Pros and Cons of Individual Agents Based on Large Trial Results: RELY, ROCKET, ARISTOTLE, AVERROES

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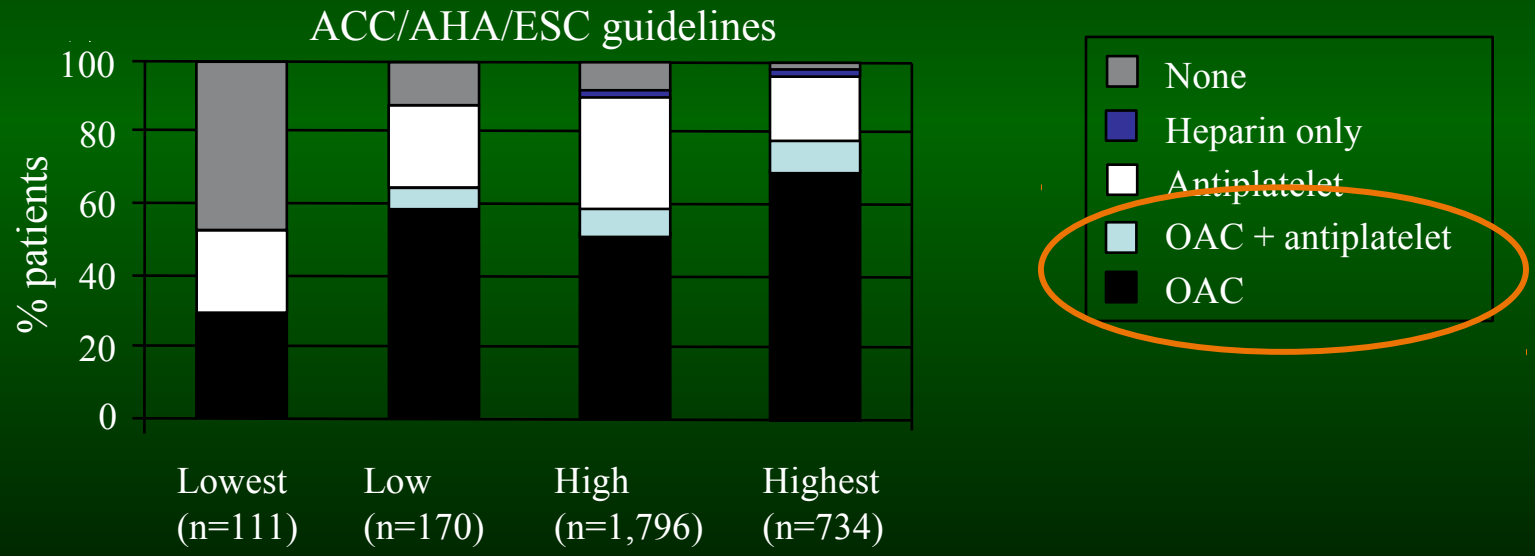
Where were we before with warfarin?



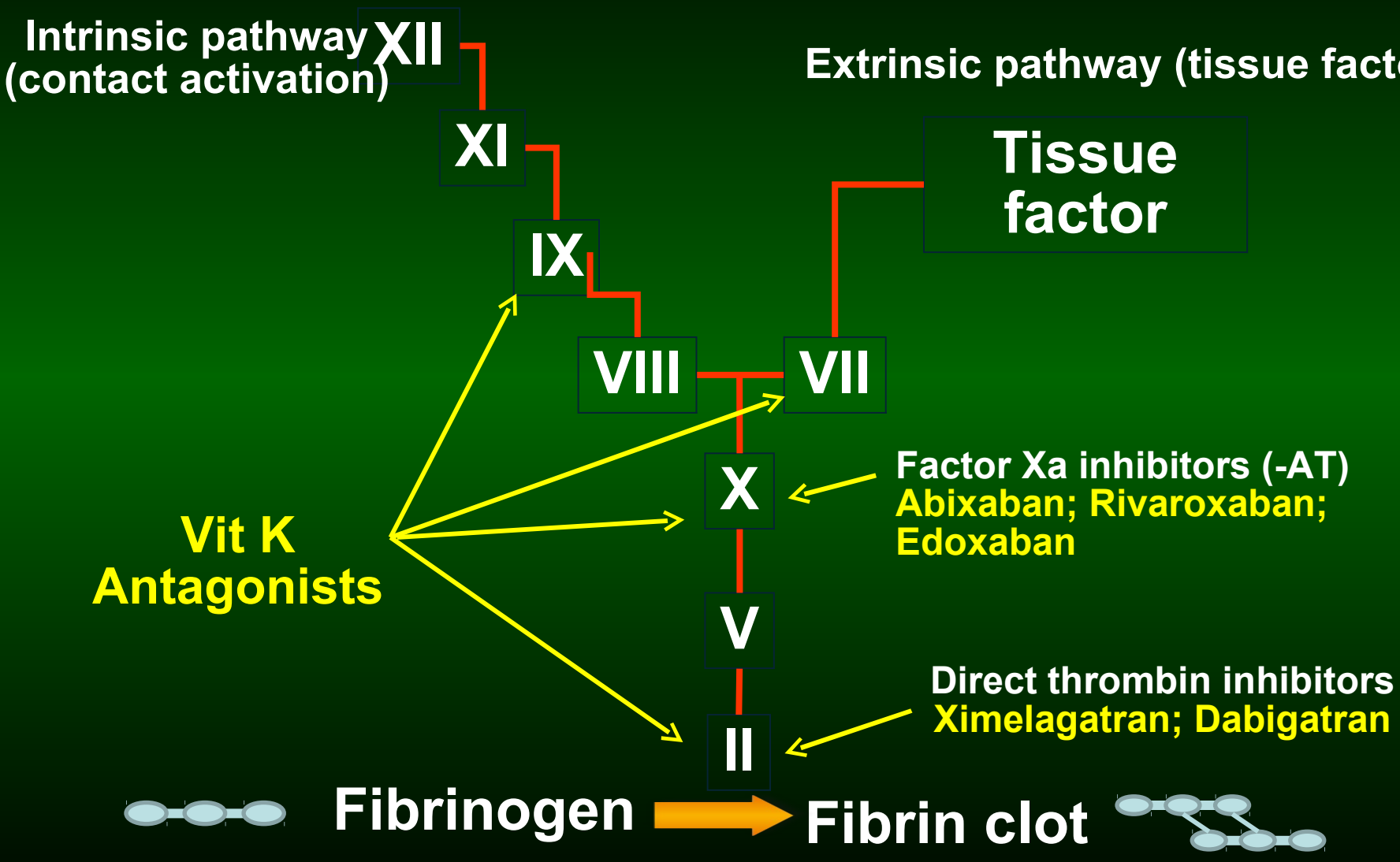
1. Nieuwlaat R, et al. Eur Heart J 2006;27:3018-26;
2. Lip GY, Tse HF. Lancet 2007;370:604-18; 3. Deplanque D, et al. Br J Clin Pharmacol 2004;57:798-806

