New oral factor Xa inhibitors. Lessons from AVERROES and ARISTOTLE trials

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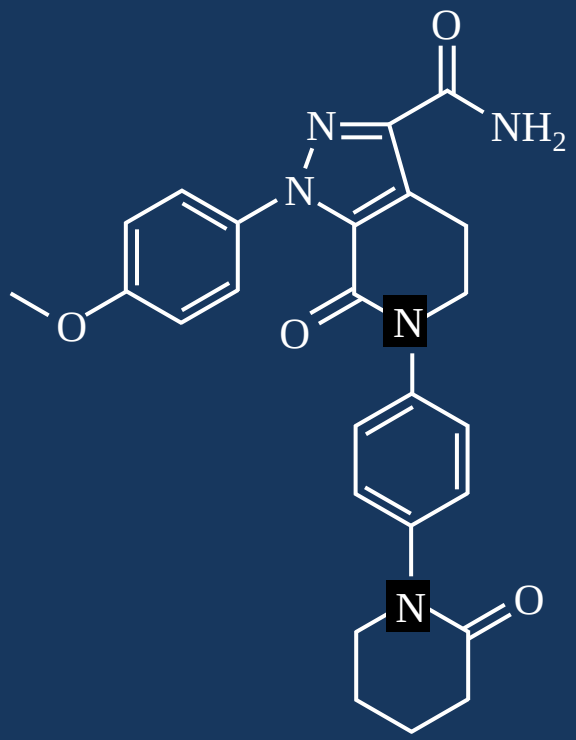
Apixaban: A novel factor Xa inhibitor

Apixaban is a structurally novel and neutral bicyclic pyrazole:



- Highly selective for factor Xa inhibition: K_i = 0.08 nM
- Oral bioavailability: ~50%
- Rapid absorption (Tmax 3-4h)
- No food effect
- Half-life: $T_{1/2}$ ~12 h
- Multiple elimination/excretion pathways: ~27% renal clearance
- Not a pro-drug; no active metabolites
- ~87% plasma protein binding

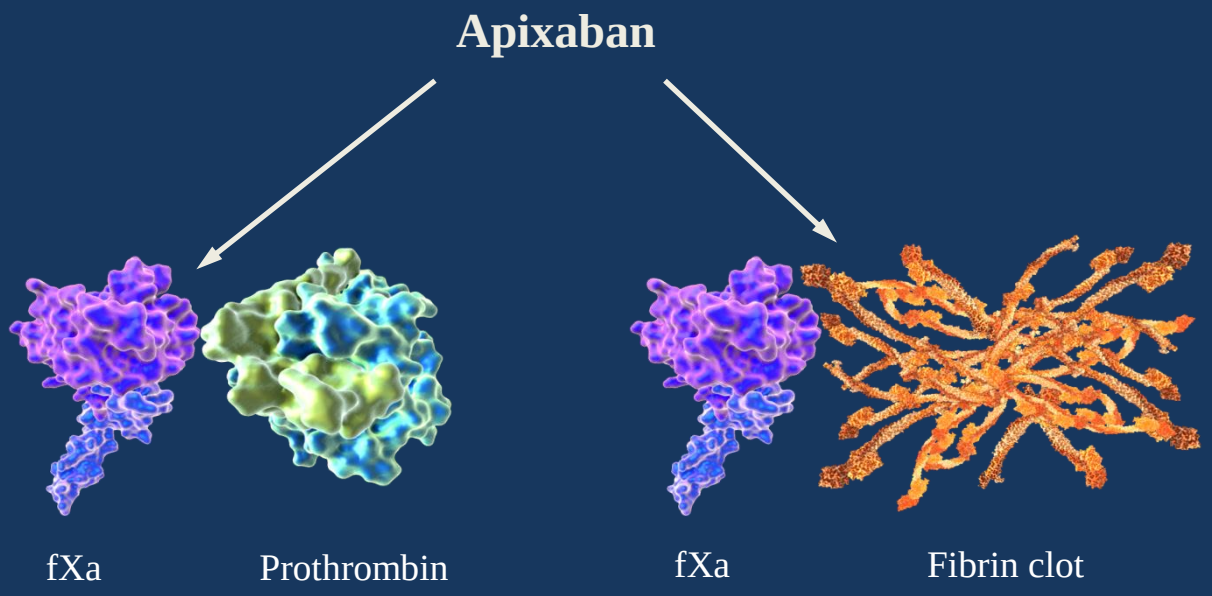
$T_{1/2}$ = elimination half-life; Ki = dissociation constant of an inhibitor: lower value indicates higher affinity

