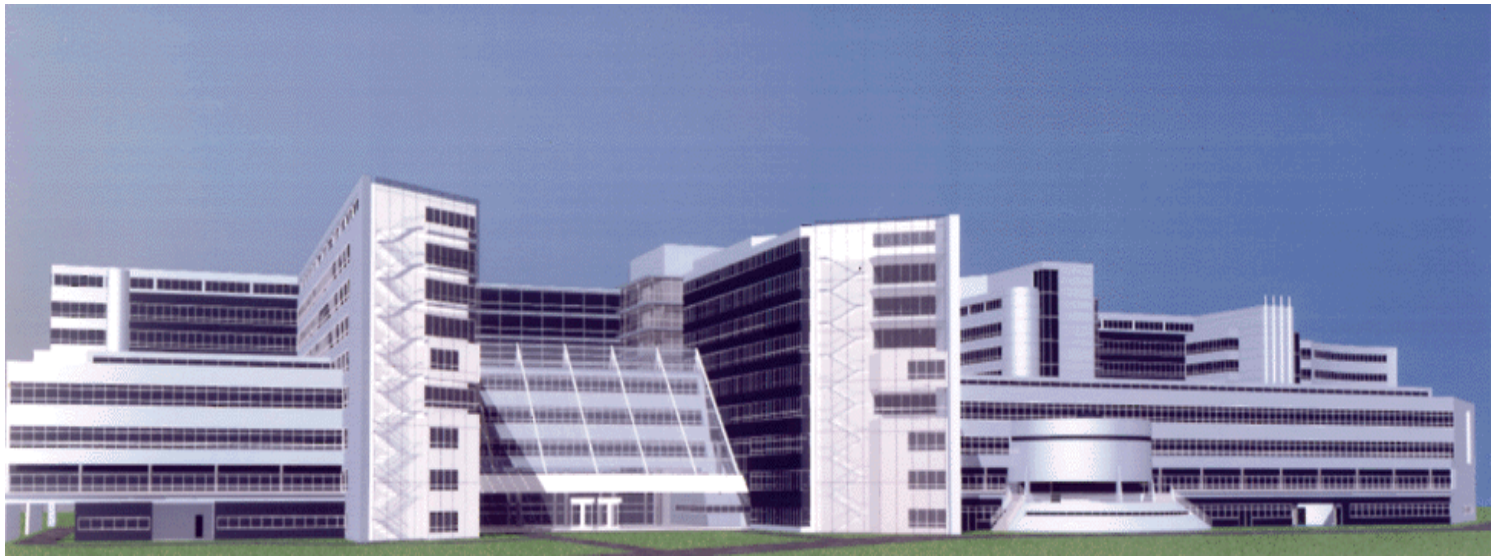
Are we protecting our patients from ischemic stroke ?

J.Y. LE HEUZEY
Georges Pompidou Hospital,
René Descartes University, Paris



Turin, October 25, 2014

Disclosures

Consultancy / conferences / research grants:

- Bristol-Myers Squibb / Pfizer
- Meda
- Boehringer Ingelheim
- Servier
- Bayer
- Daiichi Sankyo

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

Rhythm Versus Rate Control Therapy and Subsequent Stroke or Transient Ischemic Attack in Patients With Atrial Fibrillation

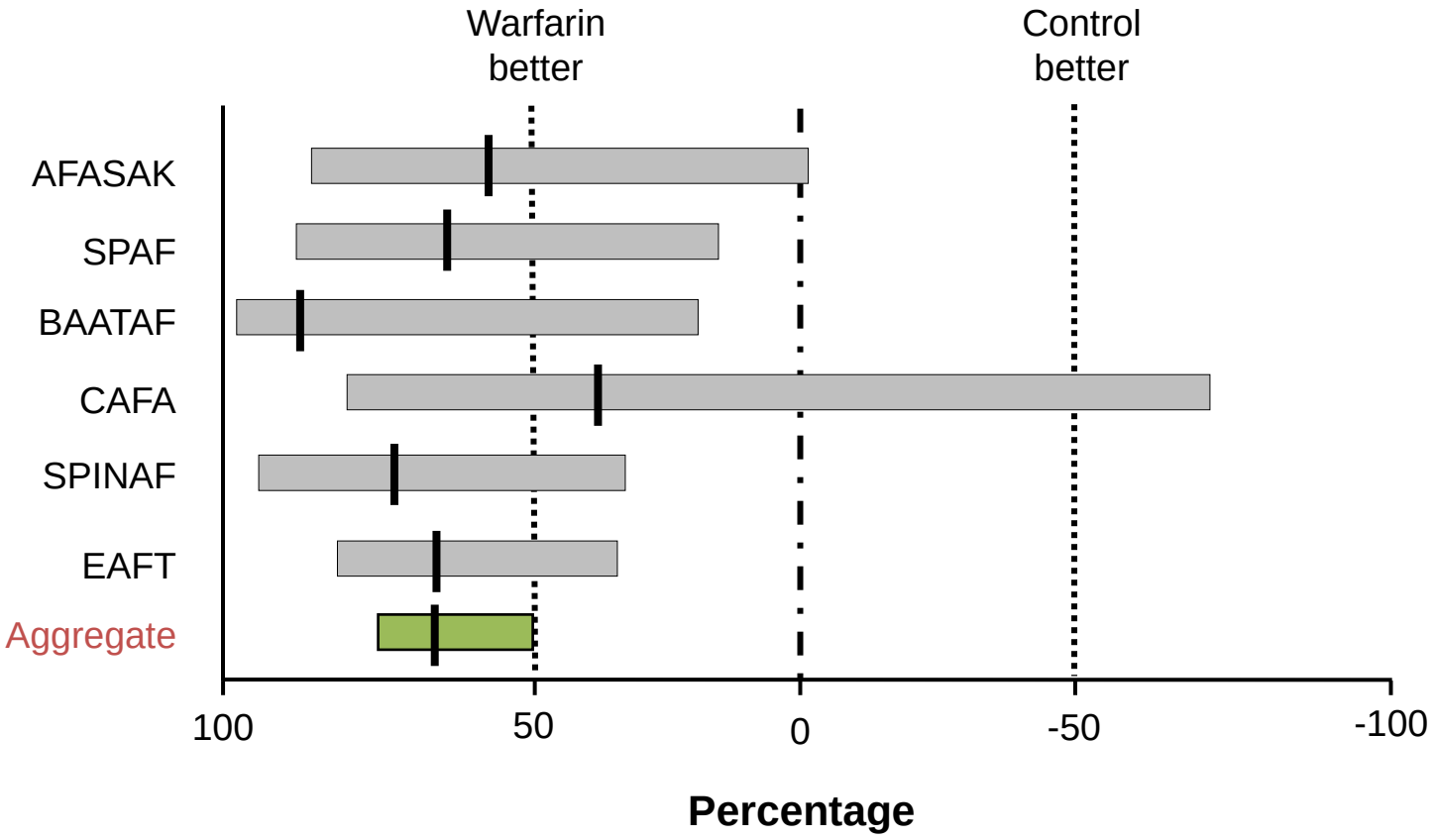
Meytal Avgil Tsadok, PhD; Cynthia A. Jackevicius, PharmD, MSc; Vidal Essebag, MD, PhD; Mark J. Eisenberg, MD, MPH; Elham Rahme, PhD; Karin H. Humphries, DSc; Jack V. Tu, MD, PhD; Hassan Behlouli, PhD; Louise Pilote, MD, PhD

Conclusions—In comparison with rate control therapy, the use of rhythm control therapy was associated with lower rates of stroke/TIA among patients with atrial fibrillation, in particular, among those with moderate and high risk of stroke. (*Circulation*. 2012;126:2680-2687.)

Table 4. Risk of Stroke/TIA in Patients Who Filled Prescriptions for Rhythm Versus Rate Control Therapy

	Unadjusted		Adjusted*	
	HR (Rhythm vs Rate Control)	95% CI	HR (Rhythm vs Rate Control)	95% CI
All patients	0.72	0.67, 0.78	0.80	0.74, 0.87
According to levels of $CHADS_2$ score†				
Low ($CHADS_2$ score=0, n=4876)	0.86	0.65, 1.13	0.93	0.70, 1.24
Moderate ($CHADS_2$ score=1, n=15 551)	0.71	0.61, 0.83	0.80	0.68, 0.93
High ($CHADS_2$ score ≥2, n=37 091)	0.77	0.70, 0.84	0.84	0.77, 0.93
Propensity score–matched cohort	0.75	0.67, 0.85	0.77	0.68, 0.87

Anticoagulation in atrial fibrillation: Stroke risk reduction



Hart et al. Ann Intern Med 1999;131:492–501

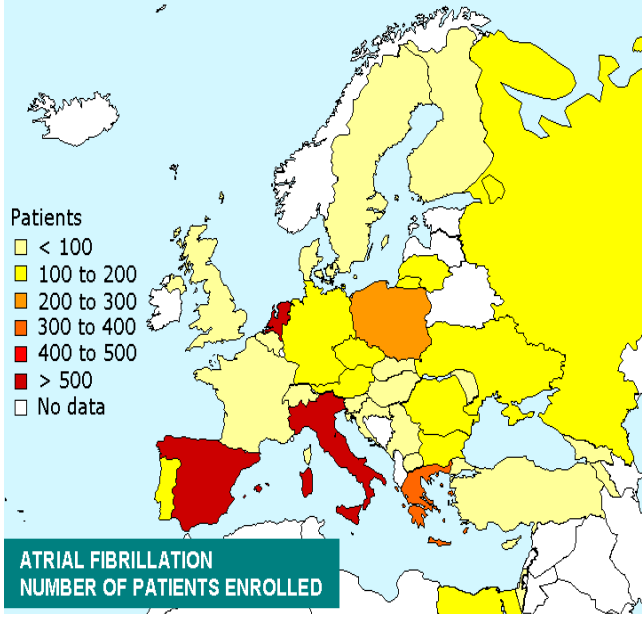
European Heart Journal
doi:10.1093/eurheartj/ehi505

