Will Apixaban Change Practice in Atrial Fibrillation? -

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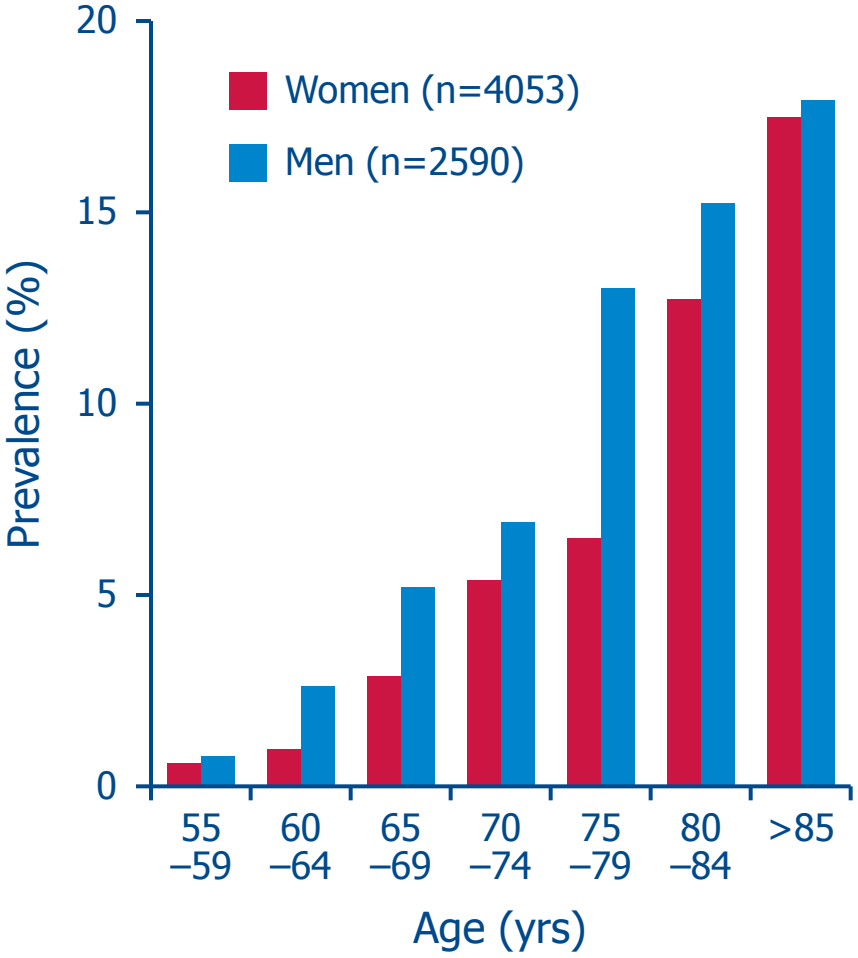
Disclosures - antithrombotic drugs

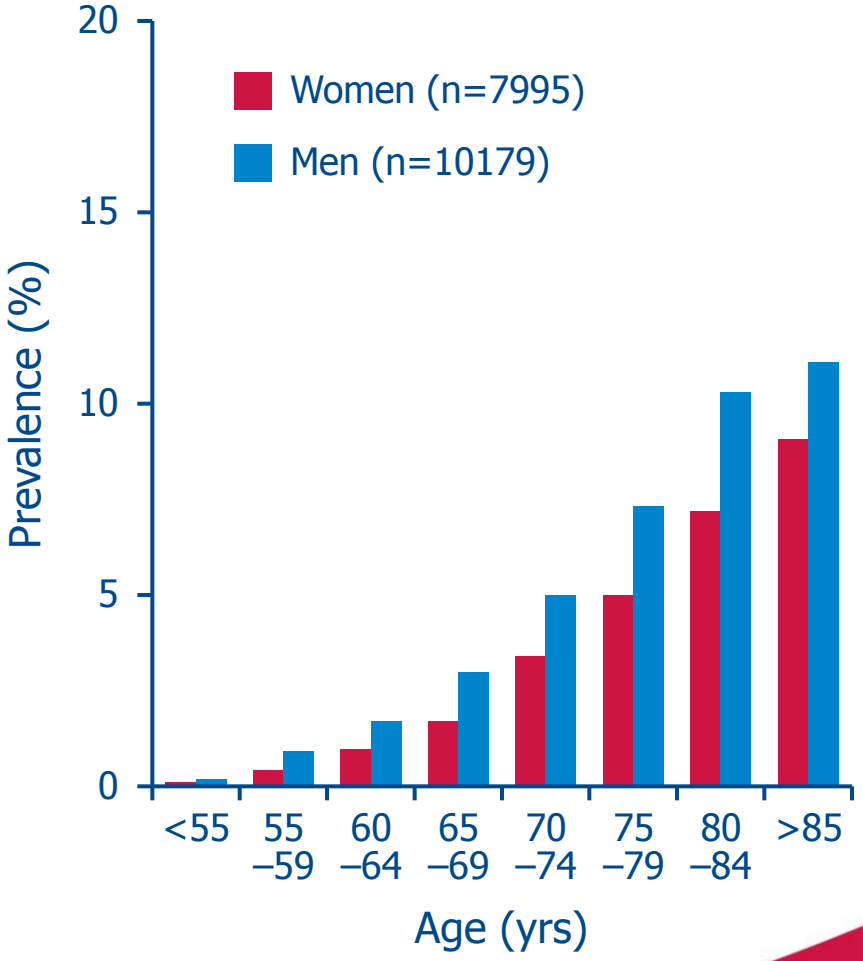
- Research support, advisory boards and consulting for
  - Boehringer-Ingelheim
  - Bayer Healthcare
  - BMS/Pfizer
  - MSD
  - AstraZeneca

Prevalence of AF increases with age

European age-related prevalence[1]



US age-related prevalence[2]



1. Heeringa J et al. Eur Heart J 2006;27:949–53; **2.** Go AS et al. JAMA 2001;285:2370–5

Estimation of stroke risk in AF: $CHADS_2$

- Validated using the National Registry of Atrial Fibrillation (NRAF)
- Most widely used to guide the choice of antithrombotic therapy

$CHADS_2$ risk criteria	**Score**
Cardiac failure	1
Hypertension	1
Age >75 yrs	1
Diabetes mellitus	1
Stroke or TIA (previous history)	**2**