Pinto DJ et al. *J Med Chem* 2007;50:5339-5356. He K et al. Poster presented at: 48th Annual Meeting of the American Society of Hematology; December 2006; Orlando, FL. Poster 38-I. Frost C et al. Poster presented at: 21st Congress of the International Society of Thrombosis and Haemostasis; July 2007; Geneva, Switzerland.(PM 664 & 665). Lassen MR et al. *J Thromb Haem* 2007;5:2368-2375. Raghavan et al. *Drug Metab Dispos* 2009;37:74-81.

Frost C et al. *Can J Clin Pharmacol* 2008;15 (3): Abstract 102. Eikelboom J et al. *Circulation* 2010;121:1523-1532. Apixaban SmPC June 2011.

Direct factor Xa inhibition with apixaban

Apixaban can neutralize FXa regardless of whether the target is clot bound or prothrombinase bound



Turpie AGG. *Arterioscler Thromb Vasc Biol* 2007;27:1238-1247.
Ansell J. *J Thromb Haemost* 2007;5(suppl1):60-64.

Apixaban pharmacokinetics

- Absorption
  - Absorption occurs primarily in the upper gastrointestinal tract
  - Oral bioavailability of ~50%
  - Peak plasma concentrations achieved at 3 to 4 hours
  - No expected effect of altered gastrointestinal pH

Frost C et al. Poster presented at: 21st Congress of the International Society of Thrombosis and Haemostasis; July 2007a; Geneva, Switzerland. P-M-664.

Frost C et al. Poster presented at: 21st Congress of the International Society of Thrombosis and Haemostasis; July 2007b; Geneva, Switzerland. P-M-665.

Frost C, et al. *Can J Clin Pharmacol* 2008;15 (3):e469. Abstract 102. Roser-Jones C, & Becker RC. *J Thromb Thrombolysis* 2010; 29;141 - 146.

Eikelboom J et al. *Circulation* 2010;121:1523-1532. Apixaban SmPC June 2011.

Apixaban pharmacokinetics (contd.)

- Metabolism/Elimination
  - Apixaban achieves steady-state concentration after ~3 days
  - Terminal half-life of approximately 12 hours
  - Elimination involves multiple mechanisms including metabolism as well as biliary and renal elimination of unchanged parent
    - Renal clearance accounted for ~27% of total clearance

Frost C et al. Poster presented at: 21st Congress of the International Society of Thrombosis and Haemostasis; July 2007a; Geneva, Switzerland. P-M-664.