Clinical research

Atrial fibrillation management: a prospective survey in ESC Member Countries

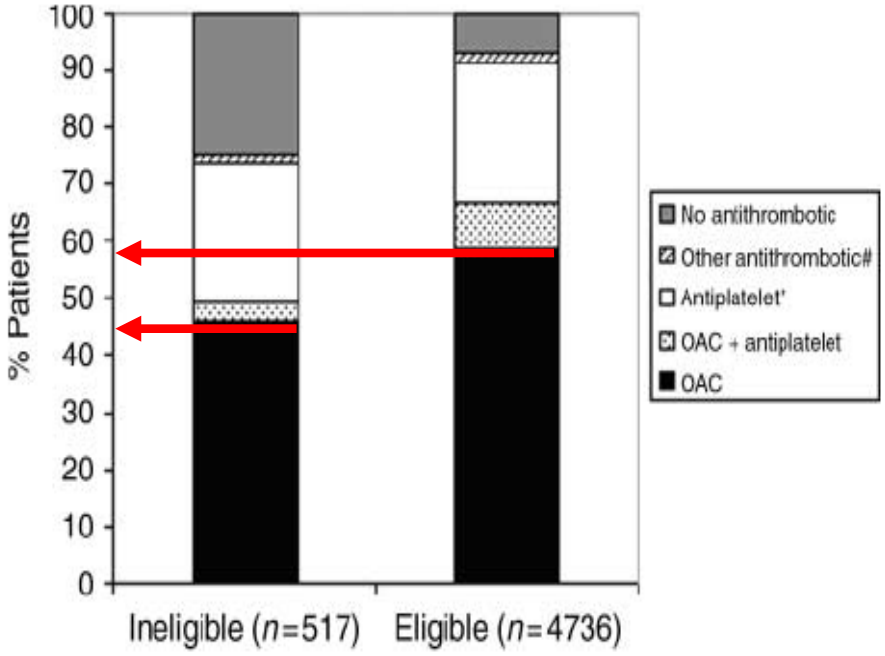
The Euro Heart Survey on Atrial Fibrillation

Robby Nieuwlaat[1*], Alessandro Capucci[2], A. John Camm[3], S. Bertil Olsson[4], Dietrich Andresen[5], D. Wyn Davies[6], Stuart Cobbe[7], Günter Breithardt[8], Jean-Yves Le Heuzey[9], Martin H. Prins[10], Samuel Lévy[11], and Harry J.G.M. Crijns[1] on behalf of the Euro Heart Survey Investigators



