14th Venice Arrhythmias October 16-18 2015

STROKE PREVENTION IN ATRIAL FIBRILLATION

Tailoring the oral acticoagulant to the individual patient - warfarin and NOACs

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MY CONFLICTS OF INTEREST ARE

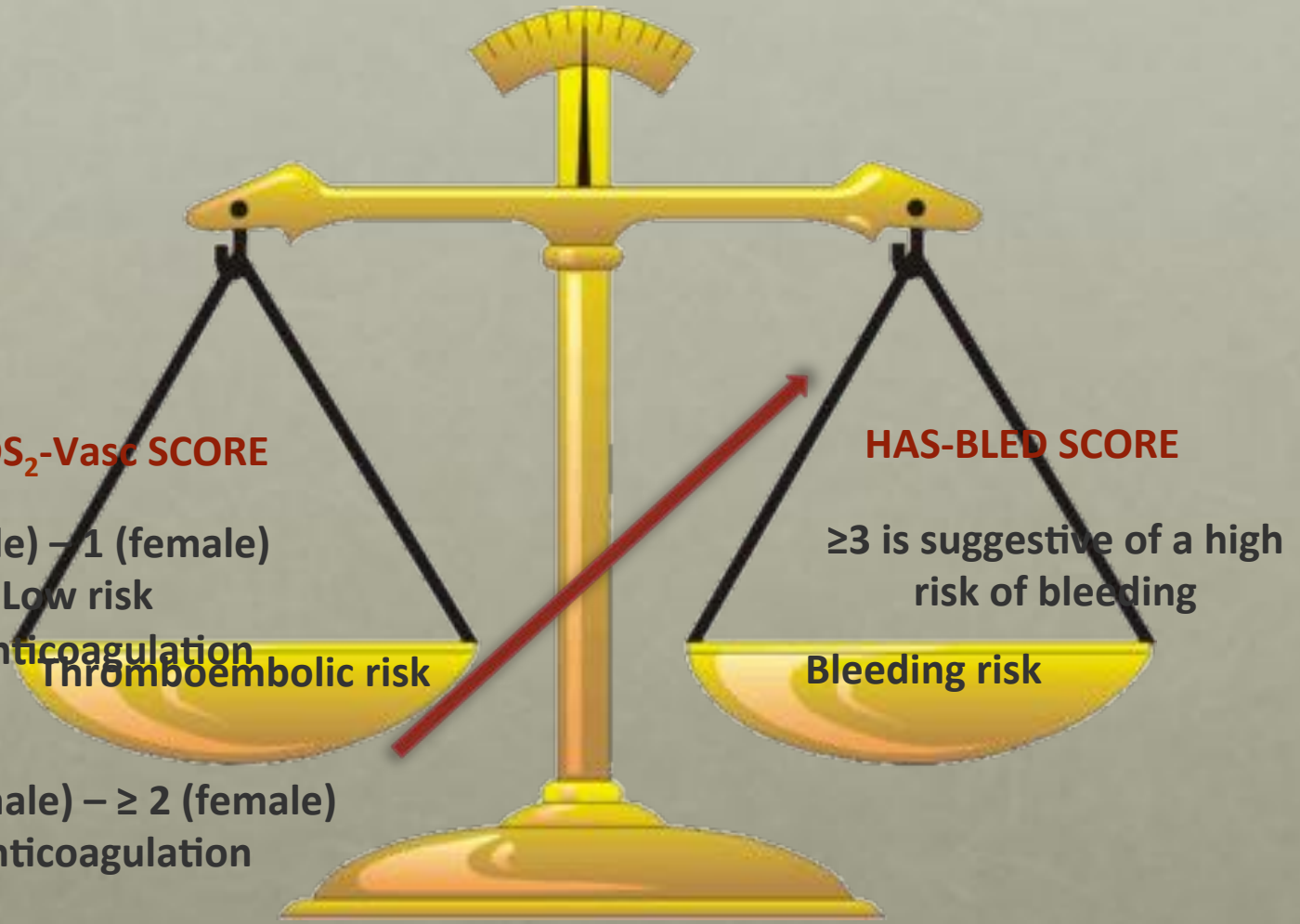
Boehringer Ingelheim

Starting Point

1. Should a patient with AF start anticoagulation treatment for thrombophylaxis?

2. Which anticoagulant should be used?

Starting Point



Overestimation of bleeding risk is a major barrier to anticoagulant therapy

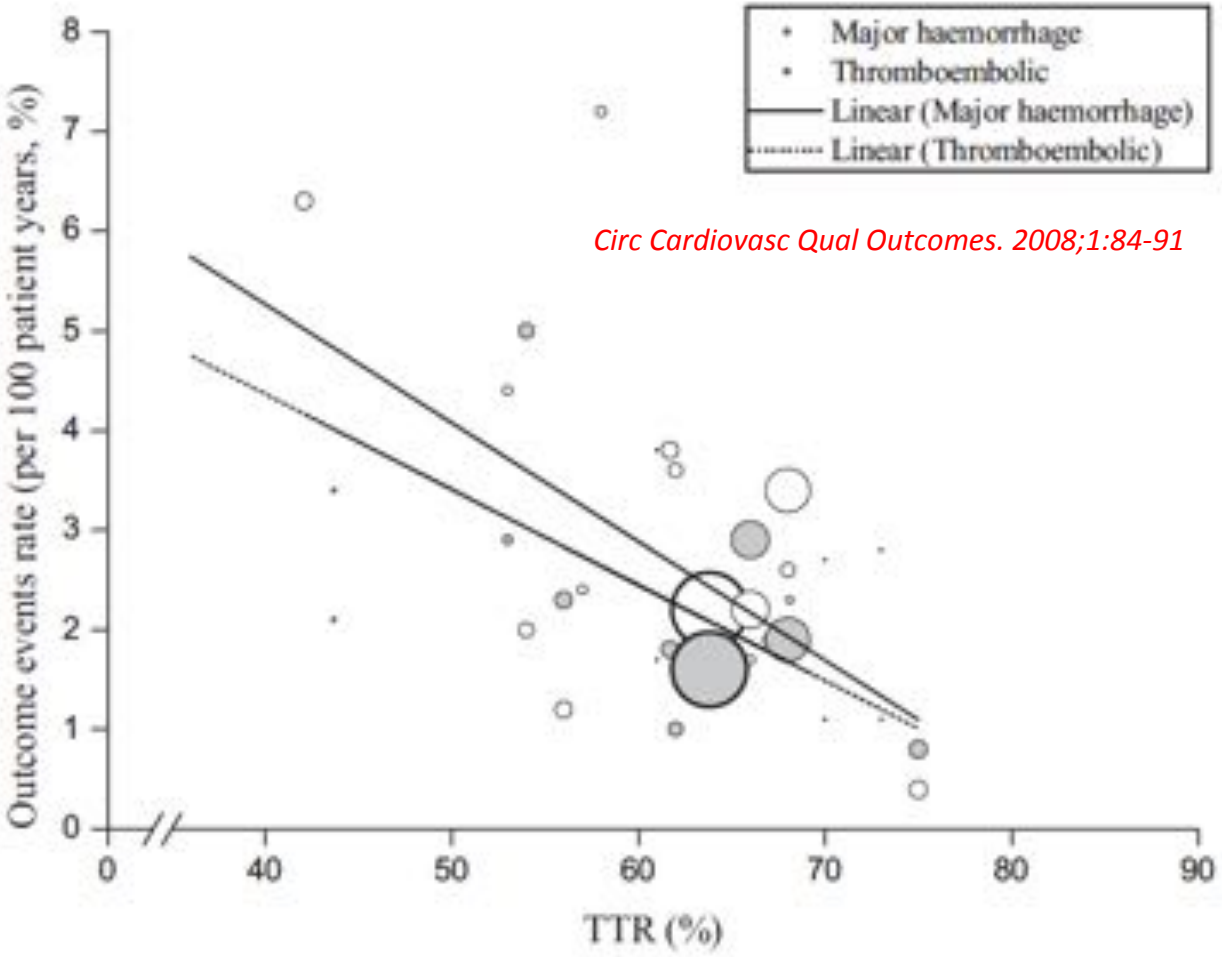
Anticoagulation Control and Prediction of Adverse Events in Patients With Atrial Fibrillation

A Systematic Review

Yi Wan, MSc; Carl Heneghan, MA, MRCGP; Rafael Perera, DPhil; Nia Roberts, MSc; Jennifer Hollowell, PhD; Paul Glasziou, PhD, FRACGP; Clare Bankhead, DPhil; Yongyong Xu, PhD

Assess

can



Circ Cardiovasc Qual Outcomes. 2008;1:84-91

Poor control of anticoagulation correlated with increased bleeding an thromboembolic risk

Warfarin treatment in patients with atrial fibrillation: observing outcomes associated with varying levels of INR control.

