysis of randomized controlled trials. *Stroke* 2012;**43**:3298–3304.

2014 ACC/AHA Atrial Fibrillation Guidelines

CHA_2DS_2-VASc	Antithrombotic Regimen
0	No therapy
1	No therapy or Aspirin or Warfarin (INR 2-3) or DOAC
≥2	Warfarin (INR 2-3) or DOAC

Circulation. 2014;129:000-000.

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Atrial Fibrillation and Flutter

- Atrial Flutter is often initiated by a brief episode of atrial tachycardia or by AF [1]
- ≥80% of patients who undergo radiofrequency catheter ablation of typical atrial flutter will have AF within the following 5 years [2]
- AF may be misdiagnosed as atrial flutter when AF activity is prominent on ECG (correctly identified as atrial fibrillation by 31%) [3]

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[1] Waldo et al. J Am Coll Cardiol. 2008 Feb 26;51(8):779-86. doi: 10.1016/j.jacc.2007.08.066
[2] Ellis et al. J Cardiovasc Electrophysiol. 2007 Aug;18(8):799-802. Epub 2007 Jun 25
[3] Knight, et al. J Electrocardiol. 1999 Oct;32(4):315-9.

Relationship between device-detected AF and stroke

Author, year, reference	No. of patients	AF burden associated with stroke	HR (95% CI) for stroke p-value	Other findings
Glotzer et al., 2003 (26)	312 (patients with sinus node dysfunction)	≥ 5 min	2.79 (1.51–5.15) p = 0.0011	
Capucci et al., 2005 (27)	725 (patients with bradyarrhythmias and history of PAF)	> 24 h	3.1 (1.1–10.5) p = 0.044	
Botto et al., 2008 (13)	568 (patients with bradyarrhythmias and history of PAF)	> 5 min		Combining AF burden and $CHADS_2$ make it possible to distinguish a subgroup at low and high risk of stroke
Glotzer et al., 2009 (28)	2486 (patients with ≥ 1 stroke risk factor implanted with a pacemaker or an ICD)	≥ 5.5 h	2.20 (0.96–5.05) p = 0.06	
Ziegler et al., 2010 (29)	163 (previous thromboembolic event, no PAF)	≥ 5 min		73% of new AF patients with previous TE experienced episodes of AF < 10% of follow-up days
Boriani et al., 2011 (30)	568 (patients with bradyarrhythmias and history of PAF)	> 5 min		Combining AF burden and $CHADS_2$ or CHA_2DS_2-VASc improves prediction of stroke, reaching C-statistics of 0.713 and 0.910, respectively
Healey et al., 2012 (31)	2580 (≥ 65 years, hypertension, no history of PAF)	> 6 min	2.49 (1.28–4.85) p = 0.007	
Shanmugam et al., 2012 (32)	560 (heart failure patients treated with CRT)	≥ 3.8 h	9.4 (1.8–47.0) p = 0.006	40% of the study population had at least 1 day with AF burden > 14 min
Boriani et al. 2013 (33)	10,016 patients with a CIED, without permanent AF, median age 70 years (pooled analysis of three studies)	≥ 1 h	2.11 (1.22–3.64) p = 0.008	

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The Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial (ASSERT)

- Enrolled 2580 PPM and ICD patients aged ≥65 years with a history of HTN but **without** a history of AF
- PPM and ICDs logged the time and duration of all episodes of sub-clinical AF (SCAF) that lasted >6 minutes and recorded electrograms that were adjudicated by experts
- Of 51 patients who experienced stroke or systemic embolism during follow-up, 26 (51%) had SCAF.

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Brambatti et al. *Circulation*. 2014;129:2094-2099.

Implantable loop Recorders

- Medtronic:
  - Reveal XT (2007)
  - Reveal Linq (02/14)
- St. Jude Medical:
  - Confirm (2008)(2016)

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Reveal Linq

- 3-year longevity
- 49.5 minutes of ECG storage
- MR Conditional
- Remote data transmission through CareLink®
- Patient activated, as well as automatic detection of abnormal heart rhythms including AF
- Daily trended diagnostics via Cardiac Compass®

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	Prior Session	Last Session
	21- Oct-2007 to 20-Nov-2007	21- Nov-2007 to 20-April-2008
	60 days	6 months

AT/AF Summary

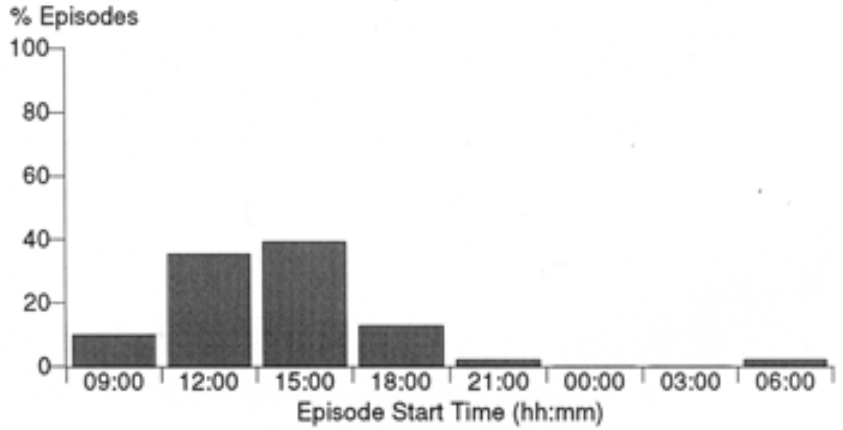
% of Time AT/AF	21.3	%	2.0	% ↓
Average AT/AF time/day	5.1	hours/day	0.5	hours/day ↓

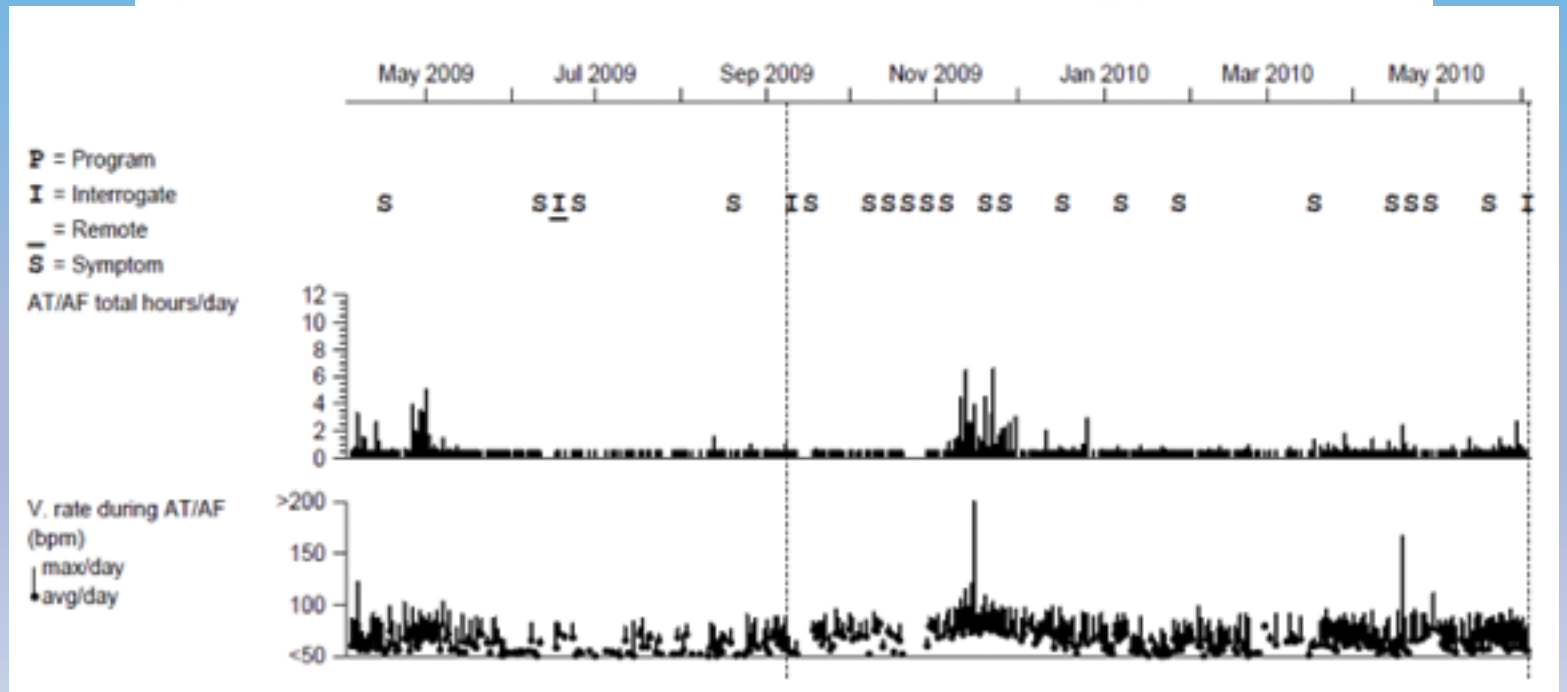
Since Last Session 20-Oct-2006 to 19-Apr-2007

AT/AF Durations

Duration	Episodes
>72 hr	0
48 hr to 72 hr	0
24 hr to 48 hr	0
12 hr to 24 hr	0
4 hr to 12 hr	5
1 hr to 4 hr	21
10 min to 1 hr	8
2 min to 10 min	0

AT/AF Episode Start Time





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The Cryptogenic Stroke and Underlying AF (CRYSTAL AF): Design

- Randomized trial (1:1 ratio) comparing the time to detection of atrial fibrillation with an ILR versus conventional follow-up
- 55 centers in Europe, Canada and USA
- Primary endpoint: time to first detection of atrial fibrillation (30 sec) at 6 months of follow-up
- Secondary end points: time to first detection of atrial fibrillation at 12 months, recurrent stroke or TIA, and the change in use of oral anticoagulant drugs
- Atrial fibrillation was defined as an episode of irregular heart rhythm, without detectable P waves, lasting more than 30 seconds