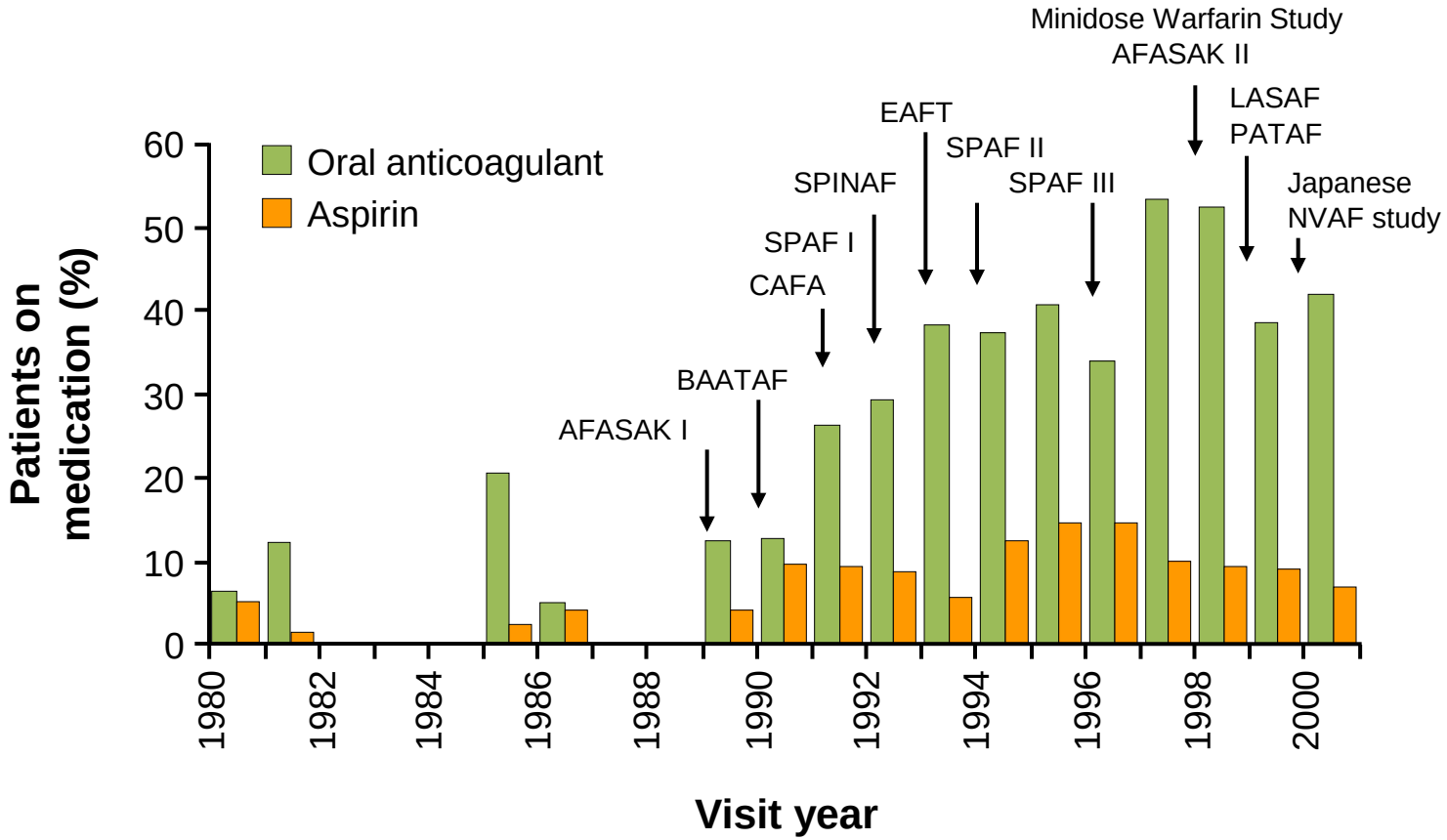
Oral anticoagulation

over utilisation in low risk patients



under utilisation in high risk patients

Oral anticoagulant and aspirin use in atrial fibrillation from 1980 to 2000



Stafford and Singer. Arch Intern Med 1996;156:2537–2541

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

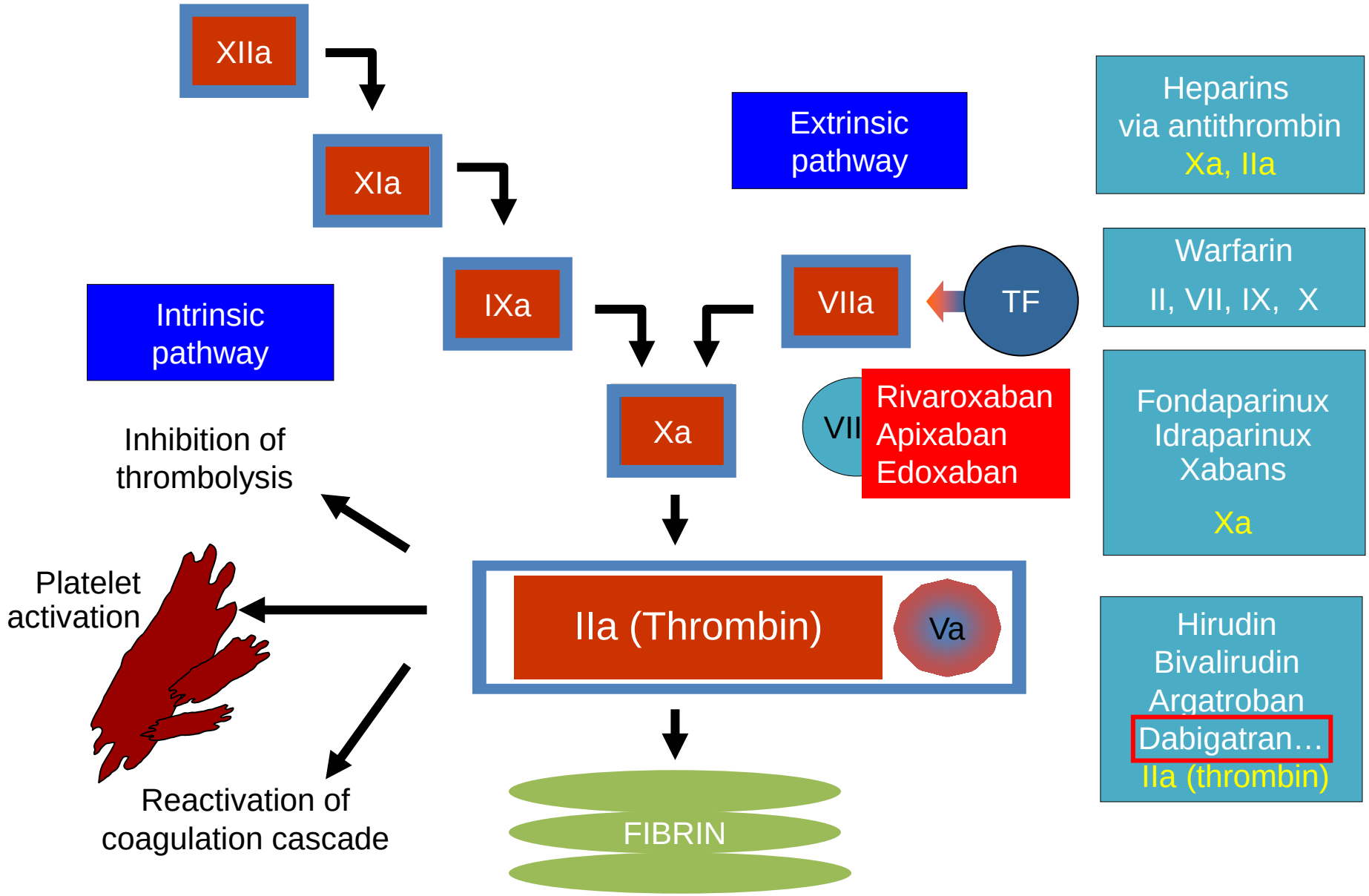
Numerous food–drug interactions

Numerous drug–drug interactions

Warfarin resistance

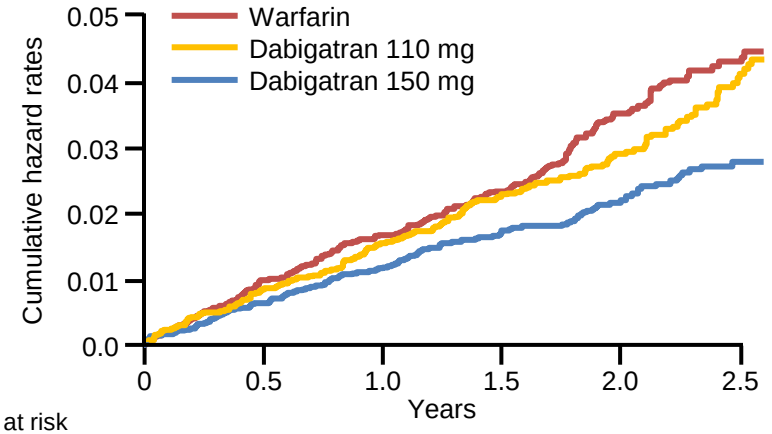
Ansell et al. Chest 2008;133;160S–198S;
Umer Ushman et al. J Interv Card Electrophysiol 2008;22:129–137;
Nutescu et al. Cardiol Clin 2008;26:169–187

Coagulation cascade



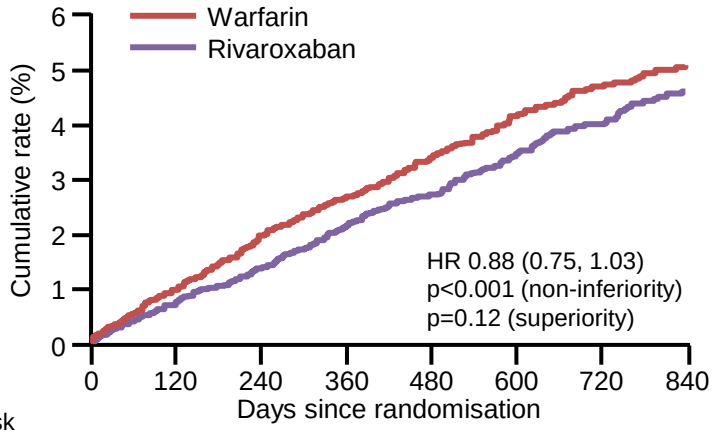
Stroke or systemic embolism (ITT)

RE-LY[1] 2009



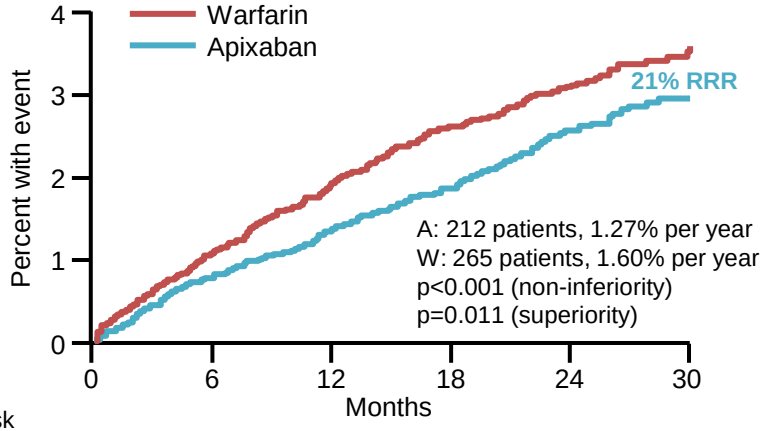
No at risk						
Warfarin	6022	5862	5718	4593	2890	1322
Dab 110 mg	6015	5862	5710	4593	2945	1385
Dab 150 mg	6076	5939	5779	4682	3044	1429

ROCKET AF[2] 2011



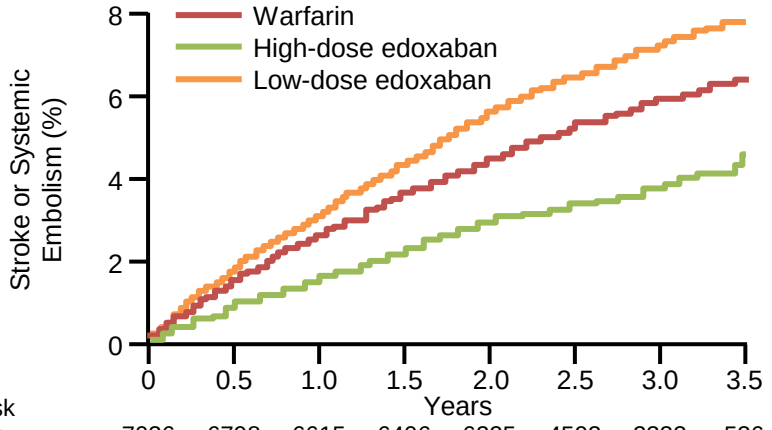
No at risk								
Rivaroxaban	7081	6879	6683	6470	5264	4105	2951	1785
Warfarin	7090	6871	6656	6440	5225	4087	2944	1783