- Significant improvement in time to stroke event in patients with INR control of greater than 70% of time in therapeutic range (2.0 to 3.0) compared with the non-warfarin treatment group.

- Overall survival was significantly improved for all warfarin treated groups with INR control of greater than 40% of time in range.

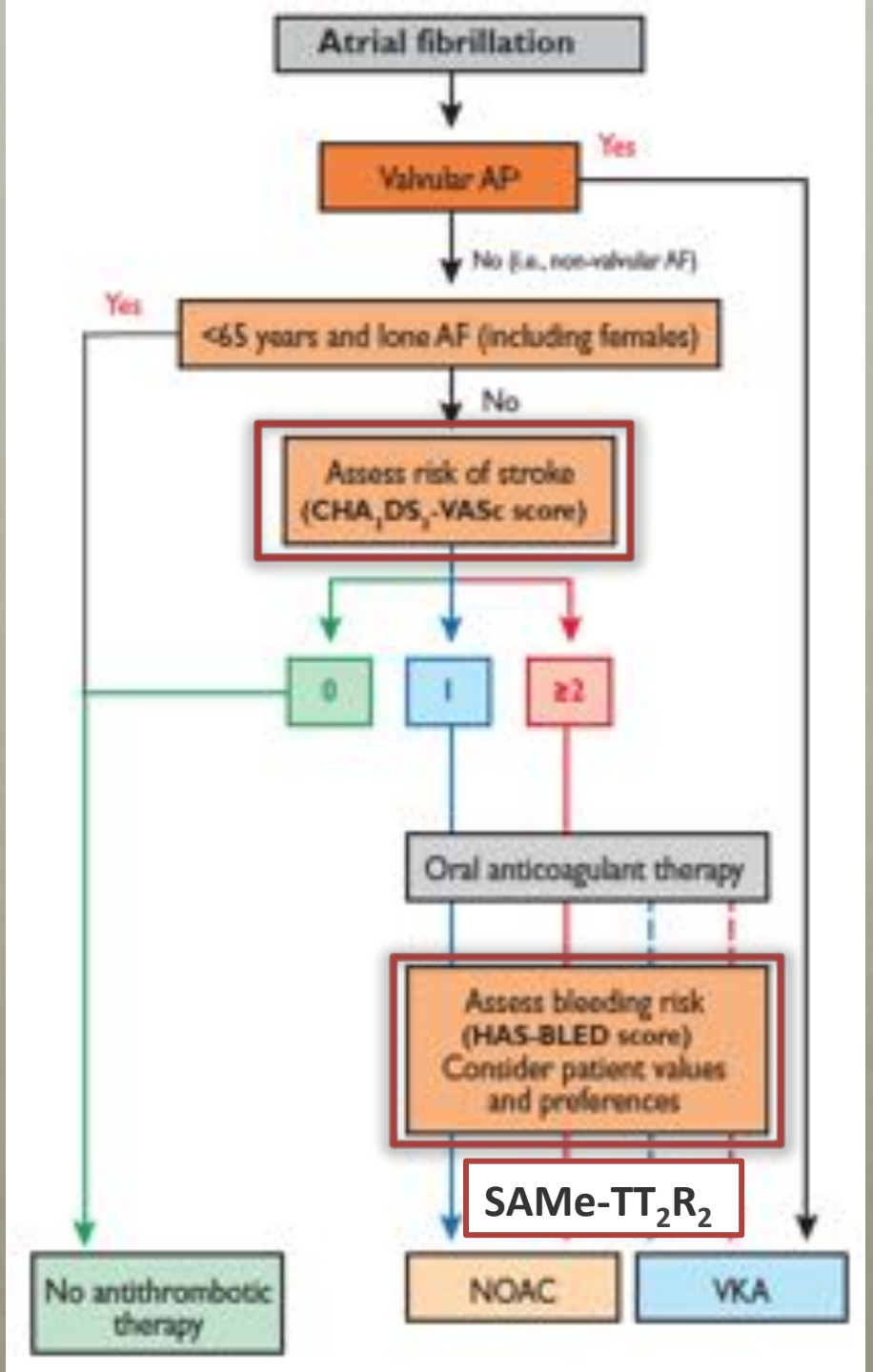
Morgan et al. Thromb Res. 2009 May;124(1):37-41

SAMe-TT_2R_2 has a significant, although moderate, ability to identify patients with a poor anticoagulation control under VKA (time-in-therapeutic range of <65%).

• Sex	1
• Age (< 60 years)	1
• Medical history	1
• Treatment	1
• Tobacco use within 2 years	2
• Race (non-Caucasian)	2

0-2 Warfarin
> 2 NOAC

ESC guidelines 2012



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

An update of the 2010 ESC Guidelines for the management of atrial fibrillation
Developed with the special contribution of the European Heart Rhythm Association

The **NOACs** so far tested in clinical trials have all shown non inferiority compared with VKAs, with better safety, consistently limiting the number of ICH. On this basis, this guideline now recommends them as broadly preferable to VKA in the vast majority of patients with non-valvular AF.

Indirect comparison analyses do not suggest profound differences in efficacy endpoints between the NOACs, but major bleeding appears lower with dabigatran 110mg b.i.d. and apixaban.

Choise of anticoagulant

- Drug Indication
- Patient's characteristics
  - Age
  - Weight
  - Race
- Concomitant disease
- Concomitant medications
- Compliance

Drugs

- **Warfarin**

Direct thrombin inhibitor

- **Dabigatran**

Activated factor Xa inhibitor

- **Rivaroxaban**
- **Apixaban**
- **Edoxaban**

NOAC advantages

- predictable effect
- no need for monitoring fewer food and drug interactions
- shorter plasma half-life
- improved efficacy/safety ratio

NOAC Indication

Non-valvular AF refers to AF that occurs in the absence of ***mechanical prosthetic heart valves*** and in the absence of ***moderate to severe mitral stenosis*** (usually of rheumatic origin). Both types of patients were excluded from all NOAC trials.

Table I Valvular indications and contraindications for NOAC therapy in AF patients

	Eligible	Contra-indicated
Mechanical prosthetic valve		✓
Moderate to severe mitral stenosis (usually of rheumatic origin)		✓
Mild to moderate other native valvular disease	✓	
Severe aortic stenosis	✓ Limited data. Most will undergo intervention	
Bioprosthetic valve[a]	✓ (except for the first 3 months post-operatively)	
Mitral valve repair[a]	✓ (except for the first 3–6 months post-operatively)	
PTAV and TAVI	✓ (but no prospective data; may require combination with single or double antiplatelets: consider bleeding risk)	
Hypertrophic cardiomyopathy	✓ (but no prospective data)	

Warfarin

Bioprosthetic valve

Clinical characteristics and outcomes with rivaroxaban vs. warfarin in patients with non-valvular atrial fibrillation but underlying native mitral and aortic valve disease participating in the ROCKET AF trial

Similar efficacy findings of NOAC vs. VKA, although bleeding rates with **rivaroxaban** were higher than with VKA in patients with valvular disease, and the rate of systemic embolism (not stroke) was marginally higher with rivaroxaban.

Breithardt G et al.Eur Heart J 2014;35:3377–85.

ef

Ezekowitz et al. J Am Coll Cardiol 2014;63(12, Supplement):A325

–32

Choise of anticoagulant

Kidney function

CrCl < 15mL/min

Activated factor Xa inhibitors are not recommended

CrCl < 30mL/min

Direct thrombin inhibitor is not recommended

Prospective data are not available in end-stage CKD patients, either with VKA, or with NOAC

Efficacy and Safety of Vitamin K-Antagonists (VKA) for Atrial Fibrillation in Non-Dialysis Dependent Chronic Kidney Disease

Table 3. Time within therapeutic range and INR variability within the entire population of 724 patients with atrial fibrillation.