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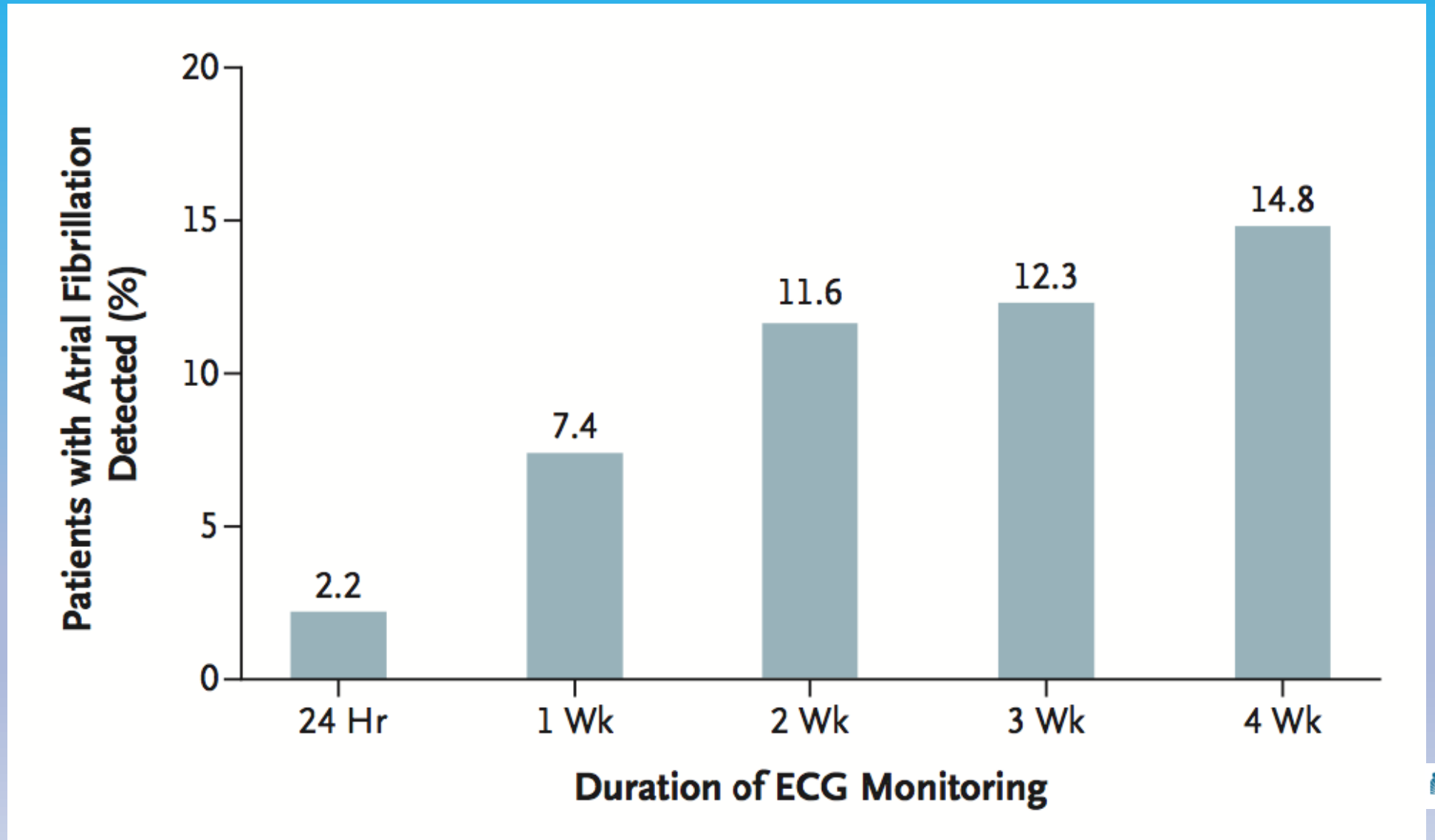
Sanna et al. N Engl J Med. 2014 Jun 26;370(26):2478-86

Incremental Yield of Prolonged ECG Monitoring for the Detection of Atrial Fibrillation in Patients with Cryptogenic Stroke or TIA



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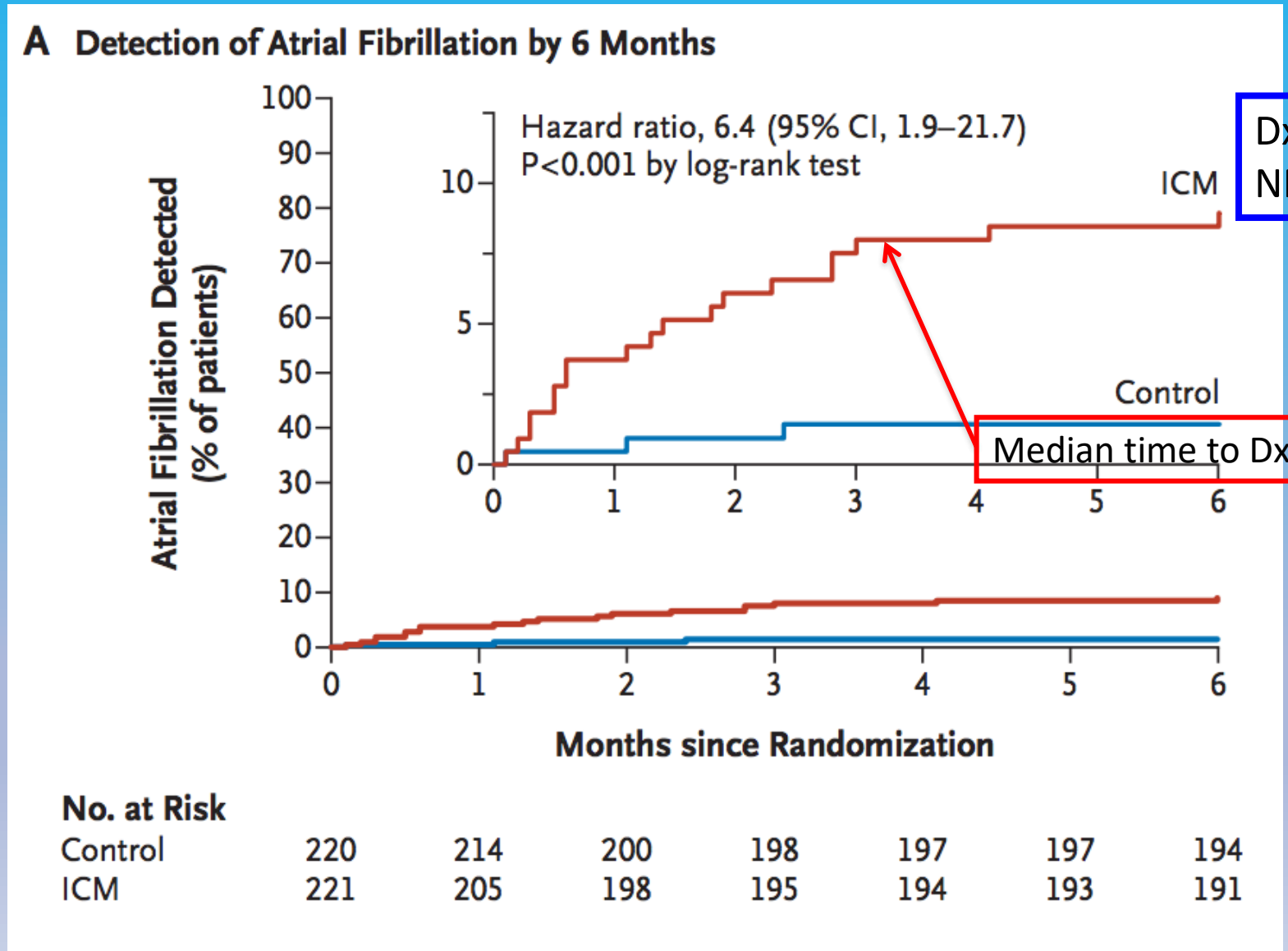
CRYSTAL AF: Results