ARISTOTLE[3] 2011



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

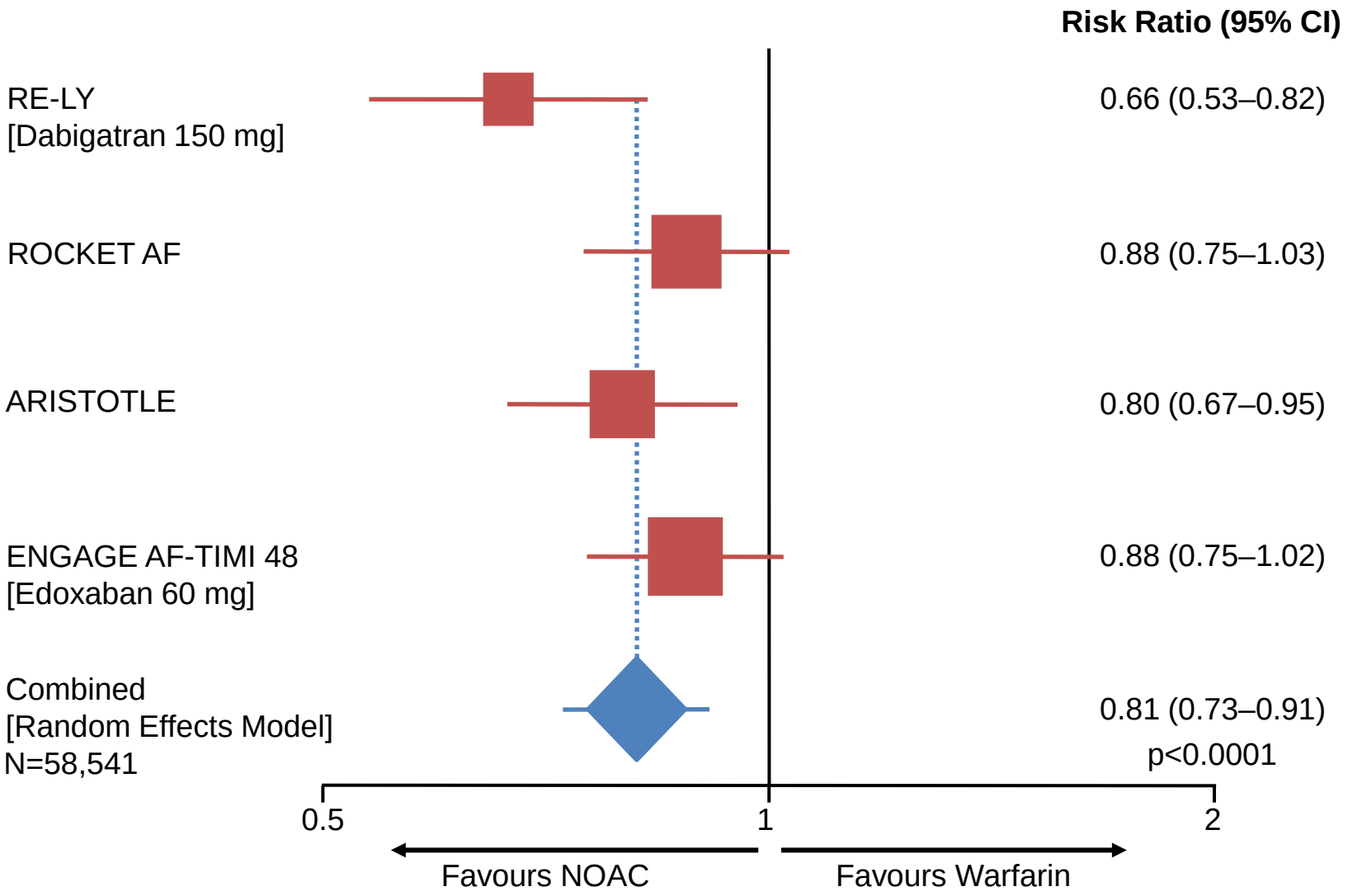
ENGAGE AF-TIMI 48[4] 2013



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

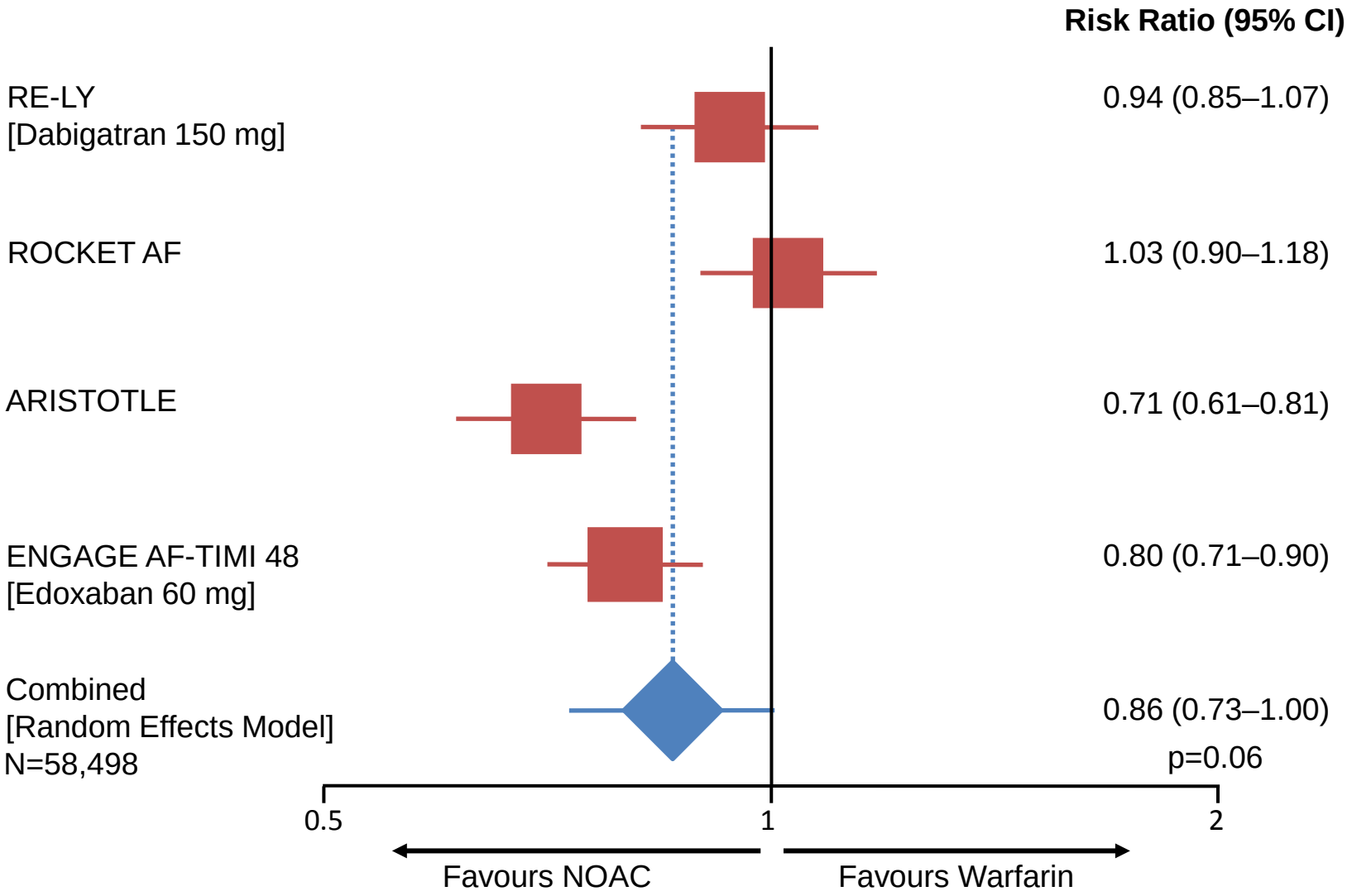
All NOACs: Stroke or SEE



Heterogeneity p=0.13

Ruff et al. Lancet 2014;383:955–962

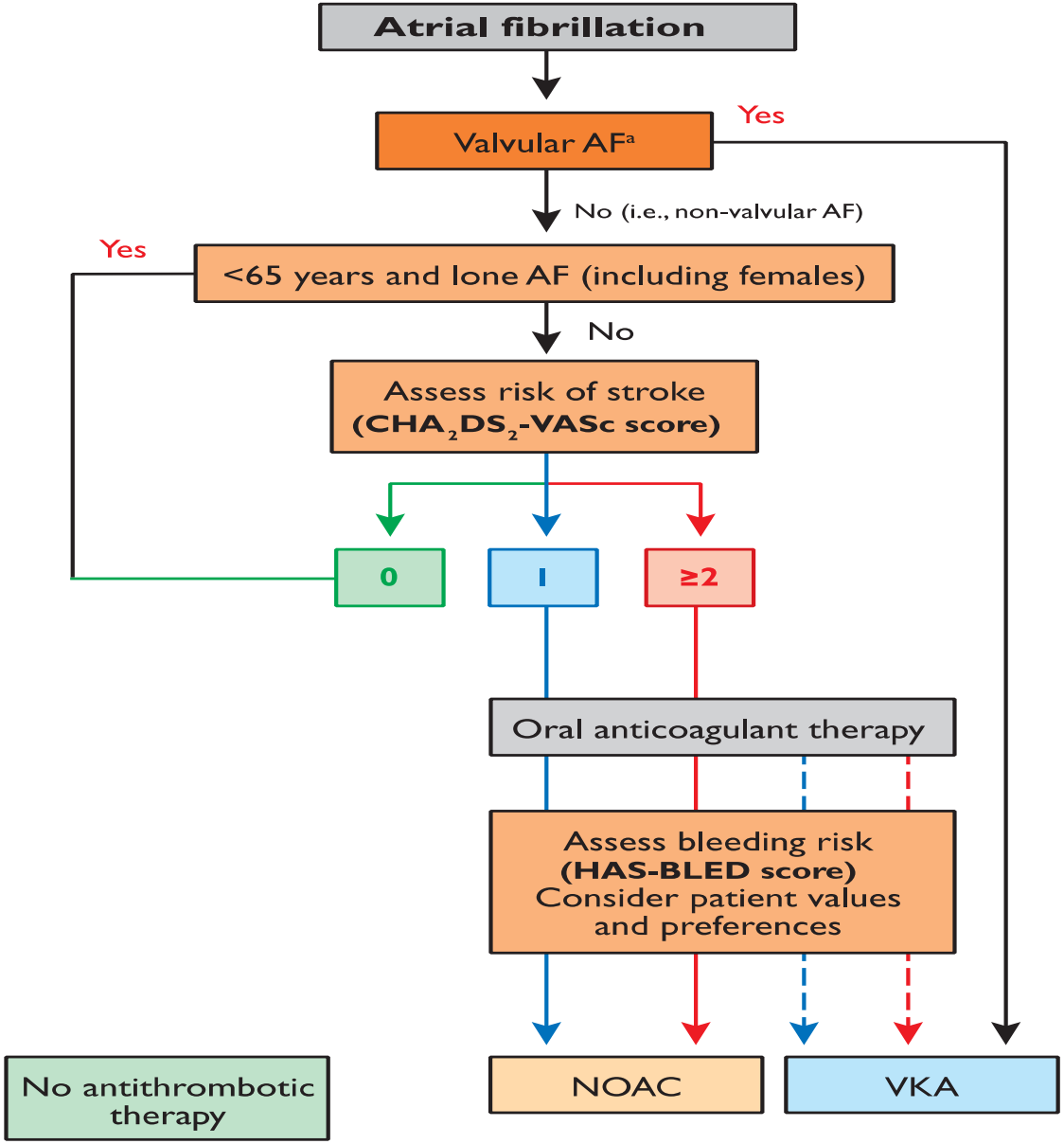
All NOACs: Major bleeding



Heterogeneity p=0.001

Ruff et al. Lancet 2014;383:955–962

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
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



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


GLORIA™ AF
Global Registry on Long-Term Oral Antithrombotic
Treatment in Patients with Atrial Fibrillation