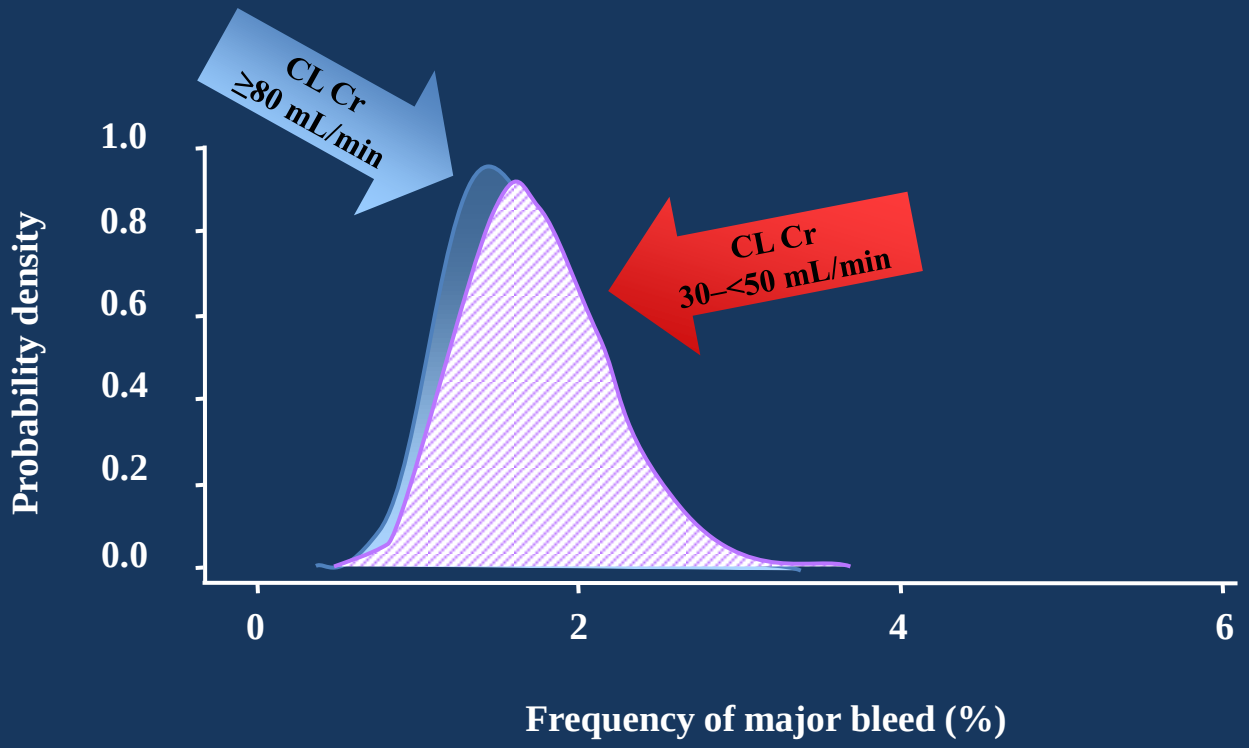
Raghavan et al. *Drug Metab Dispos* 2009;37:74-81.

Roser-Jones C & Becker RC. *J Thromb Thrombolysis* 2010; 29;141-146.

Apixaban SmPC June 2011.

The predicted effects of moderate renal impairment on the frequency of major bleeding with apixaban

- In patients treated with apixaban 2.5 mg BD, the risk of major bleeding appears comparable in patients with normal renal function and moderate renal impairment



Adapted from Leil TA et al. *Clin Pharmacol Ther* 2010;88:375-82.

Pharmacology of Apixaban, Rivaroxaban and Dabigatran

	Apixaban[1]	Rivaroxaban[2]	Dabigatran[3]
Mechanism of action	Direct factor Xa inhibitor	Direct factor Xa inhibitor	Direct thrombin inhibitor
Absolute availability	~50%	80–100%	~6.5%
Hours to C_{max}	3-4	2-4	0.5-2
Pro-drug	No	No	Yes
Food effect	No	No	No*
CYP metabolism	Yes	Yes	No**
Interaction with P-gp	Yes	Yes	Yes
Renal clearance	~27%	~33 %	85%
Mean half-life ($t_{1/2}$)	~12 h	7–11 h	~12–14 h

**But delay the time to peak plasma concentration by 2 hours*

**Dabigatran does not seem to induce, inhibit or be a substrate of the CYP450 enzyme system

1. Apixaban SmPC, 2011
2. Rivaroxaban SmPC, 2011
3. Dabigatran SmPC, 2011

AVERROES

- **Apixaban in Patients with Atrial Fibrillation Who Are Unsuitable for VKA Treatment**