Requirements of new antithrombotic agents

- At least as effective as warfarin
- Predictable response
- Wide therapeutic window
- Low incidence and severity of adverse effects
- Oral fixed dose
- No need for routine anticoagulation monitoring
- Low potential for food or drug interactions
- Fast onset and offset of action
- Cost-effective

Adapted from Lip GY et al. EHJ Suppl 2005;7:E21–5

Targets in Coagulation Pathways



Nutescu EA, et al. Cleve Clin J Med 2005; 72 Suppl 1:S2-6

AT: antithrombin;
VKAs: vitamin K antagonists

Characteristics of New OACs

	Dabigatran (RE-LY)[70,71]	Rivaroxaban (ROCKET-AF)[3]	Apixaban (ARISTOTLE)[4]
Drug characteristics			
Mechanism	Oral direct thrombin inhibitor	Oral direct factor Xa inhibitor	Oral direct factor Xa inhibitor
Bioavailability, %	6	60–80	50
Time to peak levels, h	3	3	3
Half-life, h	12–17	5–13	9–14
Excretion	80% renal	2/3 liver, 1/3 renal	25% renal, 75% faecal
Dose	150 mg b.i.d.	20 mg o.d.	5 mg b.i.d.
Dose in renal impairment	110 mg b.i.d. **FDA: 75 mg b.i.d.**	15 mg o.d. (if CrCl 30-49 mL/min)	2.5 mg b.i.d.
Special considerations	Intestinal absorption is pH-dependent and is reduced in patients taking proton pump inhibitors	Higher levels expected in patients with renal or hepatic failure	
	Increased risk of bleeding in patients taking verapamil/amiodarone/quinidine/ketoconazole	Activity lower in fasted patients so should be taken after food	

ESC Guidelines, 2012

Randomized Evaluation of Long-Term Anticoagulant Therapy (RE-LY) With Dabigatran Etexilate

Prospective, multicenter, randomized, open-label, controlled parallel group, noninferiority trial

Nonvalvular atrial fibrillation at moderate to high risk for stroke or systemic embolism (at least one high risk factor)

Warfarin	Dabigatran Etexilate	Dabigatran Etexilate
1 mg, 3 mg, 5 mg (INR 2.0 - 3.0)	110 mg bid	150 mg bid
N = 6000	N = 6000	N = 6000

Primary objective: noninferiority to warfarin

Minimum 1-year follow-up, maximum of 3 years and mean of 2 years of follow-up

Primary endpoint: stroke + systemic embolism (SE)

Safety: bleeding events during treatment

50% of enrolled patients were naïve to previous oral AC

Ezekowitz MD, et al. *Am Heart J* 2009;157:805-10.
Connolly SJ., et al. *NEJM* published online on Aug 30th 2009.
DOI 10.1056/NEJMoa0905561
http://clinicaltrials.gov/ct2/show/NCT00262600

ROCKET AF

Prevention of Stroke and Noncentral Nervous Systemic Embolism in Subjects With Nonvalvular Atrial Fibrillation

At least 2 risk factors :
- CHF
- Hypertension
- Age ≥ 75
- Diabetes

or: Stroke, TIA, or systemic embolus

Rivaroxaban
20 mg od
(15 mg for CrCl 30-49)

Prospective, randomized, double-blind, double-dummy, parallel-group, multicenter, event-driven noninferiority study (n ~ 14,000)

Warfarin
INR target - 2.5
(2.0-3.0 inclusive)

Monthly monitoring and adherence to standard of care guidelines

Primary endpoint: stroke or non-CNS systemic embolism

Other outcomes: Composite of major and non-major clinically relevant bleeding events

CLINICAL CARDIOLOGY

http://clinicaltrials.gov/ct2/show/NCT00403767

theheart.org from WebMD

ARISTOTLE: Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation

N = 15,000

AF and ≥ one other risk factor:

- Age ≥ 75 years
- Prior stroke, TIA, or SE
- CHF or LVEF ≤ 40%
- Diabetes mellitus
- Hypertension

Apixaban 5 mg oral bid + Warfarin placebo	Apixaban placebo bid + Warfarin INR 2.5 (range 2-3)

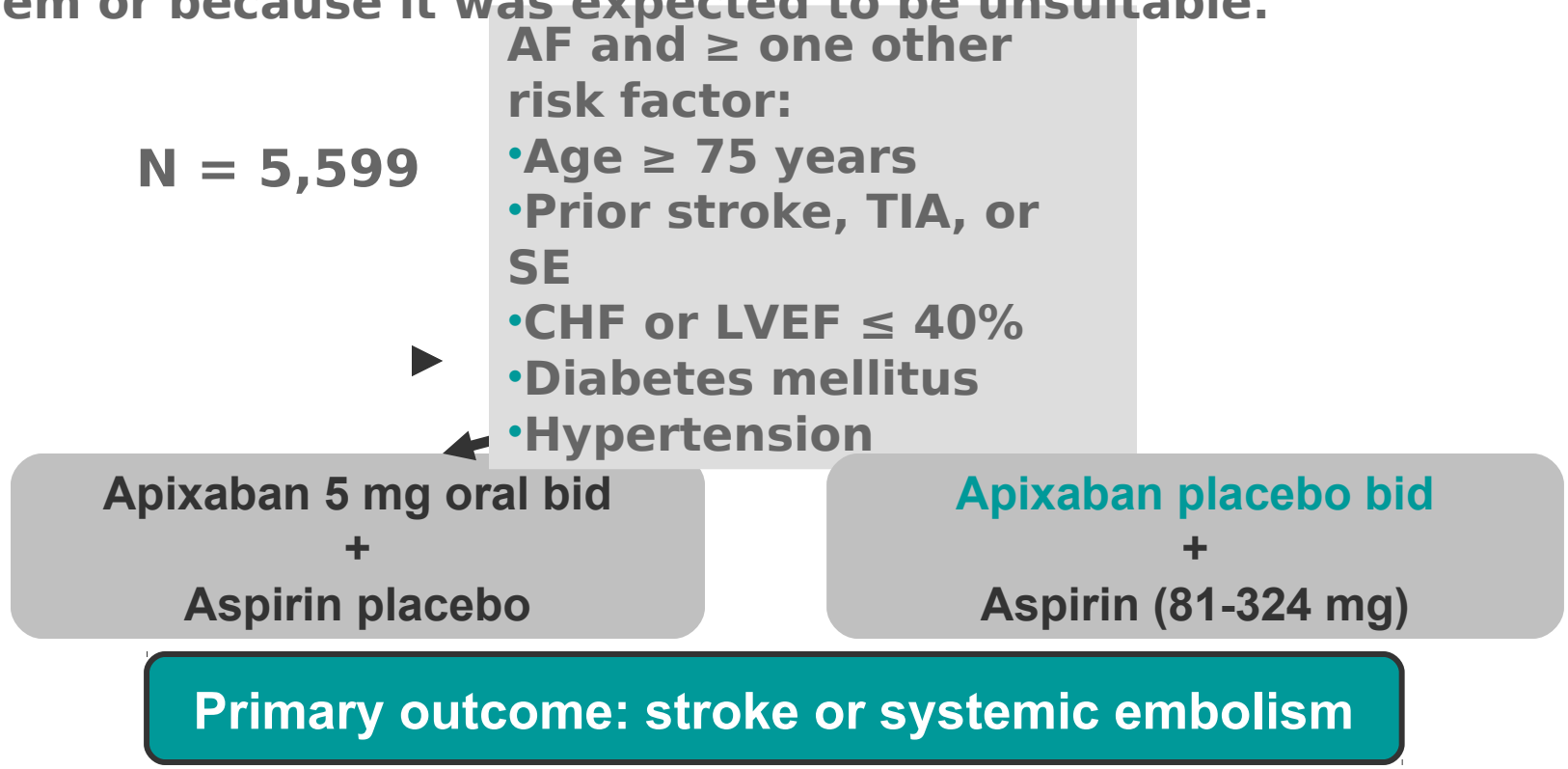
Warfarin/warfarin placebo adjusted by INR/sham INR based on encrypted point-of-care testing device

Primary outcome: stroke or systemic embolism

Other outcomes: confirmed ischemic stroke, hemorrhagic stroke, systemic embolism, all-cause death

AVERROES: Apixaban Vs ASA to Prevent Stroke in AF Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment

- patients could not be receiving vitamin K antagonist therapy, either because it had been demonstrated to be unsuitable for them or because it was expected to be unsuitable.



