INDICATIONS OF DIRECT ORAL ANTICOAGULANTS

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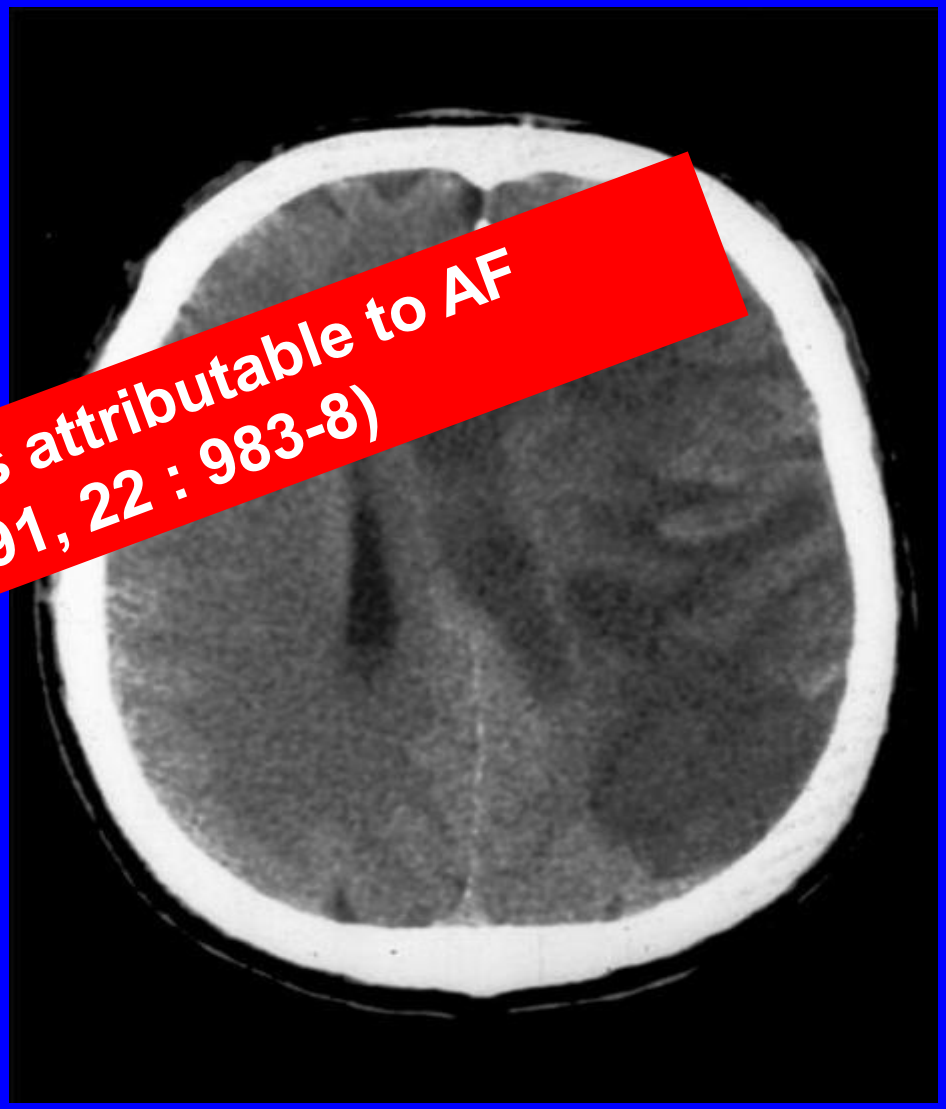
Disclosures

Fees for boards and conferences from :

Astra-Zeneca, Bayer, Boehringer Ingelheim, Bristol-Myers-Squibb/Pfizer, Correvio, Daiichi-Sankyo, Meda, Sanofi, Servier



One sixth of all strokes attributable to AF
(Wolf et al. Stroke 1991, 22 : 983-8)

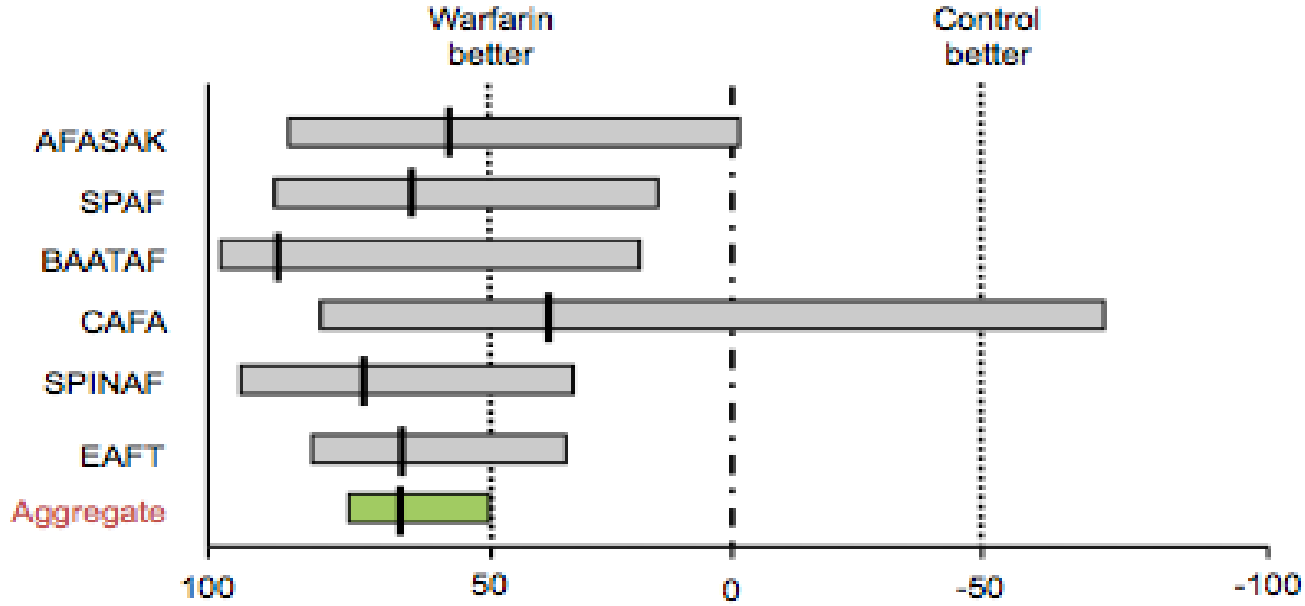
Halperin et al. Stroke 1988;19:937-941.

Antiarrhythmic prophylaxis vs. warfarin anticoagulation to prevent thromboembolic events among patients with atrial fibrillation.
A decision analysis.

Middlekauff HR, Stevenson WG, Gornbein JA.
Arch Intern Med 1995;155:913–20

CONCLUSIONS: Based on data from randomised, controlled trials of quinidine and warfarin, warfarin therapy appears to be the safest strategy for thromboembolism prevention in the patient with atrial fibrillation

Hart R.G. et al.
Ann. Intern. Med. 1999;
131 : 492 - 501.



Limitations of VKA therapy

Unpredictable response

Narrow therapeutic window (INR range 2.0–3.0)

