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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Background

- Warfarin is very effective at preventing stroke in patients with atrial fibrillation.
- Warfarin has several limitations, including drug and food interactions, a narrow therapeutic range, need for anticoagulation monitoring, and bleeding.
- Apixaban is a novel oral factor Xa inhibitor with rapid absorption, a half life of about 12 hours, and 25% renal elimination.
- Apixaban has been shown to reduce stroke and systemic embolism by 55% compared with aspirin in patients with atrial fibrillation and not suitable for warfarin.

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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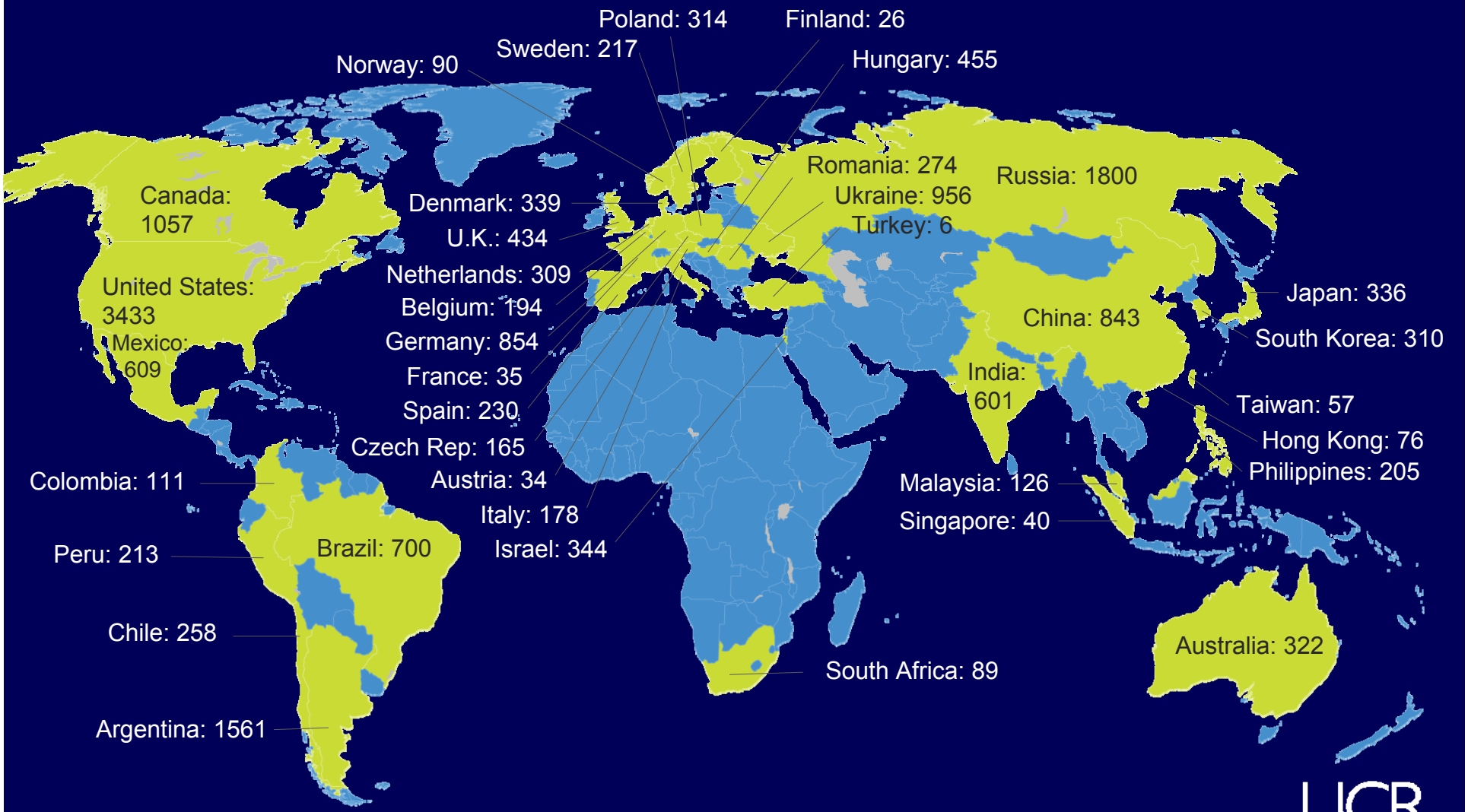
Enrollment