EORP


Garfield
global anticoagulant registry in the field


PREFER in AF

Global summary

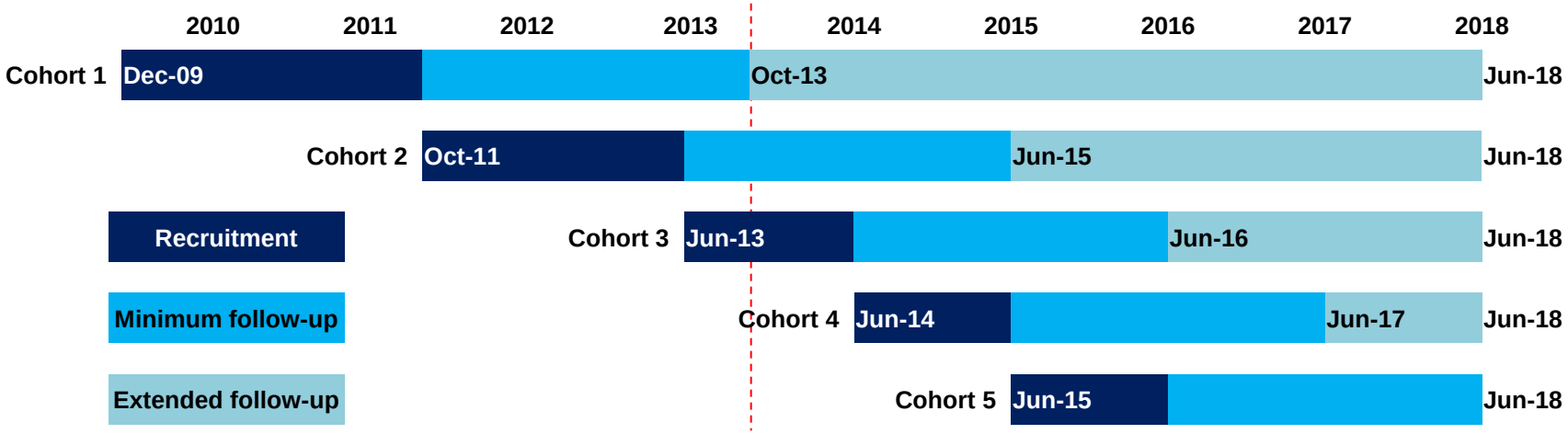
11 October 2013

Status

- 25,389 patients enrolled
  - 20,298 prospective patients
  - 11,792 patients enrolled in C2
  - 3067 patients enrolled in C3
- 30 countries active in C2 and C3
- 4 new countries being initiated
  - SWI, TUR, UAE, US

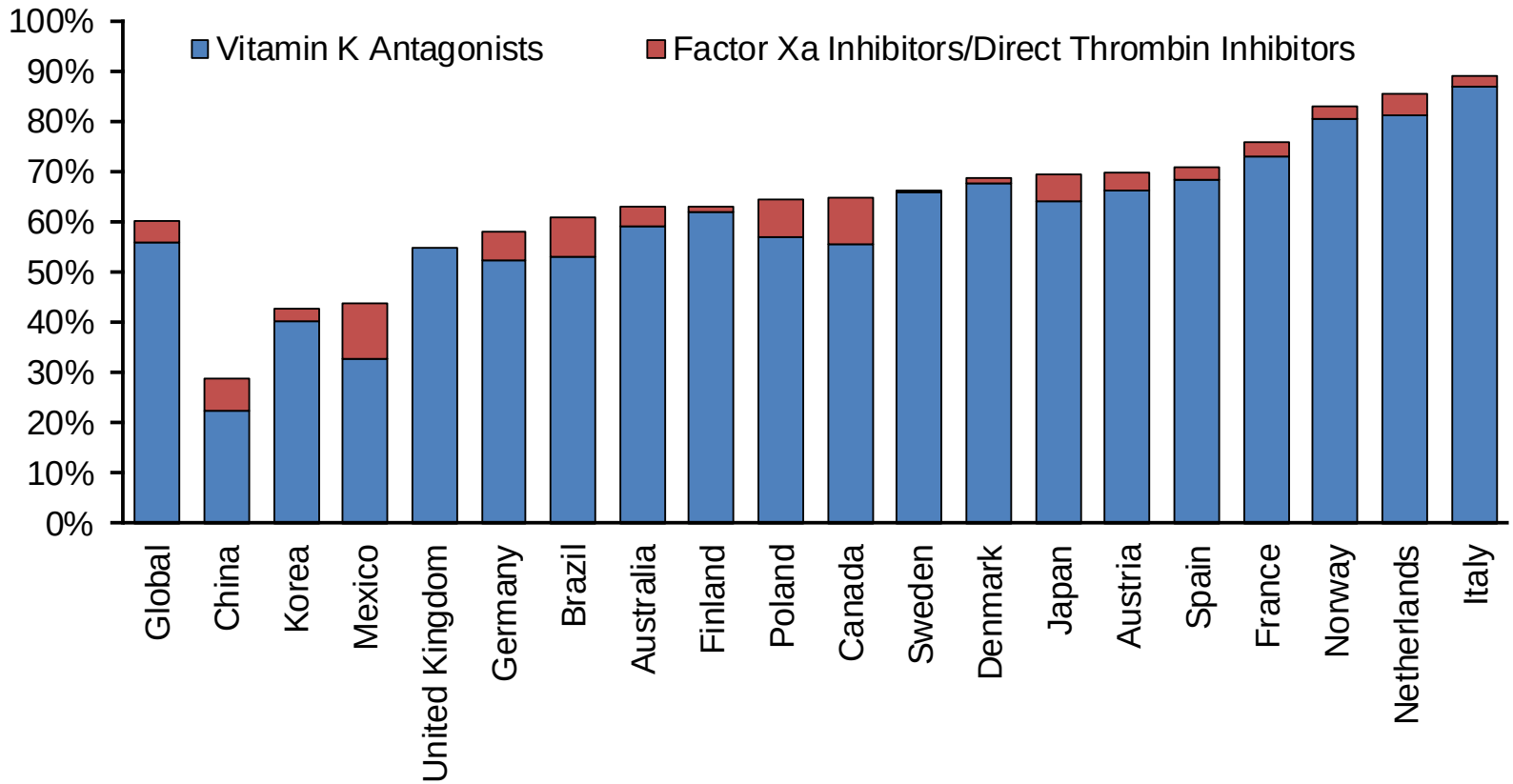
Next…

- Target is 12 month enrolment period for C3, C4, C5
- Operational priorities:
  - Initiation of 4 new countries
  - Monitoring & SDV
  - C1 database lock
  - C3 site activation & recruitment



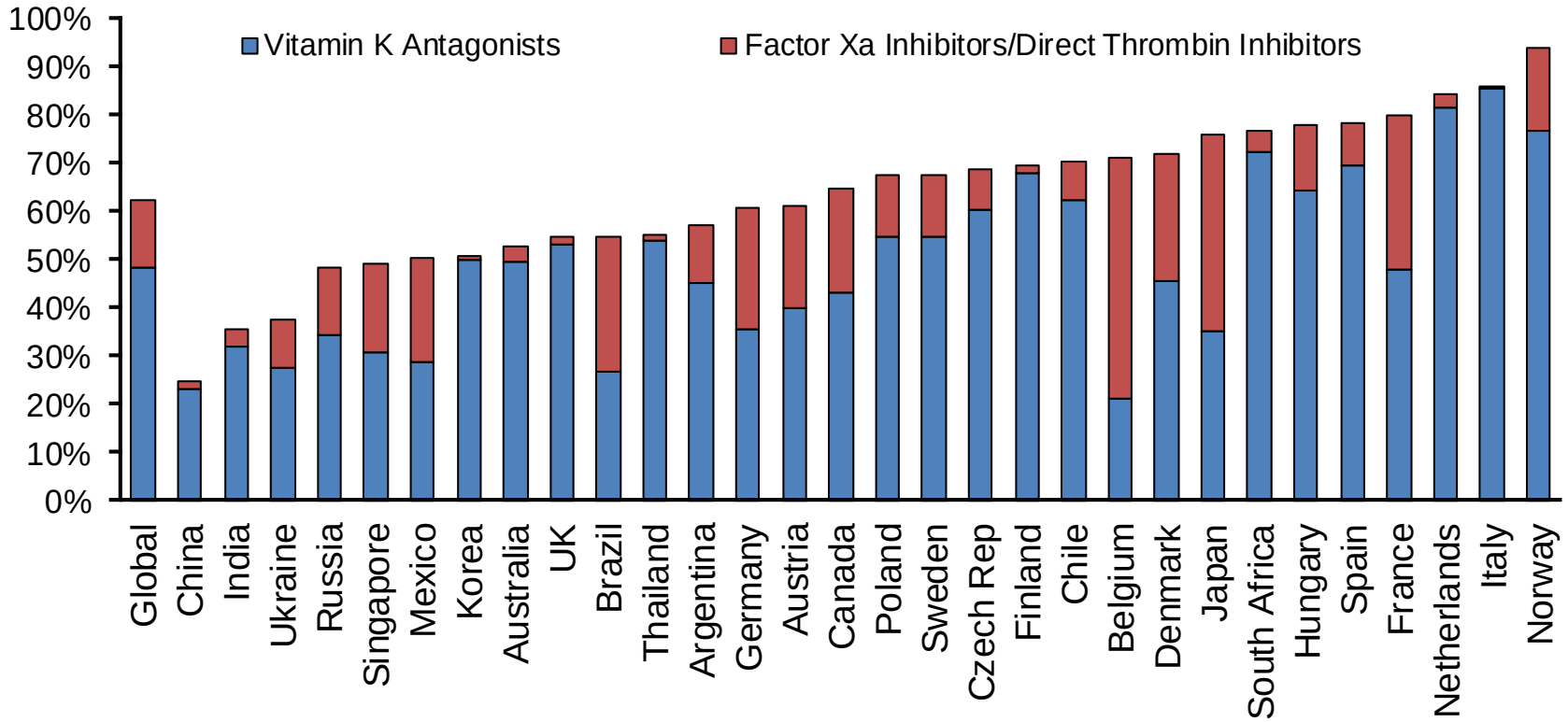
Proportion of patients receiving anticoagulant therapy varies widely between countries