TIA = transient ischaemic attack

Gage BF et al. JAMA 2001;285:2864–70

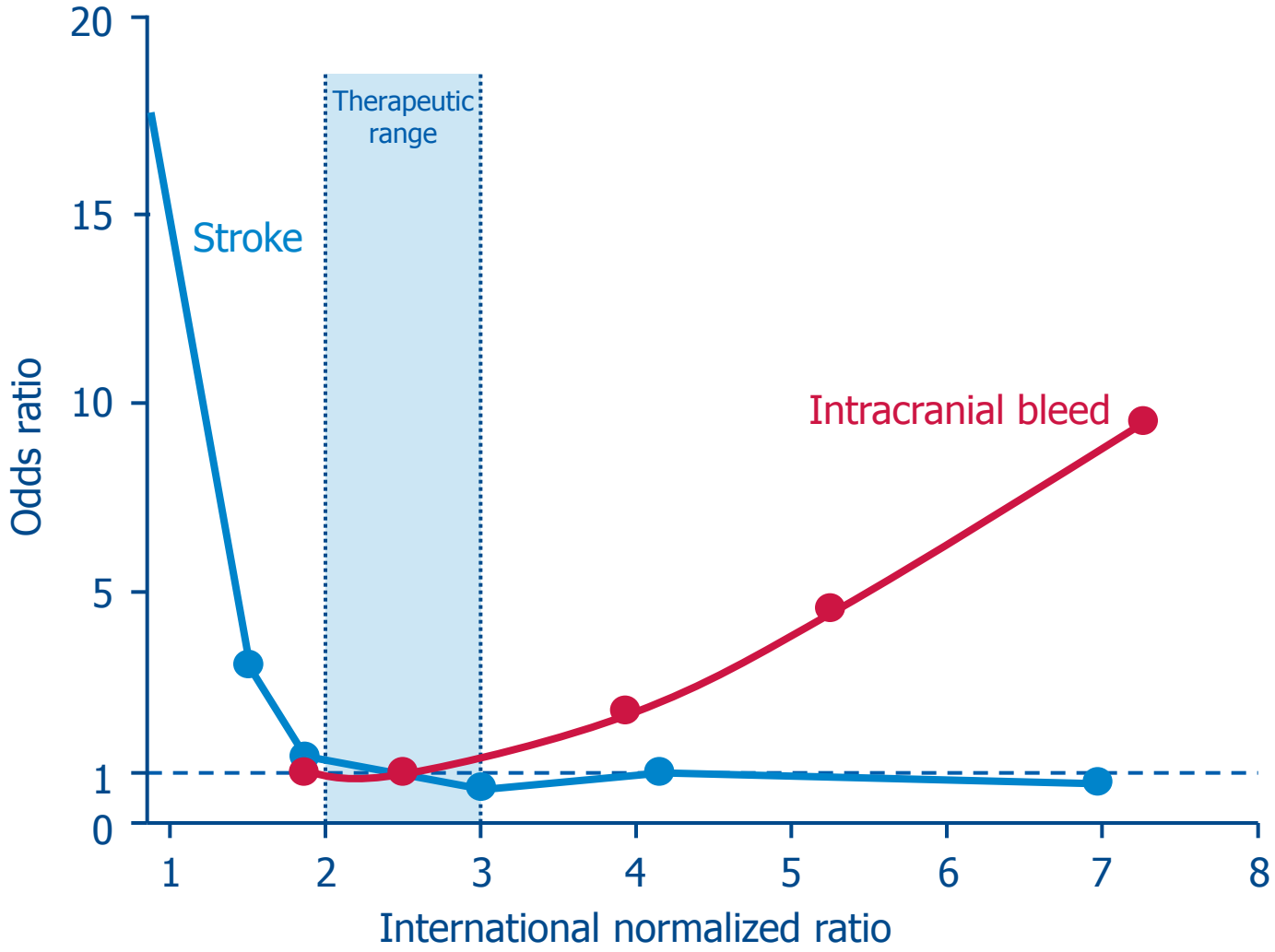
CHA_2DS_2-VASC Score – Better Predictor at Low End

Table

$CHAD_2$	**CHA_2DS_2-VASc**
Congestive heart failure	Congestive heart failure
Hypertension	Hypertension
Age ≥ 75	Age ≥ 75 *(Double Point)*
Diabetes Mellitus	Diabetes Mellitus
Previous stroke/ TIA (double point)	Previous stroke/ TIA (double point)
	Vascular disease
	Age 65-74
	Sex (female)

CHA_2DS_2-VASc scale	Stroke/thromboembolism rates at 1-y follow-up
0	0.84
1	1.79
2	3.67
3	5.75
4	8.18

VKAs have a narrow therapeutic window

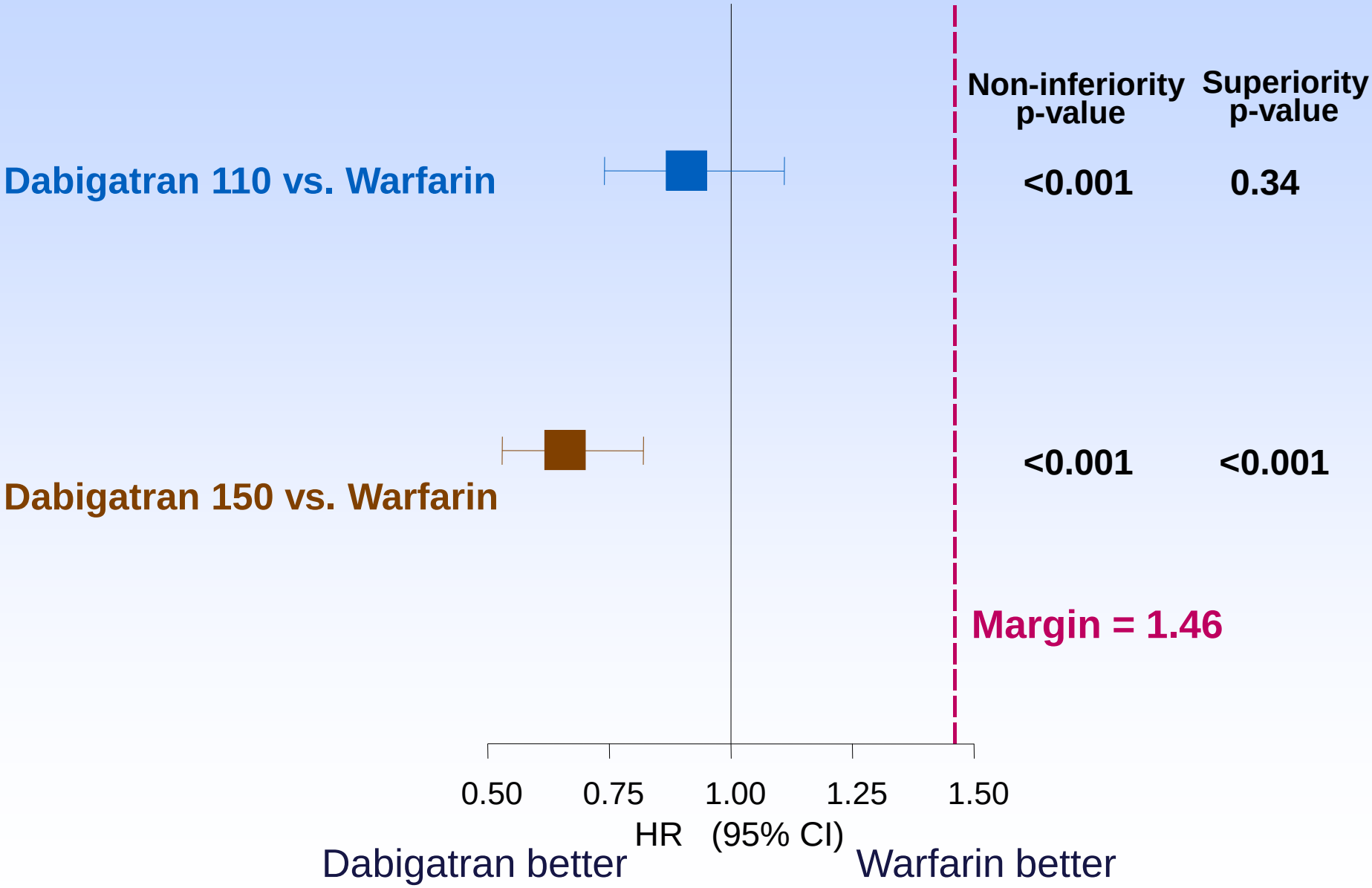


VKAs = vitamin K antagonists

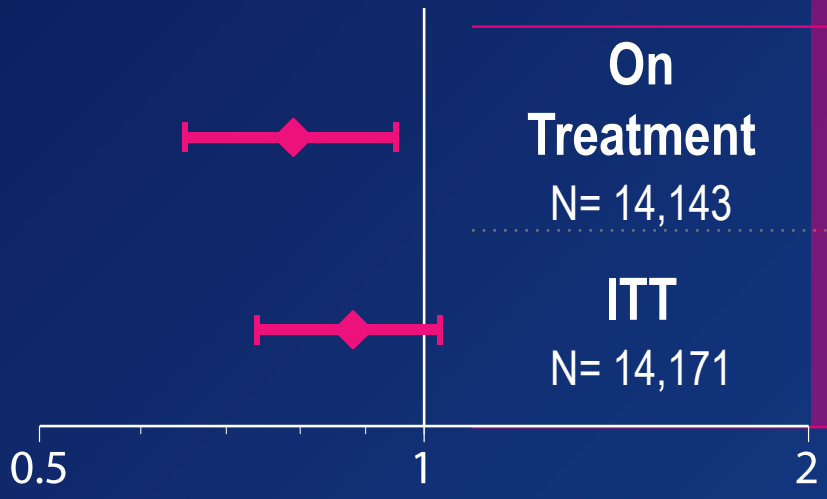
ACC/AHA/ESC guidelines: Fuster V et al. Circulation 2006;114:e257–354 & Eur Heart J 2006;27:1979–2030