Dx: 8.% vs 1.4%
NNT: 14

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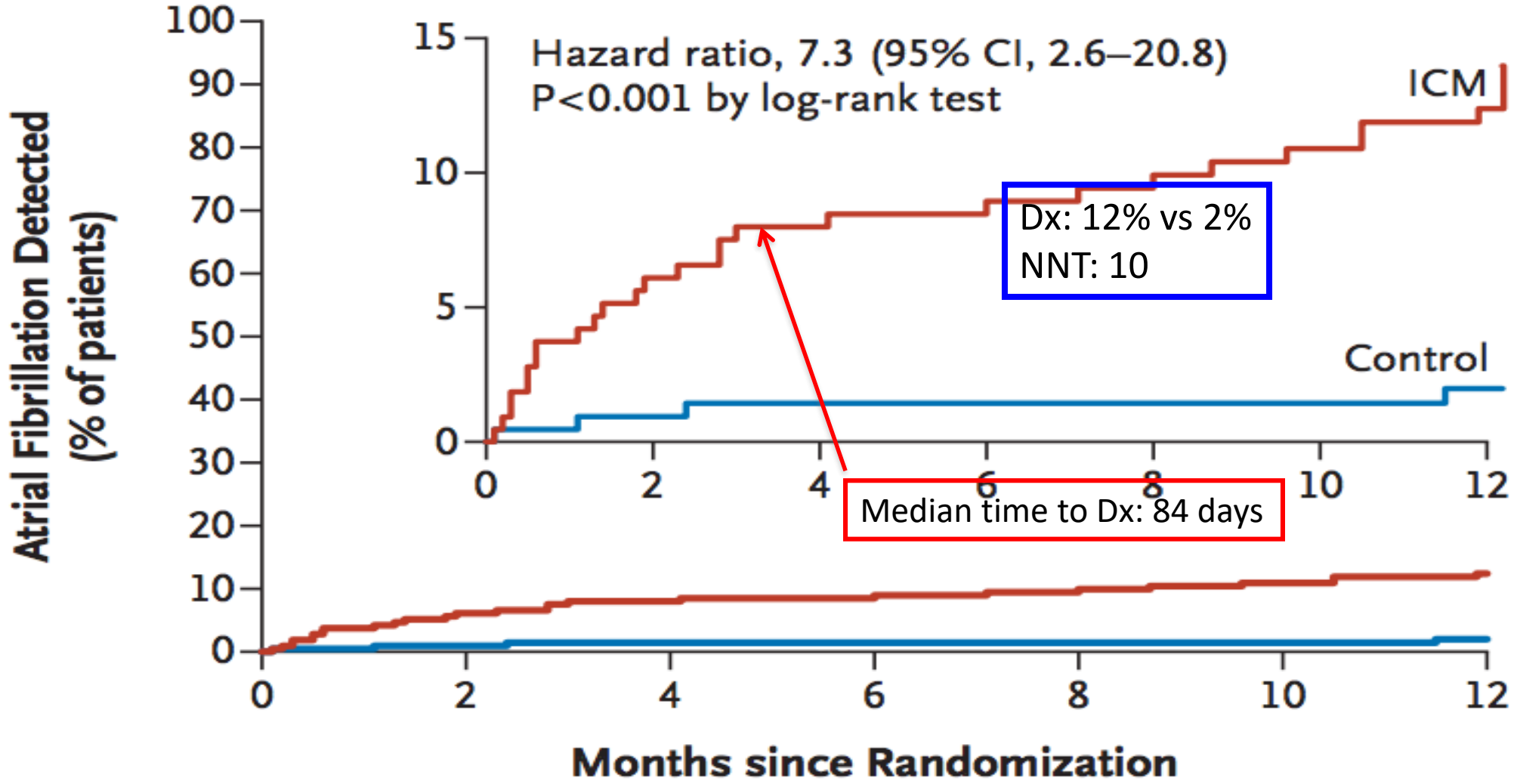
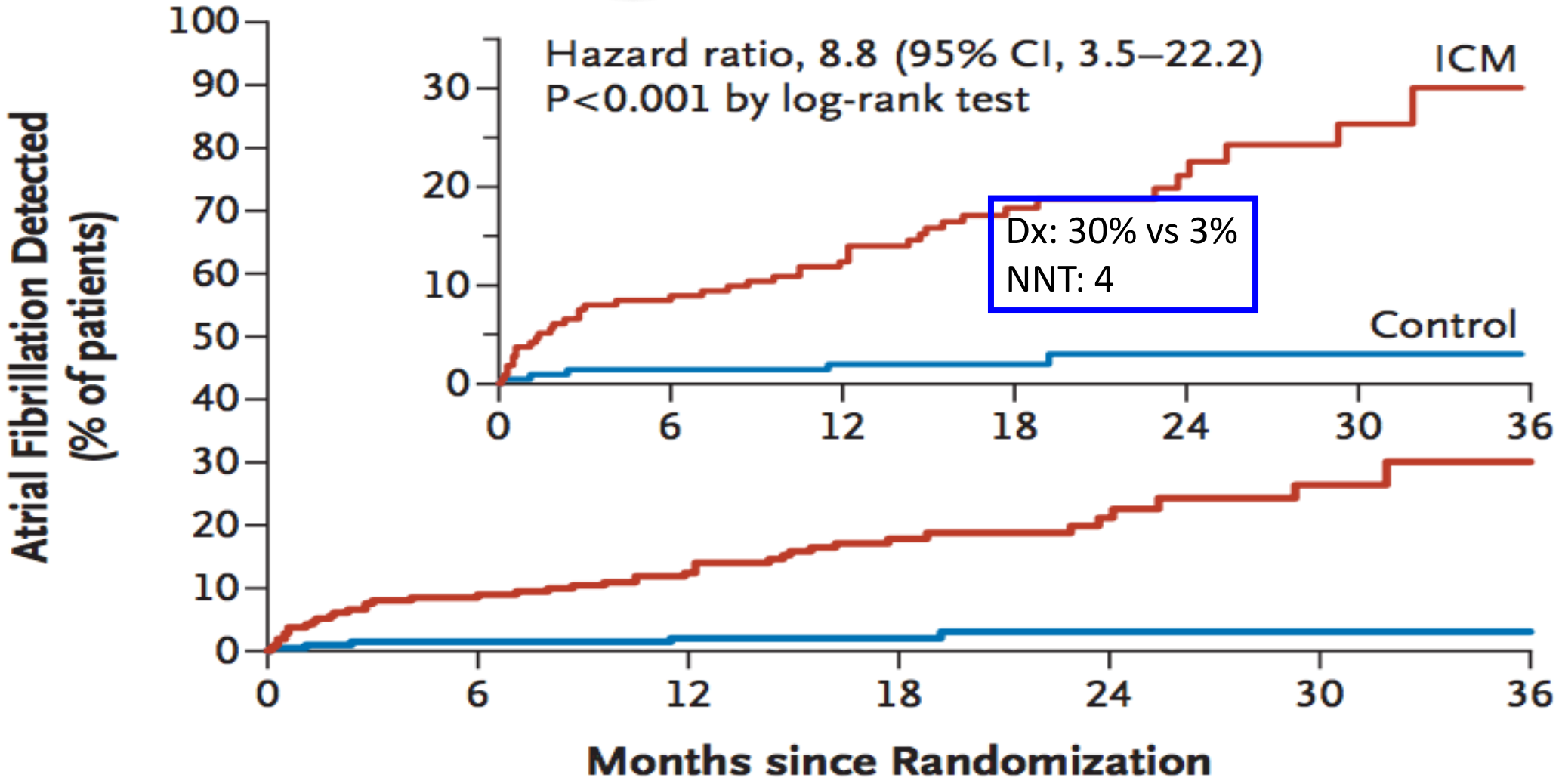
B **Detection of Atrial Fibrillation by 12 Months**



No. at Risk							
Control	220	200	197	194	184	184	167
ICM	221	198	194	191	186	182	173

C Detection of Atrial Fibrillation by 36 Months



No. at Risk							
Control	220	194	167	114	72	36	7
ICM	221	191	173	102	57	29	8

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Other findings

- AF caused no symptoms in 23/29 (79%) ILR and 2/4 patients in control group
- Recurrent CVA was observed in 5.2% pts in ILR and 8.6% in control group after 6 months post randomization, and 7.1 vs. 9.1% at 12 months
- OAC was more frequently prescribed in patients with ILR (10.1%) than in patients in the control group (4.6%) at 6 mo and at 12 months (14.7% vs 6%)

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Summary of CRYSTAL AF

- Continuous monitoring detected a significantly higher number of episodes of AF at the 6 and 12-months
- Short-term monitoring is not sufficient, as the median time to AF detection over 6 months was 41 days and over 12 months was 84 days
- Patients randomized to ILR had lower incidence of recurrent CVA (5.2 vs 8.6% at 6 mo and 7.1 vs 9.1 at 12 mo) and were more likely to be treated with OAC (10.1 vs 4.6% at 6 mo and at 12 months 14.7% vs 6%)

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SUMMARY OF DATA

- unclear what duration (30 secs, 5-6 min, 1 hour, 24 hours) of AF has to be used to consider a patient at “significantly” high risk of CVA to start anticoagulation
- High percentage of patients who experienced a stroke did not have AF around the time of event
- The NNT with a 30 day event monitor to detect an episode of AF, in patients with cryptogenic stroke, lasting more than 30s is 8 and lasting more than 2.5 min is 14
- The NNT with an ILR to detect an episode of AF lasting more than 30 sec is 16 in 6 months, 10 in 12 mo. and 4 in 36 mo.

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Take Away points thus far

- Unclear how low afib events or burden required for stroke
- Prolonged monitoring in Cryptogenic stroke more effective
- Antiplatelet therapy is not adequate for stroke prevention in Afib.

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Benefits of NOAC over VIT K antagonists

1. Can be given in fixed dosing
2. Do not require monitoring
3. Rapid onset of action 1 to 3 hours
4. Have shorter half lives 8 to 14 hours versus 36 hours
5. Have Lower incidence of intracranial hemorrhage
6. Have similar antithrombotic effect
7. Have higher GI bleeding

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Chai-Adisaksopha C, Crowther M, Isayama T, Lim W (2014) The impact of bleeding complications in patients receiving target-specific oral anticoagulants: a systemic review and meta-analysis. Blood 124(15):2450–2458

What Do We Know About the DOACs vs Warfarin for AF?

DOAC Pros

- Better, or just as good at, preventing stroke
- Less ICH
- Rapid onset
- Fixed dose
- No INR monitoring required
- Fewer drug interactions
- No dietary restrictions with regard to vitamin-K foods

DOAC Cons

- Short track record
-
- Bleeding and periprocedural management poorly defined
- Renal dosing/cutoff
- Not as easy to dose as we thought
- No readily available way to assess degree of anticoagulation
- More difficult to ensure adherence
- More expensive