Preliminary data - GARFIELD Cohort 1 (N=10,614; 19 countries)



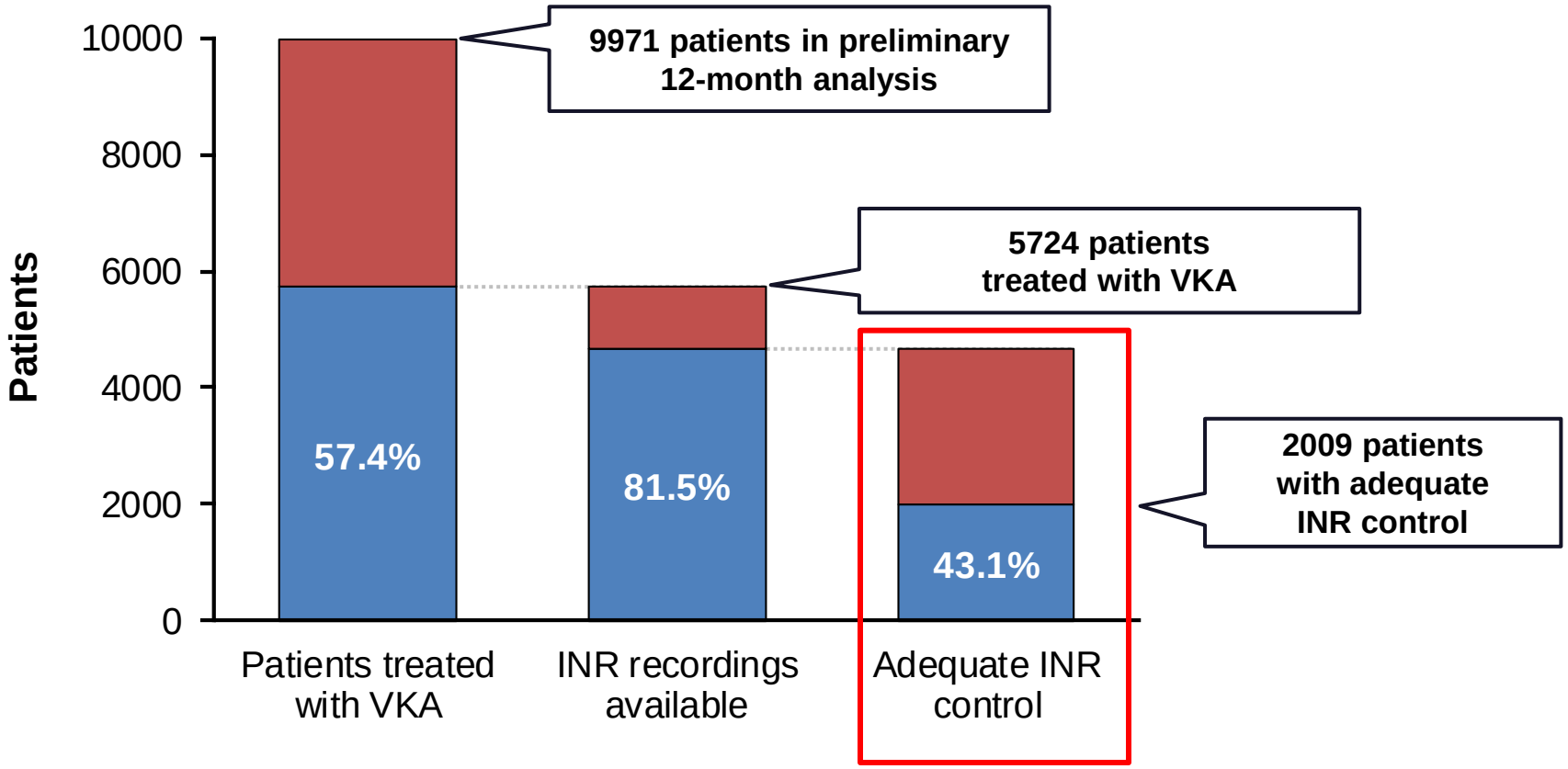
Pattern of anticoagulation therapy also influenced by approval and reimbursement of new oral anticoagulants

Preliminary data - GARFIELD Cohort 2 (N=10,544; 30 countries)



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

Preliminary data



Europace Advance Access published October 1, 2013

Europace
doi:10.1093/europace/eut263

CLINICAL RESEARCH

Management of atrial fibrillation in seven European countries after the publication of the 2010 ESC Guidelines on atrial fibrillation: primary results of the PREvention oF thromboemolic events—European Registry in Atrial Fibrillation (PREFER in AF)

Paulus Kirchhof[1,2*], Bettina Ammentorp[3], Harald Darius[4], Raffaele De Caterina[5], Jean-Yves Le Heuzey[6], Richard John Schilling[7], Josef Schmitt[3], and Jose Luis Zamorano[8]