Stroke or Systemic Embolism

RELY®
Study of stroke prevention in atrial fibrillation



Primary Efficacy Outcome
Stroke and non-CNS Embolism



	Rivaroxaban Event Rate	Warfarin Event Rate	HR (95% CI)	P-value
On Treatment N= 14,143	1.70	2.15	0.79 (0.65,0.95)	0.015
ITT N= 14,171	2.12	2.42	0.88 (0.74,1.03)	0.117

Event Rates are per 100 patient-years
Based on Safety on Treatment or Intention-to-Treat thru Site Notification populations

ROCKET AF

Apixaban versus Warfarin in Patients with Atrial Fibrillation

Results of the ARISTOTLE Trial

Presented on behalf of the ARISTOTLE Investigators and Committees

Sponsored by Bristol-Myers Squibb and Pfizer

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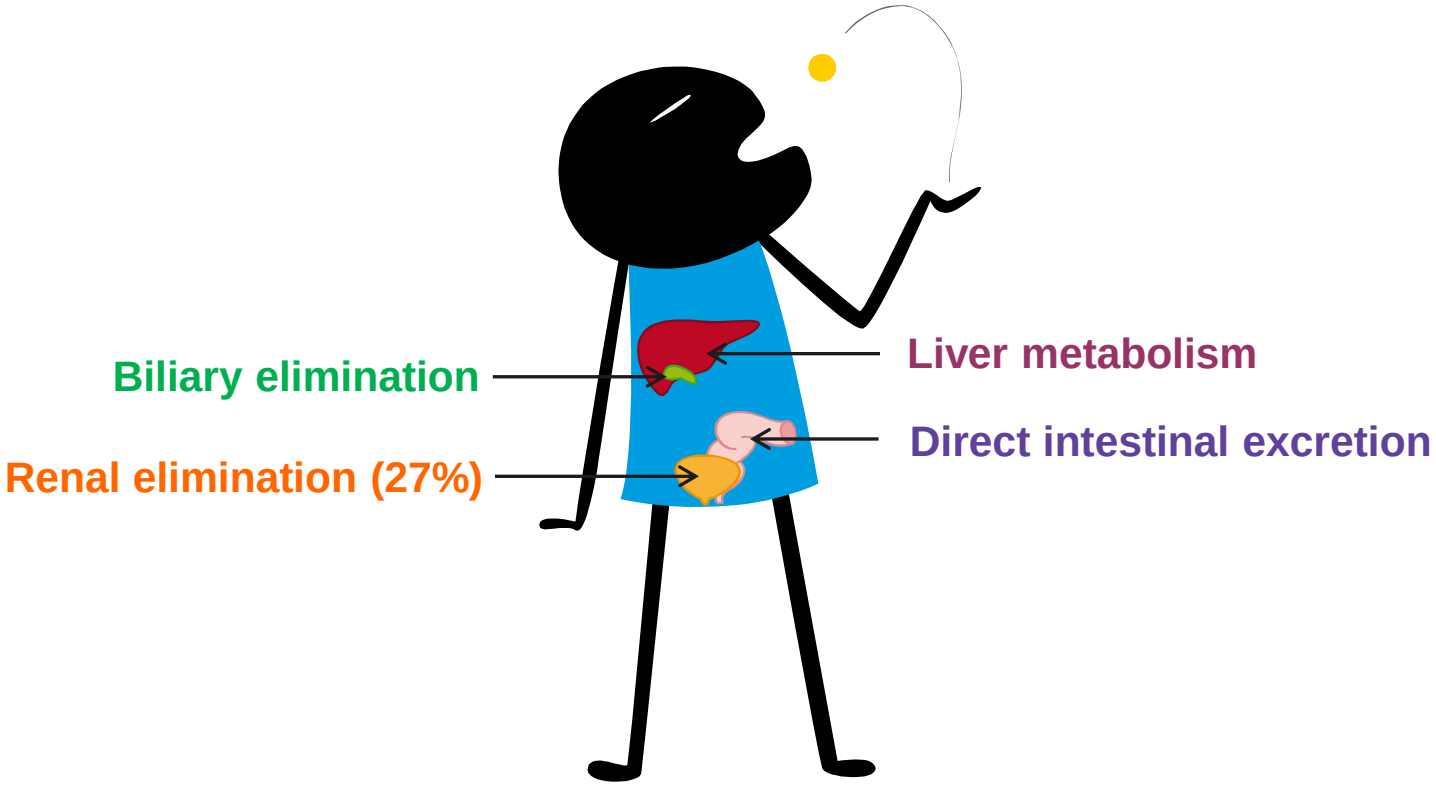
Apixaban is eliminated from the body via multiple routes

Only ~27% of apixaban is eliminated by the kidneys



Unchanged apixaban is the major drug-related component in human plasma with no active circulating metabolites present

Apixaban SmPC 2012.

Atrial Fibrillation with at Least One Additional Risk Factor for Stroke

ARISTOTLE

Inclusion risk factors
- Age ≥ 75 years
- Prior stroke, TIA, or SE
- HF or LVEF ≤ 40%
- Diabetes mellitus
- Hypertension

Randomize
double blind, double dummy
(n = 18,201)

Major exclusion criteria
- Mechanical prosthetic valve
- Severe renal insufficiency
- Need for aspirin plus thienopyridine

Apixaban 5 mg oral twice daily
(2.5 mg BID in selected patients)

Warfarin
(target INR 2-3)

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

Primary outcome: stroke or systemic embolism

Hierarchical testing: non-inferiority for primary outcome, superiority for primary outcome, major bleeding, death

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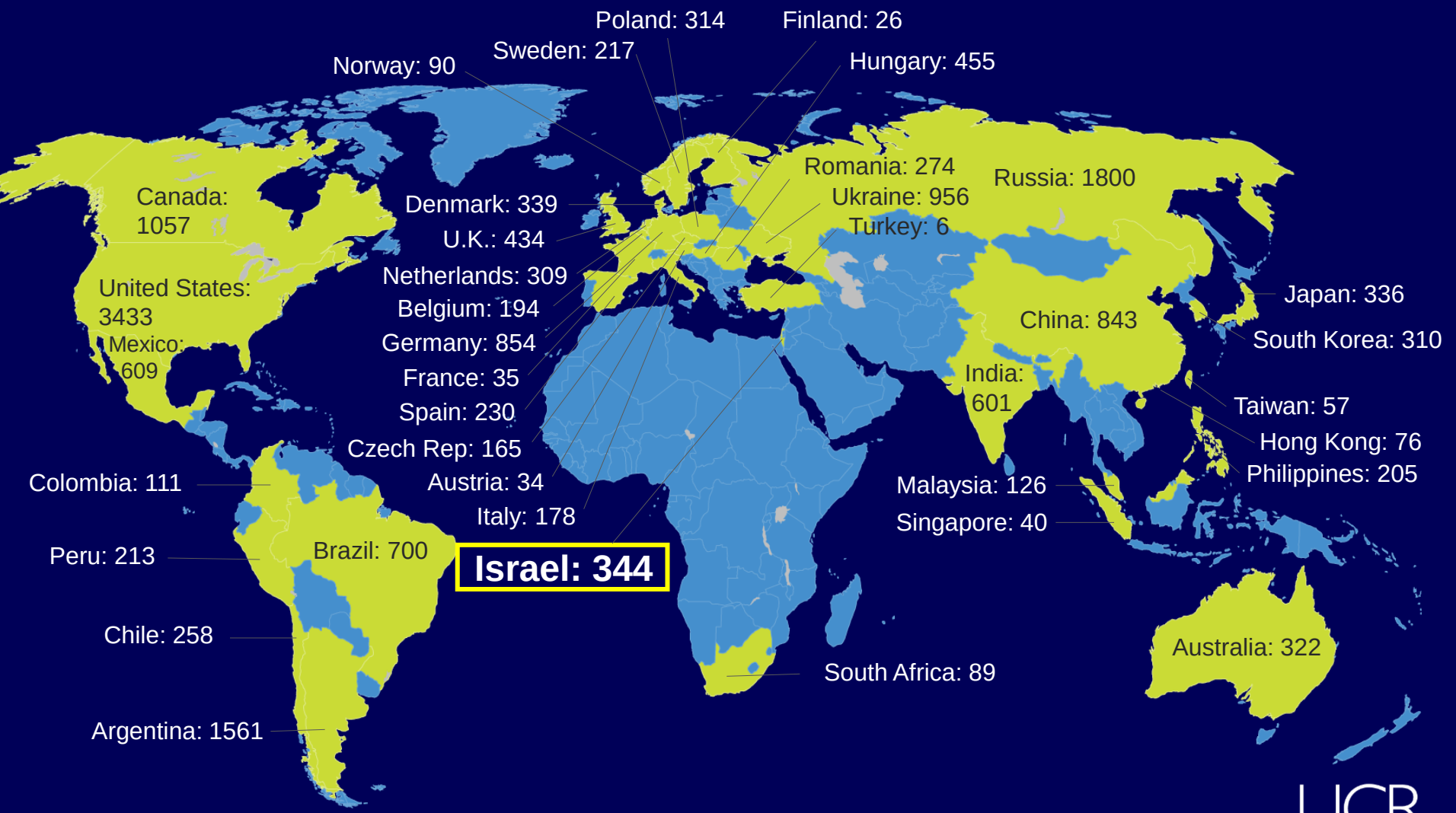
Enrollment