	No CKD	Moderate CKD	P-value comparison	Severe CKD	P-value comparison	P-value comparison with
	eGFR>60 ml/min	eGFR 30-60 ml/min	with no CKD patients	eGFR<30 ml/min	with no CKD patients	moderate CKD patients
Time spend within therapeutic range, %						
First six weeks of VKA therapy	39.4(13.2-75.5)	49.7(24.1-81.3)	0.01	44.1(26.4-77.9)	0.10	0.60
First eighteen weeks of VKA therapy	57.9(29.8-79.3)	65.5(42.1-83.9)	0.01	60.7(39.4-80.6)	0.37	0.19
First twenty-six weeks of VKA therapy	61.5(38.7-79.8)	67.1(46.7-82.4)	0.02	64.3(41.5-75.6)	0.92	0.07
Entire treatment period	67.0(43.1-81.1)	75.1(57.8-82.9)	<0.01	70.3(49.2-81.1)	0.41	0.10
Time under target range (entire treatment), %	8.7(2.6-35.5)	6.2(2.1-13.0)	<0.001	5.5(2.3-12.9)	0.001	0.77
Time above target range (entire treatment), %	11.7(3.9-21.2)	15.2(9.8-24.0)	<0.001	20.8(11.7-32.7)	<0.001	<0.01
INR variability (2.5-97.5 percentiles)						
First six weeks of VKA therapy	0.5(0.1-1.6)	0.6(0.2-1.6)	0.10	0.7(0.4-2.5)	0.001	0.03
First eighteen weeks of VKA therapy	0.4(0.2-1.3)	0.6(0.2-1.5)	0.08	0.8(0.4-1.8)	<0.001	0.01
First twenty-six weeks of VKA therapy	0.5(0.3-1.2)	0.7(0.4-1.2)	0.24	0.8(0.4-1.8)	<0.001	<0.01
Entire treatment period	0.5(0.3-1.2)	0.7 (0.4-1.2)	0.03	0.9(0.5-1.8)	<0.001	<0.01

Data are presented as median, (interquartile range). P-values were computed using Mann-Whitney test, after proof of significant differences between groups using a Kruskal-Wallis test.
CKD = chronic kidney disease, VKA = vitamin K-antagonists, eGFR = estimated glomerular filtration rate, INR = international normalized ratio.
doi:10.1371/journal.pone.0094420.t003

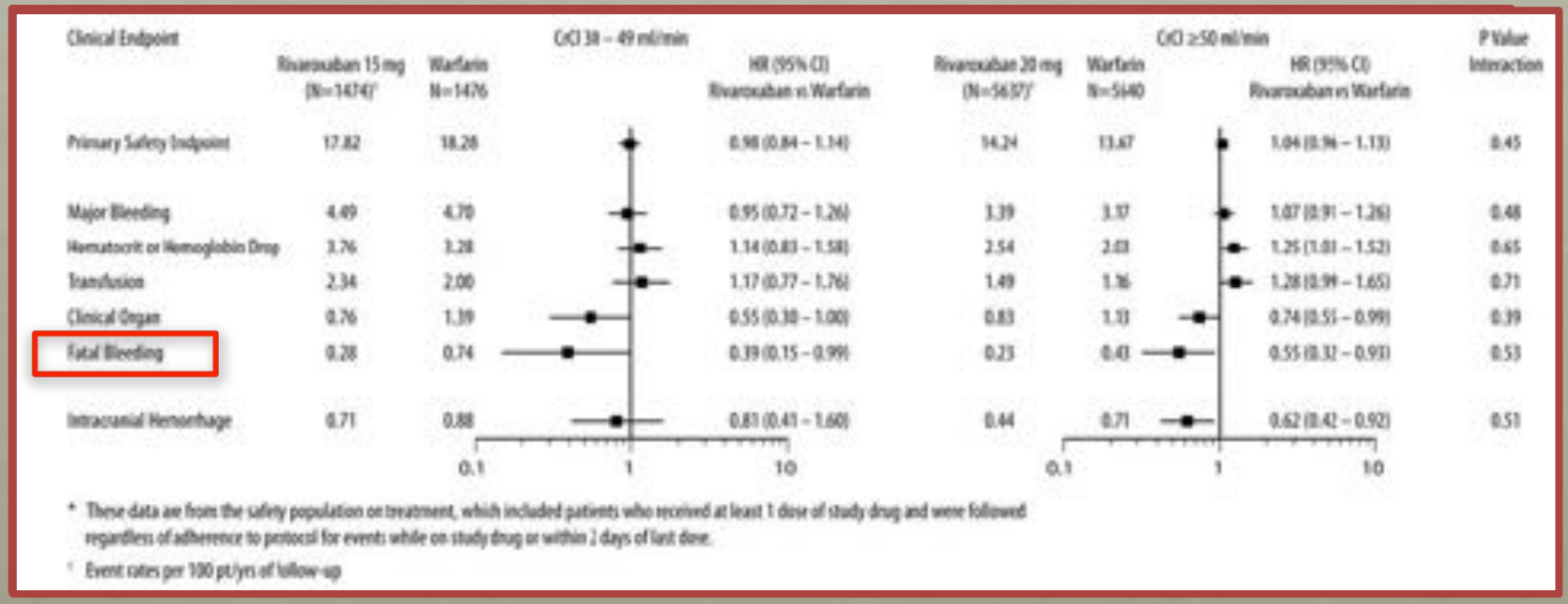
VKA treatment for AF in patients with severe CKD has a poor safety and efficacy profile, likely related to suboptimal anticoagulation control.

Kooiman et al. PLoS One. 2014 May 9;9(5):e94420

CKD and NOAC

	Dabigatran	Apixaban	Edoxaban ?	Rivaroxaban
Fraction renally excreted of absorbed dose	80%	27%	50%	35%
Bioavailability	3–7%	50%	62%	66% without food Almost 100% with food
Fraction renally excreted of administered dose	4%	12–29%	37%	33%
Approved for CrCl ≥ …	≥30 mL/min	≥15 mL/min	≥15 mL/min	≥15 mL/min
Dosing recommendation	CrCl ≥ 50 mL/min: no adjustment (i.e. 150 mg BID)	Serum creatinine ≥1.5 mg/dL: no adjustment (i.e. 5 mg BID)	CrCl ≥ 50 mL/min: no adjustment (i.e. 60 mg OD)	CrCl ≥ 50 mL/min: no adjustment (i.e. 20 mg OD)
Dosing if CKD	When CrCl 30–49 mL/min, 150 mg BID is possible (SmPC) but 110 mg BID should be considered (as per ESC guidelines) Note: 75 mg BID approved in US only If CrCl 15–30 mL/min If CrCl 30–49 mL/min and other orange factor Table 6 (e.g. verapamil)	CrCl 15–29 mL/min: 2.5 mg BID If two-out-of-three: serum creatinine ≥1.5 mg/dL, age ≥80 years, weight ≤60 kg 2.5 mg BID	30 mg OD when CrCl 15–49 mL/min	15 mg OD when CrCl 15–49 mL/min
Not recommended if	CrCl < 30 mL/min	CrCl < 15 mL/min	CrCl < 15 mL/min	CrCl < 15 mL/min

Prevention of stroke and systemic embolism with rivaroxaban compared with warfarin in patients with non-valvular atrial fibrillation and moderate renal impairment



Clinical Endpoint	CrCl 30 – 49 ml/min			CrCl ≥50 ml/min			P Value Interaction
	Rivaroxaban 15 mg (N=1474)*	Warfarin N=1476	HR (95% CI) Rivaroxaban vs Warfarin	Rivaroxaban 20 mg (N=5637)*	Warfarin N=5640	HR (95% CI) Rivaroxaban vs Warfarin	
Primary Safety Endpoint	17.82	18.26	0.98 (0.84 – 1.14)	14.24	13.67	1.04 (0.96 – 1.13)	0.45
Major Bleeding	4.49	4.70	0.95 (0.72 – 1.26)	3.39	3.37	1.07 (0.91 – 1.26)	0.48
Hematocrit or Hemoglobin Drop	3.76	3.28	1.14 (0.83 – 1.58)	2.54	2.03	1.25 (1.01 – 1.52)	0.65
Transfusion	2.34	2.00	1.17 (0.77 – 1.76)	1.49	1.16	1.28 (0.99 – 1.65)	0.71
Clinical Organ	0.76	1.39	0.55 (0.30 – 1.00)	0.83	1.13	0.74 (0.55 – 0.99)	0.39
Fatal Bleeding	0.28	0.74	0.39 (0.15 – 0.99)	0.23	0.43	0.55 (0.32 – 0.93)	0.53
Intracranial Hemorrhage	0.71	0.88	0.81 (0.41 – 1.60)	0.44	0.71	0.62 (0.42 – 0.92)	0.51