18,201 patients, 1034 sites, 39 countries



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Objectives

Primary objective

- To determine whether apixaban is non-inferior to warfarin at reducing stroke (ischemic or hemorrhagic) or systemic embolism in patients with atrial fibrillation and at least one additional risk factor for stroke.

Primary safety outcome

- Major bleeding according to the International Society of Thrombosis and Hemostasis (ISTH) definition.

Objectives and Statistics

To control the overall type I error, a pre-specified hierarchical sequential testing was performed.

1. The primary outcome (stroke or systemic embolism) for non-inferiority (upper limit of 95% CI < 1.38 and upper limit of 99% CI < 1.44)
2. If met, then the primary outcome was tested for superiority
3. If met, then major bleeding was tested for superiority
4. If met, then all-cause mortality was tested for superiority

Methods

- The primary analyses were performed using Cox proportional hazards modeling with warfarin-naïve status and world region (North America, South America, Europe, Asia/Pacific) as strata.
- Efficacy analyses included all randomized patients (intention-to-treat) and included all events from randomization until the efficacy cutoff date (predefined as January 30, 2011).
- Bleeding analyses were “on treatment” including all randomized patients who received at least 1 dose of study drug and all events from initial receipt until 2 days after the last dose of study drug.

Apixaban and Warfarin Dosing

- Apixaban (or matching placebo) was dosed at 5 mg twice daily, or 2.5 mg twice daily for a subset of patients with 2 or more of the following criteria: age ≥ 80 years, body weight ≤ 60 kg, serum creatinine ≥ 1.5 mg/dL (133 µmol/L).
- Warfarin (or matching placebo) was dosed guided by blinded encrypted INR point-of-care device, with target INR of 2.0–3.0.

Baseline Characteristics

Characteristic	Apixaban (n=9120)	Warfarin (n=9081)
Age, years, median (25th, 75th %ile)	70 (63, 76)	70 (63, 76)
Women, %	35	35
Region, %		
North America	25	25
Latin America	19	19
Europe	40	40
Asia/Pacific	16	16
Warfarin naïve, %	43	43
CHADS score, mean (+/- SD)	2.1 (+/- 1.1)	2.1 (+/- 1.1)
1, %	34	34
2, %	36	36
≥ 3, %	30	30

Baseline Characteristics

Characteristic	Apixaban (n=9120)	Warfarin (n=9081)
Qualifying risk factors, %		
Age ≥75 yrs	31	31
Prior stroke, TIA, or SE	19	20
Heart failure or reduced LV EF	35	36
Diabetes	25	25
Hypertension	87	88
Renal function (Cl_{Cr} ml/min), %		
Normal (>80)	41	41
Mild impairment (>50 – 80)	42	42
Moderate impairment (>30 – 50)	15	15
Severe impairment (≤ 30)	1.5	1.5