Patient enrolment

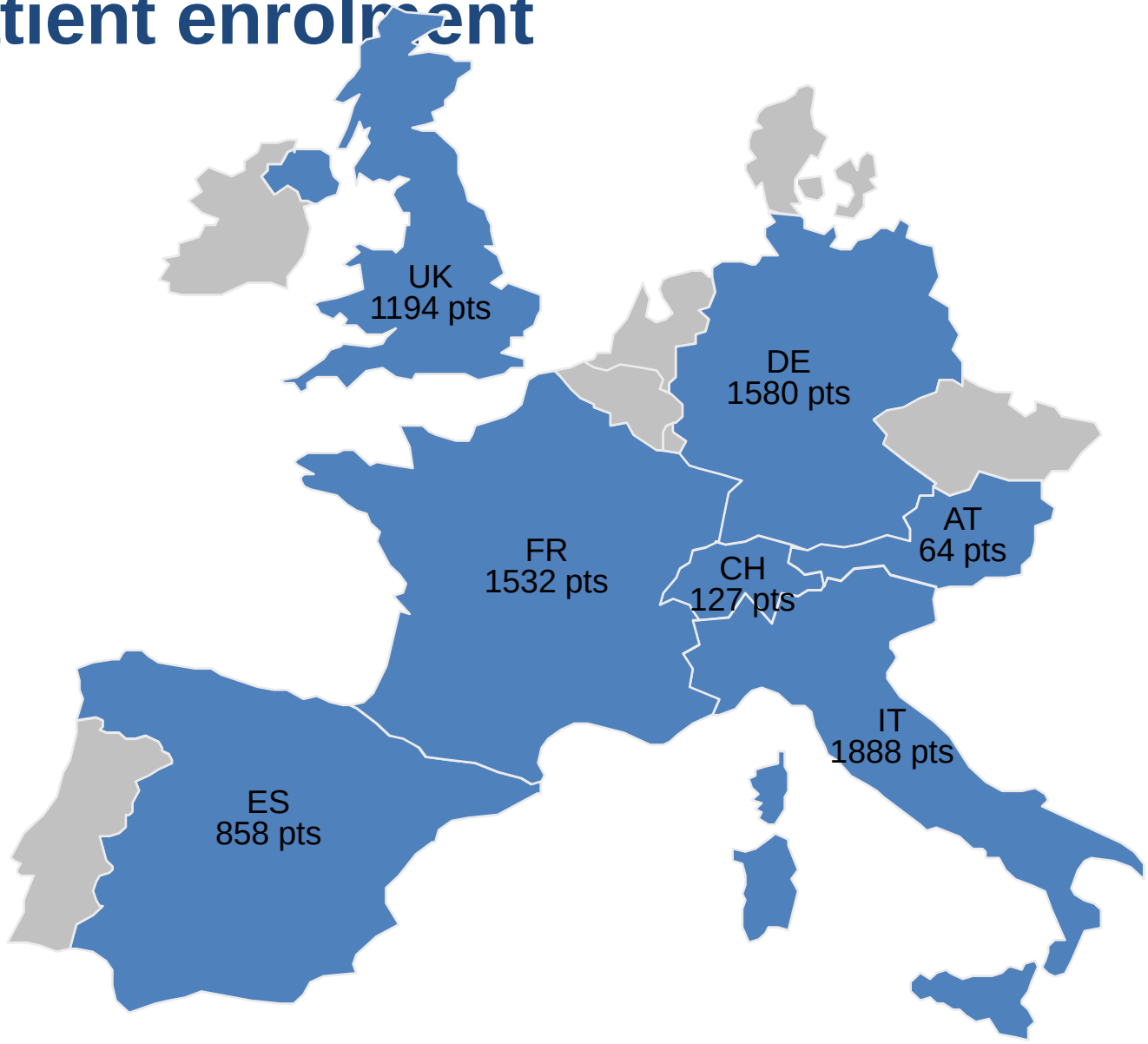


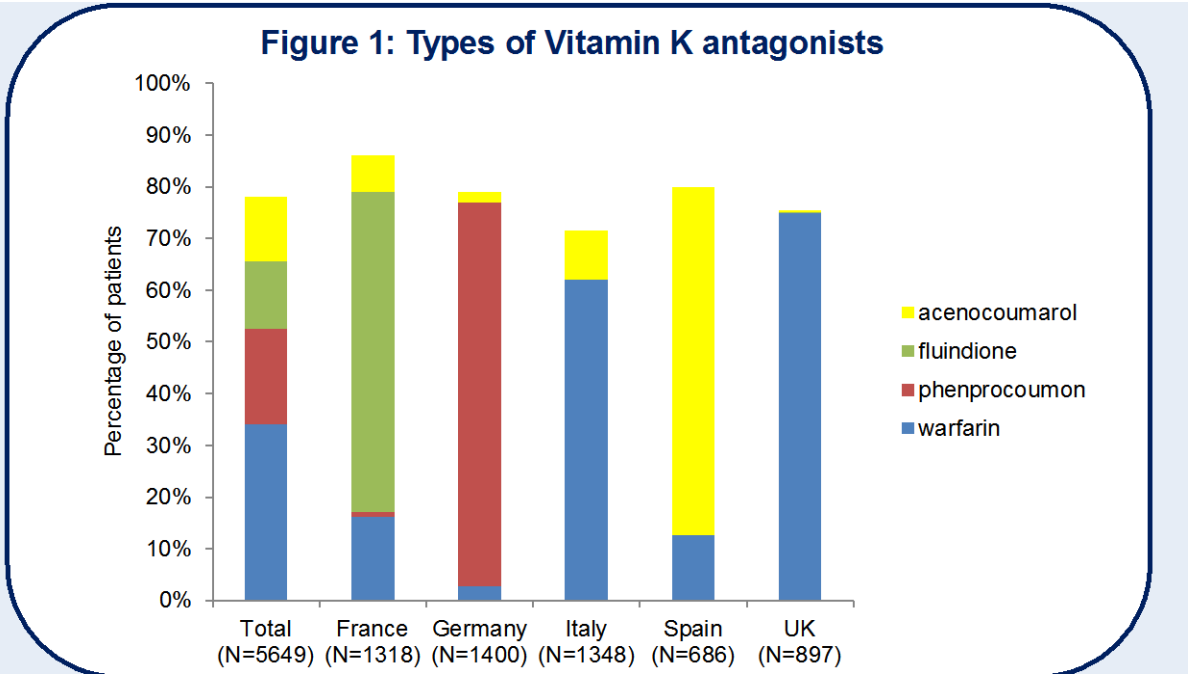
Table 3: Rate vs rhythm control and anticoagulation

	Total (N=7243)	France (N=1532)	Germany (N=1771)	Italy (N=1888)	Spain (N=858)	UK (N=1194)
Pts with rhythm control * (%)	50.7	60.7	44.1	59.2	41.8	39.5
Pts with adequate heart rate control (HR 60-100), %	78.6	79.4	81.4	78.7	79.5	72.6
Pts with acceptable heart rate control (HR 50-59 or 101-110), %	14.3	14.9	12.2	13.8	15.5	16.5
Pts without adequate heart rate control (HR<50 or >110), %	7.1	5.7	6.4	7.5	5.1	11.0
Antiplatelet agents (AP), %	22.1	16.9	17.2	27.0	18.7	30.7
Vitamin K antagonists (VKA), %	78.0	86.0	79.1	71.4	80.0	75.1
Combination therapy (VKA + AP), %	9.9	10.1	7.7	8.8	10.3	14.7
Novel oral anticoagulants, %	6.1	6.0	11.6	0.3	11.2	3.7
No antithrombotic therapy, %	6.5	4.1	5.0	10.4	5.7	6.5

** Rhythm control defined as patients with cardioversion, ablation or antiarrhythmic drugs*

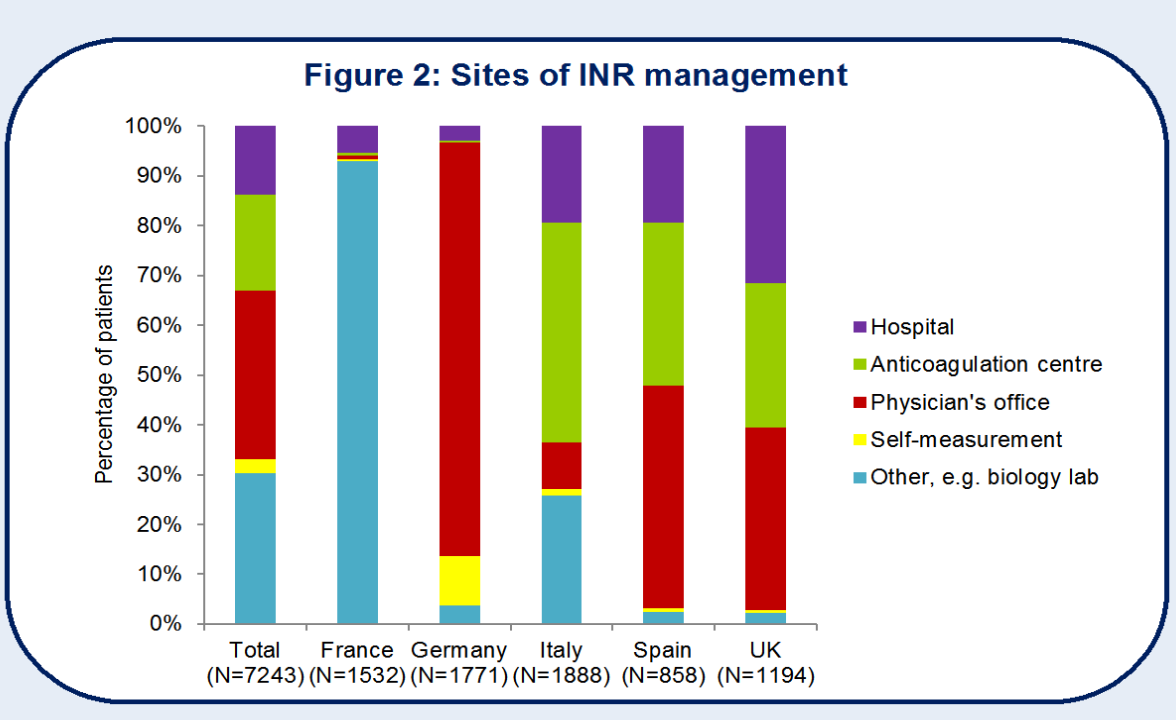
LE HEUZEY J.Y. et al. ESC 2013

PREFER *in* AF



PREFER in AF

LE HEUZEY J.Y. et al. Thrombosis and Haemostasis 2014; 111 : 833 - 41



Global Registry on Long-Term oral Anti-thrombotic Treatment in Patients with Atrial Fibrillation

Collect global information on newly diagnosed AF-patients with at least one additional risk factor for stroke prior and after the launch of dabigatran etexilate

56,000 patients

Initiation pre-launch

Launch of dabigatran

Phase I
(Pre-Launch)

Cross-Sectional Analysis:
Patient population
Treatment pattern
Regional variations

6-9 years
(dependent on dabigatran launch in respective countries)

Phase II
(Post-Launch)
Dabigatran Phase

Cross-Sectional Analysis:
Patient population
Treatment patterns

Cohort Analysis:
Collect data on dabigatran patients (safety, e.g. dyspepsia)

2 years
(dependent on comparability of initiators)

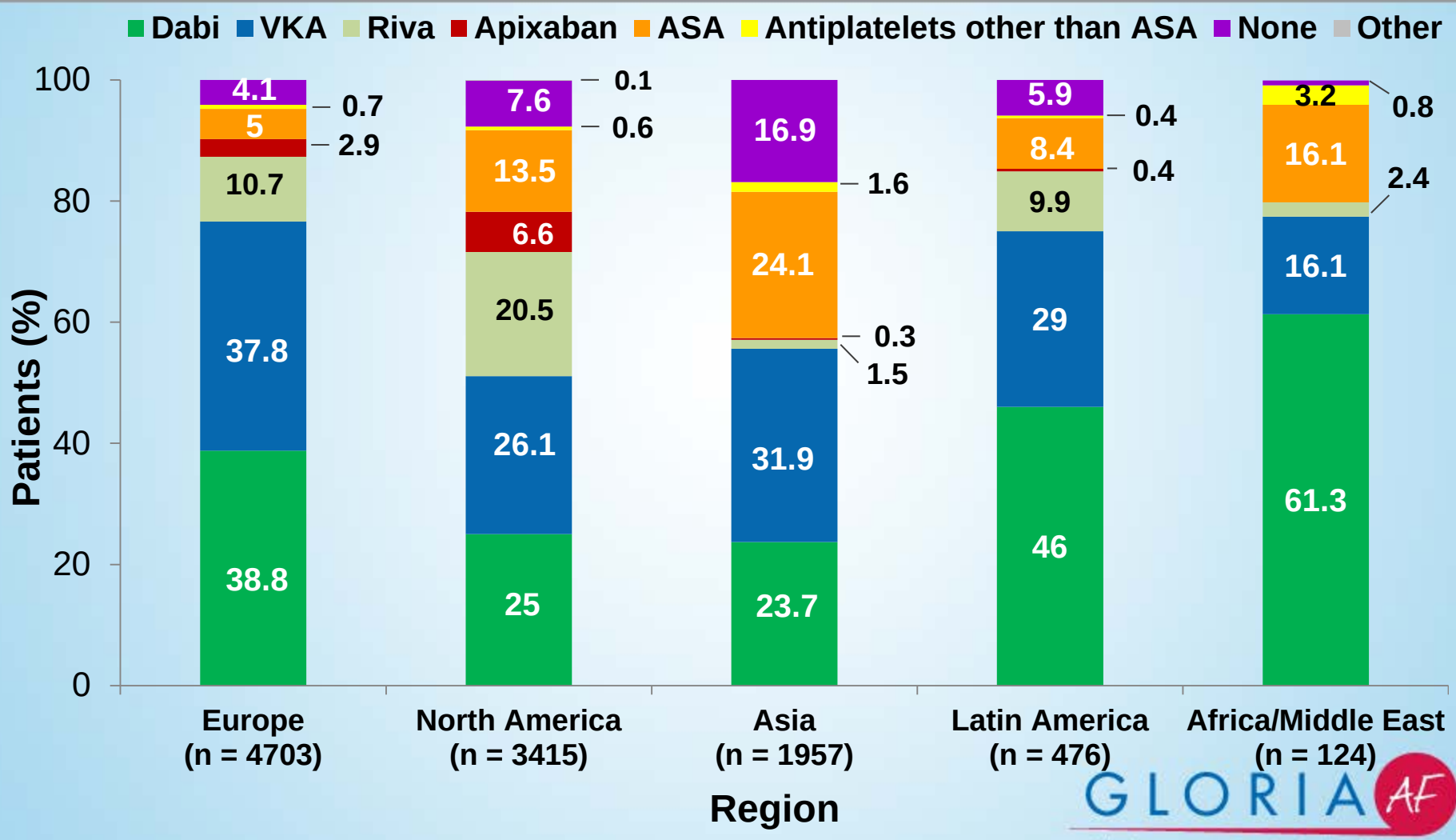
Phase III
(Post-Launch)
Comparative Phase