0.1 1 10 0.1 1 10

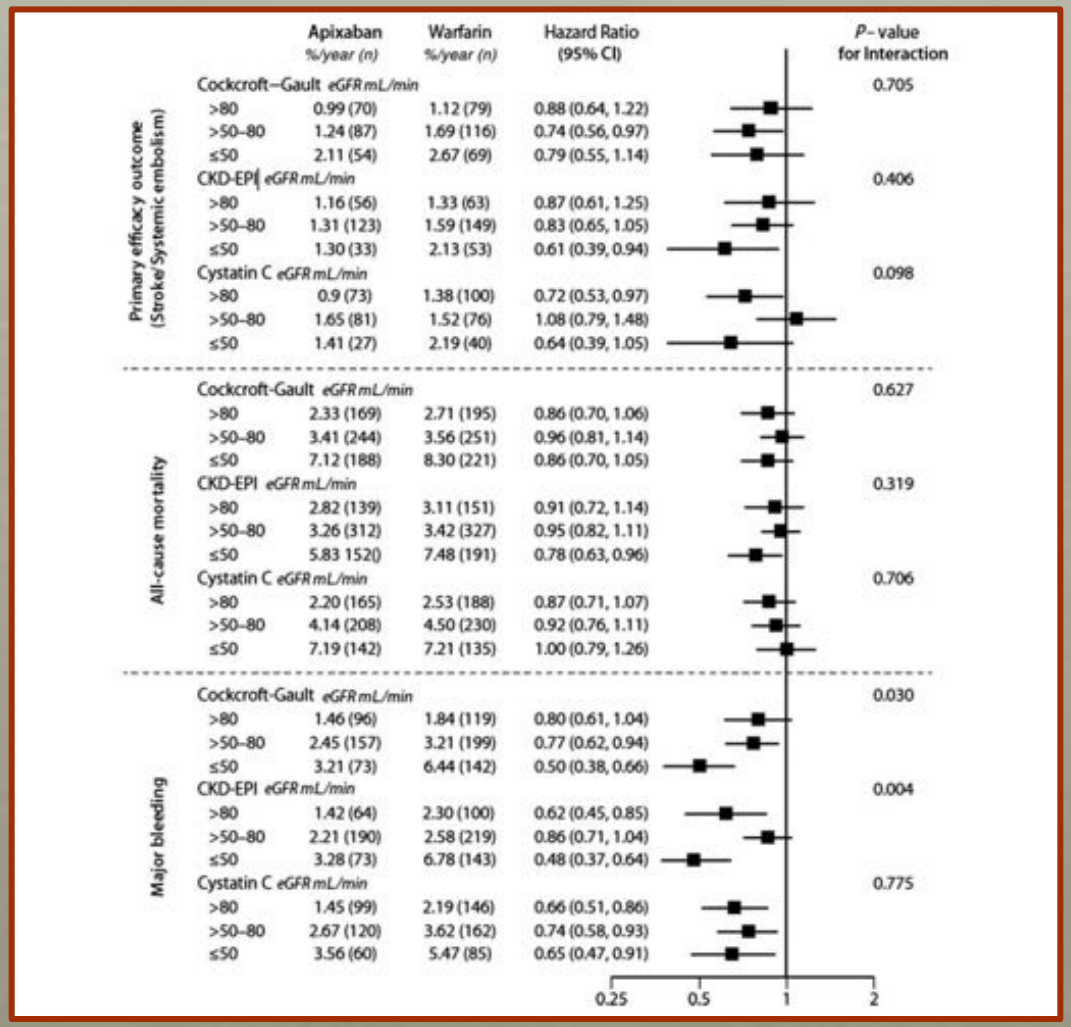
* These data are from the safety population on treatment, which included patients who received at least 1 dose of study drug and were followed regardless of adherence to protocol for events while on study drug or within 2 days of last dose.

† Event rates per 100 pt/yrs of follow-up

Rivaroxaban preserved the benefit of warfarin in preventing stroke and systemic embolus, and produced lower rates while on treatment. Bleeding rates with the reduced dose of rivaroxaban were similar to those on warfarin therapy, and there were fewer fatal bleeds with rivaroxaban.

European Heart Journal (2011) 32, 2387–2394

Efficacy of apixaban when compared with warfarin in relation to renal function in patients with atrial fibrillation: insights from the ARISTOTLE trial



Apixaban may be particularly suited to address the unmet need for a more effective and safe stroke prevention in patients with AF and renal dysfunction.

European Heart Journal (2012) 33, 2821–2830

Renal function and non-vitamin K oral anticoagulants in comparison with warfarin on safety and efficacy outcomes in atrial fibrillation patients: a systemic review and meta-regression analysis.

Five studies comprising **72,845** AF patients randomised to either a NOAC or warfarin were included in the meta-regression analysis.

- Non-vitamin K oral anticoagulants had ***similar efficacy and safety*** compared to warfarin across different levels of renal function.
- Indirect comparisons suggest that ***apixaban*** and ***edoxaban*** were associated with a *better safety profile* in patients with moderate renal impairment.
- Prescribers should fit the most appropriate NOAC to the AF patient characteristics (and vice versa) to individualise effective stroke prevention.

Clin Res Cardiol. 2015 May;104(5):418-29

Elderly Patients

Birmingham Atrial Fibrillation Treatment of the Aged (BAFTA) trial

Warfarin significantly reduces the incidence of stroke, systemic embolism or intracranial haemorrhage versus aspirin
(RR 0.48, 95% CI 0.28–0.80; P = 0.003).

Lancet 2007; 370: 493–503

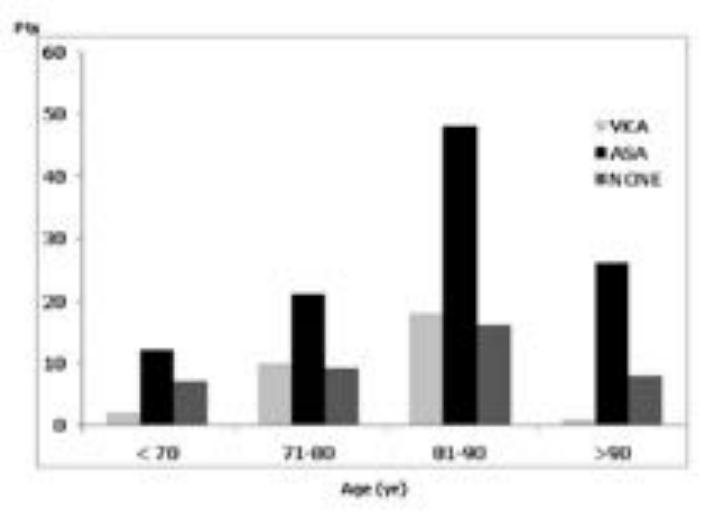
Anticoagulation and Risk Factors In Atrial Fibrillation (ATRIA) study

The net clinical benefit of well-controlled warfarin therapy increases with age.

Ann Intern Med 2009; 151: 297–305.

Stroke/Thromboembolism and Intracranial Hemorrhage in a Real-world Atrial Fibrillation Population

The Complications of Atrial Fibrillation in the Bologna Area (CAFBO) Study



- Among the patients who presented with **IE** **82.6%** were treated with ASA or did not receive any antithrombotic therapy.
- **65%** of the **ICH** events recieved VKA treatment with INR in therapeutic range in 84%.

Elderly subjects with AF should be treated with well-monitored VKA anticoagulation or possibly the novel oral anticoagulants, because antiplatelet drugs were markedly less eff ective and at least equally associated with the risk for ICH.