18,201 patients, 1034 sites, 39 countries



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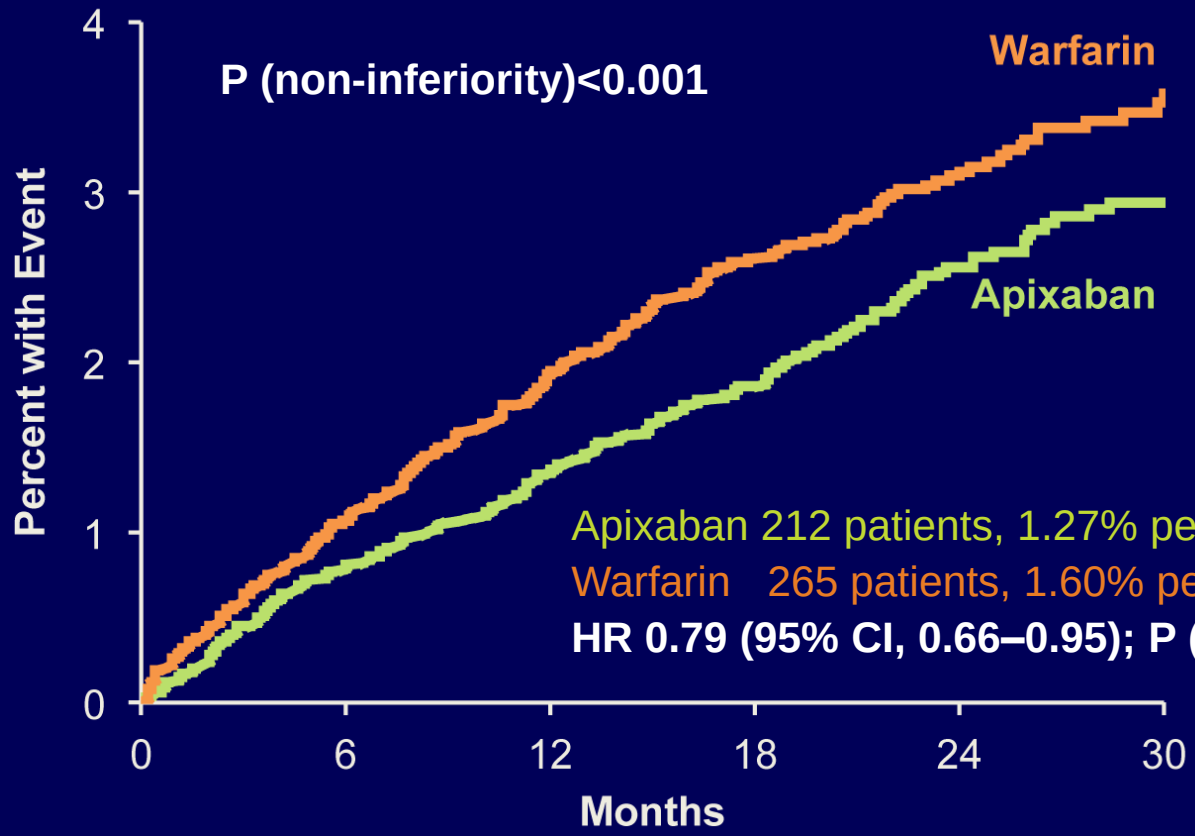
Primary Outcome

Stroke (ischemic or hemorrhagic) or systemic embolism



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

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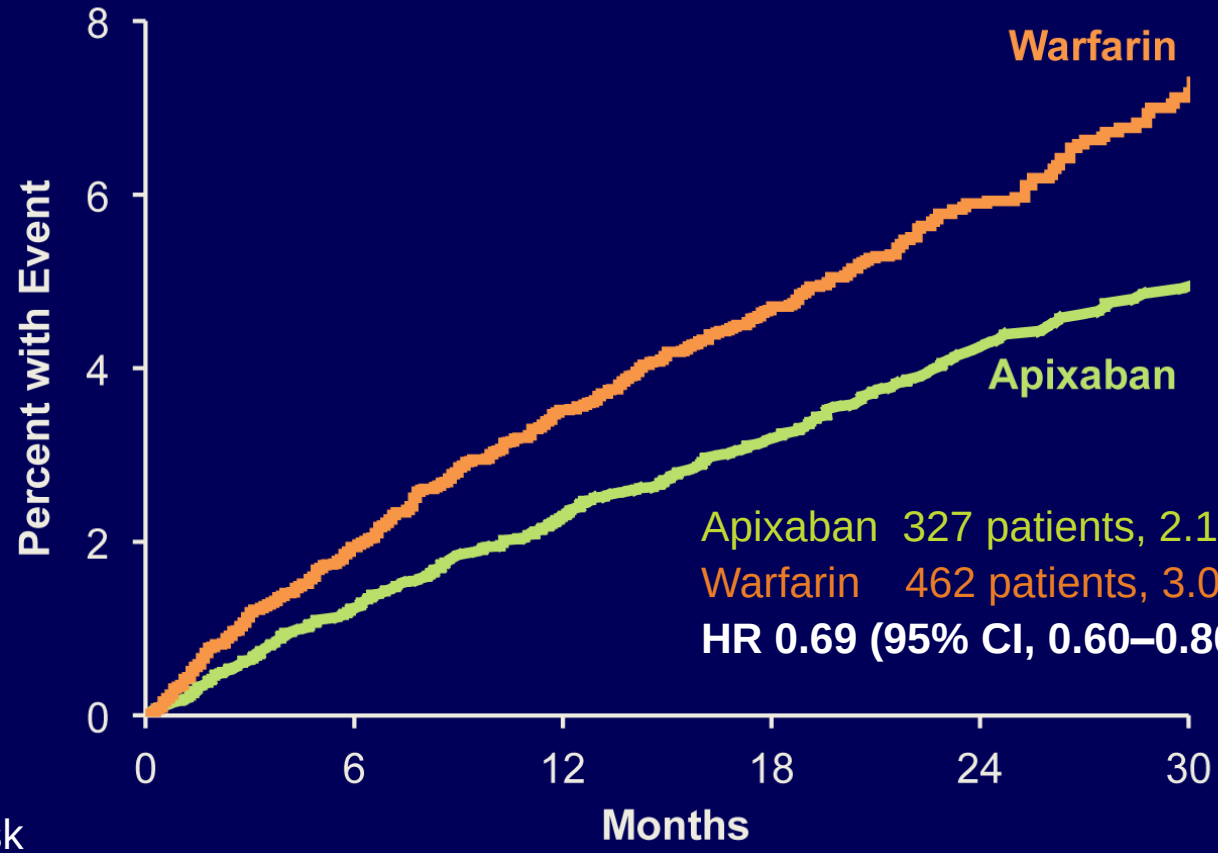
Major Bleeding

ISTH definition

ARISTOTLE



No. at Risk						
Apixaban	9088	8103	7564	5365	3048	1515
Warfarin	9052	7910	7335	5196	2956	1491