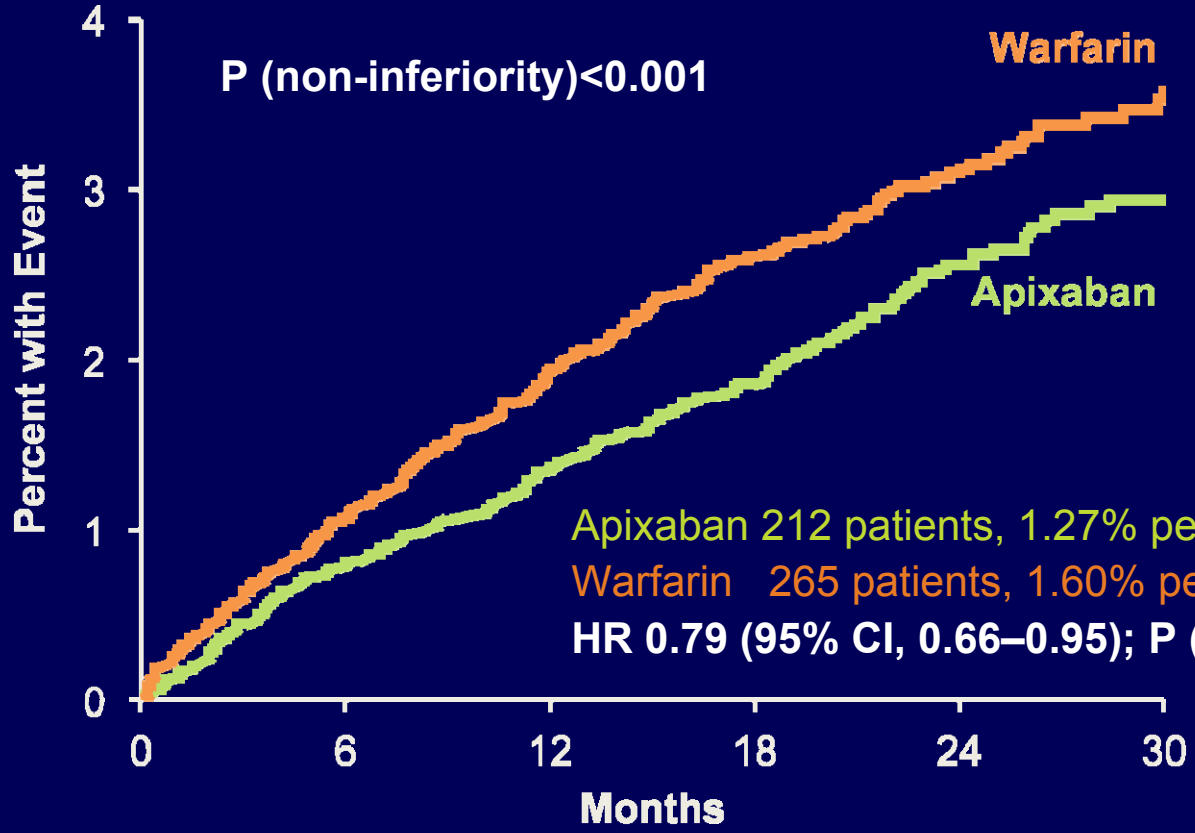
Trial Metrics

- Patients enrolled from December 2006 to April 2010
- Median duration of follow-up 1.8 years
- Drug discontinuation in 25.3% of apixaban and 27.5% of warfarin patients (p=0.001)
- Vital status at the end of the trial was missing in 380 (2.1%) patients
  - Withdrawal of consent in 199 patients
  - Loss to follow-up in 69 patients
- Median (and mean) times in therapeutic INR range among warfarin- treated patients were 66.0 (and 62.2)%.