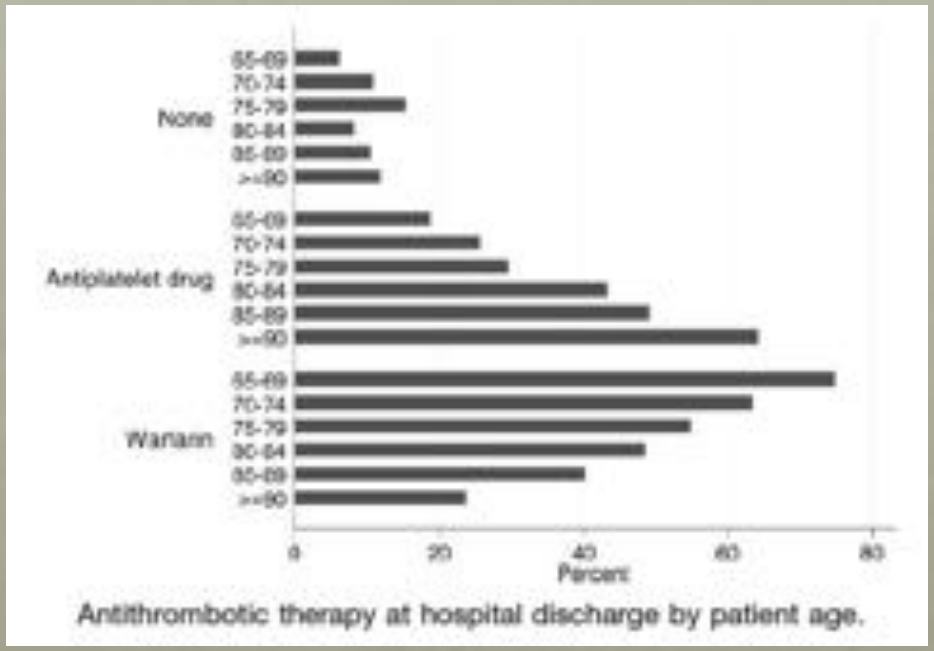
CHEST 2014; 146(4): 1073 - 1080

Translating the Results of Randomized Trials into Clinical Practice

The Challenge of Warfarin Candidacy Among Hospitalized Elderly Patients With Atrial Fibrillation

TABLE 3. Physician-Cited Reason for Not Prescribing Warfarin, Stratified by Patient Age

Reason	All, n=199*	<80 Years, n=76	≥80 Years, n=123
Hemorrhage, n (%)	66 (33)	32 (42)	34 (28)
Recurrent bleeding	31 (16)	17 (22)	14 (11)
Current bleeding	16 (8)	7 (9)	9 (7)
Past intracranial bleeding	9 (4)	3 (4)	6 (5)
Past other bleeding	10 (5)	5 (7)	5 (4)
Falls	64 (32)	14 (18)	50 (41)
Patient refused or history of nonadherence	27 (14)	13 (17)	14 (11)
Cognitive impairment	6 (3)	1 (1)	5 (4)
Active alcohol abuse	4 (2)	4 (5)	0
Advanced illness, comfort care	16 (8)	4 (5)	12 (10)
Other†	16 (8)	8 (11)	8 (7)



Antithrombotic therapy at hospital discharge by patient age.

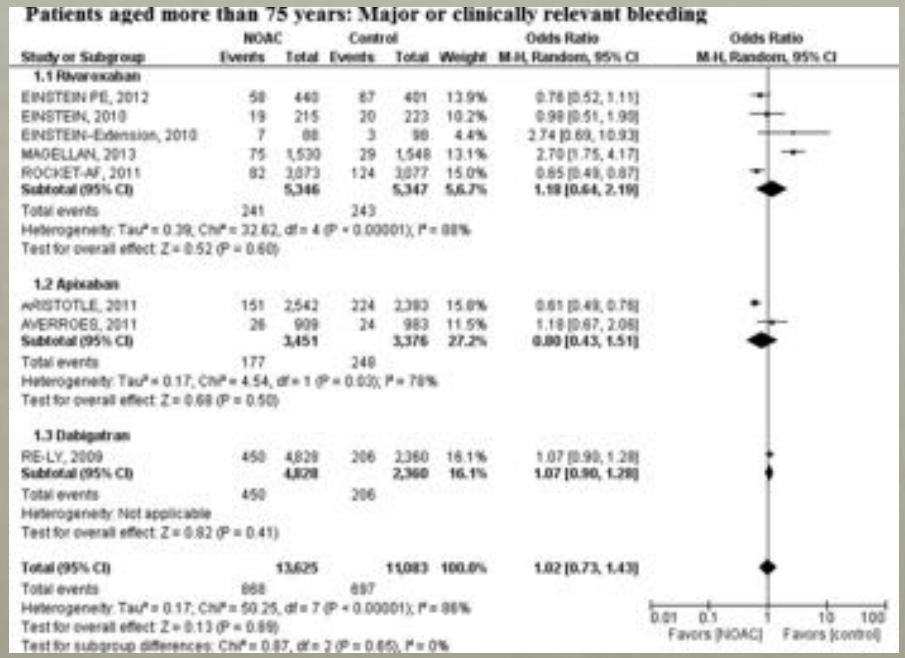
Stroke. 2006;37:1075-1080

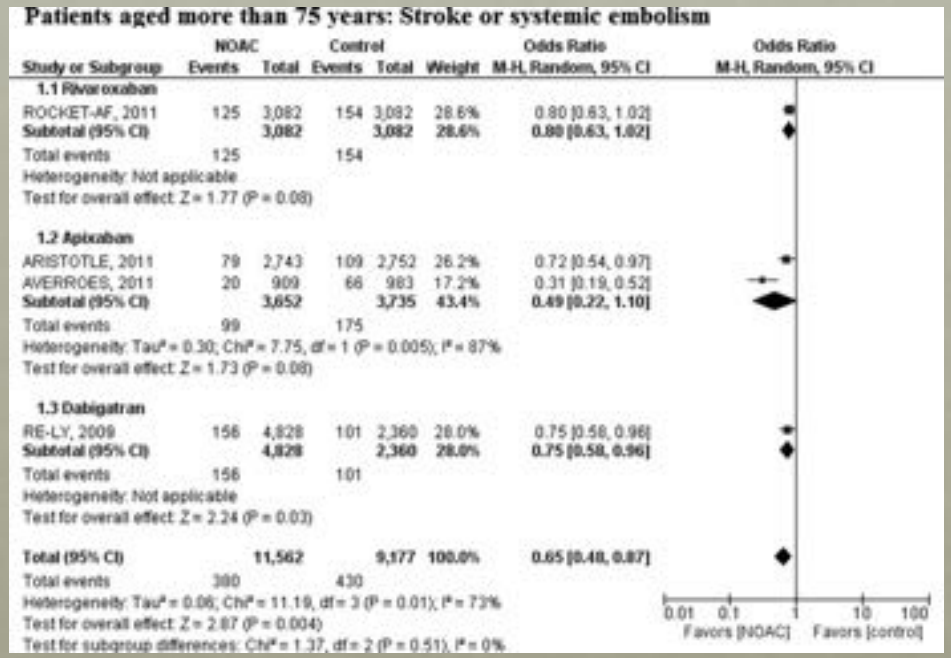
Choosing Antithrombotic Therapy for Elderly Patients With Atrial Fibrillation Who Are at Risk for Falls

"Given that the risk of subdural hematomas must be 535-fold or greater for the risks of warfarin therapy to outweigh the benefits, ***persons taking warfarin must fall about 295 (535/1.81) times in 1 year for warfarin to not be the optimal therapy***."

Arch Intern Med 1999; 159: 677–85

New Oral Anticoagulants in Elderly Adults: Evidence from a Meta-Analysis of Randomized Trials





NOACs were not associated with any increase in major or clinical relevant bleeding events in patients over 75 years of age

J Am Geriatr Soc. 2014 May;62(5):857-64

High bleeding risk

- Dabigatran
  low-dose (RR 0.80, 95% CI 0.69–0.93; P = 0.003)
- Apixaban
  high dose (RR 0.69, 95% CI 0.60–0.80; P < 0.001)
- Edoxaban
  high dose (RR 0.80, 95% CI 0.70–0.91; P < 0.001)
  low dose (RR 0.47, 95% CI 0.41–0.55; P < 0.001)

All have demonstrated a significant reduction of major haemorrhage compared to warfarin.