Routine coagulation monitoring

Slow onset/offset of action

VKA therapy has several limitations that make it difficult to use in practice

Frequent dose adjustment

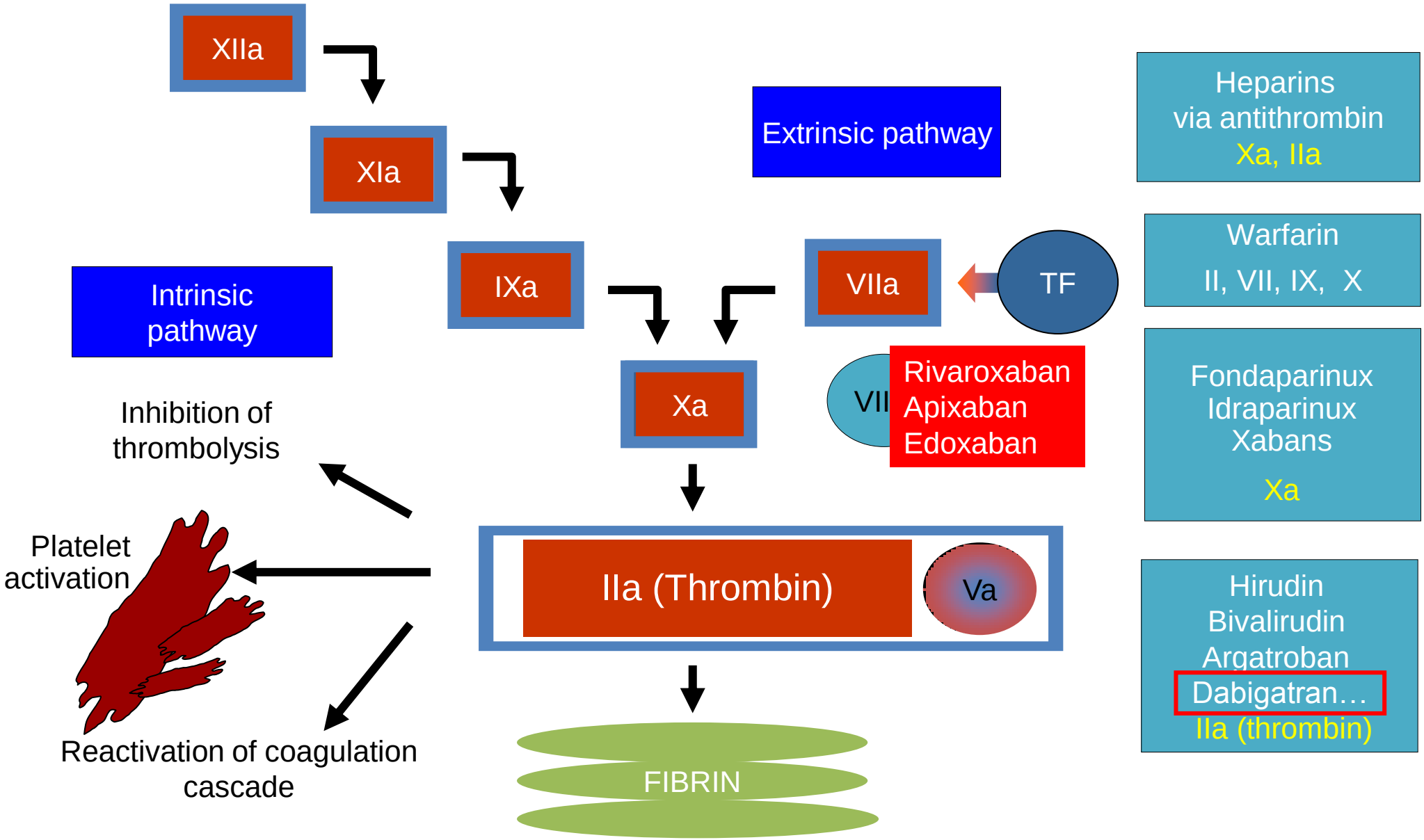
Numerous food–drug interactions

Numerous drug–drug interactions

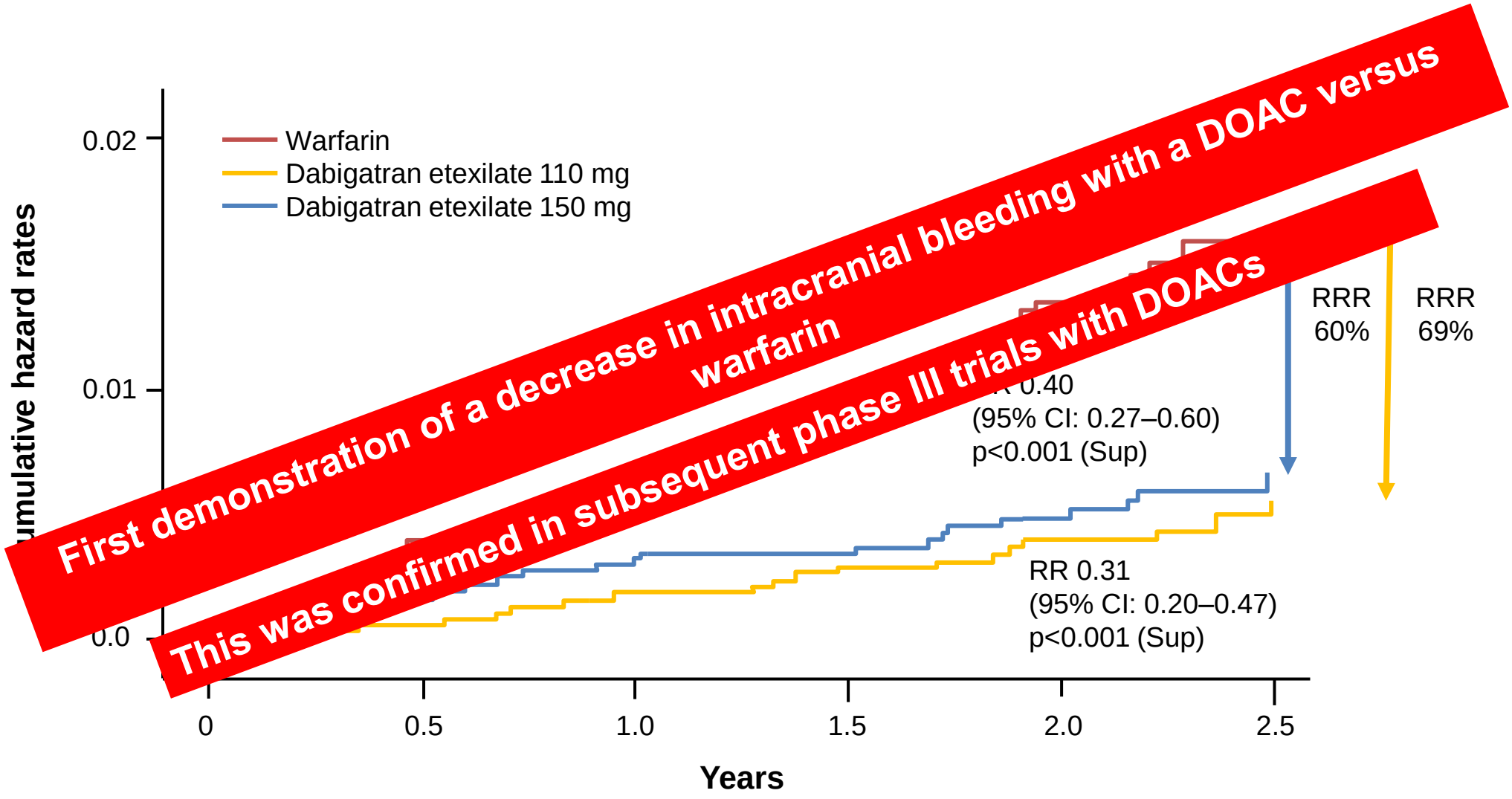
Warfarin resistance

Ansell et al. Chest 2008;133;160S–198S;
Umer Ushman et al. J Interv Card Electrophysiol 2008;22:129–137;
Nutescu et al. Cardiol Clin 2008;26:169–187

Coagulation cascade



RE-LY: Time to first intracranial bleed

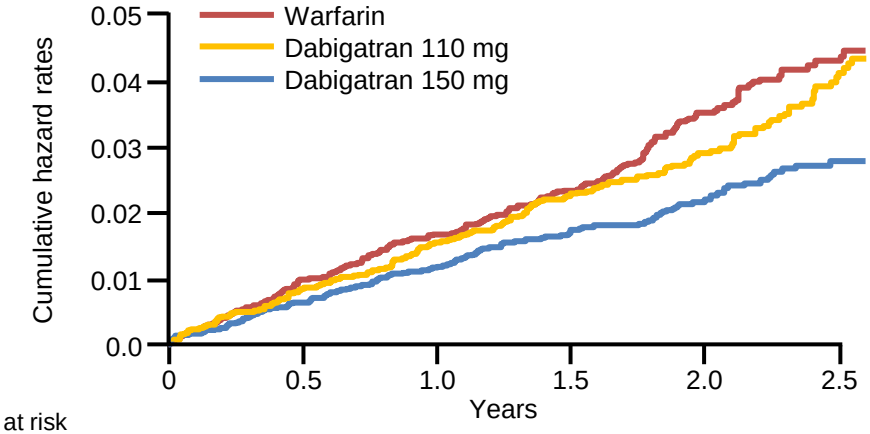


RR, relative risk; RRR, relative risk reduction; CI, confidence interval; Sup, superior