MIXED BAG

-Bleeding
-Rapid offset

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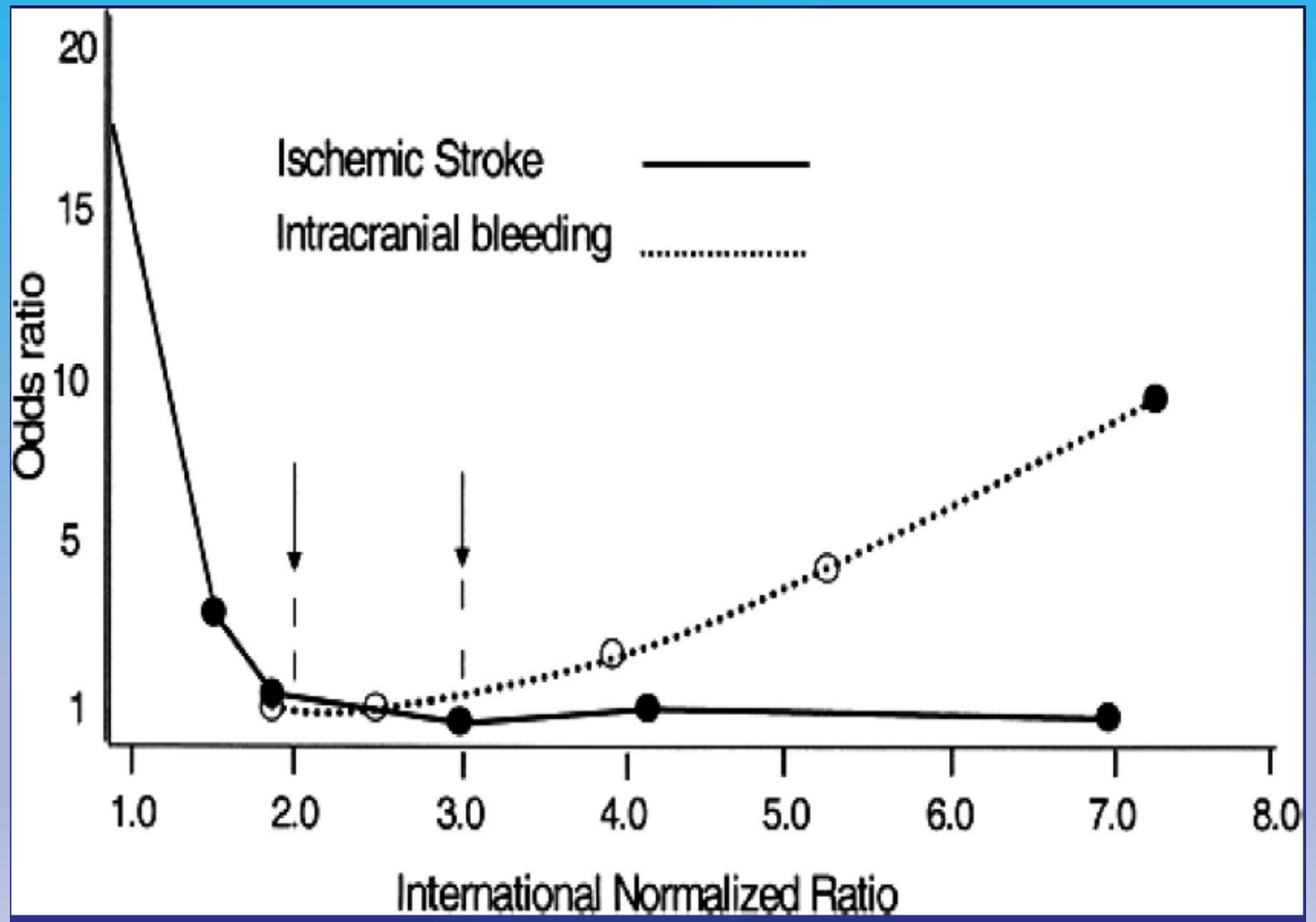
Risk Benefit of Level of Anticoagulation with VKA



Authors/Task Force Members, et al. Eur Heart J 2006 27:1979-2030; doi:10.1093/eurheartj/ehl176

Phase 3 Trials in Atrial Fibrillation: TTR and warfarin Efficacy

Study	Mean TTR (%)	Mean $CHADS_2$ Score	$CHADS_2$ ≥3 Patients (%)	Primary Efficacy Rate (warfarin Arm)*		
				Overall	$CHADS_2$ 2	$CHADS_2$ ≥3
ROCKET AF[1]	55	3.5	87.0	2.2	1.3	2.3
RE-LY[2]	64	2.1	32.5	1.7	1.4	2.7
ARISTOTLE[3]	62	2.1	30.2	1.6	1.4	2.8

- *ROCKET AF enrolled a population of patients with AF at higher risk of stroke*
- *The overall event rate for the warfarin arm in ROCKET AF was higher than those reported in RE-LY and ARISTOTLE*
- *This difference may have been driven by the greater proportion of $CHADS_2$ ≥3 patients enrolled in ROCKET AF/*

*Rate per 100 patient-years.

1. Patel MR et al. N Engl J Med. 2011;365(10):883-891
2. Connolly SJ, et al. N Engl J Med. 2009;361:1139-51. doi: 10.1056/NEJMoa0905561.
3. Granger CB, et al. N Engl J Med. 2011 [Aug 28]. ePub ahead of print. doi: 10.1056/NEJMoa1107039.

TTR for warfarin

- Mean TTR for 100 centers Vamedical centers - 57%
- Mean TTR from Quest diagnostics in 140000 in US – 54%

The DOACs

- Dabigatran (Pradaxa®) – 2010
- Rivaroxaban (Xarelto®) – 2011
- Apixaban (Eliquis®) – 2012
- Edoxaban (Savaysa®) – 2015
- Betrixiban (Bevyxxa)- VTE 2017

Year of FDA approval for non-valvular AF

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Currently Available Noacs

Table 1 | **NOAC targets, licensed indications, and considerations**[4,7,64]

Parameter	Apixaban	Betrixaban	Dabigatran	Edoxaban	Rivaroxaban
Target	Factor Xa	Factor Xa	Thrombin	Factor Xa	Factor Xa
FDA-approved indications	Nonvalvular AF, VTE (treatment*, secondary prevention, prophylaxis‡)	VTE (prophylaxis§)	Nonvalvular AF, VTE (treatment‖, secondary prevention, prophylaxis)	Nonvalvular AF, VTE (treatment§)	Nonvalvular AF, VTE (treatment*, secondary prevention, prophylaxis‡)
Safety in nonvalvular AF	Lower risk of major bleeding than with warfarin	Lower risk of major bleeding than with warfarin	Higher risk of GI bleeding than with warfarin	Lower risk of major bleeding than with warfarin; higher risk of GI bleeding (60 mg dose) than with warfarin	Higher risk of GI bleeding than with warfarin
Specific reversal agent	Andexanet alfa	Andexanet alfa	Idarucizumab	Andexanet alfa	Andexanet alfa
Half-life (h)	12	20	8–15	10–14	7–11
Renal clearance (%)	25	6–13	80	50	33
Dialysable	No	No	Yes	No	No
Prodrug	No	No	Yes	No	No
Bioavailability (%)	60	34	6	62	60–80
Time to peak effect (h)	1–2	3–4	1–3	1–2	2–4

AF, atrial fibrillation; GI, gastrointestinal; NOAC, non-vitamin K antagonist oral anticoagulant; VTE, venous thromboembolism.
*Twice daily for the first 21 days of VTE treatment; once daily for other indications for rivaroxaban or twice daily for apixaban.
‡Approved for VTE prophylaxis after knee or hip surgery only. §Prophylaxis of VTE in adult patients hospitalized for an acute medical illness and for extended use. ‖After 5–10 days of parental anticoagulant treatment only.

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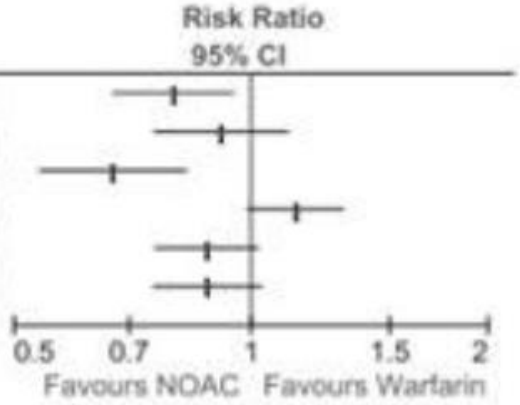
Noacs versus Warfarin

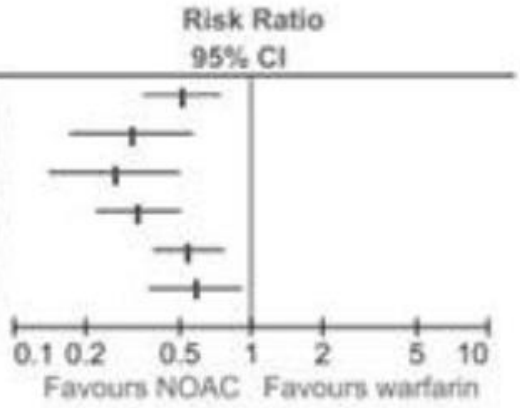
A. Primary Efficacy Outcome

Study or Subgroup	NOAC Events	NOAC Total	Warfarin Events	Warfarin Total	Risk Ratio 95% CI
Apixaban 5mg bid	212	9120	265	9081	0.80 [0.67, 0.95]
Dabigatran 110mg bid	182	6015	199	6022	0.92 [0.75, 1.12]
Dabigatran 150mg bid	134	6076	199	6022	0.67 [0.54, 0.83]
Edoxaban 30mg daily	383	7034	337	7036	1.14 [0.99, 1.31]
Edoxaban 60mg daily	296	7035	337	7036	0.88 [0.75, 1.02]
Rivaroxaban 20mg daily	269	7081	306	7090	0.88 [0.75, 1.03]



B. Haemorrhagic stroke

Study or Subgroup	NOAC Events	NOAC Total	Warfarin Events	Warfarin Total	Risk Ratio 95% CI
Apixaban 5mg bid	40	9120	78	9081	0.51 [0.35, 0.75]
Dabigatran 110mg bid	14	6015	45	6022	0.31 [0.17, 0.57]
Dabigatran 150mg bid	12	6076	45	6022	0.26 [0.14, 0.50]
Edoxaban 30mg daily	30	7034	90	7036	0.33 [0.22, 0.50]
Edoxaban 60mg daily	49	7035	90	7036	0.54 [0.39, 0.77]
Rivaroxaban 20mg daily	29	7061	50	7082	0.58 [0.37, 0.92]

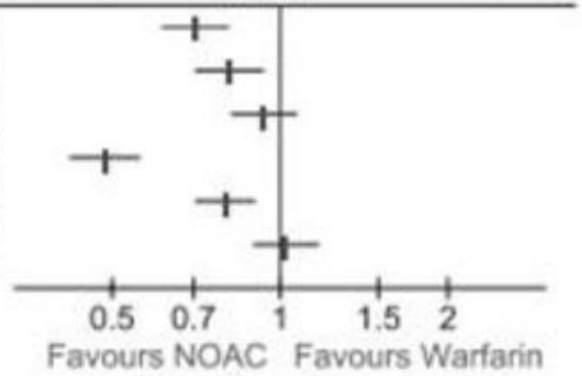


Chan et al. New oral anticoagulatns for stroke prevention in atrial fibrillation. Thromb Haemost 2014; 111: 798-807