Dabigatran high-dose and Rivaroxaban were equivalent to Warfarin

Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials

42,411 pts NOAC and 29,272 VKA

- Reduction of stroke or systemic embolic (RR 0·81, 95% CI 0·73-0·91; p<0·0001), mainly driven by a reduction in haemorrhagic stroke (0·49, 0·38-0·64; p<0·0001).
- NOACs significantly reduced all-cause mortality (0·90, 0·85-0·95; p=0·0003) and intracranial haemorrhage (0·48, 0·39-0·59; p<0·0001)
- NOACs increased gastrointestinal bleeding (1·25, 1·01-1·55; p=0·04)

Low-dose NOAC regimens showed:
similar overall reductions in stroke or systemic embolic events to warfarin
(1·03, 0·84-1·27; p=0·74)
a more favourable bleeding profile
(0·65, 0·43-1·00; p=0·05)
significantly more ischaemic strokes
(1·28, 1·02-1·60; p=0·045).

Lancet. 2014 Mar 15;383(9921):955-62

Edoxaban in the Evolving Scenario of Non Vitamin K Antagonist Oral Anticoagulants Imputed Placebo Analysis and Multiple Treatment Comparisons

Table 2. Weighted Average Effects of New Oral Anticoagulants Versus Warfarin.

		Major Bleeding	Intracranial Bleeding	Gastrointestinal Bleeding
Edoxaban 30 mg vs.	*Dabigatran 110 mg bid*	**0.581 (0.47–0.719) p<0.001**	1.033 (0.592–1.803) p = 0.909	**0.626 (0.443–0.884) p = 0.008**
	Dabigatran 150 mg bid	**0.498 (0.404–0.614) p<0.001**	0.740 (0.441–1.243) p = 0.255	**0.465 (0.334–0.649) p<0.001**
	Rivaroxaban 20 mg qd	**0.454 (0.368–0.56) p<0.001**	**0.47 (0.288–0.767) p = 0.003**	**0.421 (0.308–0.575) p<0.001**
	Apixaban 5 mg qd	**0.672 (0.544–0.829) p<0.001**	0.729 (0.451–1.177) p = 0.196	0.768 (0.543–1.087) p = 0.137
Edoxaban 60 mg vs.	*Dabigatran 110 mg bid*	0.979 (0.802–1.194) p = 0.831	1.539 (0.907–2.611) p = 0.11	1.142 (0.824–1.581) p = 0.426
	Dabigatran 150 mg bid	0.839 (0.691–1.02) p = 0.078	1.103 (0.677–1.797) p = 0.695	0.849 (0.621–1.16) p = 0.303
	Rivaroxaban 20 mg qd	**0.764 (0.628–0.93) p = 0.007**	0.700 (0.443–1.107) p = 0.127	0.768 (0.575–1.026) p = 0.074
	Apixaban 5 mg qd	1.131 (0.929–1.377) p = 0.22	1.086 (0.695–1.697) p = 0.718	**1.400 (1.009–1.944) p = 0.044**

Only endpoints available in all studies are reported. NOAC = new oral anticoagulant drug; BID = twice daily; OD = once daily; CI = confidence interval; OR = odds ratio.

doi:10.1371/journal.pone.0100478.t002

The better safety profile in terms of major bleedings compared to all other NOACs, and of gastrointestinal bleedings compared to dabigatran and rivaroxaban, would make the lower dose of edoxaban a reasonable option in patients with high or very high risk of bleeding.

PLoS One. 2014 Jun 23;9(6):e100478

CORONARY ARTERY DISEASE

- In all four trials comparing NOACs to warfarin in patients with AF, concurrent aspirin use was associated with higher incidence of major haemorrhage regardless of the treatment arm.
- However, the incidence of major haemorrhage when a NOAC was co-administered with aspirin was consistently lower than that seen with warfarin.

There is no published randomized study comparing VKAs and NOACs in pts with AF undergoing PCI for acute coronary syndromes (ACSs) or for stable CAD, i.e. patients who have an indication to receive single or DAPT.

CORONARY ARTERY DISEASE

- **Triple therapy with DAPT and NOACs at least doubles the risk of major bleeding after an ACS.**

- There are currently three **ongoing large-scale outcome studies** evaluating combinations of NOAC or VKA and antiplatelets in patients with AF that undergo a PCI with stenting (elective or due to an ACS):

  - *The PIONEER AF PCI study (rivaroxaban)*
  - *The RE-DUAL PCI study (dabigatran)*
  - *AUGUSTUS trial (apixaban)*
  - *EVOLVE-AF-PCI (edoxaban)*

Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation

"Awaiting ongoing trials, it might be assumed that the respective advantages of the NOAC over VKA are maintained in dual or triple therapy."

Risk of Stroke or Systemic Embolism in Atrial Fibrillation Patients Treated With Warfarin

A Systematic Review and Meta-analysis

Ida Ehlers Albertsen, BSc; Lars Hvilsted Rasmussen, MD, PhD; Thure Filskov Overvad, BSc; Tina Graungaard, MSc; Torben Bjerregaard Larsen, MD, PhD; Gregory Y.H. Lip, MD

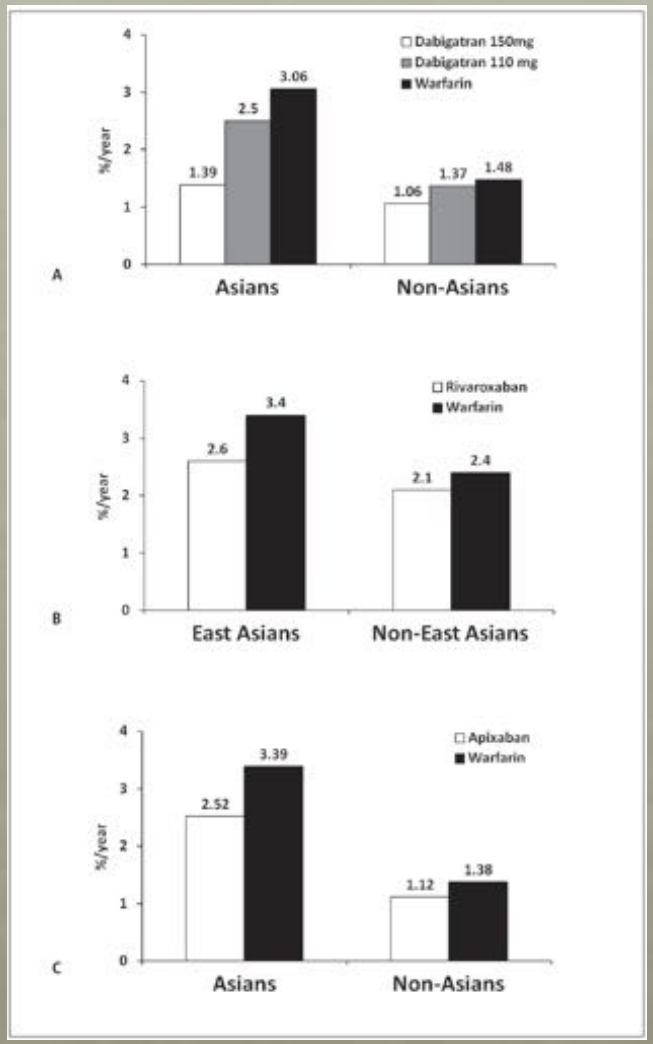
Table 2. Event Rates per 100 Person-Years (95% CI) of Stroke or Systemic Embolism in the Warfarin Arm Across Trials Stratified by Subgroups

Subgroup	SPORTIF III/V,[11,13]	BAFTA,[14]	RE-LY,[15]	ROCKET-AF,[16]	ARISTOTLE,[17]	Pooled Estimate (95% CI)		
						Event Rate	Relative Risk	*P* Value
Race								
America	NA	NA	1.55 (1.22–1.93)	2.19 (1.77–2.68)	1.51 (1.24–1.82)	1.72 (1.34–2.10)	1 [Reference]	
Europe	NA	NA	1.28 (0.98–1.66)	2.20 (1.87–2.57)	1.10 (0.92–1.46)	1.52 (0.87–2.17)	0.88 (0.75–1.04)	0.123
Asia	NA	NA	2.97 (2.23–3.86)	2.69 (2.03–3.52)	3.10 (2.42–3.79)	2.93 (2.51–3.34)	1.70 (1.42–2.03)	<0.001
Other	NA	NA	2.27 (1.28–3.64)	NA	NA	2.27 (1.17–3.39)	1.45 (0.86–2.45)	0.166

Stroke. 2013;44:1329-1336

Stroke prevention in atrial fibrillation: An Asian perspective

Chern-En Chiang[1]; Kang-Ling Wang[1]; Gregory Y. H. Lip[2]