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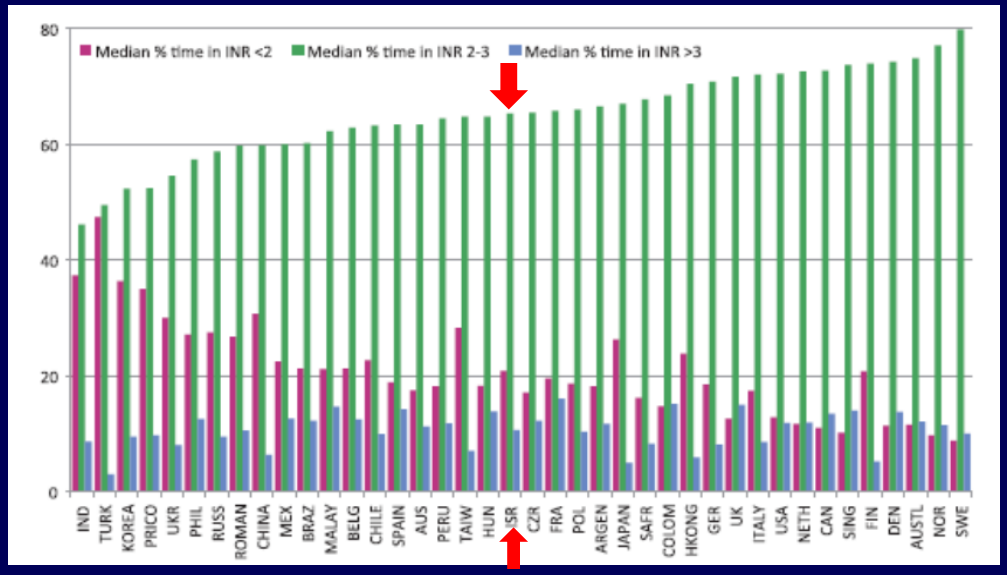
Efficacy Outcomes

Outcome	Apixaban (N=9120) Event Rate (%/yr)	Warfarin (N=9081) Event Rate (%/yr)	HR (95% CI)	P Value
Stroke or systemic embolism*	1.27	1.60	0.79 (0.66, 0.95)	0.011
Stroke	1.19	1.51	0.79 (0.65, 0.95)	0.012
Ischemic or uncertain	0.97	1.05	0.92 (0.74, 1.13)	0.42
Hemorrhagic	0.24	0.47	0.51 (0.35, 0.75)	<0.001
Systemic embolism (SE)	0.09	0.10	0.87 (0.44, 1.75)	0.70
All-cause death*	3.52	3.94	0.89 (0.80, 0.998)	0.047
Stroke, SE, or all-cause death	4.49	5.04	0.89 (0.81, 0.98)	0.019
Myocardial infarction	0.53	0.61	0.88 (0.66, 1.17)	0.37

* Part of sequential testing sequence preserving the overall type I error

Results in Relation to TTR (by center)



Predicted cTTR	Apixaban N	Apixaban Events (%/yr)	Warfarin N	Warfarin Events (%/yr)	HR (95% CI)	P Interacti
Primary outcome (SSE)						0.078
24.3 - 60.5	2243	68 (1.72)	2251	92 (2.36)	0.73 (0.53-1.00)	
60.6 - 66.3	2287	68 (1.61)	2266	72 (1.72)	0.94 (0.67-1.31)	
66.4 - 71.1	2301	36 (0.86)	2301	56 (1.35)	0.64 (0.42-0.97)	
71.2 - 83.2	2289	40 (0.91)	2263	45 (1.04)	0.88 (0.57-1.35)	
All cause death						0.34
24.3 - 60.5	2243	163 (4.00)	2251	178 (4.39)	0.91 (0.74-1.13)	
60.6 - 66.3	2287	175 (4.04)	2266	185 (4.30)	0.94 (0.76-1.15)	
66.4 - 71.1	2301	140 (3.29)	2301	170 (4.01)	0.82 (0.66-1.03)	
71.2 - 83.2	2289	125 (2.81)	2263	136 (3.10)	0.91 (0.71-1.16)	
Major bleeding						0.095
24.3 - 60.5	2232	52 (1.44)	2245	102 (2.89)	0.50 (0.36-0.70)	
60.6 - 66.3	2284	77 (1.97)	2261	116 (3.07)	0.64 (0.48-0.86)	
66.4 - 71.1	2290	99 (2.61)	2292	113 (3.06)	0.85 (0.65-1.11)	
71.2 - 83.2	2282	99 (2.48)	2254	131 (3.31)	0.75 (0.58-0.97)	

Wallentin et al, Circulation 2013

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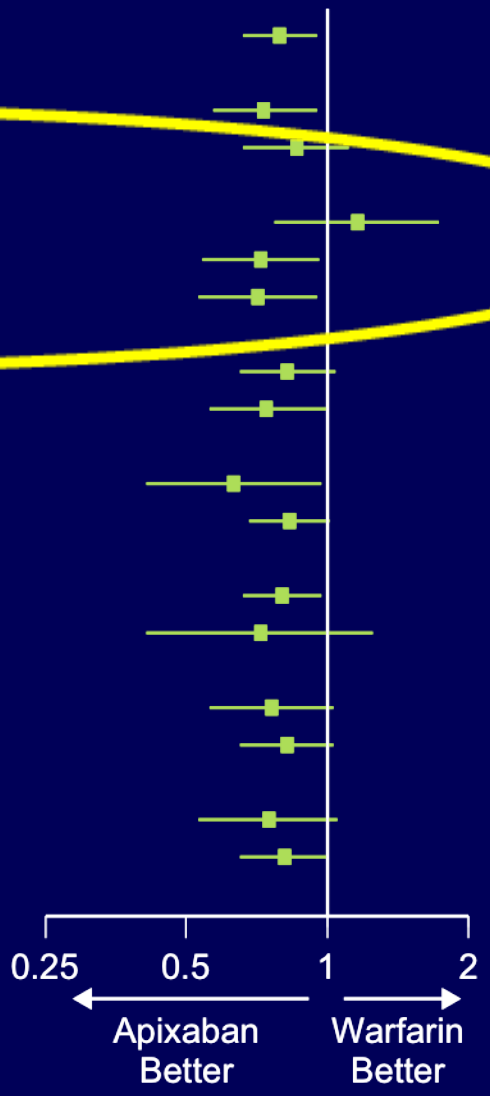
Subgroups for Stroke and Systemic Embolism
(1 of 2)

ARISTOTLE

Characteristics	No. of Patients	Apixaban no. of events (%/yr)	Warfarin no. of events (%/yr)	P-value for Interaction
All Patients	18201	212 (1.27)	265 (1.60)	
Prior Warfarin/VKA Status				0.39
Experienced	10401	102 (1.1)	138 (1.5)	
Naïve	7800	110 (1.5)	127 (1.8)	
Age				0.12
<65 yrs	5471	51 (1.0)	44 (0.9)	
≥65 to < 75 yrs	7052	82 (1.3)	112 (1.7)	
≥75 yrs	5678	79 (1.6)	109 (2.2)	
Sex				0.60
Male	11785	132 (1.2)	160 (1.5)	
Female	6416	80 (1.4)	105 (1.8)	
Weight				0.26
≤60 kg	1985	34 (2.0)	52 (3.2)	
>60 kg	16154	177 (1.2)	212 (1.4)	
Type of Atrial Fibrillation				0.70
Permanent/Persistent	15412	191 (1.4)	235 (1.7)	
Paroxysmal	2786	21 (0.8)	30 (1.1)	
Prior Stroke or TIA				0.71
Yes	3436	73 (2.5)	98 (3.2)	
No	14765	139 (1.0)	167 (1.2)	
Diabetes Mellitus				0.71
Yes	4547	57 (1.4)	75 (1.9)	
No	13654	155 (1.2)	190 (1.5)	