Connolly et al. ,ESC meeting, Barcelona 2009

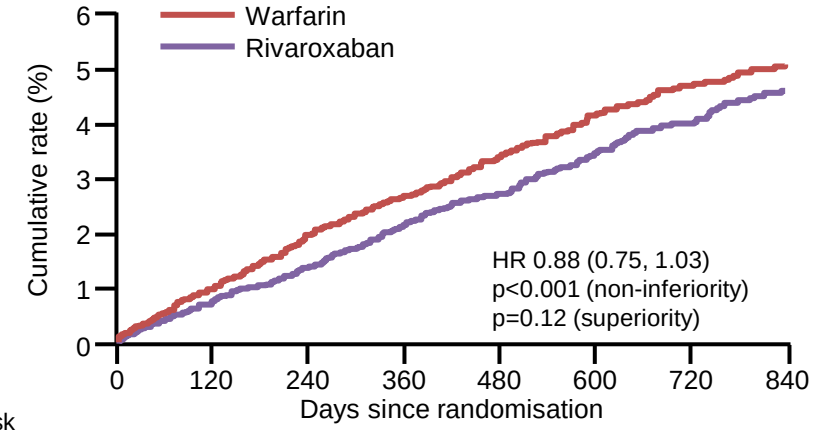
Stroke or systemic embolism (ITT)

RE-LY[1] 2009



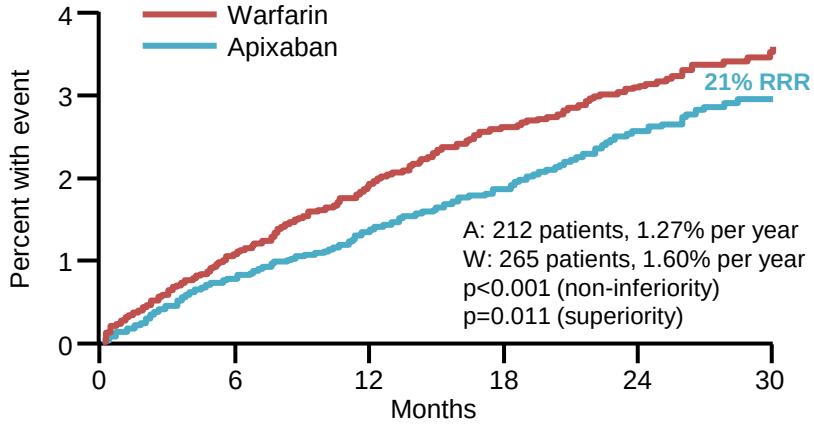
No at risk						
Warfarin	6022	5862	5718	4593	2890	1322
Dab 110 mg	6015	5862	5710	4593	2945	1385
Dab 150 mg	6076	5939	5779	4682	3044	1429

ROCKET AF[2] 2011



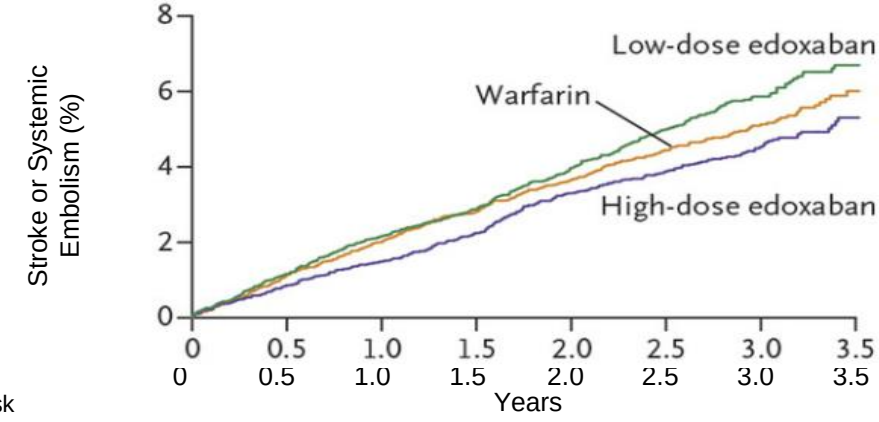
No at risk								
Rivaroxaban	7081	6879	6683	6470	5264	4105	2951	1785
Warfarin	7090	6871	6656	6440	5225	4087	2944	1783

ARISTOTLE[3] 2011



No at risk						
Apixaban	9120	8726	8440	6051	3464	1754
Warfarin	9081	8620	8301	5972	3405	1768

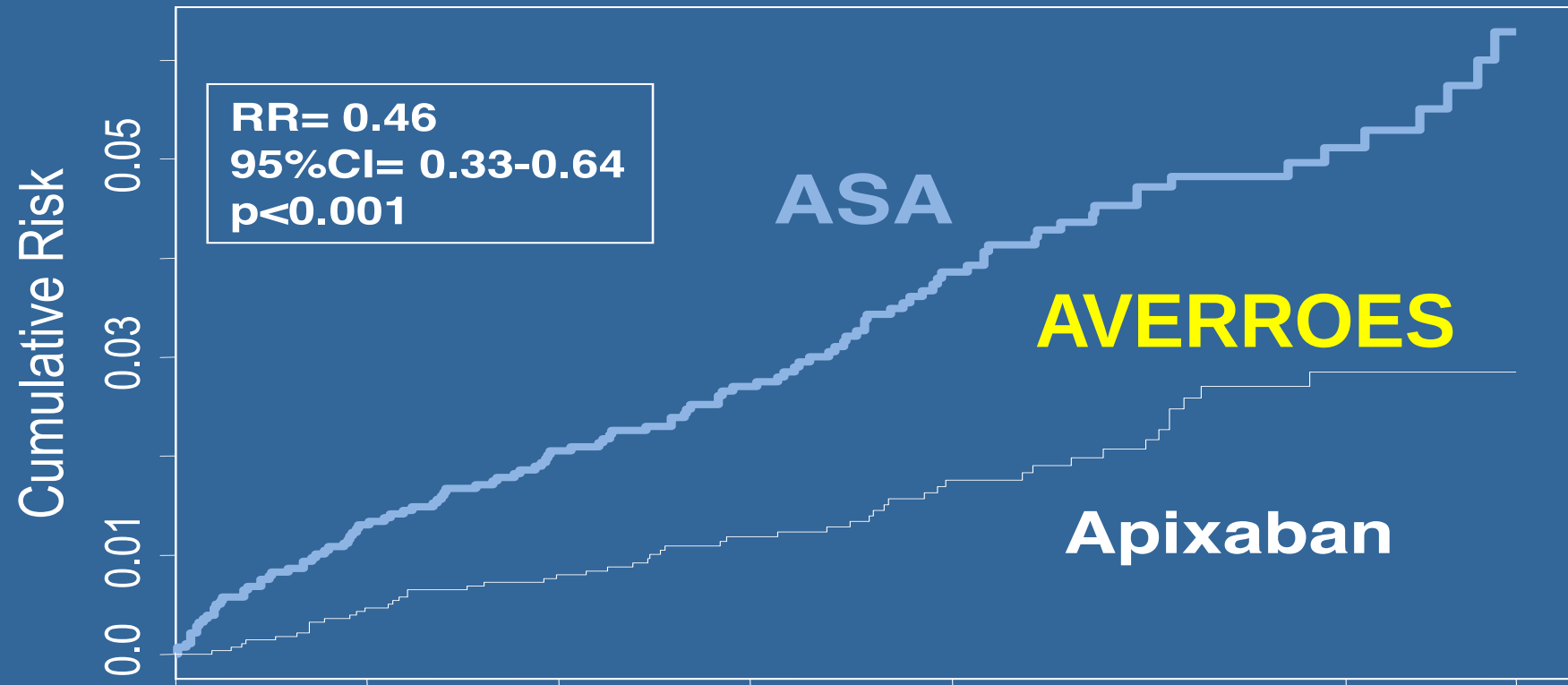
ENGAGE AF-TIMI 48[4] 2013



No at risk								
Warfarin	7036	6798	6615	6406	6225	4593	2333	536
High-dose edoxaban	7035	6816	6650	6480	6283	4659	2401	551
Low-dose edoxaban	7034	6815	6631	6461	6277	4608	2358	534