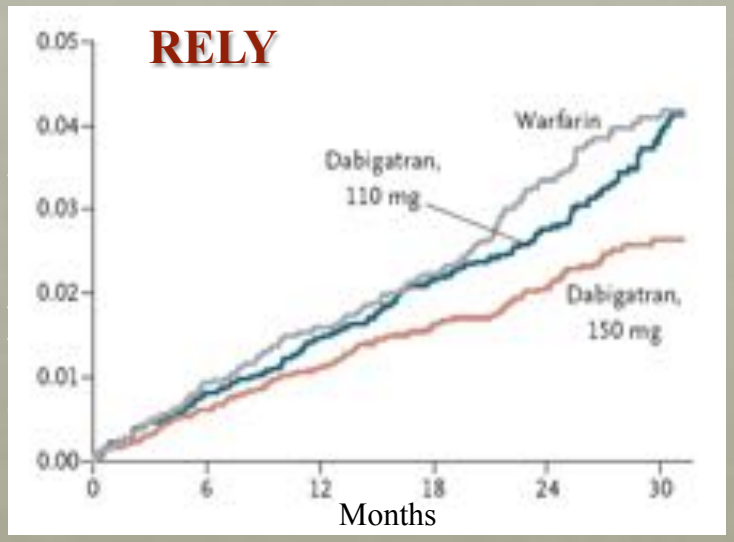
	Asians	Non-Asians
RE-LY		
TTR (INR=2.0–3.0)	56.5%	68.9%
INR<2.0	30.8%	15.4%
INR>3.0	8.1%	11.6%
ROCKET AF		
TTR (INR=2.0–3.0)	52.4%	55.2%*
INR<2.0	33.9%	29.1%*
INR>3.0	13.7%	15.7%*
ARISTOTLE		
TTR (INR=2.0–3.0)	60%	67%
INR<2.0	28.6%	18.0%
INR>3.0	11.4%	15.0%

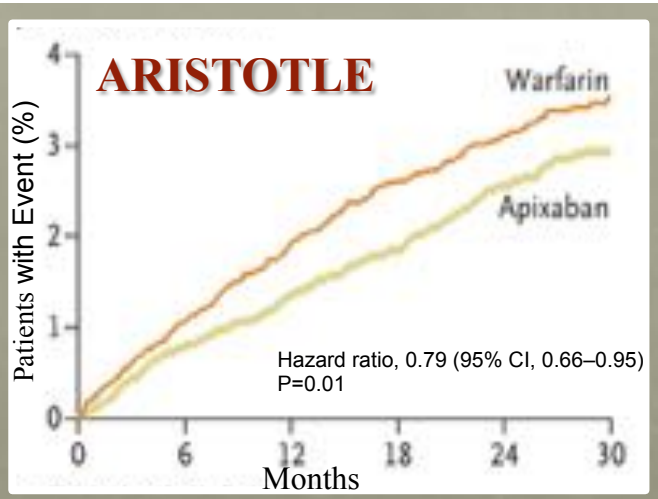
Data from recent trials show that warfarin is difficult to use in Asians due to higher risk of bleeding and stroke than non-Asians.

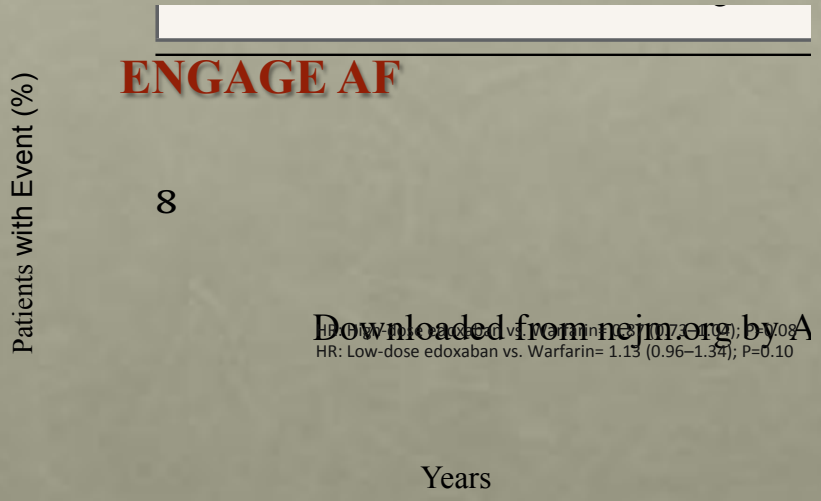
Thromb Haemost 2014; 111: 789–797

NOAC vs Warfarin in Patients with AF

Stroke or systemic embolism:







Connolly et al. *NEJM* 2009. Patel et al. *NEJM* 2011, Granger et al. *NEJM* 2011 ; Giugliano et al. NEJM 2013

Compliance

Table 2 Non-VKA oral anticoagulant drugs, approved for prevention of systemic embolism or stroke in patients with non-valvular AF

	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Action	Direct thrombin inhibitor	Activated factor Xa inhibitor	Activated factor Xa inhibitor	Activated factor Xa inhibitor
Dose	150 mg BID 110 mg BID[a,b] (75 mg BID)[b]	5 mg BID 2.5 mg BID[a]	60 mg OD[c] 30 mg OD[a]	20 mg OD 15 mg OD[a]
Phase III clinical trial	RE-LY[25]	ARISTOTLE[26] AVERROES[27]	ENGAGE-AF[28]	ROCKET-AF[29]

Non-vitamin K antagonist oral anticoagulants: considerations on once- vs. twice-daily regimens and their potential impact on medication adherence

(rivarox ...an: *n* = 265)

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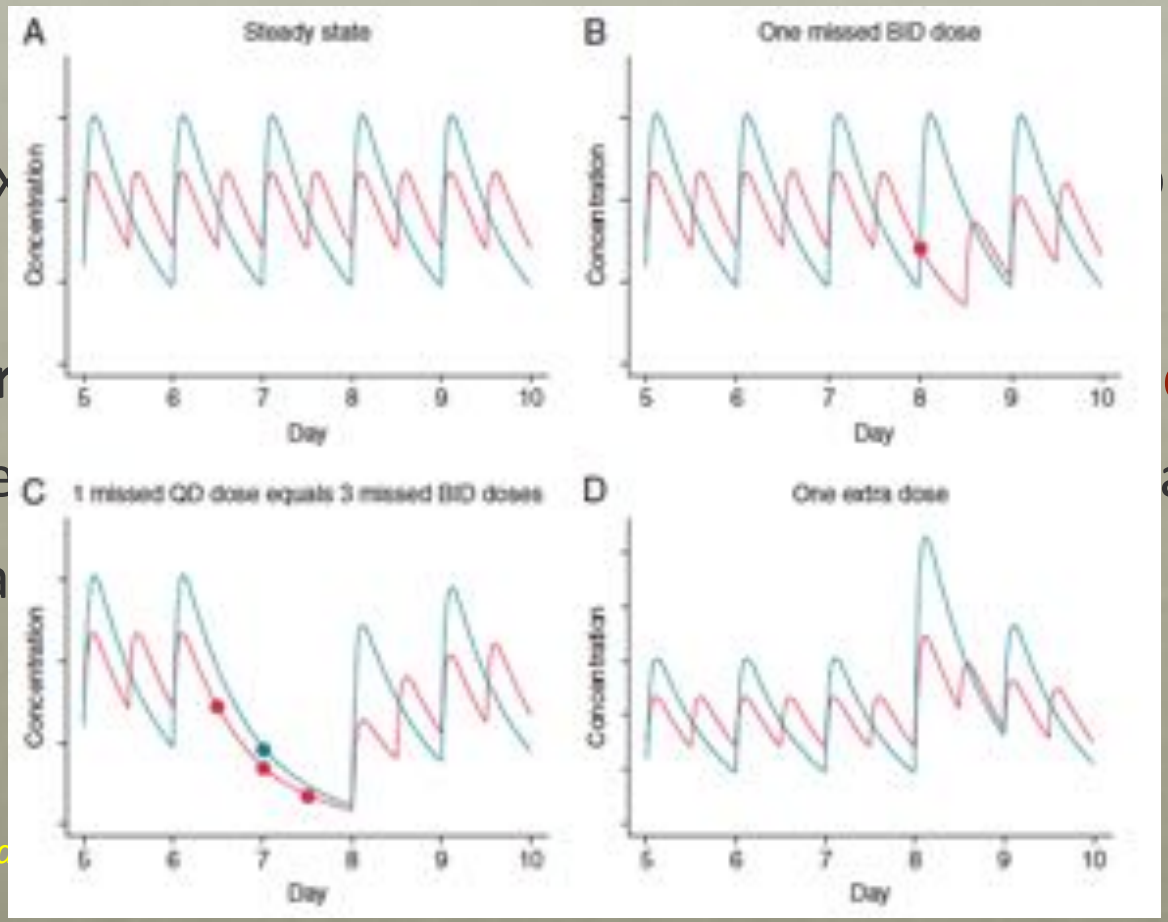