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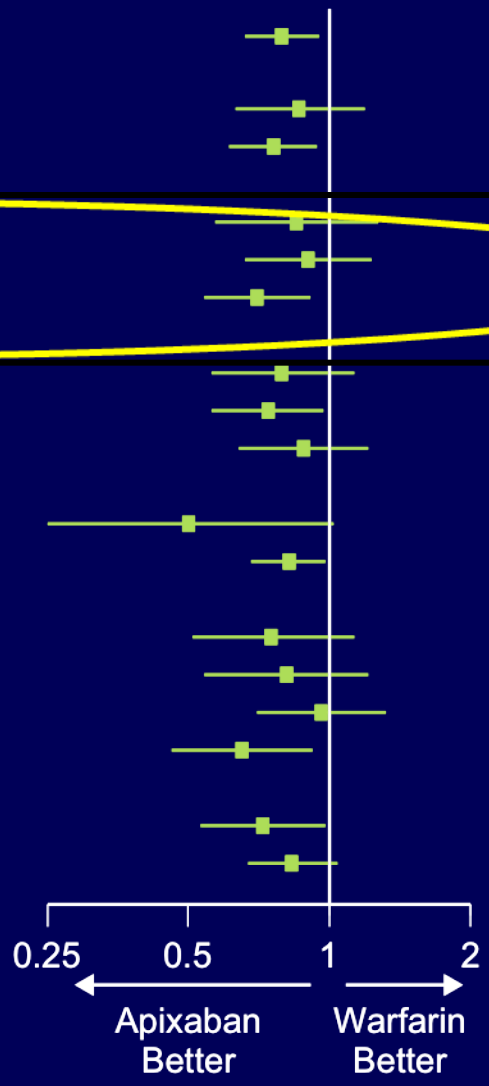
Subgroups for Stroke and Systemic Embolism
(2 of 2)

ARISTOTLE

Characteristics	No. of Patients	Apixaban no. of events (%/yr)	Warfarin no. of events (%/yr)	P-value for Interaction
All Patients	18201	212 (1.27)	265 (1.60)	
Heart Failure				0.50
Yes	5541	70 (1.4)	79 (1.6)	
No	12660	142 (1.2)	186 (1.6)	
CHADs Score				0.45
≤1	6183	44 (0.7)	51 (0.9)	
=2	6516	74 (1.2)	82 (1.4)	
≥3	5502	94 (1.9)	132 (2.8)	
Level of Renal Impairment				0.72
Severe or Moderate	3017	54 (2.1)	69 (2.7)	
Mild	7587	87 (1.2)	116 (1.7)	
No impairment	7518	70 (1.0)	79 (1.1)	
Apixaban Dose				0.22
2.5 mg BID or placebo	831	12 (1.7)	22 (3.3)	
5 mg BID or placebo	17370	200 (1.3)	243 (1.5)	
Geographic Region				0.44
North America	4474	42 (1.0)	56 (1.3)	
Latin America	3468	43 (1.4)	52 (1.8)	
Europe	7343	75 (1.1)	77 (1.1)	
Asia/Pacific	2916	52 (2.0)	80 (3.1)	
Aspirin at Randomization				0.44
Yes	5632	70 (1.3)	94 (1.9)	
No	12569	142 (1.2)	171 (1.5)	



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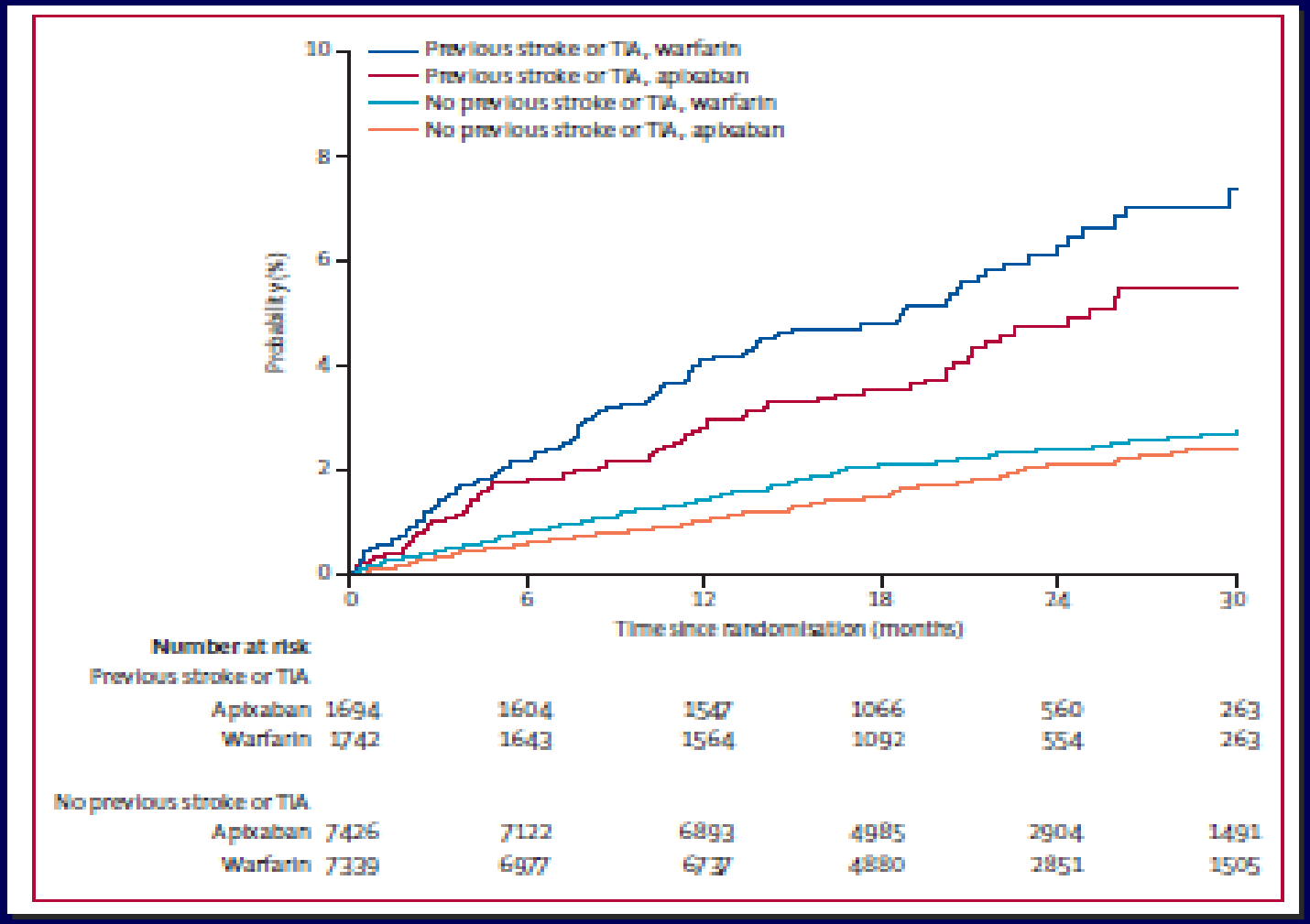
Patients with $CHADS_2$ ≥3 Results:

Table 3. Primary Efficacy and Safety in Subgroups of Trial Patients With CHADS2 Score ≥3

	New Anticoagulant			Warfarin			
	Subjects	Events	Event Rate per 100 Person-Years	Subjects	Events	Event Rate (95% CI) per 100 Person-Years*	Hazard Ratio (95% CI)
Primary efficacy end point: stroke or systemic embolism (intention-to-treat analysis)							
Apixaban (ARISTOTLE)	2758	94	1.9†	2744	132	2.8† (2.35–3.31)	0.68 (0.52–0.88)
Dabigatran 110 mg (RE-LY)‡	1968	82‡	2.12	1933	101§	2.68 (2.19–3.24)	0.79 (0.59, 1.05)‖
Dabigatran 150 mg (RE-LY)‡	1981	74‡	1.88	1933	101§	2.68 (2.19–3.24)	0.70 (0.52, 0.95)‖
Rivaroxaban (ROCKET-AF)¶	6156	239	2.25	6155	270	2.56 (2.27–2.88)	0.88 (0.74, 1.05)
Major Hemorrhage (on-treatment analysis)							
Apixaban (ARISTOTLE)	NR#	126	2.9†	NR#	173	4.2† (3.61–4.86)	0.69 (0.55–0.87)
Dabigatran 110 mg (RE-LY) approximated**	1966	147	3.80	1931	172	4.61 (3.96–5.34)	0.82 (0.66–1.03)‖
Dabigatran 150 mg (RE-LY) approximated**	1979	188	4.86	1931	172	4.61 (3.96–5.34)	1.05 (0.86–1.30)‖
Rivaroxaban (ROCKET-AF)††	6187	337	3.64	6191	337	3.60 (3.23–4.00)	1.01 (0.87–1.18)