Study Design

Event driven*

Patient population (N=5599)

- Patients aged ≥ 50 years with AF and ≥1 risk factor for stroke
- Not receiving VKA therapy (expected to be unsuitable or have previously failed VKA therapy)

Apixaban 5.0 mg twice daily (2.5 mg in selected patients†) (n=2808)

Aspirin 81–324 mg once daily (n=2791)

Primary efficacy outcome

- Stroke (ischemic or hemorrhagic) or systemic embolism

Primary safety outcome

- Major bleeding

All outcomes were centrally adjudicated by an independent committee

522 centers
36 countries

* 226 primary study events were needed.

† Two or more of the following: age ≥80 years; body weight ≤60 kg; serum creatinine ≥1.5 mg/dL (133 µmol/L).

AF, atrial fibrillation; MI, myocardial infarction; VKA, vitamin K antagonist.

Eikelboom JW, et al. *Am Heart J.* 2010;159:348–353.

Inclusion Criteria

- Age ≥ 50 years
- Documented permanent, persistent, or paroxysmal atrial fibrillation
- One or more risk factor for stroke:
  - prior stroke or TIA
  - age ≥75 years
  - treated arterial hypertension
  - treated diabetes mellitus
  - heart failure (NYHA class ≥ 2)
  - left ventricular ejection fraction ≤ 35%
  - documented peripheral arterial disease
- Not currently receiving VKA therapy (demonstrated or expected to be unsuitable)

Eikelboom JW, et al. *Am Heart J.* 2010;159:348–353.

Baseline Characteristics

Variable - mean ± SD or n (%)	Apixaban (n=2808)	Aspirin (n=2791)
Age, years	70 ± 9	70 ± 10
Male sex	1660 (59)	1617 (58)
Heart rate — beats/min	74 ± 14	74 ± 14
Systolic blood pressure — mm Hg	132 ± 16	132 ± 16
Body mass index - kg / m^2	28 ± 5	28 ± 5
$CHADS_2$ score	2.0 ± 1.1	2.1 ± 1.1
0 or 1	1004 (36)	1022 (37)
2	1045 (37)	954 (34)
≥3	758 (27)	812 (29)
VKA within 30 days before screening	401 (14)	426 (15)
Aspirin within 30 days before screening	2137 (76)	2081 (75)

VKA, Vitamin K antagonist

Connolly SJ, et al. *N Engl J Med*. 2011;364:806–817.

Baseline Characteristics (Continued)

Variable - n (%)	Apixaban (n=2808)	Aspirin (n=2791)
Risk factors for stroke		
Prior stroke or TIA	390 (14)	374 (13)
Hypertension, receiving treatment	2408 (86)	2429 (87)
Heart failure	1118 (40)	1053 (38)
NYHA class 1 or 2	932 (33)	878 (31)
NYHA class 3 or 4	186 (7)	175 (6)
LVEF ≤35%	144 (5)	144 (5)
Peripheral artery disease	66 (2)	87 (3)
Diabetes, receiving treatment	537 (19)	559 (20)
Mitral stenosis	64 (2)	50 (2)

LVEF, left ventricular ejection fraction; TIA, transient ischemic attack; NYHA, New York Heart Association

Connolly SJ, et al. *N Engl J Med*. 2011;364:806–817.