Other outcomes: confirmed ischemic stroke, hemorrhagic stroke, systemic embolism, all-cause death

ENGAGE-AF TIMI 48
Endoxaban vs Warfarin

- Double-blind, double-dummy
- AF plus 1 or more stroke risk factors
- Stroke or Systemic Embolus
- Non-inferiority
- 16,500 subjects
- Results expected soon

Trial Characteristics of New OACs

Table 2. Comparison of the Design of Phase III Trials of New Oral Anticoagulants

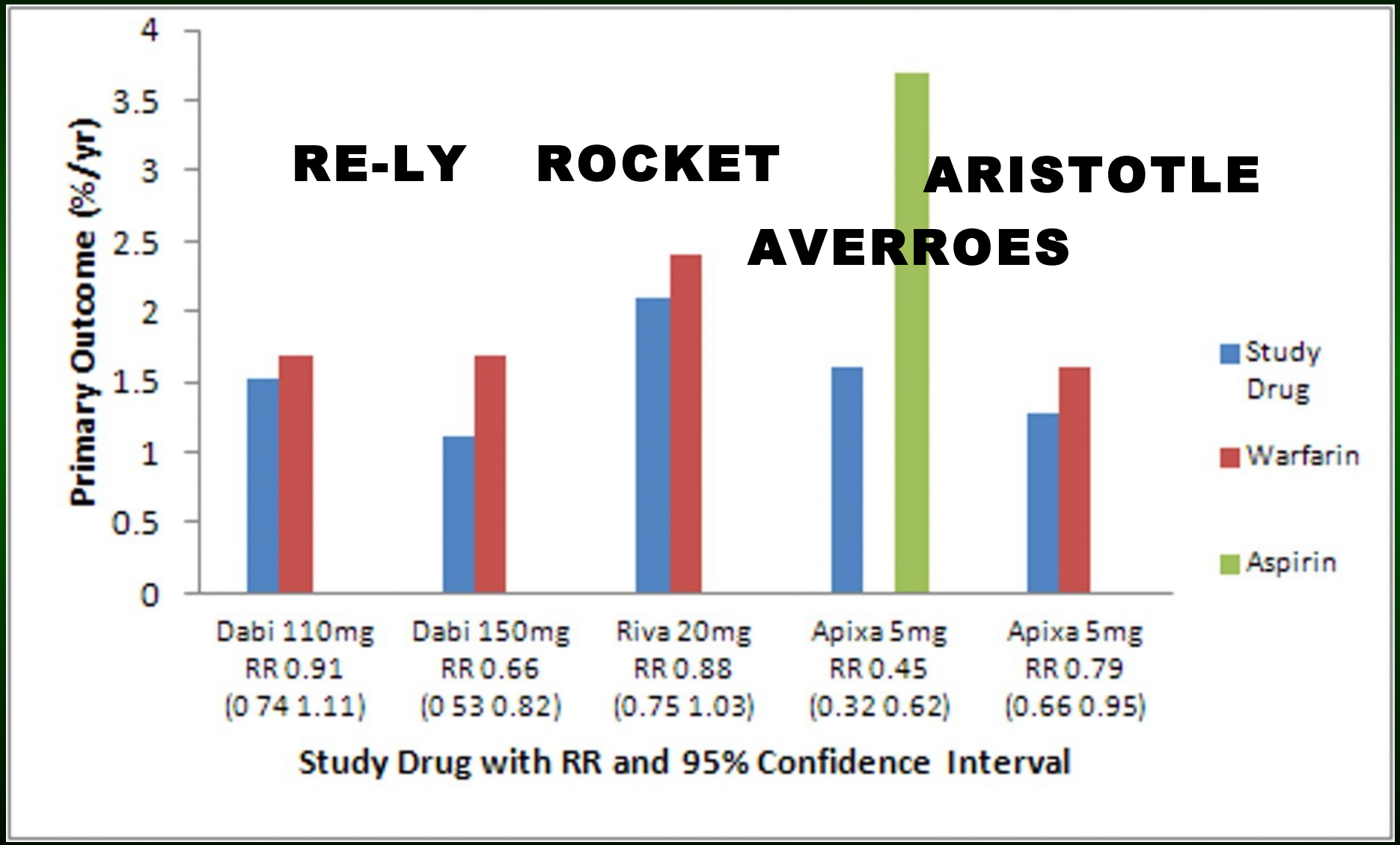
	RE-LY	ROCKET-AF	ARISTOTLE
Inclusion criteria	AF and at least 1 additional risk factor for stroke	AF and at least ≥3 or more risk factors or previous thromboembolism (90% of subjects)	AF and at least 1 additional risk factor for stroke
Exclusion criteria	CrCl <30 mL/min, liver disease, recent stroke	CrCl <30 mL/min, Plt <90 000, uncontrolled HTN, recent stroke	CrCl <25 mL/min, mitral valve stenosis, recent stroke
Design	PROBE	Randomized double-blind, double dummy	Randomized double-blind
Primary stroke	Any stroke or systemic embolism	Any stroke or systemic embolism	Any stroke or systemic embolism
Mean age, y	71.5	73	70
Mean time in treatment range TTR	64%	55%	62%

RE-LY indicates The Randomized Evaluation of Long-Term Anticoagulation Therapy; ROCKET-AF, Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation; ARISTOTLE, Apixaban versus Warfarin in Patients with Atrial Fibrillation; AF, atrial fibrillation; CrCl, creatine clearance; PROBE, prospective, randomized, open-label, blinded end point evaluation; Plt, platelets; HTN, hypertension.

MEAN CHADS2 SCORE 2.1 3.5 2.1

Katsnelson M, Sacco RL, Moscucci M. Progress for stroke prevention with atrial fibrillation: emergence of alternative oral anticoagulants. Stroke. 2012 ;43:1179-85.