Noacs and Bleeding versus VKA

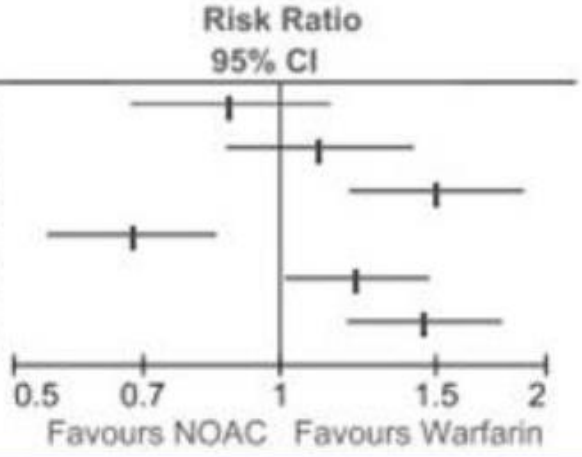
A. Major bleeding

Study or Subgroup	NOAC Events	NOAC Total	Control Events	Control Total	Risk Ratio 95% CI
Apixaban 5mg bid	327	9088	462	9052	0.70 [0.61, 0.81]
Dabigatran 110mg bid	322	6015	397	6022	0.81 [0.70, 0.94]
Dabigatran 150mg bid	375	6076	397	6022	0.94 [0.82, 1.07]
Edoxaban 30mg daily	254	7002	524	7012	0.49 [0.42, 0.56]
Edoxaban 60mg daily	418	7012	524	7012	0.80 [0.70, 0.90]
Rivaroxaban 20mg daily	395	7111	386	7125	1.03 [0.89, 1.18]



B. Major gastrointestinal bleeding

Study or Subgroup	NOAC Events	NOAC Total	Warfarin Events	Warfarin Total	Risk Ratio 95% CI
Apixaban 5mg bid	105	9088	119	9052	0.88 [0.68, 1.14]
Dabigatran 110mg bid	133	6015	120	6022	1.11 [0.87, 1.42]
Dabigatran 150mg bid	182	6076	120	6022	1.50 [1.20, 1.89]
Edoxaban 30mg daily	129	7002	190	7012	0.68 [0.55, 0.85]
Edoxaban 60mg daily	232	7012	190	7012	1.22 [1.01, 1.47]
Rivaroxaban 20mg daily	224	7111	154	7125	1.46 [1.19, 1.78]

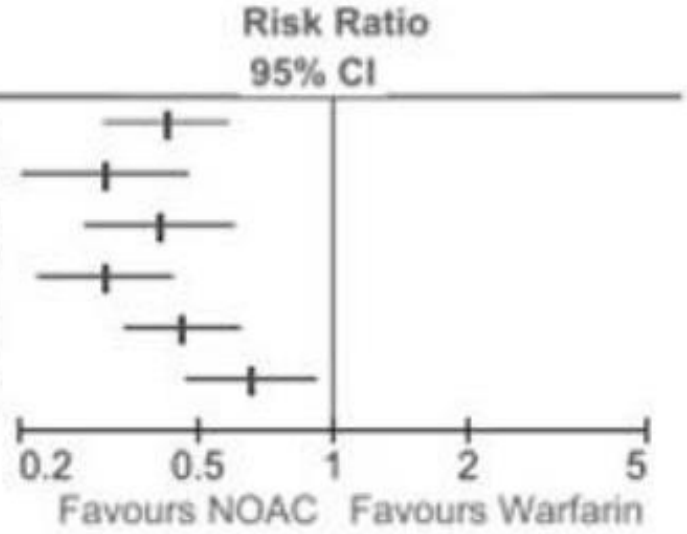


Chan et al. New oral anticoagulatns for stroke prevention in atrial fibrillation. Thromb Haemost 2014; 111: 798-807

Noacs and Intracranial Bleeding

C. Intracranial bleeding

Study or Subgroup	NOAC Events	NOAC Total	Warfarin Events	Warfarin Total	Risk Ratio 95% CI
Apixaban 5mg bid	52	9088	122	9052	0.42 [0.31, 0.59]
Dabigatran 110mg bid	27	6015	87	6022	0.31 [0.20, 0.48]
Dabigatran 150mg bid	36	6076	87	6022	0.41 [0.28, 0.60]
Edoxaban 30mg daily	41	7002	132	7012	0.31 [0.22, 0.44]
Edoxaban 60mg daily	61	7012	132	7012	0.46 [0.34, 0.62]
Rivaroxaban 20mg daily	55	7111	84	7125	0.66 [0.47, 0.92]



Chan et al. New oral anticoagulatns for stroke prevention in atrial fibrillation. Thromb Haemost 2014; 111: 798-807

FDA-Approved Indications

Anticoagulant	Stroke Prevention in Non-Valvular AF	VTE (DVT/PE) Treatment (Acute and Longterm)	Mechanical Heart Valve
Warfarin (Coumadin®)	YES	YES	YES
Dabigatran (Pradaxa®)	YES	YES, but requires 5-10 days of parenteral first	NO, contraindicated (RE-ALIGN)
Rivaroxaban (Xarelto®)	YES	YES	NO, do not use (RE-ALIGN)
Apixaban (Eliquis®)	YES	YES	NO, do not use (RE-ALIGN)
Edoxaban (Savaysa®)	YES	YES, but requires 5-10 days of parenteral first	NO, do not use (RE-ALIGN)

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Pharmacology and Pharmacokinetics

	Warfarin (Coumadin®)	Dabigatran (Pradaxa®)	Rivaroxaban (Xarelto®)	Apixaban (Eliquis®)	Edoxaban (Savaysa®)
Mechanism of Action	Inhibits synthesis of vitamin K-dependent clotting factors	Direct IIa (thrombin) Inhibitor	Direct Factor Xa Inhibitor	Direct Factor Xa Inhibitor	Direct Factor Xa Inhibitor
Onset to full, therapeutic anticoagulation	5-9 days	0.5-2 hr	3-5 hr	2-4 hr	1-2hr
Elimination Half-life	20-60 hr	12-17 hr	5-9 hr	8-15 hr	10-14 hr
Dosing frequency	Daily	BID	Daily	BID	Daily

Pradaxa® [package insert]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals; 2011.
Xarelto® [package insert.]. Titusville, NJ: Janssen Pharmaceuticals; 2011.
Eliquis® [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 2012.
N Engl J Med 2011;365:981-9.
Savaysa® [package insert]. Parsippany, NJ: Daiichi-Sankyo, Inc; 2015.

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Renal Dosing Approved but Not Studied

Agent	Trial	Renal Function Exclusions
Apixaban	ARISTOTLE	<25 ml/min
Rivaroxaban	ROCKET-AF	<30 ml/min
Dabigatran	RE-LY	<30 ml/min

- KPCO does not recommends NOAC use in patients with CrCl below what was studied
- AHA/ASA agrees

N Engl J Med 2009;361:1139-51
N Engl J Med 2011;365:981-9
N Engl J Med 2011; 365:883-91

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Preferred/Formulary DOAC at KPCO: Pradaxa

- **"Warfarin remains the preferred anticoagulant at KPCO."**
  Excellent INR control at KPCO: TTR 72%
- **Why**
  - Pradaxa is the only DOAC superior to warfarin at preventing ischemic stroke
  - Less expensive for patient and KP vs other DOACs
  - Reversal agent/antidote: Praxbind;

    Reversal agent/ andexanet not available
- **Clinical**
  - 150mg BID standard AF dose
  - Take with full glass of water and remain upright for 30 minutes to mitigate potential dyspepsia

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Effect of TTR on Comparison to Dabigatran

Format: Abstract Send to

Lancet. 2010 Sep 18;376(9745):975-83. doi: 10.1016/S0140-6736(10)61194-4.

Efficacy and safety of dabigatran compared with warfarin at different levels of international normalised ratio control for stroke prevention in atrial fibrillation: an analysis of the RE-LY trial.

Wallentin L[1], Yusuf S, Ezekowitz MD, Alings M, Flather M, Franzosi MG, Pais P, Dans A, Eikelboom J, Oldgren J, Pogue J, Reilly PA, Yang S, Connolly SJ; RE-LY investigators.

Author information

Abstract

BACKGROUND: Effectiveness and safety of warfarin is associated with the time in therapeutic range (TTR) with an international normalised ratio (INR) of 2·0-3·0. In the Randomised Evaluation of Long-term Anticoagulation Therapy (RE-LY) trial, dabigatran versus warfarin reduced both stroke and haemorrhage. We aimed to investigate the primary and secondary outcomes of the RE-LY trial in relation to each centre's mean TTR (cTTR) in the warfarin population.

METHODS: In the RE-LY trial, 18 113 patients at 951 sites were randomly assigned to 110 mg or 150 mg dabigatran twice daily versus warfarin dose adjusted to INR 2·0-3·0. Median follow-up was 2·0 years. For 18 024 patients at 906 sites, the cTTR was estimated by averaging TTR for individual warfarin-treated patients calculated by the Rosendaal method. We compared the outcomes of RE-LY across the three treatment groups within four groups defined by the quartiles of cTTR. RE-LY is registered with ClinicalTrials.gov, number NCT00262600.

FINDINGS: The quartiles of cTTR for patients in the warfarin group were: less than 57·1%, 57·1-65·5%, 65·5-72·6%, and greater than 72·6%. There were no significant interactions between cTTR and prevention of stroke and systemic embolism with either 110 mg dabigatran (interaction p=0·89) or 150 mg dabigatran (interaction p=0·20) versus warfarin. Neither were any significant interactions recorded with cTTR with regards to intracranial bleeding with 110 mg dabigatran (interaction p=0·71) or 150 mg dabigatran (interaction p=0·89) versus warfarin. There was a significant interaction between cTTR and major bleeding when comparing 150 mg dabigatran with warfarin (interaction p=0·03), with less bleeding events at lower cTTR but similar events at higher cTTR, whereas rates of major bleeding were lower with 110 mg dabigatran than with warfarin irrespective of cTTR. There were significant interactions between cTTR and effects of both 110 mg and 150 mg dabigatran versus warfarin on the composite of all cardiovascular events (interaction p=0·036 and p=0·0006, respectively) and total mortality (interaction p=0·066 and p=0·052, respectively) with reduced event rates at low cTTR, and similar rates at high cTTR.