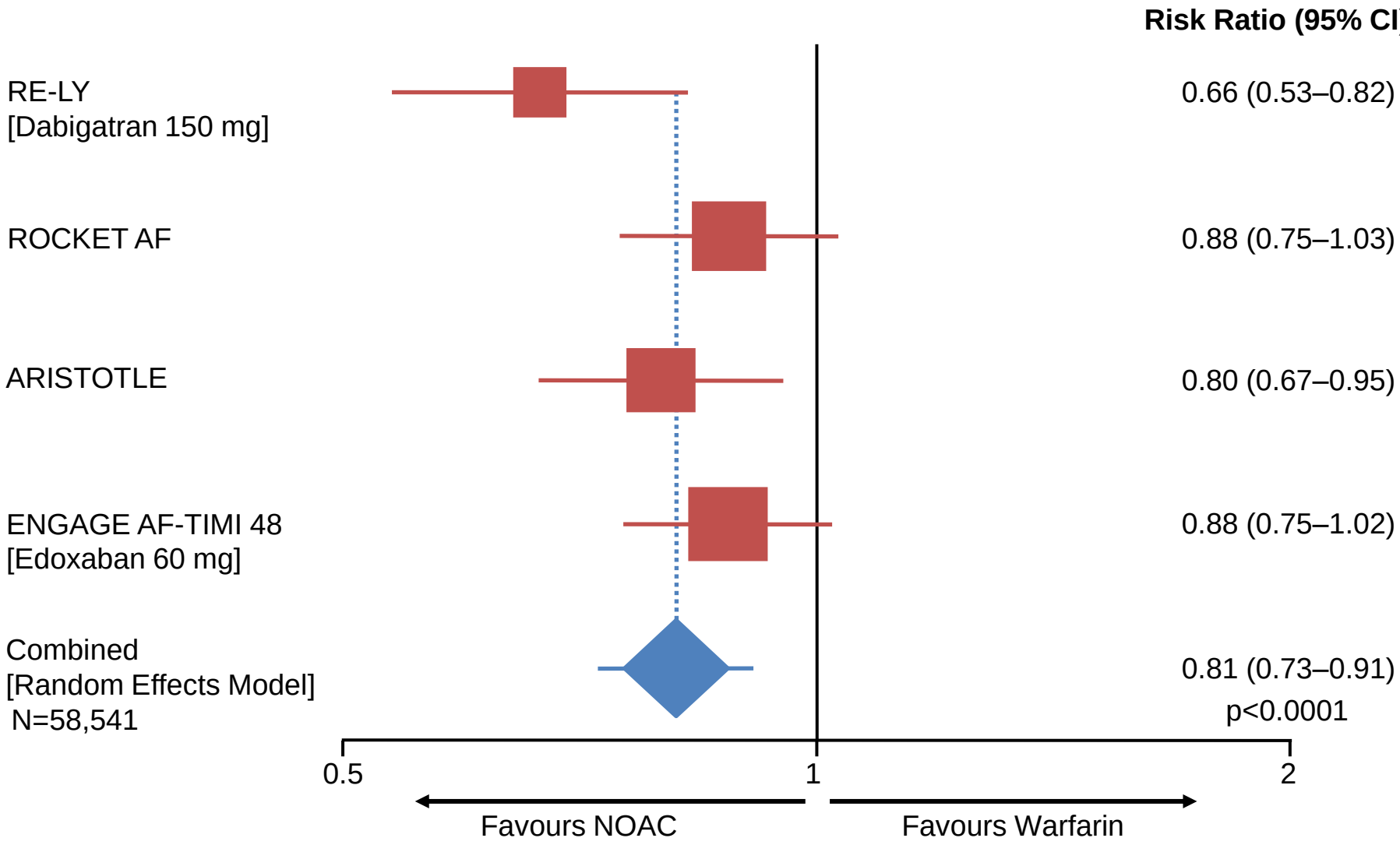
1. Connolly et al. N Eng J Med 2009;361:1139–1151
2. Patel et al. N Eng J Med 2011;365:883–891
3. Granger et al. N Eng J Med 2011;365:981–992
4. Giugliano et al. N Eng J Med 2013;369:2093–2104

Stroke or Systemic Embolic Event



No. at Risk							
ASA	2791	2720	2541	2124	1541	626	329
Apix	2809	2761	2567	2127	1523	617	353