Comparison of Primary Outcomes Stroke of Systemic Embolism



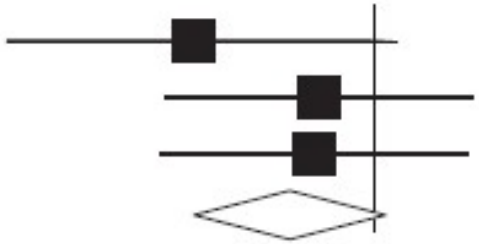
Katsnelson M et al. Stroke 2012;43:1179-1185

Comparison of Secondary Outcomes Ischemic Stroke

B Ischemic Stroke

Study Name	Events / Total	
	New Agents	Warfarin
RE-LY, 2009	111 / 6076	142 / 6022
ROCKET-AF, 2011	149 / 7061	161 / 7082
ARISTOTLE, 2011	162 / 9120	175 / 9081
TOTAL	422 / 22257	478 / 22185

$p = 0.054$
$I^2 = 0\%$
Egger p = NA



Risk Ratio and 99% CI

0.5 1

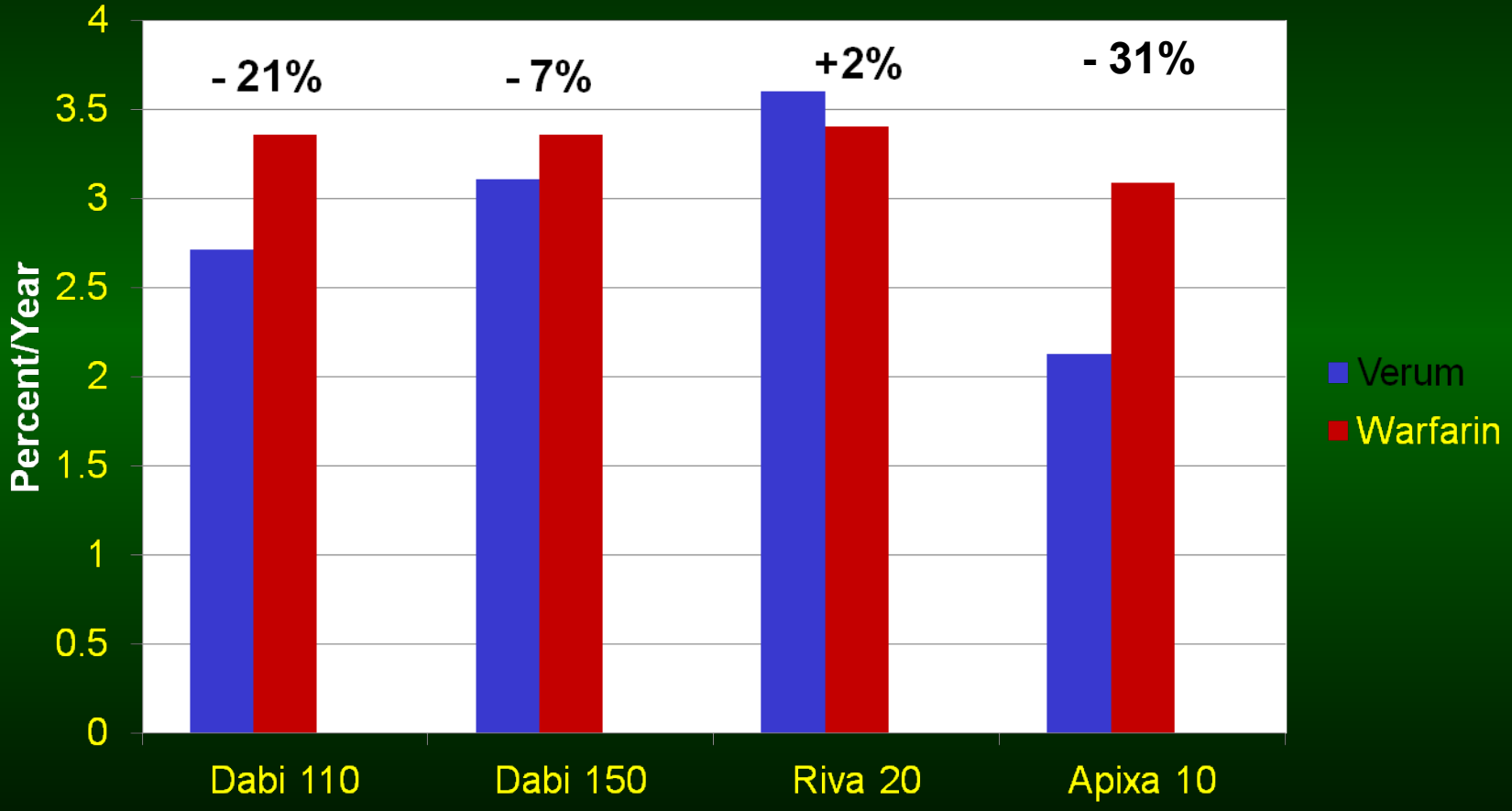
Favors New Agents Favors Warfarin

Baker and Phung, Circ Cardiovasc Qual Outcomes 2012;5:711-19

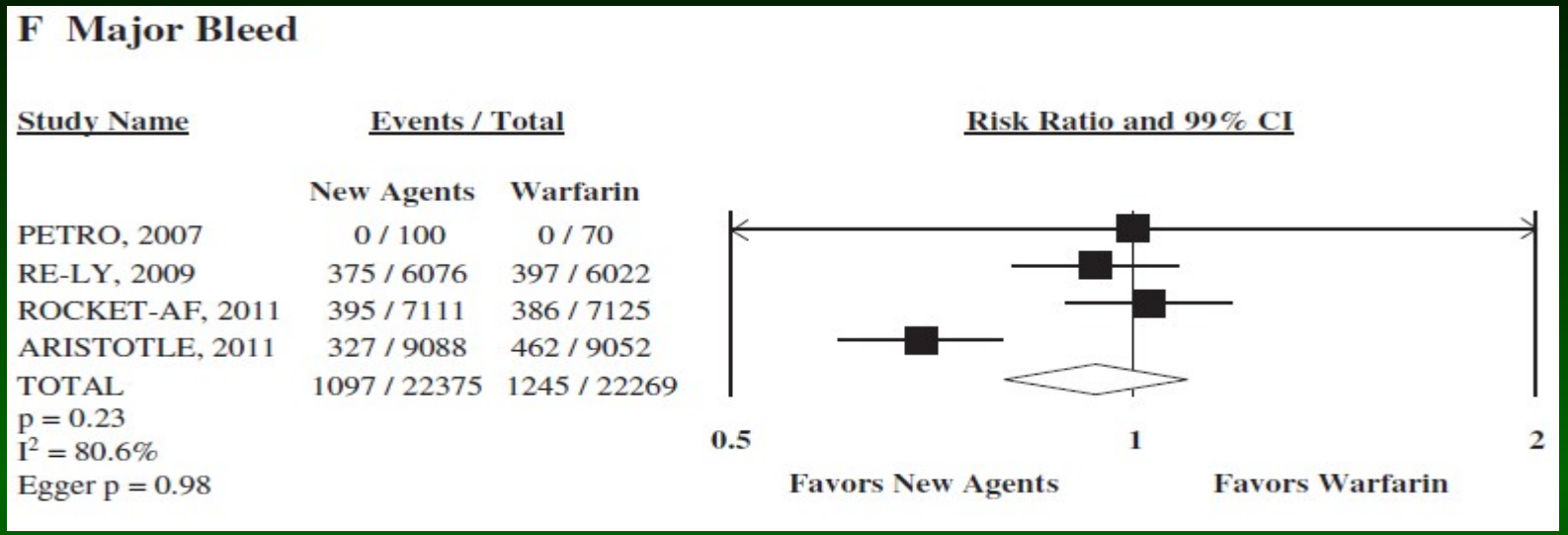
Major Bleeding Definitions

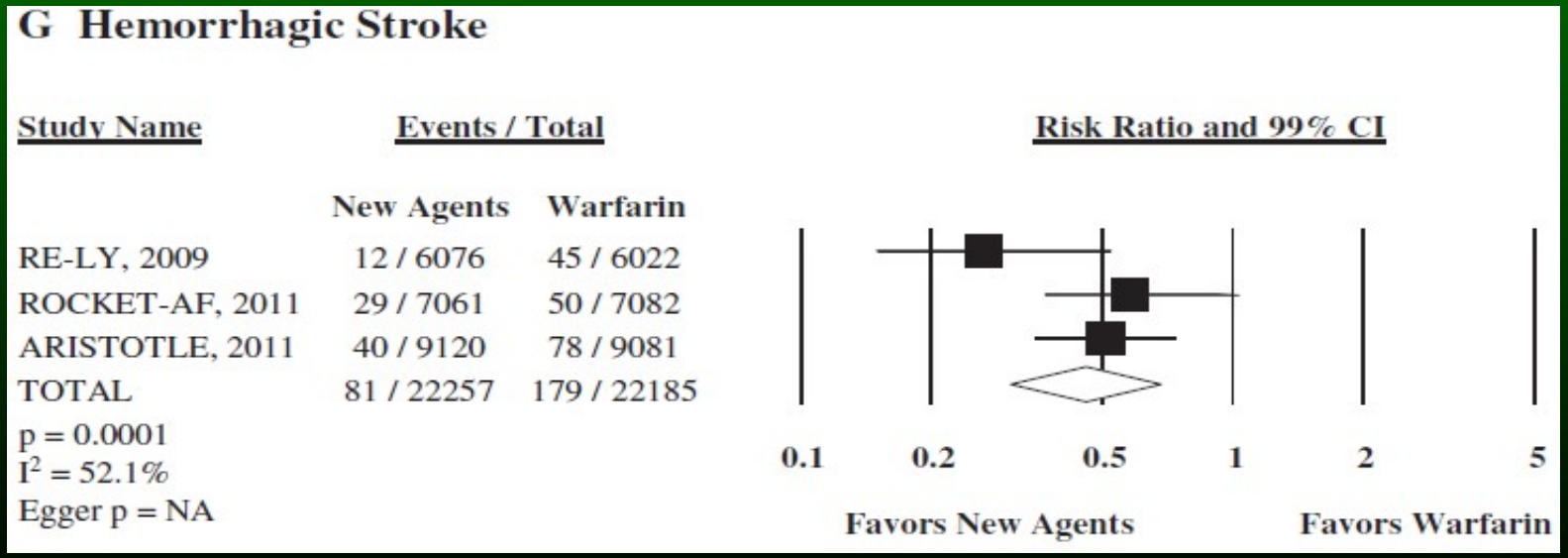
- **RE-LY**: Reduction in Hgb level of at least 2 g/dL, transfusion of at least 2 units of blood, or symptomatic bleeding in a critical area or organ.
- **ROCKET**: Clinically overt bleeding associated with any of the following: fatal outcome, involvement of a critical anatomic site (intracranial, spinal, ocular, pericardial, articular, retroperitoneal, or intramuscular with compartment syndrome), fall in hemoglobin concentration >2 g/dL, transfusion of >2 units of whole blood or packed red blood cells, or permanent disability.
- **ARISTOTLE**: Clinically overt bleeding accompanied by a decrease in the hemoglobin level of at least 2 g/dL or transfusion of at least 2 units of packed red cells, occurring at a critical site, or resulting in death.