INTERPRETATION: The benefits of 150 mg dabigatran at reducing stroke, 110 mg dabigatran at reducing bleeding, and both doses at reducing intracranial bleeding versus warfarin were consistent irrespective of centres' quality of INR control. For all vascular events, non-haemorrhagic events, and mortality, advantages of dabigatran were greater at sites with poor INR control than at those with good INR control. Overall, these results show that local standards of care affect the benefits of use of new treatment alternatives.

Renal clearance for NOACS

- Apixaban -25%
- Betrixaban 6-13%
- Edoxaban 50%
- Rivaroxaban 33%
- Dabigatran 80%

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Interactions for Dabigitran and Rivaroxiban

Table 4. Drug interactions with at least 50% change in the exposure to Dabigatran or Rivaroxaban. Reproduced with permission from *Blood* 2012; **119**(13): 3016-23.[7]

	Dabigatran		Rivaroxaban	
	Interacting drug	Exposure, %		Exposure, %
P-gp inhibition	Ketoconazole*	150	Ketoconazole*	160
	Quinidine	53		
	Amiodarone	60		
	Verapamil	50†		
P-gp induction	Rifampicin	-67	Rifampicin	-50
	St John's wort	ND	St John's wort	ND
CYP3A4 inhibition			Ketoconazole*	160
			Clarithromycin	50
			Ritonavir	50
CYP3A4 induction			Rifampicin	50
			St John's wort	ND

*Contraindicated

†Variable depending on verapamil formulation

ND = not determined

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Strong P –GP

Strong P-glycoprotein Inhibitors			Strong P-glycoprotein Inducers
Alfentanil	Indinavir	Quinidine	Barbiturates
Amiodarone	Itraconazole	Ritonavir	Carbamazepine
Bepridil	Ketoconazole	Saquinavir	Dexamethasone
Carvedilol	Lapatinib	Tacrolimus	Phenytoin
Clarithromycin	Lovastatin	Tamoxifen	Rifampin
Conivaptan	Mefloquine	Telaprevir	St John's Wort
Cyclosporine	Mifepristone	Telithromycin	
Diltiazem	Nelfinavir	Testosterone	
Dronedarone	Nicardipine	Ticagrelor	
Duloxetine	Posaconazole	Verapamil	
Fenofibrate	Propafenone		

P –GP and CYP3A4 drugs to avoid with Rivaroxaban and Apixaban

Combined Strong P-glycoprotein AND CYP3A4 Inhibitors		Combined Strong P-glycoprotein AND CYP3A4 Inducers
amiodarone	nelfinavir	barbiturates
clarithromycin	posaconazole	carbamazepine
conivaptan	ritonavir	dexamethasone
cyclosporine	saquinavir	phenytoin
indinavir	tamoxifen	rifampin
itraconazole	telaprevir	St John's wort
ketoconazole	telithromycin	
mifepristone		

Testing for presence and excess NOAC

Clinical objective						
Drug	Determine if clinically relevant below on-therapy drug levels are present		Estimate drug levels within on-therapy range		Determine if above on-therapy drug levels are present	
	Suggested test	Interpretation	Suggested test	Interpretation	Suggested test	Interpretation
Dabigatran	TT	Normal TT likely excludes clinically relevant drug levels	Dilute TT, ECA, ECT		aPTT, dilute TT, ECA, ECT	Normal aPTT likely excludes excess drug levels; only dilute TT, ECA, and ECT are suitable for quantitation
Rivaroxaban	Anti-Xa	Normal anti-Xa activity likely excludes clinically relevant drug levels	Anti-Xa		Anti-Xa, PT	Normal PT likely excludes excess drug levels; only Anti-Xa is suitable for quantitation
Apixaban	Anti-Xa	Normal anti-Xa activity likely excludes clinically relevant drug levels	Anti-Xa		Anti-Xa	Normal PT may not exclude excess drug levels; only Anti-Xa is suitable for quantitation
Edoxaban	Anti-Xa	Normal anti-Xa activity likely excludes clinically relevant drug levels	Anti-Xa		Anti-Xa, PT	Normal PT likely excludes excess drug levels; only Anti-Xa is suitable for quantitation

aPTT Activated partial thromboplastin time, *ECA* ecarin chromogenic assay, *ECT* ecarin clotting time, *PT* prothrombin time, *TT* thrombin time, need permission from Cuker et al. JACC 2014 [40]

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J Thromb Thrombolysis (2016) 41:206–232
DOI 10.1007/s11239-015-1310-7

Summary conclusion for Testing of NOACs

- Dabigatran - the a(PTT) is prolonged in dose dependent fashion but but plateaus at higher concentration.
  - Serious bleeding or urgent surgery in a patient on Dabigatran (Pradaxa) with a prolonged a(PTT) is an indication for reversal
  - **A normal a(PTT) with sensitive reagent excludes clinically significant presence of Dabigatran**
  - **A normal thrombin time excludes the presence of Dabigatran**

Pollack, C. V. Jr *et al.* Idarucizumab for dabigatran reversal — full cohort analysis. *N. Engl. J. Med.* **377**, 431–441 (2017).

Summary conclusion for Testing of NOACs

- Rivaroxaban – a normal PT excludes excess drug levels
- Edoxaban - a normal PT excludes excess drug levels

- Apixaban - a normal PT does not exclude excess drug levels..

J Thromb Thrombolysis (2016) 41:206–232
DOI 10.1007/s11239-015-1310-7

Individual NOAC Selection

- Avoid Dabigatran and Rivaroxaban if previous GI bleeding
- Avoid NOACS if complicating medications
  - P-GP inhibitors with Pradaxa and Rivaroxaban, Apixaban,edoxaban
  - CYP3a4 inhibitors factor 10a inhibitors.
- Avoid NOACS I pregnancy and breast feeding

- Avoid NOACS in extremes of weight < 50 kg or greater than BMI 35
  - Extremes of weight appears not to effect peak concentration of Dabigatran
  - Elevates concentration in 10a inhibitors in low an reduced BMI and in high BMI greater than 35

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NOACS in Renal Failure

Outcomes Associated with Apixaban Use in End-Stage Kidney Disease Patients with Atrial Fibrillation in the United States

Konstantinos C. Siontis ✉, Xiaosong Zhang, Ashley Eckard, Nicole Bhave, Doug E. Schaubel, Kevin He, Anca Tilea, Austin G. Stack, Rajesh Balkrishnan, Xiaoxi Yao, Peter A. Noseworthy, Nilay D. Shah, Rajiv Saran, and Brahmajee K. Nallamothu

Originally published 24 Jul 2018 | Circulation. 2018;0:CIRCULATIONAHA.118.035418

Abstract

Background—Patients with end-stage kidney disease (ESKD) on dialysis were excluded from clinical trials of direct o anticoagulants for atrial fibrillation (AF). Recent data have raised concern regarding the safety of dabigatran and rivaroxaban, but apixaban has not been evaluated despite current labeling supporting its use in this population. The go of this study was to determine patterns of apixaban use and its associated outcomes in dialysis-dependent ESKD patients with AF.

Methods—We performed a retrospective cohort study of Medicare beneficiaries included in the United States Renal Data System (October 2010 to December 2015). Eligible patients were those with ESKD and AF undergoing dialysis who initiated treatment with an oral anticoagulant. Due to the small number of dabigatran and rivaroxaban users, outcomes were assessed only in patients treated with apixaban or warfarin. Apixaban and warfarin patients were matched (1:3) based on prognostic score. Differences between groups in survival free of stroke or systemic embolism, major bleeding, gastrointestinal bleeding, intracranial bleeding, and death were assessed using Kaplan-Meier analyses Hazard ratios (HR) and 95% confidence intervals (CI) were derived from Cox regression analyses.

Results—The study population consisted of 25,523 patients (45.7% women; age 68.2±11.9 years), including 2,351 patients on apixaban and 23,172 patients on warfarin. An annual increase in apixaban prescriptions was observed following its marketing approval in the end of 2012, such that 26.6% of new anticoagulant prescriptions in 2015 were fo apixaban. In matched cohorts, there was no difference in the risks of stroke/systemic embolism between apixaban and warfarin (HR 0.88, 95% CI 0.69-1.12; P=0.29), but apixaban was associated with significantly lower risk of major bleeding (HR 0.72, 95% CI 0.59-0.87; P<0.001). In sensitivity analyses, standard dose apixaban (5 mg twice a day; n=1,034) was associated with significantly lower risks of stroke/systemic embolism and death as compared with either reduced dose apixaban (2.5 mg twice a day; n=1,317; HR 0.61, 95% CI 0.37-0.98, P=0.04 for stroke/systemic embolism; and HR 0.64, 95% CI 0.45-0.92, P=0.01 for death) or warfarin (HR 0.64, 95% CI 0.42-0.97, P=0.04 for stroke/systemic embolism; and HR 0.63, 95% CI 0.46-0.85, P=0.003 for death).

Conclusions—Among ESKD patients with AF on dialysis, apixaban use may be associated with lower risk of major bleeding compared with warfarin, with a standard 5 mg twice a day dose also associated with reductions in thromboembolic and mortality risk.