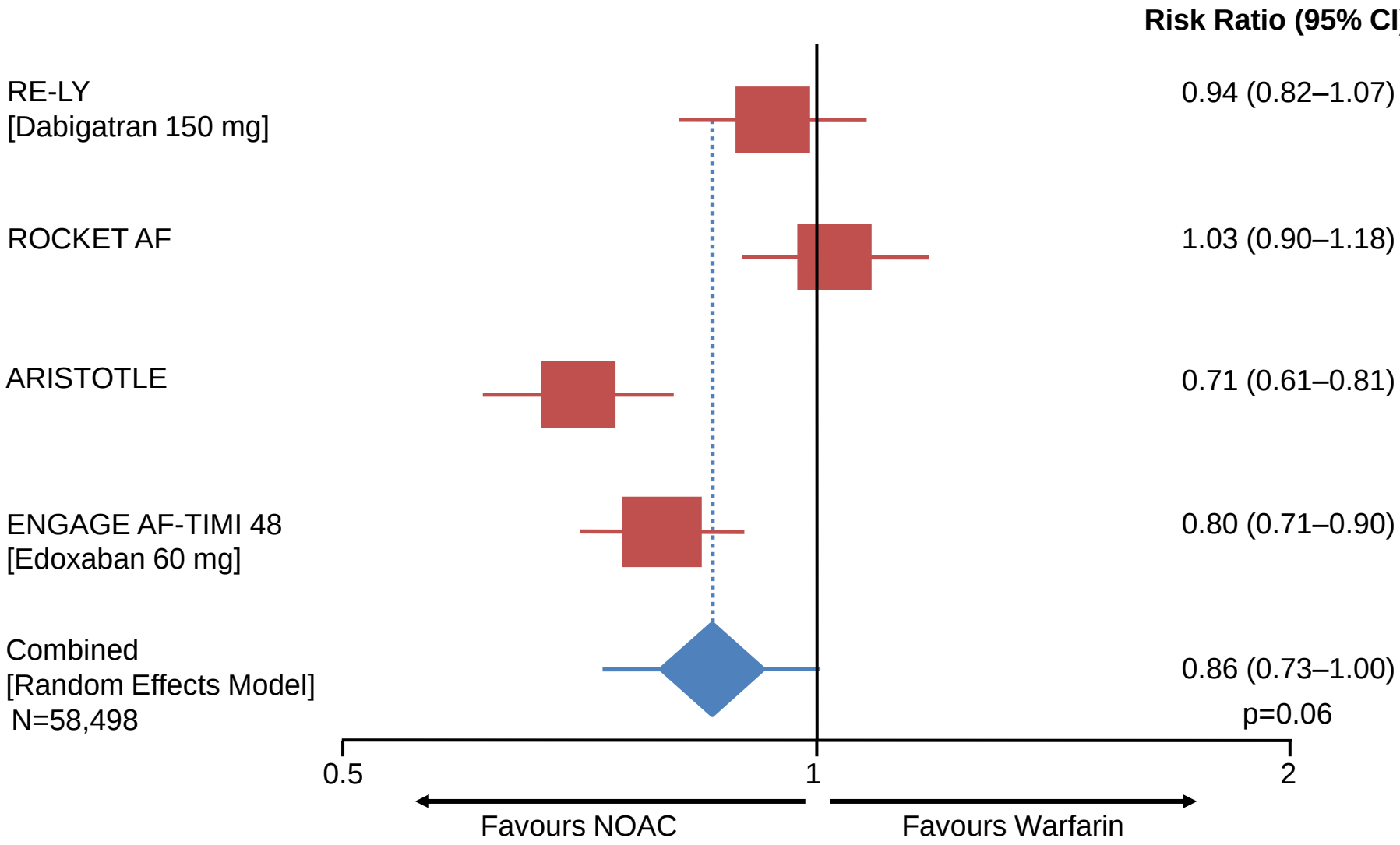
All NOACs: Stroke or SEE



Heterogeneity p=0.13

Ruff et al. Lancet 2014;383:955–962

All NOACs: Major bleeding

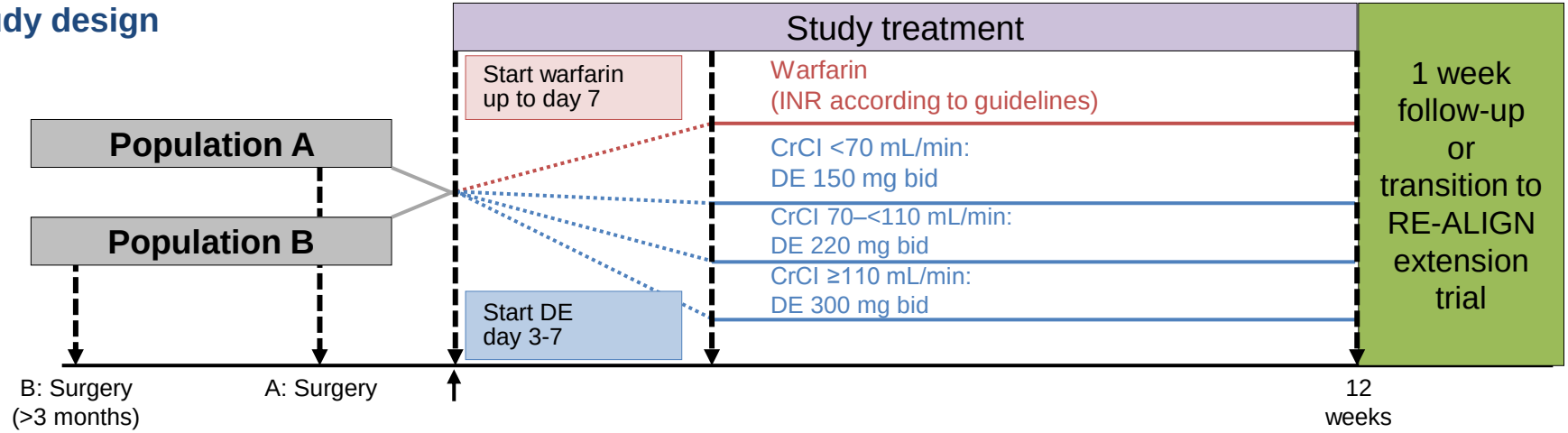


Heterogeneity p=0.001

Ruff et al. Lancet 2014;383:955–962

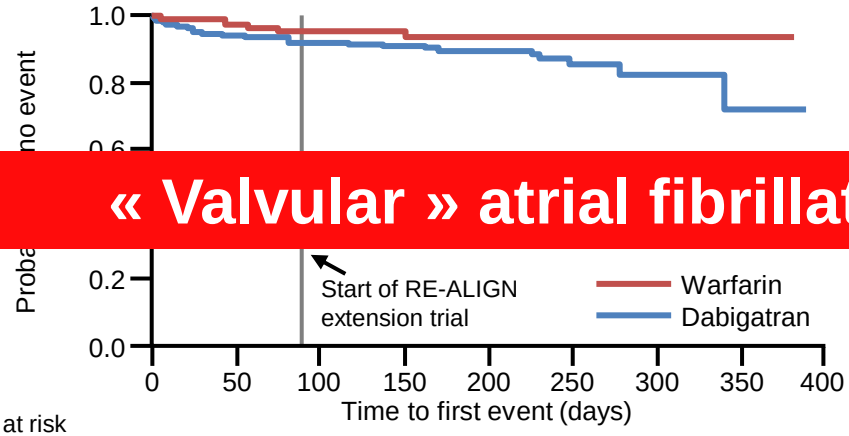
RE-ALIGN

Study design



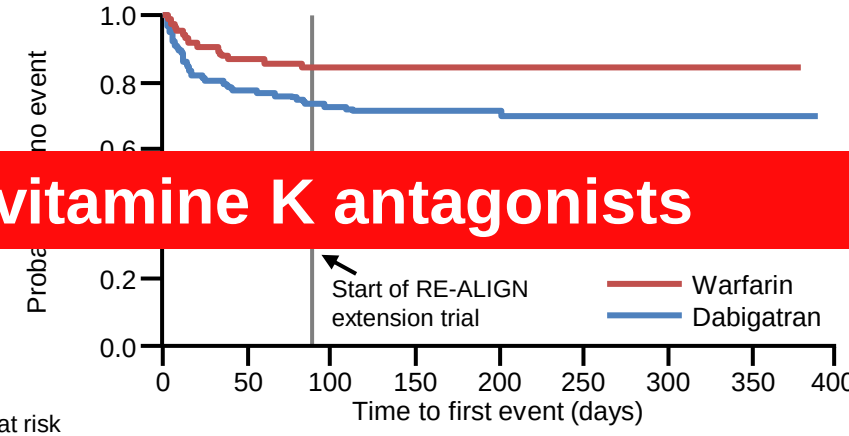
*Increased dose of dabigatran when trough plasma level <50 ng/mL (by Hemoclot®)

Composite of a first thromboembolic event or death



No at risk								
Dabigatran	168	156	126	108	73	44	15	7
Warfarin	84	82	66	55	40	22	9	4

First bleeding event (any bleeding)



No at risk								
Dabigatran	168	129	103	86	58	32	11	6
Warfarin	84	73	56	50	38	22	11	4

« Valvular » atrial fibrillation : vitamine K antagonists

First thromboembolic event includes stroke, systemic embolism, TIA, myocardial infarction

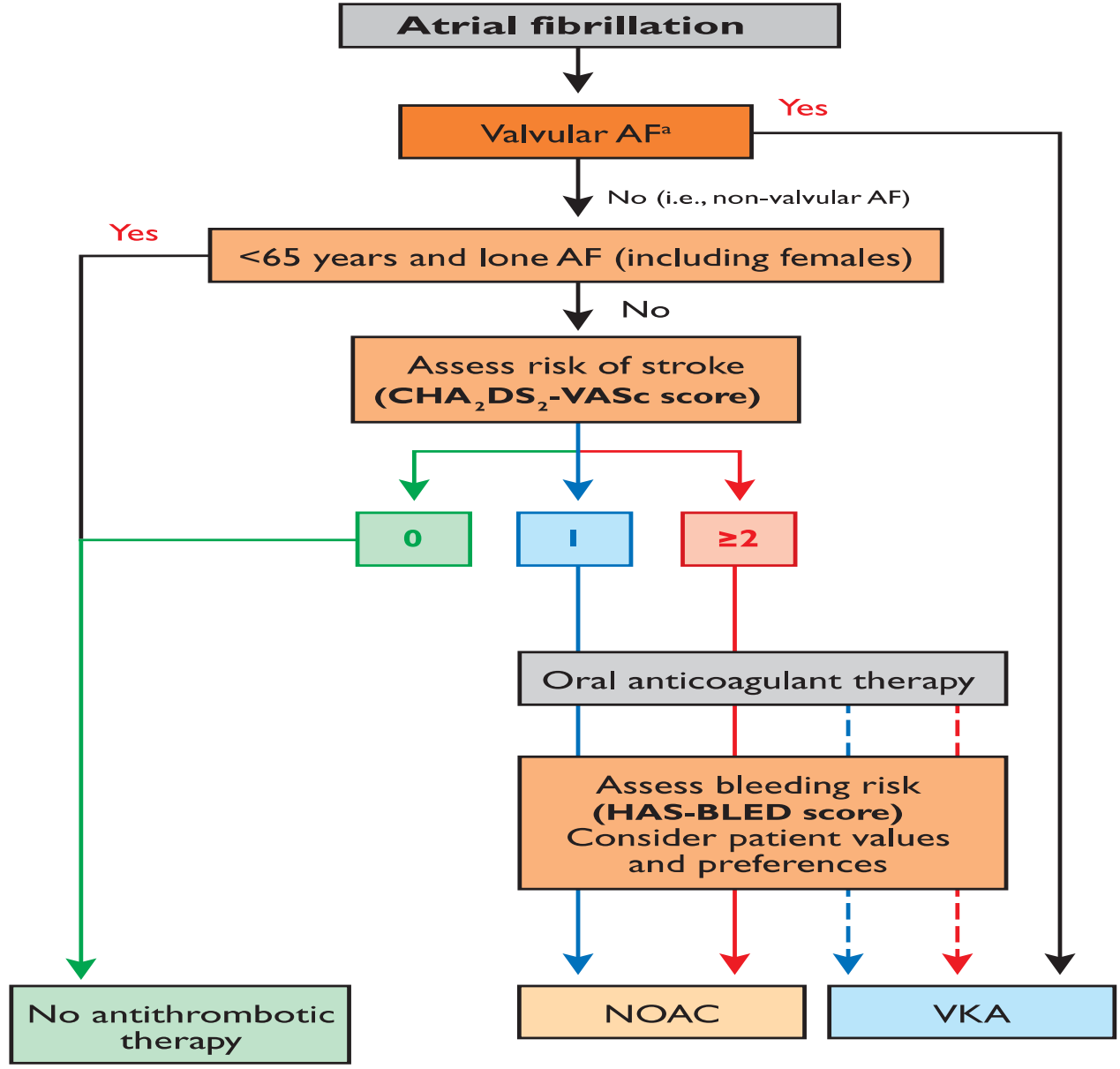
Van de Werf ESC 2013;
Eikelboom et al. N Eng J Med 2013;369:1206–14