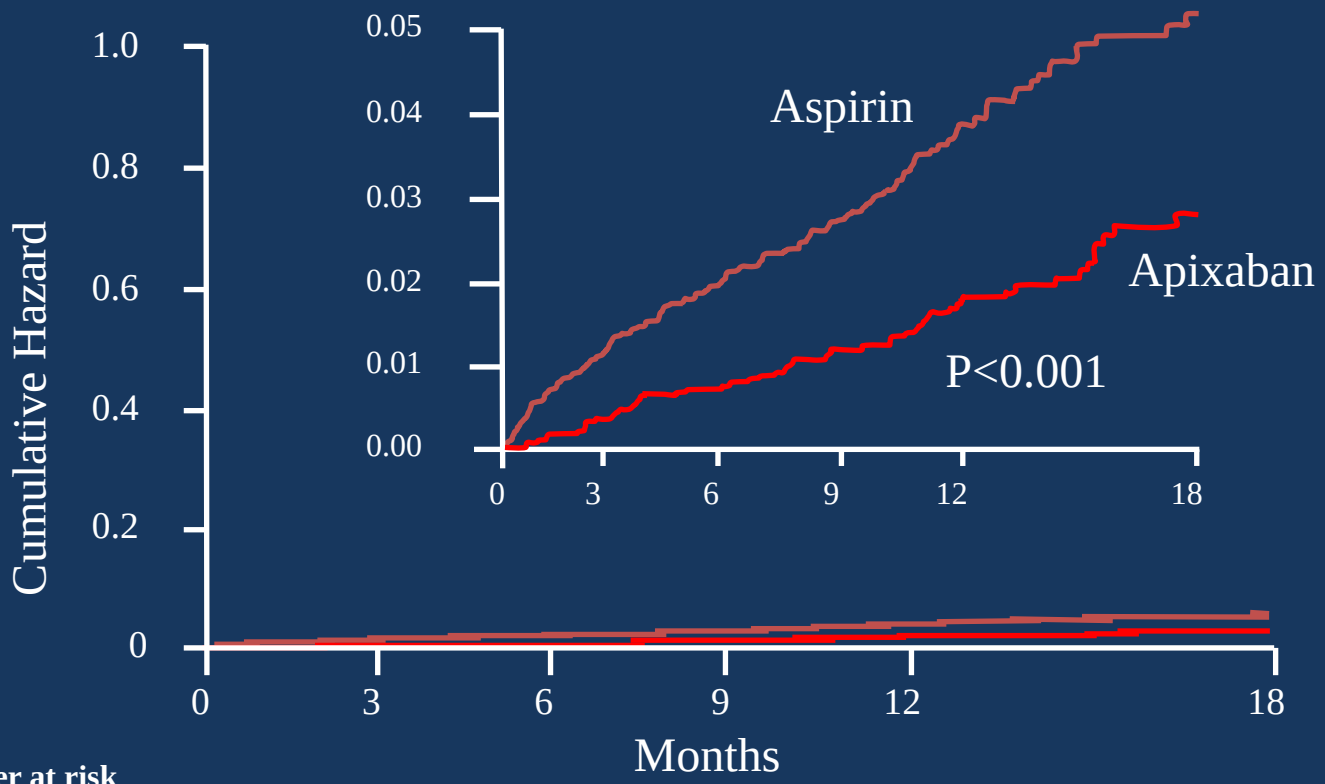
Early Termination of Study: Clear Benefit of Apixaban

- Data and safety monitoring committee recommended early termination of AVERROES trial because of a clear benefit in favor of apixaban
- First planned interim analysis of efficacy (Feb 19, 2010)
  - Treatment benefit in favor of apixaban for the primary outcome (stroke or systemic embolism) exceeded 4 SD
- Confirmatory analysis (May 28, 2010)
  - *P*=0.000002 for primary outcome (z=4.76)
- Events occurring through May 28, 2010 were included in the primary analyses

Connolly SJ, et al. *N Engl J Med.* 2011;364:806–817.
Pfizer/Bristol-Myers Squibb. AVERROES study of investigational agent apixaban closes early due to clear evidence of efficacy. Princeton, NJ and New York, NY. June 10, 2010.