Sebastian Sc, et.al, Circ Cardiovasc Qual Outcomes July (2012)

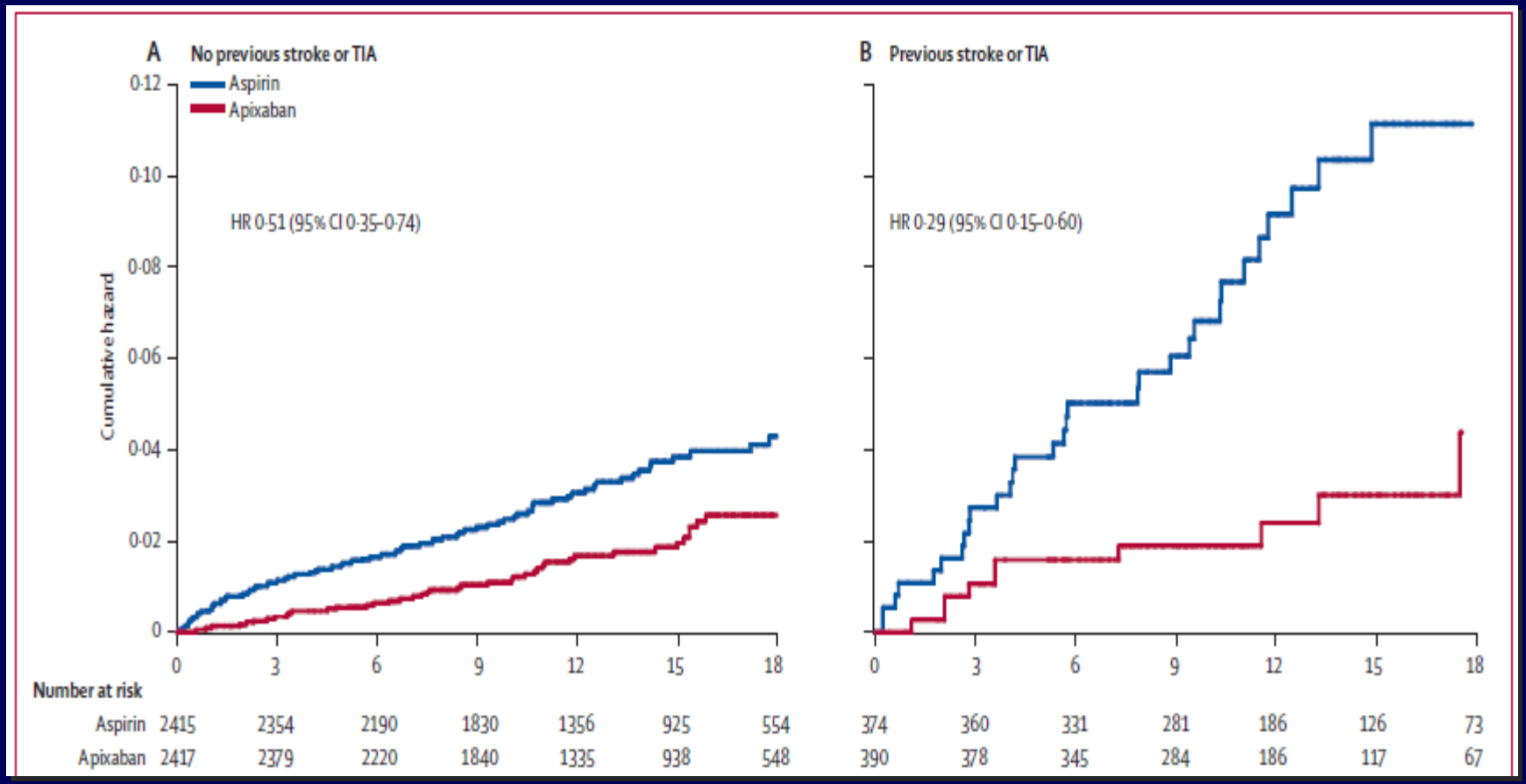
Stroke/TIA in pts with previous cerebrovascular event



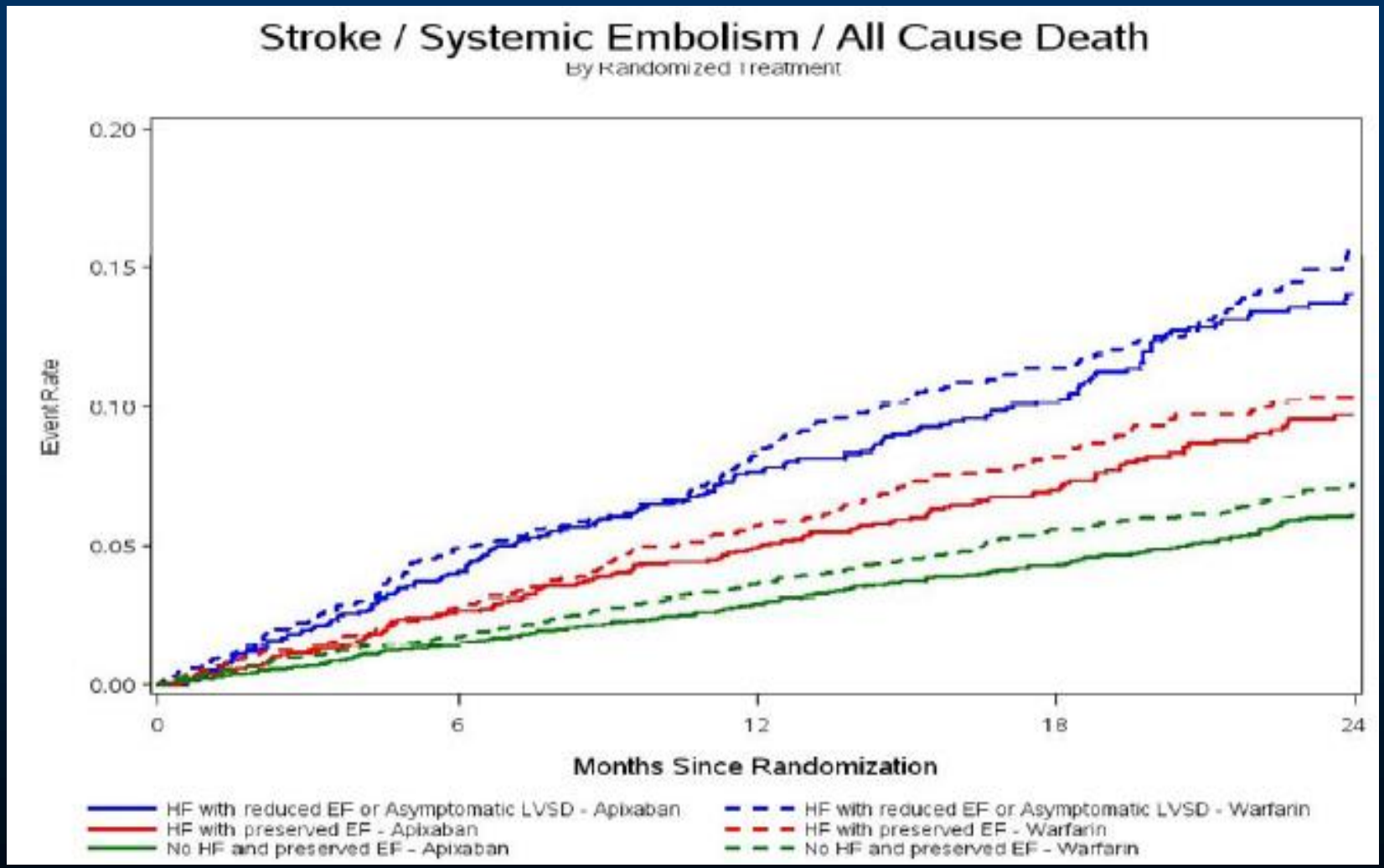
Number at risk						
Previous stroke or TIA						
Apixaban	1694	1604	1547	1066	560	263
Warfarin	1742	1643	1564	1092	554	263
No previous stroke or TIA						
Apixaban	7426	7122	6893	4985	2904	1491
Warfarin	7339	6977	6737	4880	2851	1505

Easton et al, Lancet Neurology, online May 8 2012

Previous stroke/TIA subgroup from AVERROES study (vs aspirin)



Effect of Apixaban by HF/EF Status



Conclusion

ARISTOTLE

In patients with atrial fibrillation, apixaban is superior to warfarin:

- **less stroke/SE (-21%, p=0.01)**
- **less bleeding (-31%, p<0.001)**
- **lower mortality (-11%, p=0.04)**

ARISTOTLE

Compared with warfarin, apixaban (over 1.8 years) prevented

- 6 Strokes
  - 4 hemorrhagic
  - 2 ischemic/uncertain type
- 15 Major bleeds
- 8 Deaths

per 1000 patients treated.