Recommendations	Class[a]	Level[b]	Ref[c]
Recommendations for prevention of thromboembolism in non-valvular AF—general			
Antithrombotic therapy to prevent thromboembolism is recommended for all patients with AF, except in those patients (both male and female) who are at low risk (aged <65 years and lone AF), or with contraindications.	I	A	21, 63, 104, 105, 106
The choice of antithrombotic therapy should be based upon the absolute risks of stroke/thromboembolism and bleeding and the net clinical benefit for a given patient.	I	A	21, 63, 105
The CHA_2DS_2-VASc score is recommended as a means of assessing stroke risk in non-valvular AF.	I	A	25, 36 ,39
In patients with a CHA_2DS_2-VASc score of 0 (i.e., aged <65 years with lone AF) who are at low risk, with none of the risk factors, no antithrombotic therapy is recommended.	I	B	21, 36, 82
In patients with a CHA_2DS_2-VASc score ≥2, OAC therapy with: • adjusted-dose VKA (INR 2–3); or • a direct thrombin inhibitor (dabigatran); or • an oral factor Xa inhibitor (e.g. rivaroxaban, apixaban)[d] … is recommended, unless contraindicated.	I	A	3, 4, 70, 82
In patients with a CHA_2DS_2-VASc score of 1, OAC therapy with • adjusted-dose VKA (INR 2–3); or • a direct thrombin inhibitor (dabigatran); or • an oral factor Xa inhibitor (e.g. rivaroxaban, apixaban)[d] …. should be considered, based upon an assessment of the risk of bleeding complications and patient preferences.	IIa	A	33, 44
Female patients who are aged <65 and have lone AF (but still have a CHA_2DS_2-VASc score of 1 by virtue of their gender) are low risk and no antithrombotic therapy should be considered.	IIa	B	33, 44
When patients refuse the use of any OAC (whether VKAs or NOACs), antiplatelet therapy should be considered, using combination therapy with aspirin 75–100 mg plus clopidogrel 75 mg daily (where there is a low risk of bleeding) or—less effectively—aspirin 75–325 mg daily.	IIa	B	21, 26, 51, 109

Eur. Heart J. 2012; 33 : 2719 - 47

Recommendations for prevention of thromboembolism in non-valvular AF—NOACs			
When adjusted-dose VKA (INR 2–3) cannot be used in a patient with AF where an OAC is recommended, due to difficulties in keeping within therapeutic anticoagulation, experiencing side effects of VKAs, or inability to attend or undertake INR monitoring, one of the NOACs, either: • a direct thrombin inhibitor (dabigatran); or • an oral factor Xa inhibitor (e.g. rivaroxaban, apixaban)[d] … is recommended.	I	B	2, 28, 65, 107
Where OAC is recommended, one of the NOACs, either: • a direct thrombin inhibitor (dabigatran); or • an oral factor Xa inhibitor (e.g. rivaroxaban, apixaban)[d] … should be considered rather than adjusted-dose VKA (INR 2–3) for most patients with non-valvular AF, based on their net clinical benefit.	IIa	A	3, 4, 70, 82
Where dabigatran is prescribed, a dose of 150 mg b.i.d. should be considered for most patients in preference to 110 mg b.i.d., with the latter dose recommended in: • elderly patients, age ≥ 80 • concomitant use of interacting drugs (e.g. verapamil) • high bleeding risk (HAS-BLED score ≥3) • moderate renal impairment (CrCl 30–49 mL/min).	IIa	B	85, 96
Where rivaroxaban is being considered, a dose of 20 mg o.d. should be considered for most patients in preference to 15 mg o.d., with the latter dose recommended in: • high bleeding risk (HAS-BLED score ≥3) • moderate renal impairment (CrCl 30–49 mL/min).	IIa	C	3, 108
Baseline and subsequent regular assessment of renal function (by CrCl) is recommended in patients following initiation of any NOAC, which should be done annually but more frequently in those with moderate renal impairment where CrCl should be assessed 2–3 times per year.	IIa	B	85
NOACs (dabigatran, rivaroxaban, and apixaban) are not recommended in patients with severe renal impairment (CrCl <30 mL/min).	III	A	3, 24, 70