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NOAC use in Dialysis patients

- Retrospective Medicare review of patients with AF and Dialysis.
- 25523 patients over 5 years
- Similar stroke and systemic embolism compared to warfarin
- Reduced incidence of major bleeding with Apixaban

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Circulation. 2018;0:CIRCULATIONAHA.118.035418

Switching to NOAC

Warfarin to DOAC	
Dabigatran[a]	Start when INR < 2.0
Rivaroxaban[a]	Start when INR < 3.0
Apixaban[a]	Start when INR < 2.0
Edoxaban[a]	Start when INR ≤ 2.5
LMWH to DOAC	
Dabigatran	Start DOAC within 0–2 h of the time of next scheduled dose of LMWH
Rivaroxaban	
Apixaban	
Edoxaban	
(iv) UFH to DOAC	
Dabigatran[a]	Start DOAC immediately after stopping iv UFH
Rivaroxaban[a]	
Apixaban[a]	
Edoxaban[a]	Start edoxaban 4 h after stopping iv UFH

As a general rule, we suggest that as INR drops below 2.5, a DOAC can be started

As a general rule, we suggest that each DOAC can be started within 30 min after stopping (iv) UFH

[a] Recommendations adapted from company's package insert

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J Thromb Thrombolysis (2016) 41:206–232
DOI 10.1007/s11239-015-1310-7

Switching to warfarin

DOAC to warfarin	
Dabigatran[a]	Start warfarin and overlap with dabigatran; CrCl ≥50 mL/min, overlap 3 days CrCl 30–50 mL/min, overlap 2 days CrCl 15–30 mL/min, overlap 1 day
Rivaroxaban[a] Apixaban[a]	Stop DOAC; start warfarin and LMWH at time of next scheduled DOAC dose and bridge until INR ≥ 2.0
Edoxaban[a]	For 60 mg dose, reduce dose to 30 mg and start warfarin concomitantly For 30 mg dose reduce dose to 15 mg and start warfarin concomitantly Stop edoxaban when INR ≥ 2.0

Overlap intended to avoid under-anticoagulation while warfarin effect developing. When DOAC overlapped with warfarin, measure INR just before next DOAC dose since DOAC can influence INR

As a general rule, we believe either approach (i.e. stop DOAC then start LMWH and warfarin; or overlap warfarin with DOAC, measure INR just before next DOAC dose and stop DOAC when INR ≥ 2.0) can be used for all DOAC to warfarin transitions

CrCl creatinine clearance

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J Thromb Thrombolysis (2016) 41:206–232
DOI 10.1007/s11239-015-1310-7

Hold times prior to procedures

TABLE 2 Recommended Durations for Withholding DOACs Based on Procedural Bleed Risk and Estimated CrCl When There Are No Increased Patient Bleed Risk Factors

	Dabigatran					Apixaban, Edoxaban, or Rivaroxaban		
CrCl, mL/min	≥80	50-79	30-49	15-29	<15	≥30	15-29	<15
Estimated drug half-life, h	13	15	18	27	30 (off dialysis)	6-15	Apixaban: 17 Edoxaban: 17 Rivaroxaban: 9	Apixaban: 17 (off dialysis) Edoxaban: 10-17 (off dialysis) Rivaroxaban: 13 (off dialysis)
Procedural bleed risk								
Low	≥24 h	≥36 h	≥48 h	≥72 h	No data. Consider measuring dTT and/or withholding ≥96 h.	≥24 h	≥36 h	No data. Consider measuring agent-specific anti Xa level and/or withholding ≥48 h
Uncertain, intermediate, or high	≥48 h	≥72 h	≥96 h	≥120 h	No data. Consider measuring dTT.	≥48 h	No data. Consider measuring agent-specific anti Xa level and/or withholding ≥72 h.	

JACC VOL. 69, NO. 7, 2017
FEBRUARY 21, 2017:871-98

Bruise Control 2

- Interrupted versus continued NOAC use during device implantation
- Apixaban , Rivaroxaban , Dabigitran
  prior to implantation of devices

Major hematoma both arms 2.1%

Hematoma requiring discontinuation of drug
  no difference
Hematoma prolonging hospitalization
  no difference
Hematoma requiring drainage
  no difference.

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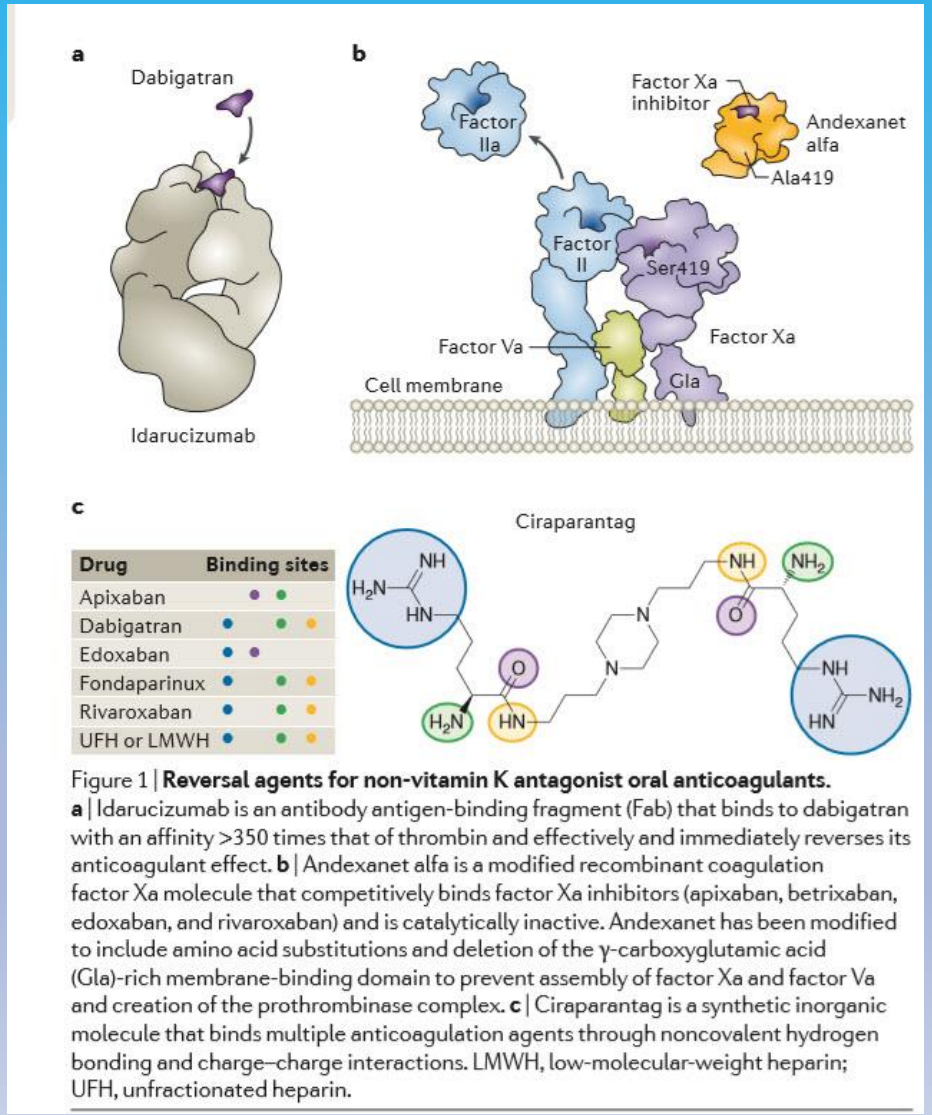
. *Eur Heart J* 2018:Jul 25:

Reversal Agents

- Idarucizumab- Fab fragment binds Dabigitran 350 times that of thrombin
- Andexanet alpha-recombinant modified factor 10a
- Ciraparantag - binds low molecular weight and unfractionated
  - heparin and thrombin and 10a inhibitors.

Reversal mechanisms



Drug	Binding sites
Apixaban	
Dabigatran	
Edoxaban	
Fondaparinux	
Rivaroxaban	
UFH or LMWH	

Figure 1 | **Reversal agents for non-vitamin K antagonist oral anticoagulants.** **a** | Idarucizumab is an antibody antigen-binding fragment (Fab) that binds to dabigatran with an affinity >350 times that of thrombin and effectively and immediately reverses its anticoagulant effect. **b** | Andexanet alfa is a modified recombinant coagulation factor Xa molecule that competitively binds factor Xa inhibitors (apixaban, betrixaban, edoxaban, and rivaroxaban) and is catalytically inactive. Andexanet has been modified to include amino acid substitutions and deletion of the γ-carboxyglutamic acid (Gla)-rich membrane-binding domain to prevent assembly of factor Xa and factor Va and creation of the prothrombinase complex. **c** | Ciraparantag is a synthetic inorganic molecule that binds multiple anticoagulation agents through noncovalent hydrogen bonding and charge–charge interactions. LMWH, low-molecular-weight heparin; UFH, unfractionated heparin.

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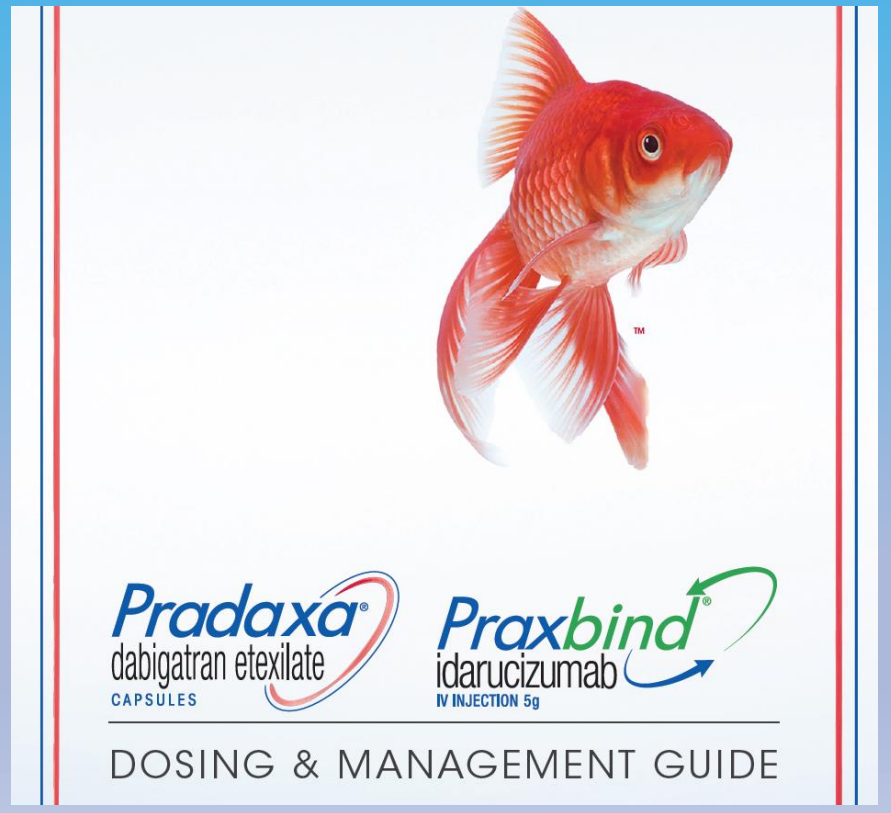
Indarucizumbab-(Praxabind)