Curr Med

Europace (2015) 17, 514–523

Drugs Interaction

Table 6 Effect on NOAC plasma levels (AUC) from drug–drug interactions and clinical factors, and recommendations towards NOAC dose adaptation

	via	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Antiarrhythmic drugs:					
Amiodarone	moderate P-gp competition	+12–60%	No PK data	+40%	Minor effect (use with caution if CrCl <50 mL/min)
Digoxin	P-gp competition	No effect	No data yet	No effect	No effect
Diltiazem	P-gp competition and weak CYP3A4 inhibition	No effect	+40%	No data yet	Minor effect (use with caution if CrCl 15–50 mL/min)
Dronedarone	P-gp competition and CYP3A4 inhibition	+70–100% (US: 2 x 75 mg if CrCl 30–50 mL/min)	No PK or PD data: caution	+85% (Reduce NOAC dose by 50%)	Moderate effect but no PK or PD data: caution and try to avoid
Quinidine	P-gp competition	+53%	No data yet	+77% (No dose reduction required by label)	Extent of increase unknown
Verapamil	P-gp competition (and weak CYP3A4 inhibition)	+12–180% (reduce NOAC dose and take simultaneously)	No PK data	+53% (SR) (No dose reduction required by label)	Minor effect (use with caution if CrCl 15–50 mL/min)
Other cardiovascular drugs					
Atorvastatin	P-gp competition and CYP3A4 inhibition	+18%	No data yet	No effect	No effect
Antibiotics					
Clarithromycin; Erythromycin	moderate P-gp competition and CYP3A4 inhibition	+15–20%	No data yet	+90% (reduce NOAC dose by 50%)	+30–54%
Rifampicin***	P-gp/ BCRP and CYP3A4/CYP2J2 inducers	minus 66%	minus 54%	avoid if possible: minus 35%, but with compensatory increase of active metabolites	Up to minus 50%
Antiviral drugs					
HIV protease inhibitors (e.g. ritonavir)	P-gp and BCRP competition or inducer; CYP3A4 inhibition	No data yet	Strong increase	No data yet	Up to +153%

Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation

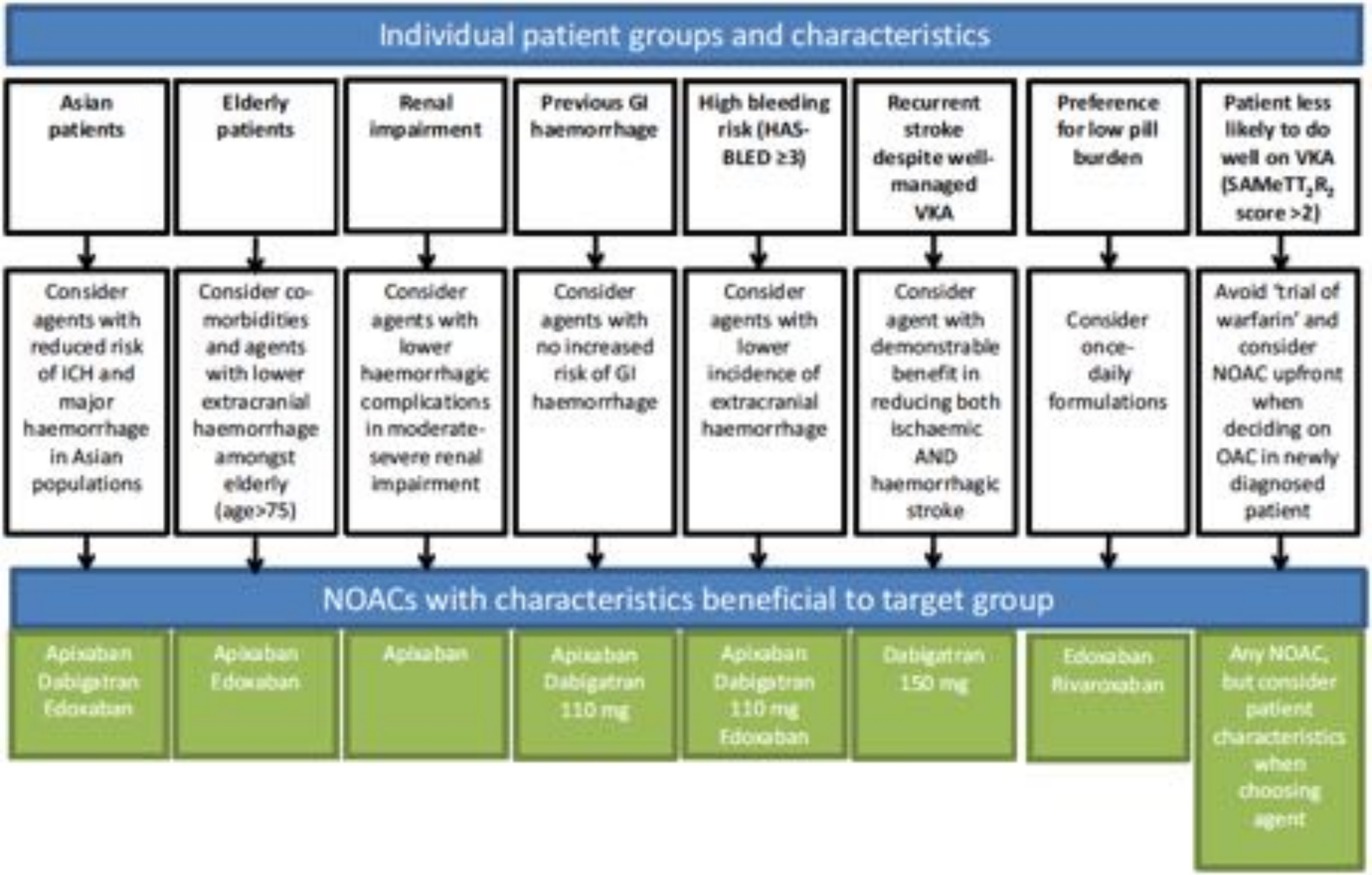
Table 6 Continued

	via	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Fungostatics					
Fluconazole	Moderate CYP3A4 inhibition	No data yet	No data yet	No data yet	+42% (if systemically administered)
Itraconazole; Ketoconazole; Posaconazole; Voriconazole;	potent P-gp and BCRP competition; CYP3A4 inhibition	+140–150% (US: 2 x 75 mg if CrCl 30–50 mL/min)	+100%	+87–95% (reduce NOAC dose by 50%)	Up to +160%
Immunosuppressive					
Cyclosporin; Tacrolimus	P-gp competition	[illegible]	No data yet	+73%	Extent of increase unknown
Antiphlogistics					
Naproxen	P-gp competition	No data yet	+55%	No effect (but pharmacodynamically increased bleeding time)	No data yet
Antacids					
H2B; PPI; Al-Mg-hydroxide	GI absorption	Minus 12–30%	No effect	No effect	No effect
Others					
Carbamazepine***; Phenobarbital***; Phenytoin***; St John's wort***	P-gp/ BCRP and CYP3A4/CYP2J2 inducers	minus 66%	minus 54%	minus 35%	Up to minus 50%

Malignancies

The presence of a malignancy in patients with AF increases stroke risk. If the AF patients are on prior NOAC therapy, ***its continuation may be possible***, even in patients with malignancies who receive moderately myelosuppressive therapies.

When anticoagulant therapy needs to be **newly** initiated in a patient with malignancy developing AF, therapy with **VKAs or heparins** should be considered over NOACs, because of the clinical experience with these substances, the possibility of close monitoring, and reversal options.



Shields et al. J Int Med2015;278:1-8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