**Rosendaal FR et al. Throb Haemost 1993;69:236–39.*

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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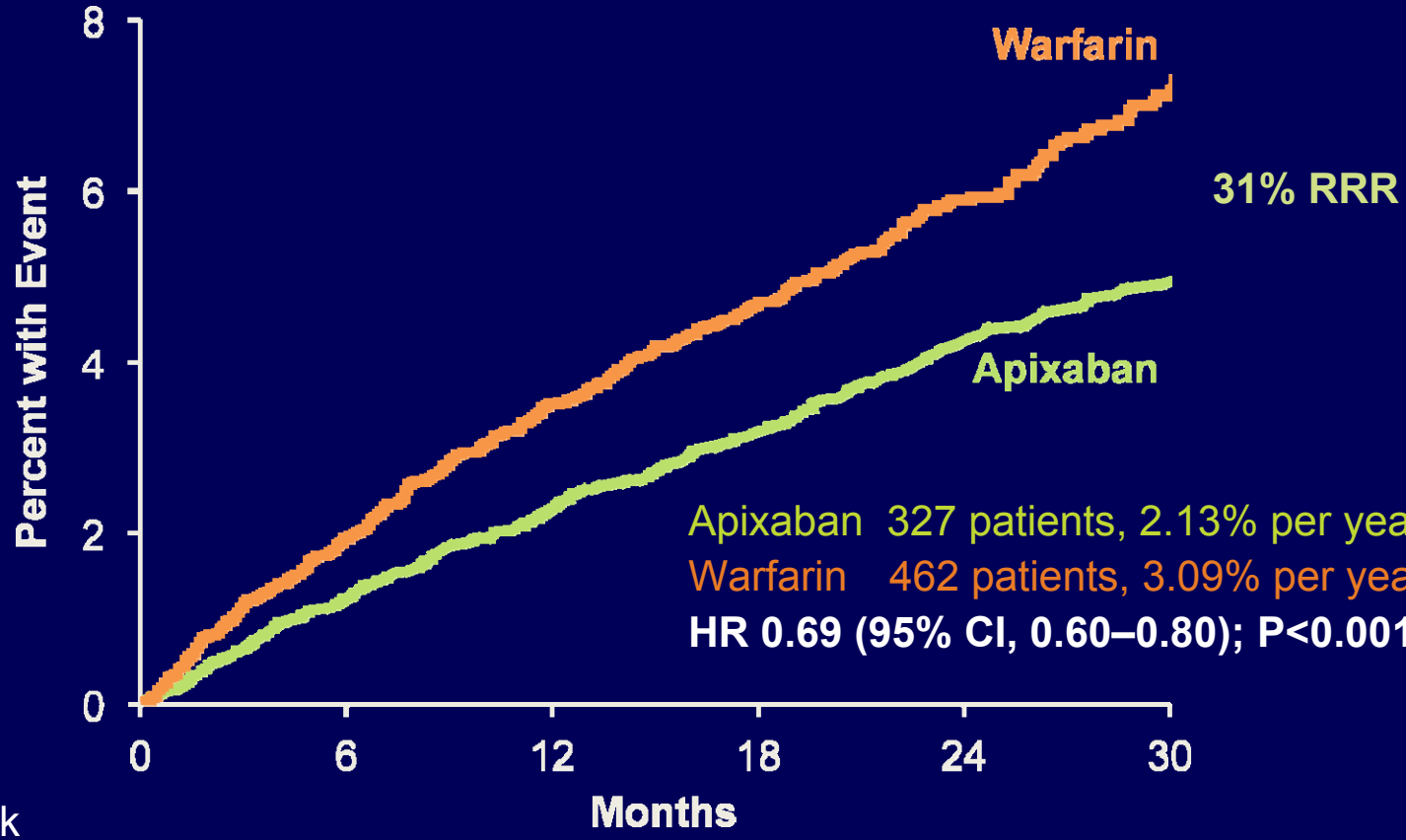
Efficacy Outcomes