Major bleeding
RE-LY, ROCKET and ARISTOTLE



Comparison of Secondary Outcomes Major Bleeding and Hemorrhagic Stroke





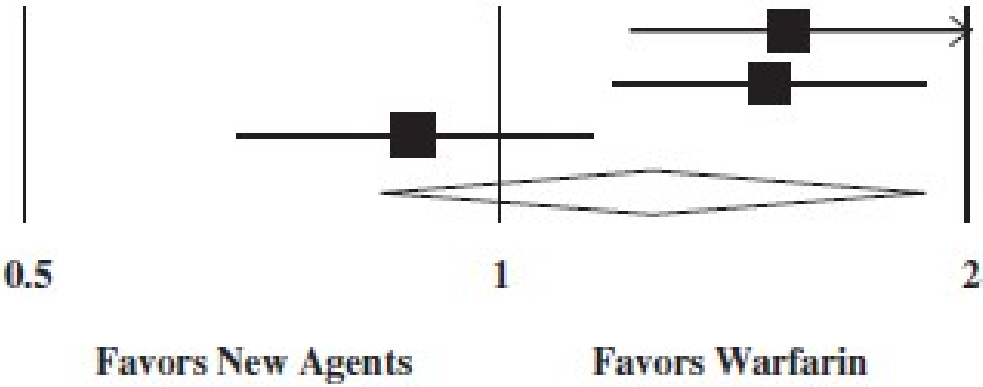
Baker and Phung, Circ Cardiovasc Qual Outcomes 2012;5:711-19

Comparison of Secondary Outcomes
GI Bleeding

H Gastrointestinal Bleed

Study Name	Events / Total	
	New Agents	Warfarin
RE-LY, 2009	182 / 6076	120 / 6022
ROCKET-AF, 2011	224 / 7111	154 / 7125
ARISTOTLE,2011	105 / 9088	119 / 9052
TOTAL	511 / 22275	393 / 22199

p = 0.16
I^2 = 82.5%
Egger p = NA

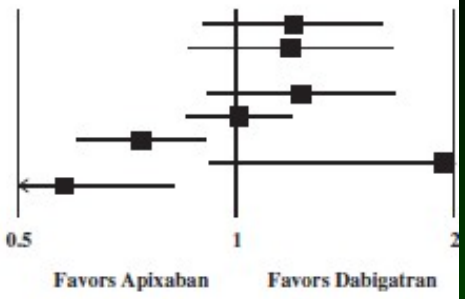


Baker and Phung, Circ Cardiovasc Qual Outcomes 2012;5:711-19

INDIRECT COMPARISONS

A Forest Plots Comparing Apixaban vs Dabigatran

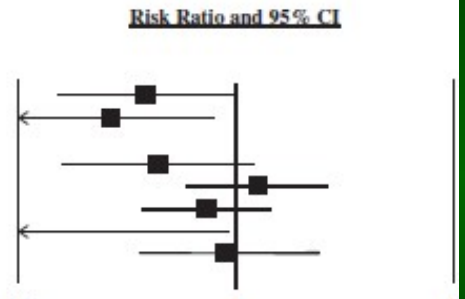
Outcome	Statistics For Each Outcome		
	Risk ratio	Lower limit	Upper limit
Stroke or Systemic Emboli	1.193	0.902	1.579
Ischemic Stroke	1.190	0.860	1.645
Systemic Emboli	Not Available		
Any Stroke	1.213	0.907	1.622
Mortality	1.007	0.855	1.185
Major Bleed	0.753	0.619	0.916
Hemorrhagic Stroke	1.933	0.929	4.017
GI Bleed	0.603	0.434	0.838



Apixaban lowers the risk of major and gastrointestinal bleeding versus dabigatran and rivaroxaban.

B Forest Plots Comparing Dabigatran vs Rivaroxaban

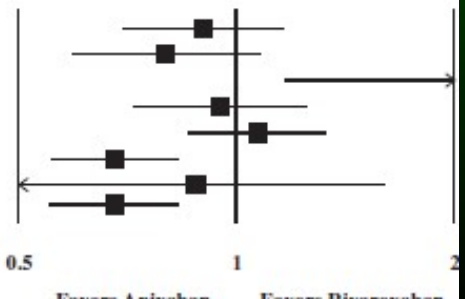
Outcome	Statistics For Each Outcome		
	Risk ratio	Lower limit	Upper limit
Stroke or Systemic Emboli	0.758	0.580	0.992
Ischemic Stroke	0.676	0.490	0.933
Systemic Emboli	Not Available		
Any Stroke	0.783	0.582	1.053
Mortality	1.069	0.859	1.331
Major Bleed	0.913	0.753	1.107
Hemorrhagic Stroke	0.454	0.210	0.983
GI Bleed	0.970	0.715	1.314



Dabigatran lowers the composite of stroke or systemic emboli, and ischemic stroke versus rivaroxaban.