Primary Efficacy Outcome: Stroke or Systemic Embolism

Hazard ratio with apixaban, 0.45 (95% CI, 0.32, 0.62)

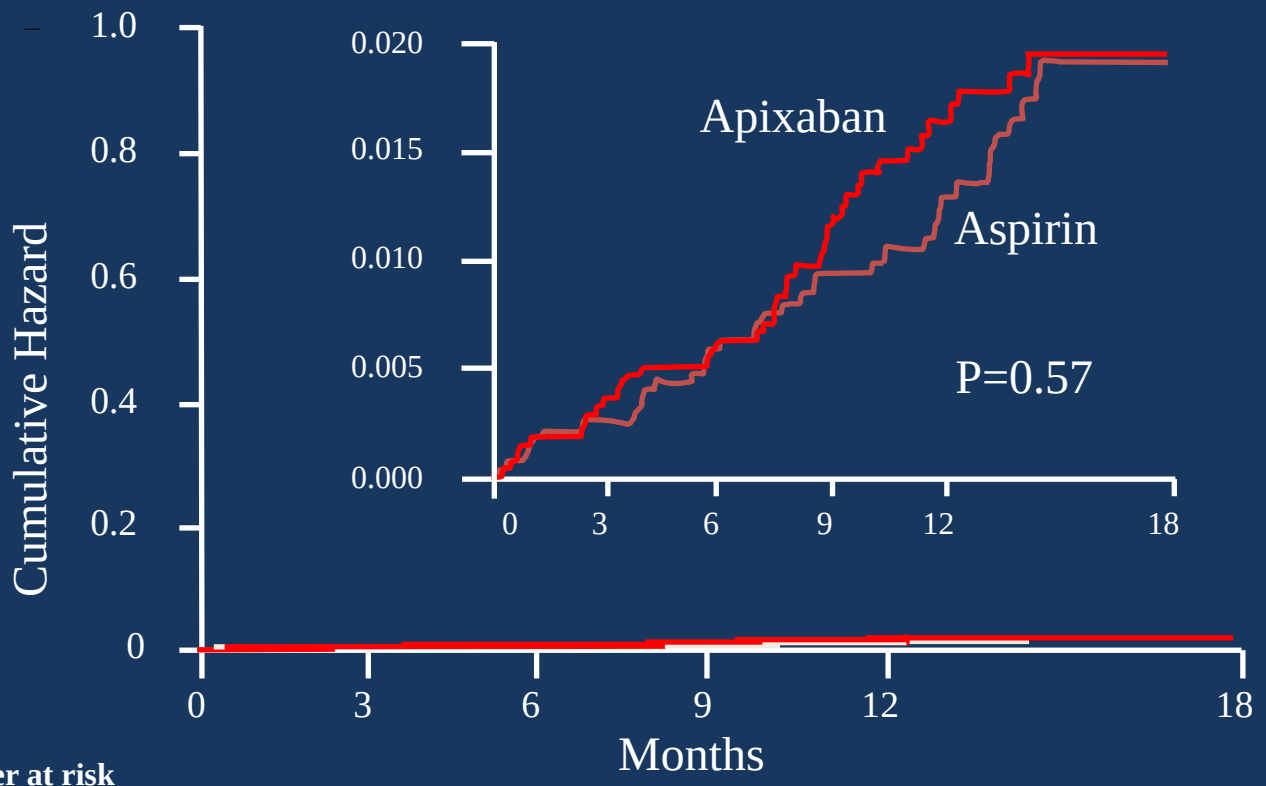


Number at risk						
Aspirin	**2791**	**2716**	**2530**	**2112**	**1543**	**628**
Apixaban	**2808**	**2758**	**2566**	**2125**	**1522**	**615**

Connolly SJ, et al. *N Engl J Med*. 2011;364:806–817.

Primary Safety Outcome: Major Bleeding

Hazard ratio with apixaban, 1.13 (95% CI, 0.74, 1.75)



Number at risk						
Aspirin	2791	2738	2557	2140	1571	642
Apixaban	2808	2759	2566	2120	1521	622

Connolly SJ, et al. *N Engl J Med*. 2011;364:806–817.