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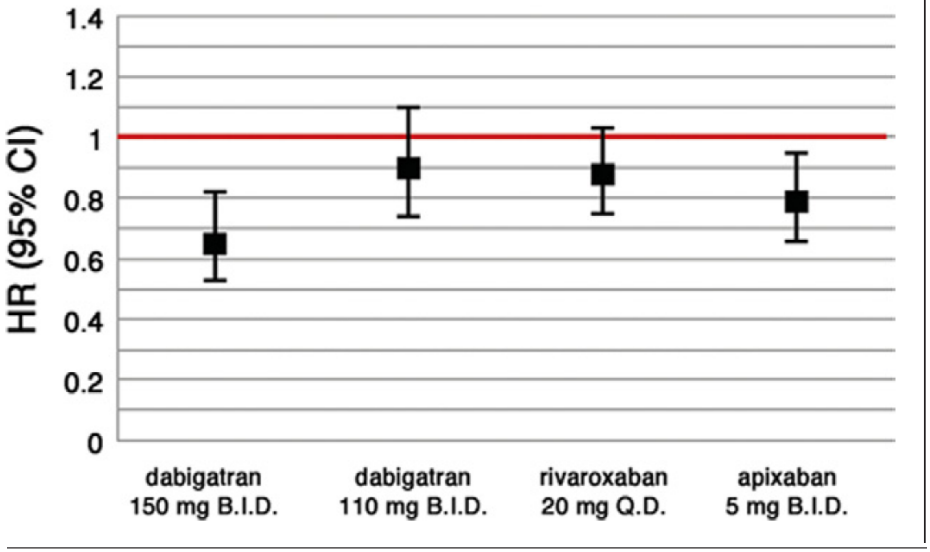
STATE-OF-THE-ART PAPER

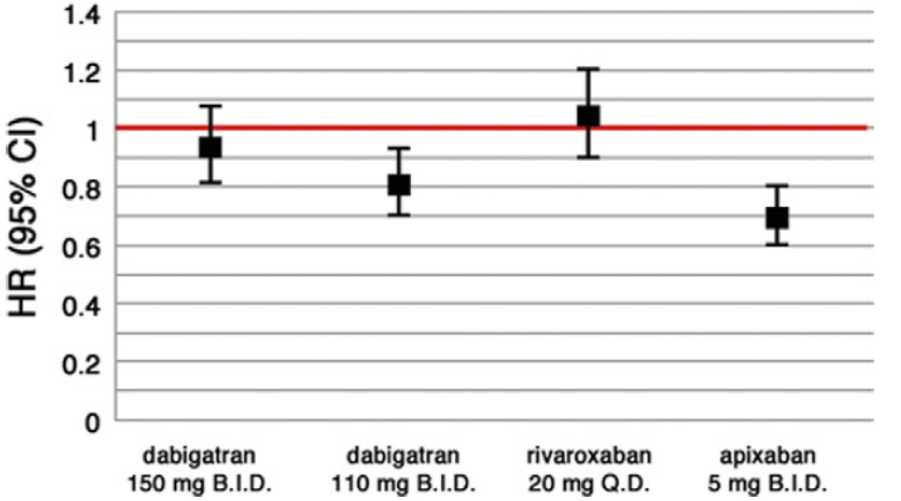
New Oral Anticoagulants in Atrial Fibrillation and Acute Coronary Syndromes

ESC Working Group on Thrombosis—Task Force on Anticoagulants in Heart Disease Position Paper

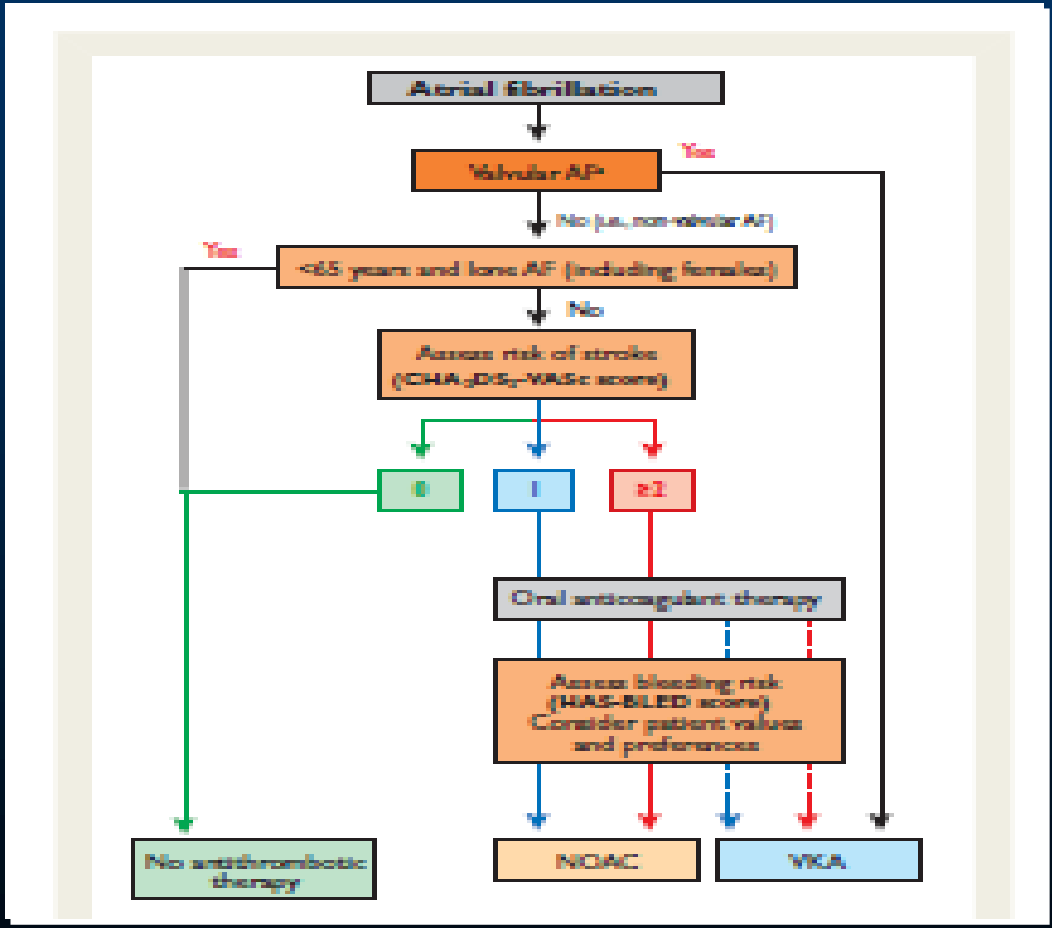
Comparable Primary Efficacy Endpoints of Stroke or Systemic Embolism



Comparable Primary Safety Endpoints of Major Bleeding



ESC AF Guidelines 2012



The New Questions

- Bleeding and how to treat it
  - Kcentra (prothrombin complex concentrate (PCC)) = urgent reversal of VKA (warfarin)
  - Anti-II, Anti-Xa?
- Valves
  - Mechanical
  - Biological
- Drug interactions
  - Antiplatelets - Which? New?
  - Others

European Heart Journal Advance Access published April 26, 2013

European Heart Journal
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EHRA Practical Guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation: executive summary†

Hein Heidbuchel[1]*, Peter Verhamme[1], Marco Alings[2], Matthias Antz[3], Werner Hacke[4], Jonas Oldgren[5], Peter Sinnaeve[1], A. John Camm[6], and Paulus Kirchhof[7,8]

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New oral anticoagulants (NOACs) are an alternative for vitamin K antagonists (VKAs) to prevent stroke in patients with non-valvular atrial