Cross-Sectional Analysis:
Patient population
Treatment pattern

Comparative Analysis:
Efficacy and safety of different treatment regimens

4-6 years
(observation time per patient 3 years)

Antithrombotic Treatment at Baseline – By Region



•'Other' includes combination of oral anticoagulants.

GLORIA AF
Global Registry on Long-Term Oral Antithrombotic Treatment in Patients with Atrial Fibrillation

A prospective survey in European Society of Cardiology member countries of atrial fibrillation management : baseline results of EuroObservational Research Programme Atrial Fibrillation (EORP-AF) Pilot General Registry

G. LIP et al. Europace, December 17, 2013

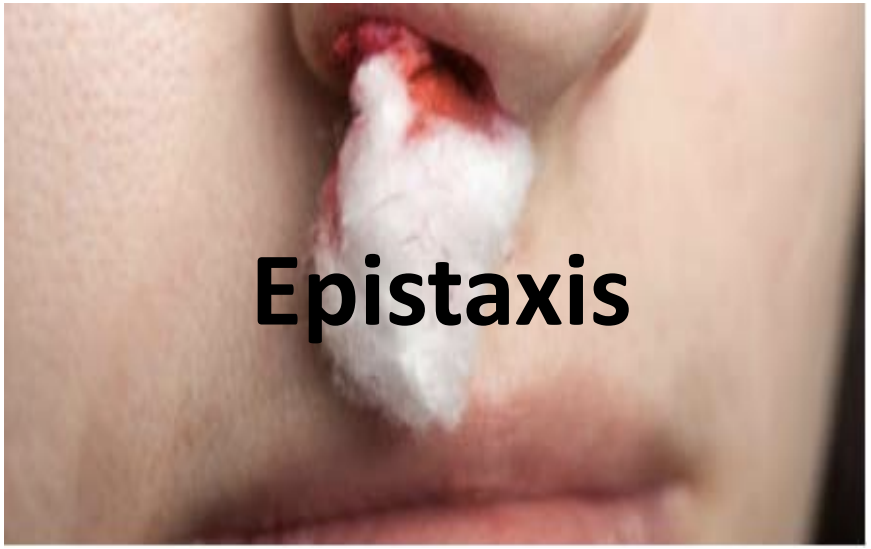
- 3119 patients, from February 2012 to March 2013
- 40.4% female, mean age 68.8 years, lone AF 3.9%, amiodarone most common antiarrhythmic agent (20%), OAC in 80% overall, NOACs in 8.4%, other antithrombotics 33%
- In CHA_2DS_2-VASc = 0, OACs used in 56.4% and 26.3% had no antithrombotic therapy

Bristol-Myers Squibb

Pfizer

EUROPEAN SOCIETY OF CARDIOLOGY

FEAR OF BLEEDING



… Hematuria

Menorrhagia

Rectorrhagia …

Advantages of Direct Oral Anticoagulants

- No routine monitoring
- Less intracranial hemorrhages in the trials
- Superiority versus Warfarine in some cases
- Short half lifes
- Less inter and intraindividual variability of the effect
- Simplification or suppression of bridging
- No major interaction with food

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?

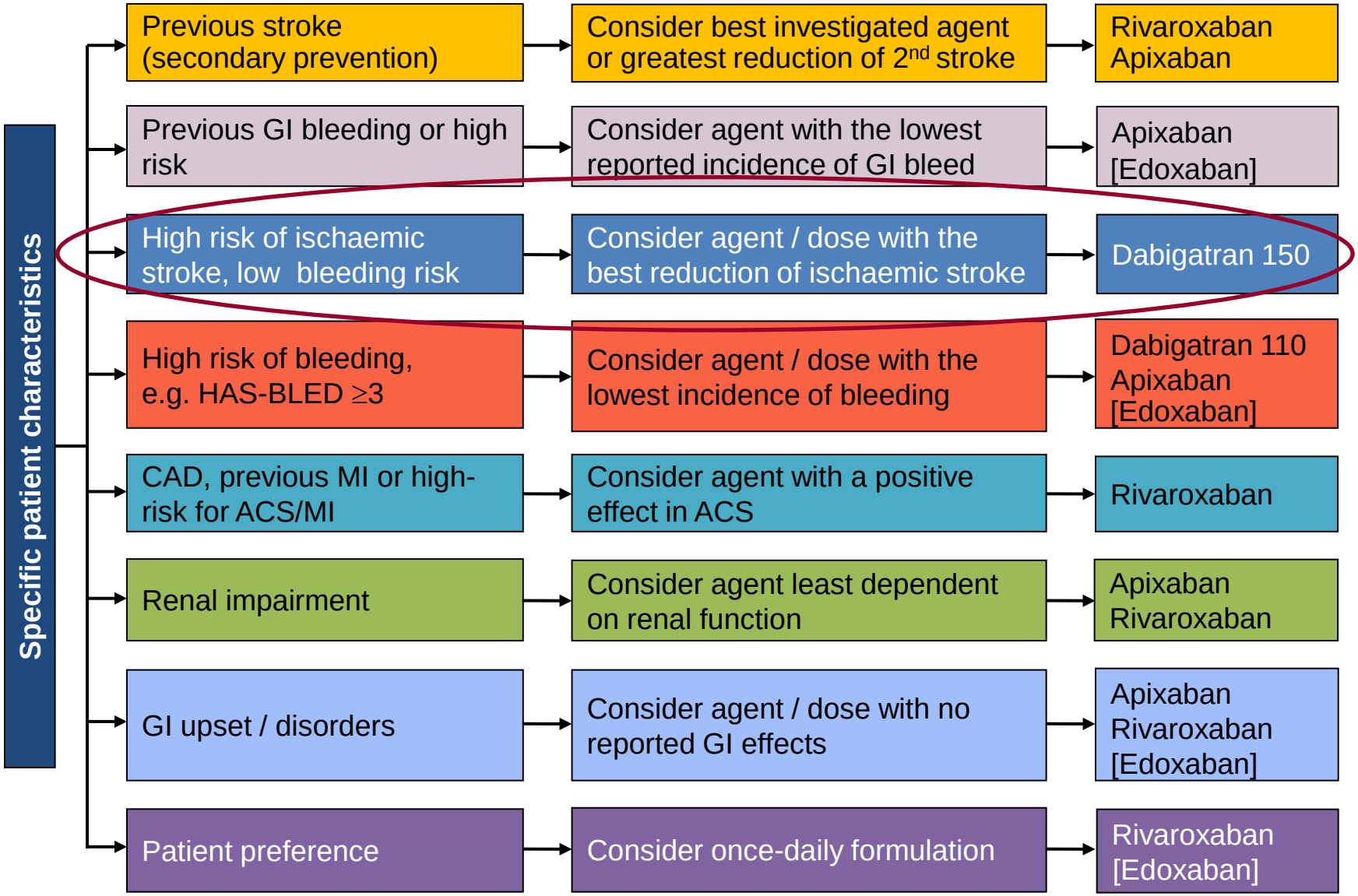
NO HEAD TO HEAD COMPARISON

- 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 BID
- 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

Pointers towards which NOAC to choose



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

Comparisons?

Conclusions

1- The rate of anticoagulation in atrial fibrillation patients, on a global perspective, remains low

2- This rate is higher in western countries and when the patient is treated by a cardiologist

3- In patients treated by vitamine K antagonists, the INRs are often out of the target

4- Direct oral anticoagulants are easier to use, induce less intracranial hemorrhages but have not completely changed the landscape, mainly because of their high cost and the difficulties to afford these drugs in many countries

5- Fear of bleeding, both from patients and practitioners, is also a reason for this low rate of anticoagulation