Primary and Secondary Efficacy Outcomes

Outcome	Apixaban (n=2808)		Aspirin (n=2791)		Apixaban vs aspirin		
	Events	Rate*	Events	Rate*	HR	95% CI	*P*
Stroke or systemic embolism	51	1.6	113	3.7	0.45	0.32–0.62	<0.001
Stroke†	49	1.6	105	3.4	0.46	0.33–0.65	<0.001
Ischemic	35	1.1	93	3.0	0.37	0.25–0.55	<0.001
Hemorrhagic	6	0.2	9	0.3	0.67	0.24–1.88	0.45
Unspecified	9	0.3	4	0.1	2.24	0.69–7.27	0.18
Disabling or fatal	31	1.0	72	2.3	0.43	0.28–0.65	<0.001
Systemic embolism	2	0.1	13	0.4	0.15	0.03–0.68	0.01

*The annual rate is the rate per 100 patient-years of follow-up. All analyses were based on the time to a first event;.
†Stroke included ischemic and hemorrhagic (ie, primary intracerebral bleeding) types; some strokes could not be classified (unspecified). Hemorrhagic stroke is also included in the categories of major bleeding and intracranial bleeding. Disabling or fatal stroke was defined by a modified Rankin score of 3 to 6.

Connolly SJ, et al. *N Engl J Med*. 2011;364:806–817.

Secondary Efficacy Outcomes

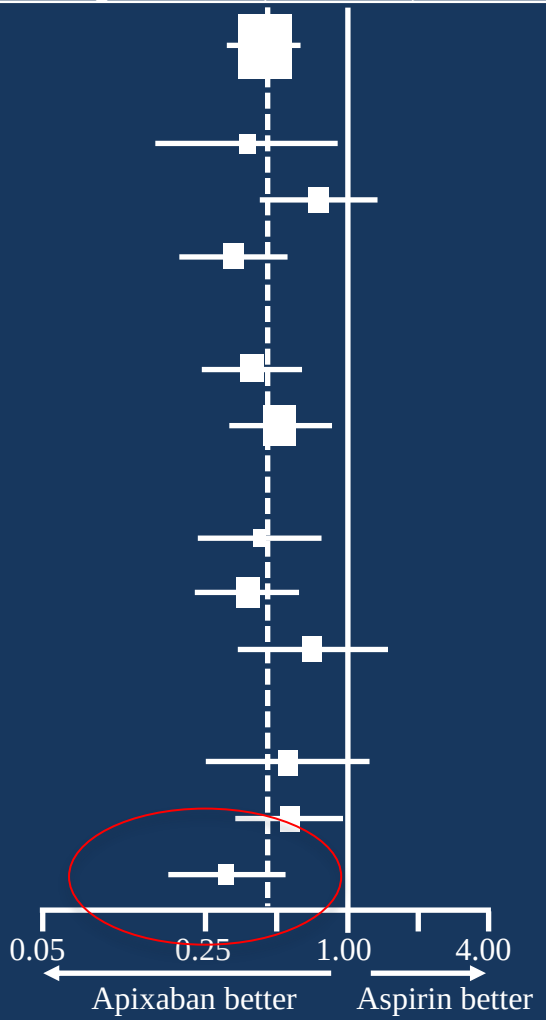
	Apixaban (n=2808)		Aspirin (n=2791)		Apixaban vs aspirin		
Outcome	Events	Rate*	Events	Rate*	HR	95% CI	*P*
Stroke, systemic embolism, or death	143	4.6	223	7.2	0.64	0.51–0.78	<0.001
Stroke, systemic embolism, MI, or vascular death	132	4.2	197	6.4	0.66	0.53–0.83	<0.001
Stroke, systemic embolism, MI, vascular death, or major bleeding	163	5.3	220	7.2	0.74	0.60–0.90	0.003
MI	24	0.8	28	0.9	0.86	0.50–1.48	0.59
Death	111	3.5	140	4.4	0.79	0.62–1.02	0.07
Vascular death	84	2.7	96	3.1	0.87	0.65–1.17	0.37
CV Hospitalization	367	12.6	455	15.9	0.79	0.69–0.91	<0.001

* The percent per year is the rate per 100 patient-years of follow-up. All analyses were based on time to first event; patients could have more than one event. CV, cardiovascular; HR, hazard ratio; MI, myocardial infarction.