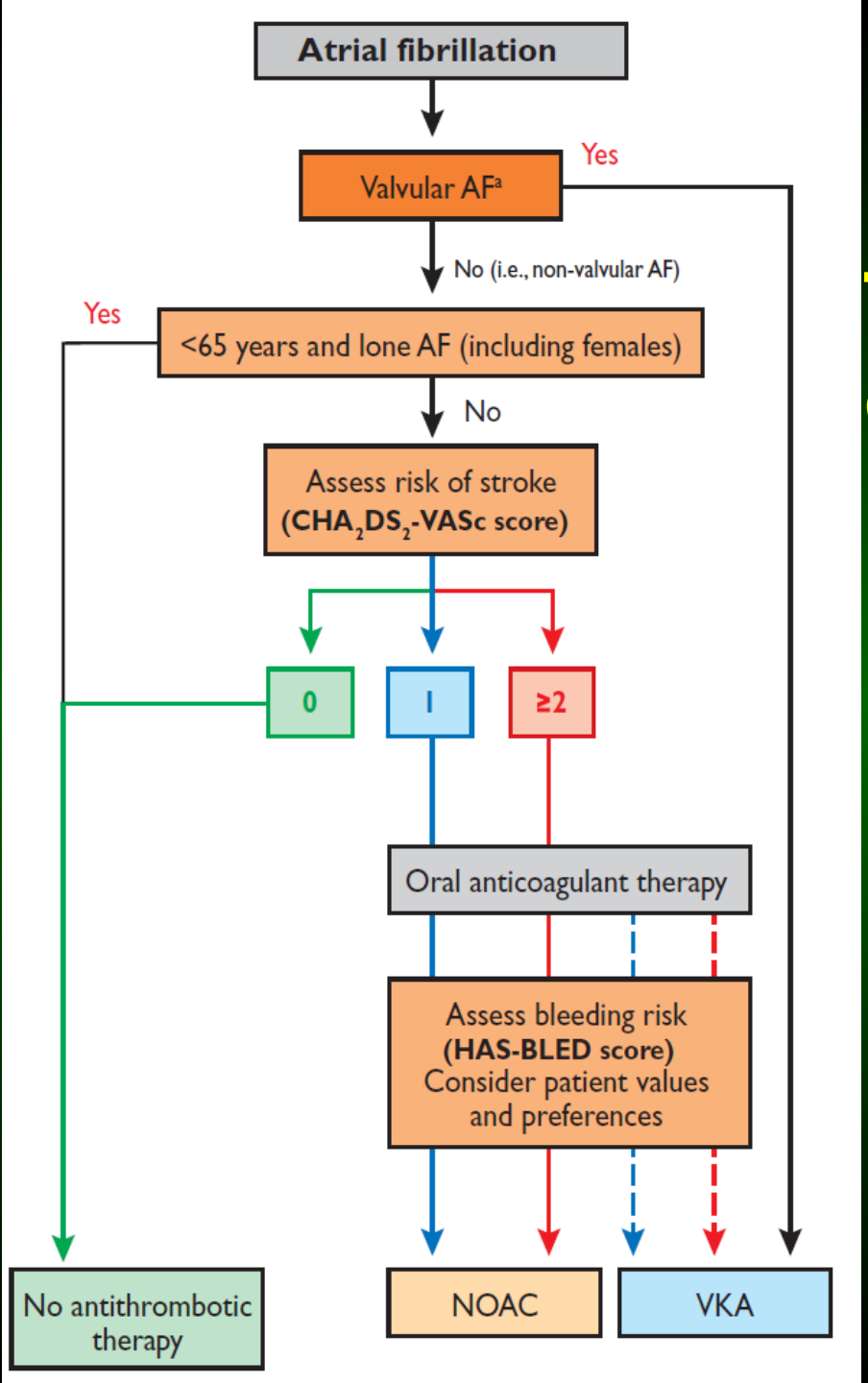
C Forest Plots Comparing Apixaban vs Rivaroxaban

Outcome	Statistics For Each Outcome		
	Risk ratio	Lower limit	Upper limit
Stroke or Systemic Emboli	0.905	0.712	1.150
Ischemic Stroke	0.804	0.598	1.082
Systemic Emboli	3.854	1.202	12.356
Any Stroke	0.949	0.727	1.238
Mortality	1.077	0.873	1.328
Major Bleed	0.688	0.566	0.835
Hemorrhagic Stroke	0.878	0.487	1.583
GI Bleed	0.585	0.414	0.826



Head-to-head clinical trials are required to confirm these findings.

Baker and Phung, Circ Cardiovasc Qual Outcomes 2012;5:711-19



ESC Guidelines for Management of AF

Color: CHA2DS2-VASc: green = 0, blue = 1, red ≥2

Line: solid = best option; dashed = alternative option

AHA/ASA Recommendations

- Warfarin (Class I, Level of Evidence A), dabigatran (Class I, Level of Evidence B), apixaban (Class I, Level of Evidence B), and rivaroxaban (Class IIa, Level of Evidence B) are all indicated for the prevention of first and recurrent stroke in patients with non-valvular atrial fibrillation.

Furie et al. Stroke 2012

Comparisons of NOAC

- All are NON-INFERIOR to Warfarin
- Dabigatran & Apixaban are SUPERIOR to warfarin
- Apixaban has significantly lower bleeding than warfarin; Dabigatran has significantly lower hemorrhagic stroke than warfarin
- Rivaroxaban is once a day; dabigatran and apixaban are twice a day
- Cost-neutral, not cost-saving yet
- Only direct comparison trials can define differential efficacy

Comparisons of NOAC

- Adherence could be an issue in community settings without monitoring
- Concurrent use with antiplatelets increases bleeding risk
- All have no antidotes or easily measured tests
- All need dose adjustment for renal insufficiency
- More post-marketing surveillance needed