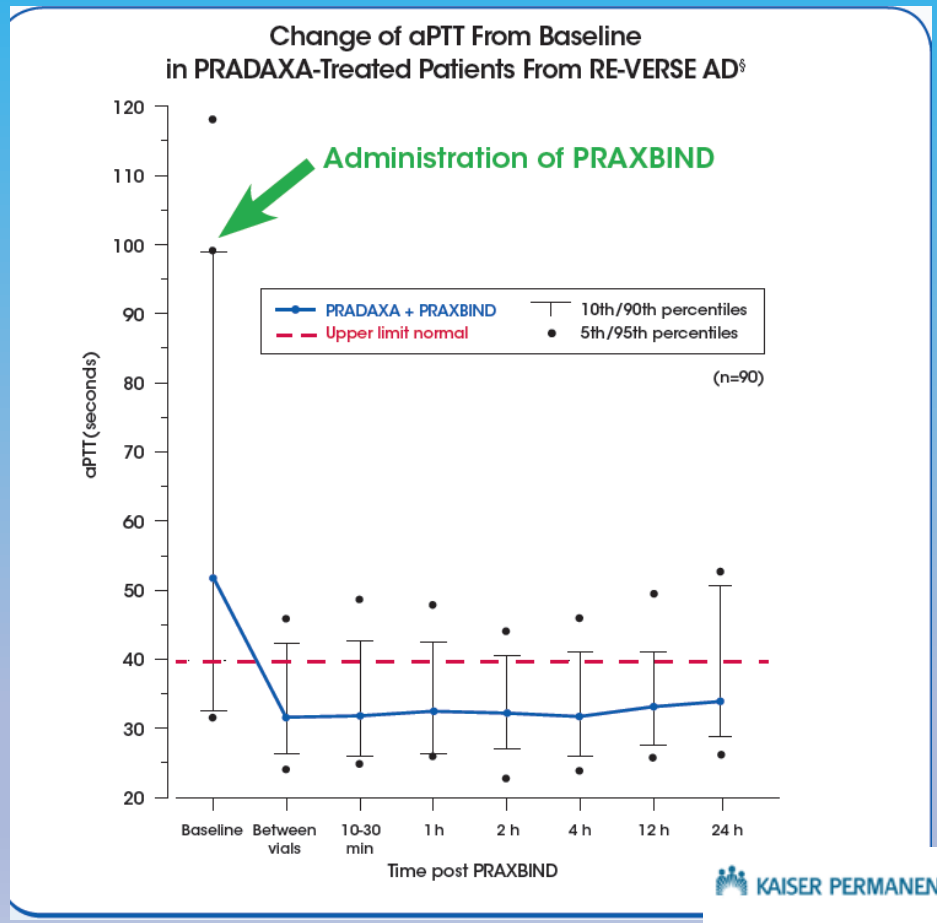
- Indicated for emergency lifethreatening bleeding
- Indicated for emergency surgery
- Administered as 2 2.5 mg infusions

- Can reinitiate Pradaxa after 24 hours



Reverse –AD trial

- Group A serious bleeding , Group B urgent surgery in less than 8 hours
- Median reversal with Praxabind in 4 hours 100%
- Median time to cessation of non cranial bleeding 2.4 hours
- Assessment of normal of coagulation by surgeons at 1.5 hours 94%
- Median time to surgery 1.6 hours.
- 5% thromboembolic event in 30 days



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Pollack, C. V. Jr *et al.* Idarucizumab for dabigatran reversal. *N. Engl. J. Med.* **373**, 511–520 (2015).

FDA approval for factor 10-A inhibitors

Andexanet Alfa, First Reversal Agent for Factor Xa Inhibitors, Finally Gains FDA Approval

The agent is the second antidote approved for the NOACs, joining idarucizumab, dabigatran's reversal agent.

By Todd Neale | May 04, 2018

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Andexanet Alpha

- Indicated for emergent surgery or life threatening bleeding in patient with Apixaban , and Rivaroxaban. (also reverses heparins)
- Recombinant factor (10A)

Table 1: ANDEXXA Dosing Regimens

Dose*	Initial IV Bolus	Follow-On IV Infusion
Low Dose	400 mg at a target rate of 30 mg/min	4 mg/min for up to 120 minutes
High Dose	800 mg at a target rate of 30 mg/min	8 mg/min for up to 120 minutes

*The safety and effectiveness of more than one dose have not been evaluated.

The recommended dosing of ANDEXXA is based on the specific FXa inhibitor, dose of FXa inhibitor, and time since the patient's last dose of FXa inhibitor (see Table 2).

Table 2: ANDEXXA Dose Based on Rivaroxaban or Apixaban Dose (Timing of FXa Inhibitor Last Dose Before ANDEXXA Initiation)

FXa Inhibitor	FXa Inhibitor Last Dose	< 8 Hours or Unknown	≥ 8 Hours
Rivaroxaban	≤ 10 mg	Low Dose	Low Dose
Rivaroxaban	> 10 mg / Unknown	High Dose	
Apixaban	≤ 5 mg	Low Dose	
Apixaban	> 5 mg / Unknown	High Dose	

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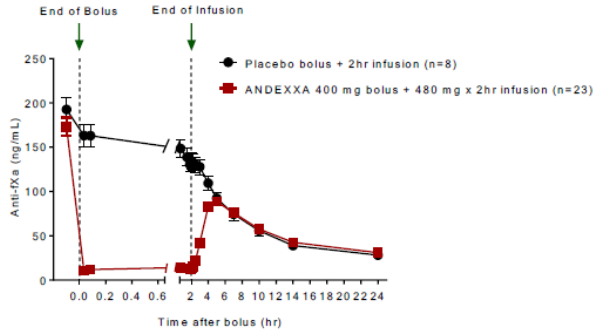
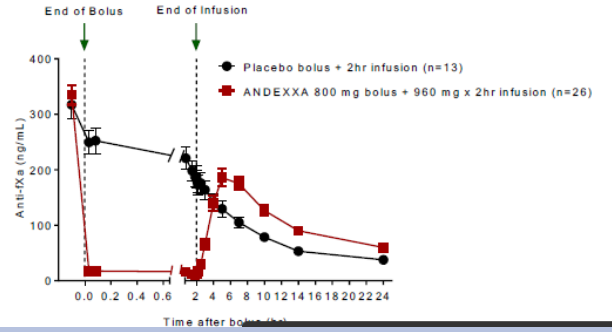
Andexanet Alpha

- Rapid reversal of 10A inhibition with bolus and sustained with infusion
- Recovery of 10A inhibition occurred and peaked 4 hours after infusion, with resolution according to ½ life 10A inhibitor.
- 17.8% of patients with reversal had thrombotic complications.

Figure 1: Change in Anti-FXa Activity (ng/mL) in Subjects Anticoagulated with Apixaban (A – Study 1) and Rivaroxaban (B – Study 2)



(A)



KAISER PERMANENTE

Ciraparantag

- Not FDA approved
- Appears to reverse 10a, IIA(thrombin) and all heparins.
- Phase 1 trial full reversal of Edoxaban in 10 minutes

Price of Reversal

- Indarucizumab – wholesale $4200.00

- Andexanet alpha (Portola)- $58,000.00

Summary Points

- Atrial fibrillation is associated with significant morbidity
- Detection is elevated with prolonged monitoring
- Risk factors correlate with increased risk of Stroke
- NOACS are associated with similar or lower stroke and intracranial bleeding compared to warfarin
  - But higher GI bleeding (Dabigitran, Rivaroxiban)

Summary II

- PRADAXA – may be best choice for Low and High BMI patients (controversial)
- Apixaban – less bleeding than warfarin with dialysis in retrospective evaluation.
- Avoid –combination of P-GP and CYP3a4 inhibitors and inducers with factor 10 a inhibitors
- Avoid – (Ketoconazole) with rivaroxaban, Rivaroxaban, and Dabigatran
- Hold NOAC 24 hours for low , 48 hours for high risk bleeding procedures.
  - Alter hold time based on GFR
- Idaricuzimab – 5 mg for life threatening bleeding with Dabigatran
- Andexanet Alpha- low or high dose for Factor 10 A I with bleeding
  - Low or high base dose on dose and if greater than 8 hours since last dose.

Anticoagulation always has Risks

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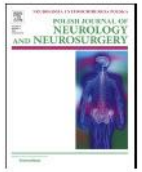

Case report

Fatal consequences of climbing a ladder under apixaban and drunken

Claudia Stöllberger *, *Josef Finsterer*

Krankenanstalt Rudolfstiftung, Wien, Austria

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ABSTRACT

Background: Apixaban, a factor-Xa-inhibitor, is one of the non-vitamin-K-antagonist oral anticoagulants (NOACs) which are increasingly used in atrial fibrillation (AF). In real life even patients with contraindications to vitamin K antagonists (VKAs) receive NOAC because NOAC are considered as "safer" than VKAs.

Case description: In a 61-years-old man with hypertension, heart failure and paroxysmal AF apixaban was started. Despite advices from his physicians, he continued alcohol abuse and suffered from recurrent falls. After 9 months he fell from a ladder and suffered from extensive subarachnoidal and intraparenchymal hemorrhages, subdural hematoma, brain edema with midline shift and a left-sided skull fracture. Because of the inability to reverse the anticoagulant therapy, no neurosurgical intervention was carried out and the patient died without regaining consciousness.

Conclusions: Patients with recurrent falls or chronic alcohol abuse should not be considered as candidates for NOACs. If anticoagulation is deemed necessary, VKA with its potential for prompt reversibility should be favored.

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1. Introduction

Apixaban, a factor-Xa-inhibitor, is one of the non-vitamin-K-antagonist oral anticoagulants (NOACs) which are increasingly

patients nonetheless receive NOACs because NOACs are considered as "safer" than VKAs.

2. Case report

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Risk can only be mitigated not eliminated

P- GP and Dabigatran

- Rifampin reduces exposure to Dabigatran and should be avoided
- P-GP inbitors amiodarone, Verapamil ,quinidine and clarithromycin
  - Do not require Dabigatran dose adjustment