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

Major Bleeding

ISTH definition



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

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Bleeding Outcomes

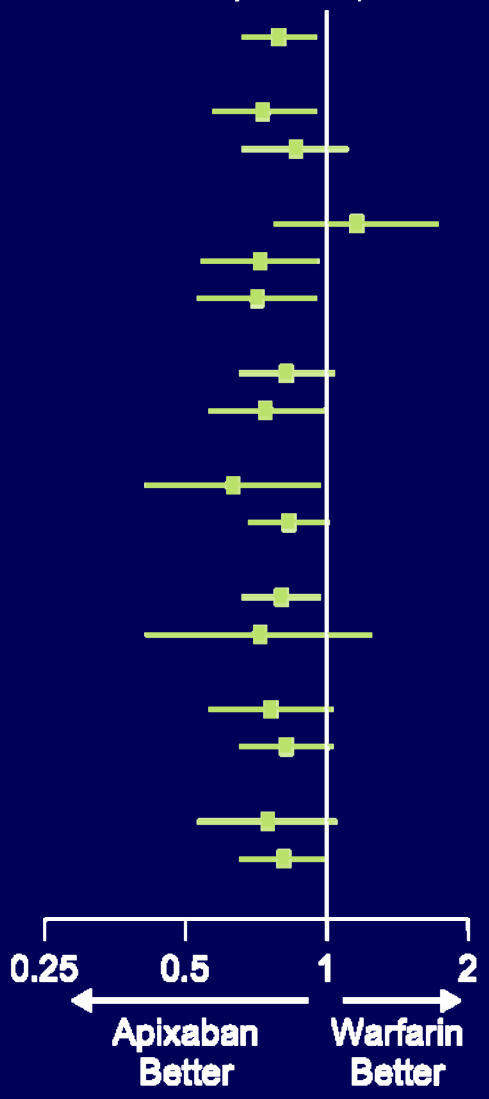
Outcome	Apixaban (N=9088) Event Rate (%/yr)	Warfarin (N=9052) Event Rate (%/yr)	HR (95% CI)	P Value
Primary safety outcome: ISTH major bleeding*	2.13	3.09	0.69 (0.60, 0.80)	<0.001
Intracranial	0.33	0.80	0.42 (0.30, 0.58)	<0.001
Gastrointestinal	0.76	0.86	0.89 (0.70, 1.15)	0.37
Major or clinically relevant non-major bleeding	4.07	6.01	0.68 (0.61, 0.75)	<0.001
GUSTO severe bleeding	0.52	1.13	0.46 (0.35, 0.60)	<0.001
TIMI major bleeding	0.96	1.69	0.57 (0.46, 0.70)	<0.001
Any bleeding	18.1	25.8	0.71 (0.68, 0.75)	<0.001

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

Subgroups for Stroke and Systemic Embolism

(1 of 2)

Characteristics	No. of Patients	Apixaban no. of events (%/yr)	Warfarin	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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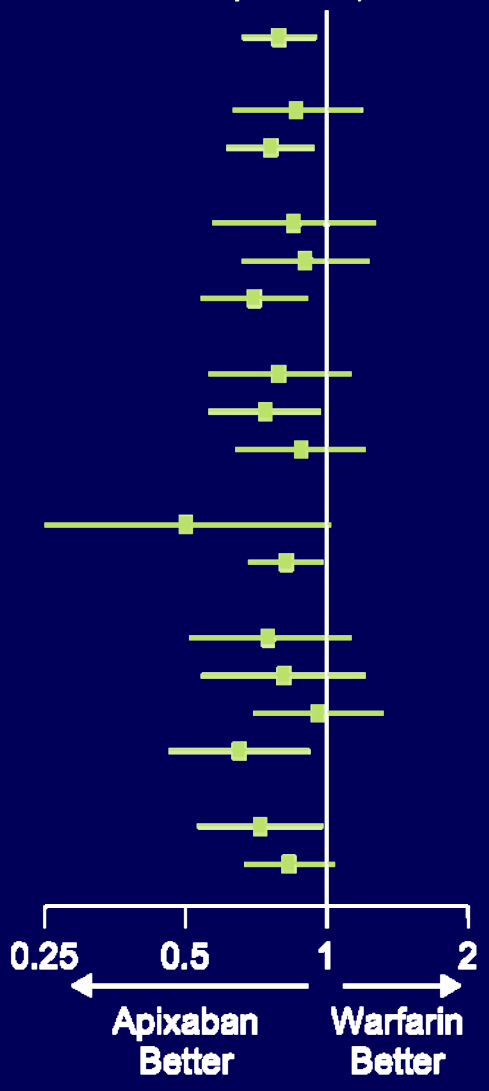
Subgroups for Stroke and Systemic Embolism

(2 of 2)