Eur. Heart J. 2012; 33 : 2719 - 47



Eur. Heart J. 2012; 33 : 2719 - 47

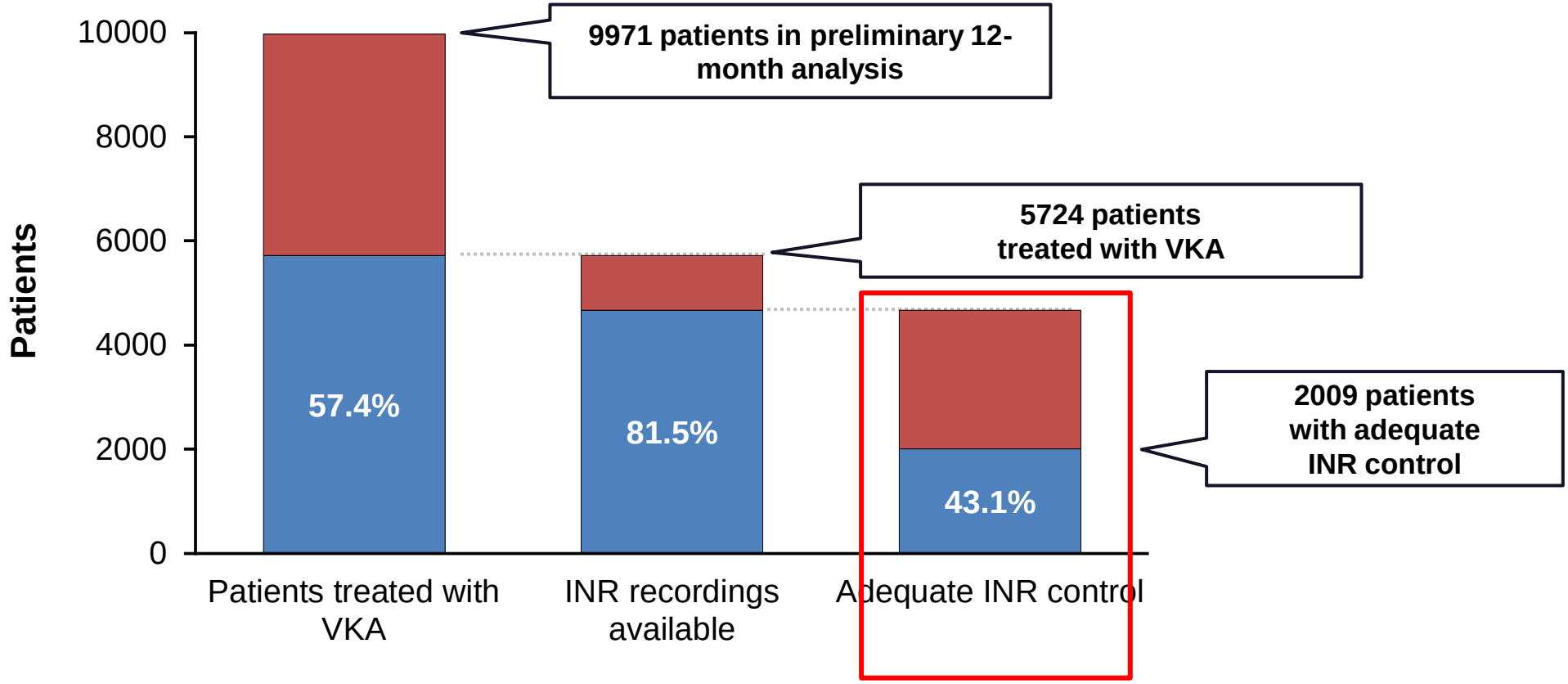
Circulation 2014, 130 : 2071 - 104

Table 6. Summary of Recommendations for Risk-Based Antithrombotic Therapy

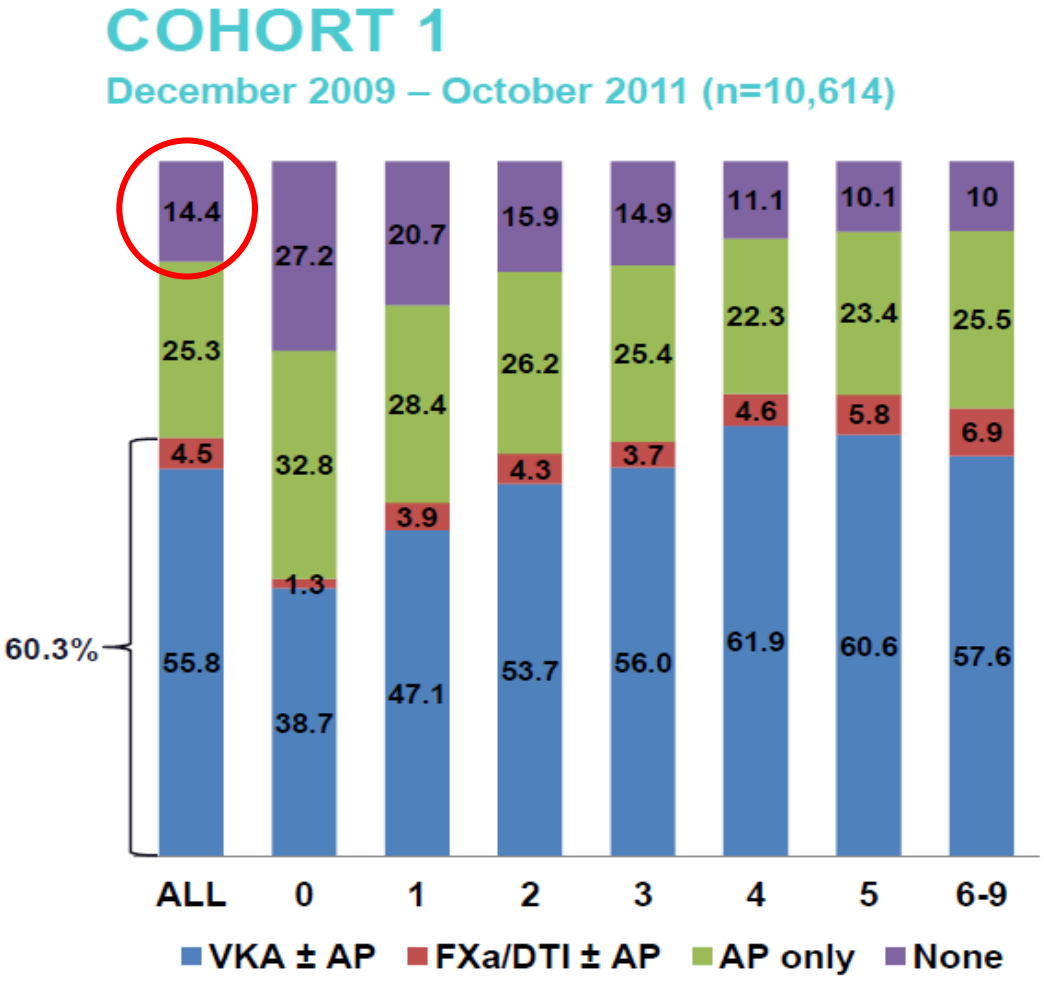
Recommendations	COR	LOE	References
Antithrombotic therapy based on shared decision making, discussion of risks of stroke and bleeding, and patient's preferences	I	C	N/A
Selection of antithrombotic therapy based on risk of thromboembolism	I	B	167–170
CHA_2DS_2-VASc score recommended to assess stroke risk	I	B	171–173
Warfarin recommended for mechanical heart valves and target INR intensity based on type and location of prosthesis	I	B	174–176
With prior stroke, TIA, or CHA_2DS_2-VASc score ≥2, oral anticoagulants recommended. Options include:			
Warfarin	I	A	171–173
Dabigatran, rivaroxaban, or apixaban	I	B	177–179
With warfarin, determine INR at least weekly during initiation of therapy and monthly when stable	I	A	180–182
Direct thrombin or factor Xa inhibitor recommended if unable to maintain therapeutic INR	I	C	N/A
Reevaluate the need for anticoagulation at periodic intervals	I	C	N/A
Bridging therapy with UFH or LMWH recommended with a mechanical heart valve if warfarin is interrupted. Bridging therapy should balance risks of stroke and bleeding	I	C	N/A
For patients without mechanical heart valves, bridging therapy decisions should balance stroke and bleeding risks against duration of time patient will not be anticoagulated	I	C	N/A
Evaluate renal function before initiation of direct thrombin or factor Xa inhibitors, and reevaluate when clinically indicated and at least annually	I	B	183–185
For atrial flutter, antithrombotic therapy is recommended as for AF	I	C	N/A
With nonvalvular AF and CHA_2DS_2-VASc score of 0, it is reasonable to omit antithrombotic therapy	IIa	B	183, 184
With CHA_2DS_2-VASc score ≥2 and end-stage CKD (CrCl <15 mL/min) or on hemodialysis, it is reasonable to prescribe warfarin for oral anticoagulation	IIa	B	185
With nonvalvular AF and a CHA_2DS_2-VASc score of 1, no antithrombotic therapy or treatment with oral anticoagulant or aspirin may be considered	IIb	C	N/A

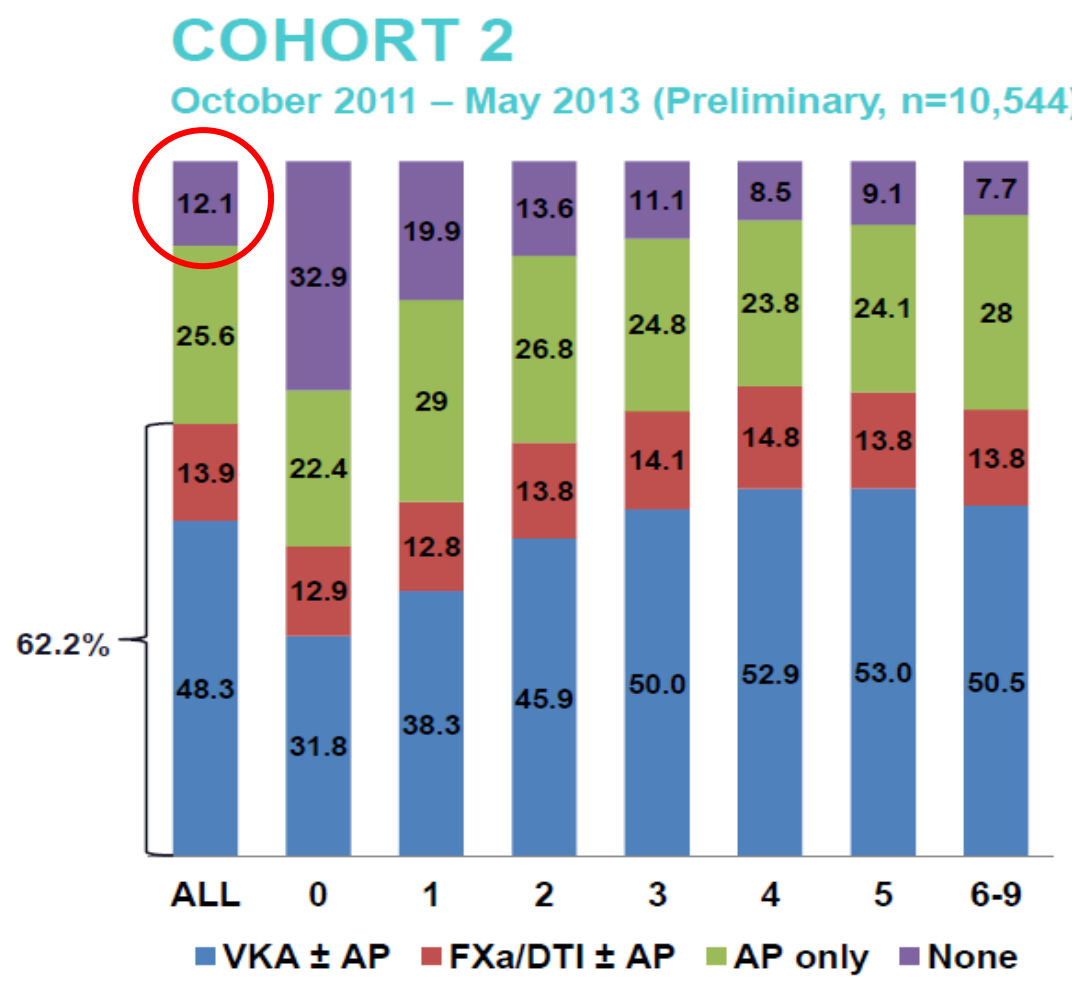
A minority of patients treated with VKAs in GARFIELD achieved adequate INR control over first 12 months