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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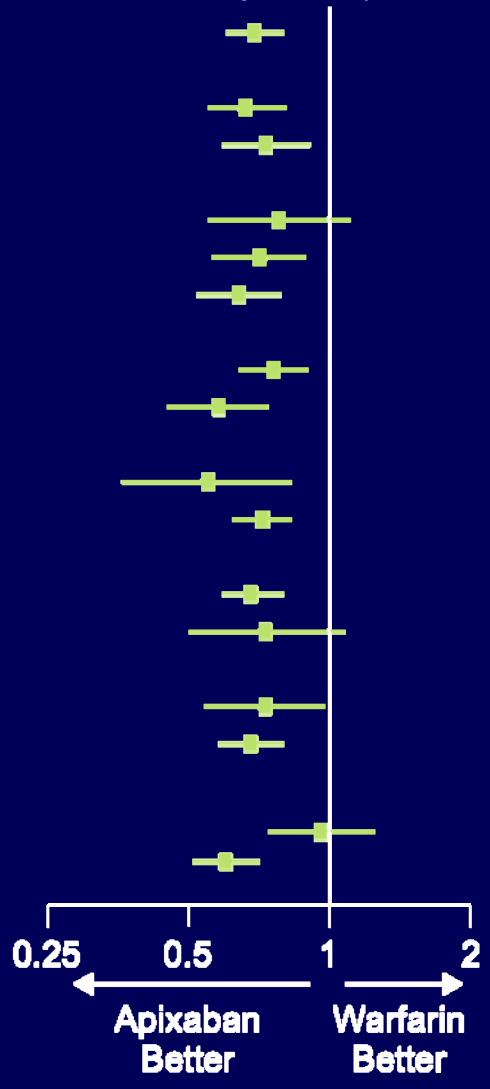
Subgroups for Major Bleeding

(1 of 2)

Characteristics	No. of Patients	Apixaban no. of events (%/yr)	Warfarin no. of events (%/yr)	P-value for Interaction
All Patients	18140	327 (2.13)	462 (3.09)	
Prior Warfarin/VKA Status				0.50
Experienced	10376	185 (2.1)	274 (3.2)	
Naïve	7764	142 (2.2)	188 (3.0)	
Age				0.64
<65 yrs	5455	56 (1.2)	72 (1.5)	
≥65 to < 75 yrs	7030	120 (2.0)	166 (2.8)	
≥75 yrs	5655	151 (3.3)	224 (5.2)	
Sex				0.08
Male	11747	225 (2.3)	294 (3.0)	
Female	6393	102 (1.9)	168 (3.3)	
Weight				0.22
≤60 kg	1978	36 (2.3)	62 (4.3)	
>60 kg	16102	290 (2.1)	398 (3.0)	
Type of Atrial Fibrillation				0.75
Permanent/Persistent	15361	283 (2.2)	402 (3.2)	
Paroxysmal	2776	44 (1.9)	60 (2.6)	
Prior Stroke or TIA				0.71
Yes	3422	77 (2.8)	106 (3.9)	
No	14718	250 (2.0)	356 (2.9)	
Diabetes Mellitus				0.003
Yes	4526	112 (3.0)	114 (3.1)	
No	13614	215 (1.9)	348 (3.1)	



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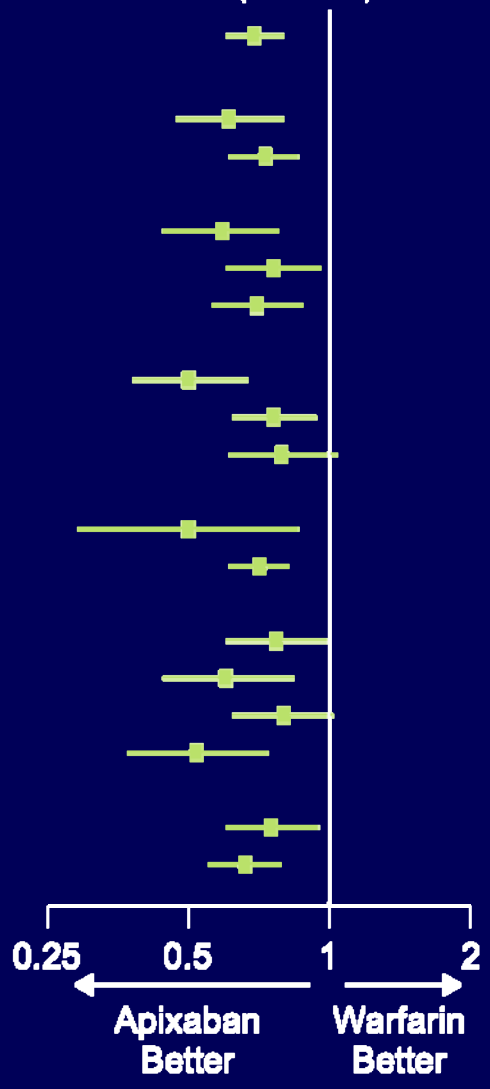
Subgroups for Major Bleeding