Preliminary data



Kakkar AK *et al. Am Heart Assoc* 2012;Abstr





1- Kakkar AK, et al. Risk Profiles and Antithrombotic Treatment of Patients Newly Diagnosed with Atrial Fibrillation at Risk of Stroke: Perspectives from the International, Observational, Prospective GARFIELD Registry. PLoS One. 2013

FEAR OF BLEEDING

… Hematuria

Menorrhagia

Rectorrhagia …

Advantages of Direct Oral Anticoagulants

- No routine coagulation monitoring
- Less intracranial hemorrhages in the trials
- At least as effective as Warfarine
- Short half lifes
- Less inter and intraindividual variability of the effect
- Simplification or suppression of bridging
- No major interaction with food
- Fixed doses and more predictable response

Limitations of Direct Oral Anticoagulants

- No specific antidote at that time, difficulties in bleeding management
- Biological tests difficult to interprete
- Drug-drug interactions (PgP and CYP)
- Precaution +++ in patients with moderate renal failure (elderly), contraindication if more severe failure (creatinine clearance less than 30 ml/min with the Cockroft method)
- Therapeutics schemes to redefine in specific situations (for example coronary heart disease)
- Cost ++++++++

Which is the best direct oral anticoagulant?

NO HEAD TO HEAD COMPARISON

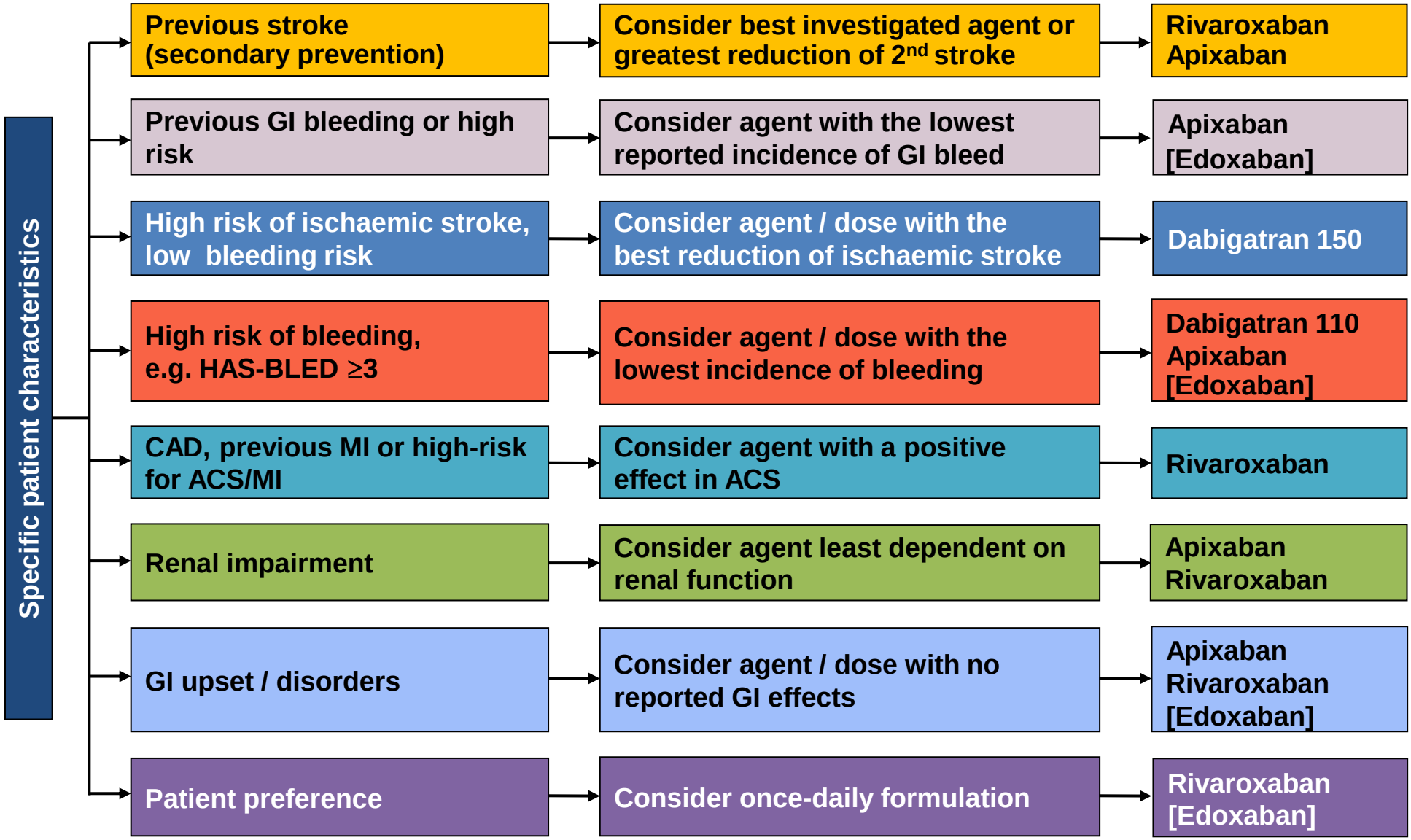
- Slightly different populations in the trials: higher $CHADS_2$ score and more secondary prevention patients in ROCKET AF
- Ischaemic stroke reduction only with dabigatran 150 mg
- In the trials increase in gastrointestinal bleeding with dabigatran, rivaroxaban and high-dose edoxaban, not with apixaban and low-dose edoxaban
- Decrease in total mortality with apixaban and low-dose edoxaban

Which is the best direct oral anticoagulant?

- Discussion on dabigatran and myocardial infarction increased risk
- Lower discontinuation rate with apixaban in ARISTOTLE and edoxaban in ENGAGE AF
- Different rates of renal excretion (dabigatran > edoxaban > rivaroxaban > apixaban)
- Higher difficulty in switching QD vitamin K antagonist for a BID new oral anticoagulant than for a QD one

Comparisons?

Pointers towards which NOAC to choose



Adapted from Savelieva and Camm. Clin Cardiol 2014;37:32–47

CONCLUSIONS

1- The landscape of anticoagulant treatment in atrial fibrillation has dramatically changed in the last years

2- All patients with a CHA_2DS_2VASC score ≥ 2 must be anticoagulated, if they have no contraindication

3- Patients with a CHA_2DS_2VASC score 0 do not need any antithrombotic treatment

4- The choice for patients with a CHA_2DS_2VASC score 1 must be made case by case

5- Direct oral anticoaguants are often preferred to Vitamine K antagonists (unstable INR, patient's preference) but their prescription may be limited by several factors, mainly including renal failure and economic considerations.