(2 of 2)

Characteristics	No. of Patients	Apixaban no. of events (%/yr)	Warfarin no. of events (%/yr)	P-value for Interaction
All Patients	18140	327 (2.13)	462 (3.09)	
Heart Failure				0.30
Yes	5527	87 (1.9)	137 (3.1)	
No	12613	240 (2.2)	325 (3.1)	
CHADs Score				0.40
≤ 1	6169	76 (1.4)	126 (2.3)	
=2	6492	125 (2.3)	163 (3.0)	
≥3	5479	126 (2.9)	173 (4.2)	
Level of Renal Impairment				0.03
Severe or Moderate	3005	73 (3.2)	142 (6.4)	
Mild	7565	157 (2.5)	199 (3.2)	
No impairment	7496	96 (1.5)	119 (1.8)	
Apixaban Dose				0.21
2.5 mg BID or placebo	826	20 (3.3)	37 (6.7)	
5 mg BID or placebo	17314	307 (2.1)	425 (3.0)	
Geographic Region				0.16
North America	4463	106 (2.8)	137 (3.6)	
Latin America	3460	60 (2.1)	94 (3.5)	
Europe	7313	110 (1.7)	135 (2.2)	
Asia/Pacific	2904	51 (2.1)	96 (4.1)	
Aspirin at Randomization				0.40
Yes	5608	129 (2.7)	164 (3.7)	
No	12532	198 (1.9)	298 (2.8)	



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Adverse Events and Liver Function Tests

N (%)	Apixaban (N=9088)	Warfarin (N=9052)
Total patients with an adverse event	7406 (81.5)	7521 (83.1)
Total patients with a serious adverse event	3182 (35.0)	3302 (36.5)
Serious adverse events reported in ≥ 1% of patients in either treatment group		
Atrial fibrillation	301 (3.3)	287 (3.2)
Pneumonia	202 (2.2)	231 (2.6)
Discontinuations due to an adverse event	688 (7.6)	758 (8.4)
ALT or AST > 3X ULN and total bilirubin > 2X ULN	30/ 8788 (0.3)	31/ 8756 (0.4)
ALT elevation		
> 3X ULN	100/ 8790 (1.1)	89/ 8759 (1.0)
> 5X ULN	45/ 8790 (0.5)	47/ 8759 (0.5)
> 10X ULN	16/ 8790 (0.2)	20/ 8759 (0.2)
> 20X ULN	8/ 8790 (<0.1)	12/ 8759 (0.1)

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.

Summary

Treatment with apixaban as compared to warfarin in patients with AF and at least one additional risk factor for stroke:

- Reduces stroke and systemic embolism by 21% (p=0.01)
- Reduces major bleeding by 31% (p<0.001)
- Reduces mortality by 11% (p=0.047)

with consistent effects across all major subgroups and with fewer study drug discontinuations on apixaban than on warfarin, consistent with good tolerability.

Conclusion

In patients with atrial fibrillation, apixaban is superior to warfarin at preventing stroke or systemic embolism, causes less bleeding, and results in lower mortality.

THANKS to all investigators and patients

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