Connolly SJ, et al. *N Engl J Med*. 2011;364:806–817.

Relative Risk of Stroke or Systemic Embolism by Subgroup

Characteristic	No. of Patients	Aspirin no. of events (%/yr)	Apixaban no. of events (%/yr)	HR with Apixaban (95% CI)	P Value
Overall	5599	113 (3.7)	51 (1.6)		
Age					0.08
<65 yr	1714	19 (2.0)	7 (0.7)		
65 to <75 yr	1987	28 (2.7)	24 (2.0)		
≥75 yr	1897	66 (6.1)	20 (2.0)		
Sex					0.42
Female	2321	64 (4.9)	25 (1.9)		
Male	3277	49 (2.7)	26 (1.4)		
Estimated GFR					0.36
<50 ml/min	1198	36 (5.8)	16 (2.5)		
50 to <80 ml/min	2374	59 (4.5)	22 (1.7)		
≥80 ml/min	2021	18 (1.6)	13 (1.1)		
$CHADS_2$ 0-score					0.23
1	2026	18 (1.6)	10 (0.9)		
2	1999	40 (3.7)	25 (2.1)		
≥3	1570	55 (6.3)	16 (1.9)		



Connolly SJ, et al. *N Engl J Med.* 2011;364:806–817.

Discontinuation of Study Medication

- At 2 years, rates of permanent discontinuation of study medication were lower in the apixaban group
  - 17.9% per year in the apixaban group
  - 20.5% per year in the aspirin group
  - HR: 0.88 (95% CI: 0.78–0.99), p=0.03

Connolly SJ, et al. *N Engl J Med*. 2011;364:806–817.

ARISTOTLE

Atrial Fibrillation with at Least One Additional Risk Factor for Stroke

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

Design of NOAC Trials

	RELY	ROCKET	ARISTOTLE	AVERROES
N	**18,113**	**14,264**	**18,201**	**5,599***
Enrolment	**Dec 22, 2005 – Dec 15,2007**	**Dec18, 2006 – June 17, 2009**	**Dec19, 2006 – April 2, 2010**	Sept 10, 2007 – Dec 23, 2009
Design	Randomized **Open-Label** use of warfarin	Randomized, double-blind, double-dummy	Randomized, double-blind, double-dummy	Randomized, double-blind, double-dummy
Treatments	- **Dabigatran** 110x2 - **Dabigatran** 150x2 - Warfarin (INR)	- **Rivaroxaban** 20 mgx1 (15 mg if CrCl=30-49) - Warfarin (INR)	- **Apixaban** 5 mgx2 (2.5 mgx2 if[1]) - Warfarin (INR)	- **Apixaban** 5 mgx2 (2.5 mgx2 if[1]) - Aspirin 81-324 mg
Objective	**Non-inferiority**	**Non-inferiority**	**Non-inferiority**	**Superiority**

[1]Patients with ≥2 of the following criteria: age ≥80 years, body weight <60 kg, or a serum creatinine level ≥1.5 mg/dL (133 µmol/L): used in 4.6% ARISTOTLE patients; used in 6.5% of patients in AVERROES patients.

Study Outcomes in NOAC Trials

(Central Blinded Adjudication in All)

	RELY	ROCKET	ARISTOTLE	AVERROES
Primary study outcome	**Stroke or SE**	**Stroke or SE**	**Stroke or SE**	**Stroke or SE**
Primary safety outcome	**Major** bleeding Life-threatening bleeding	**Major*** and non-major clinically relevant bleeding	**Major** and non-major clinically relevant bleeding	**Major** and non-major clinically relevant bleeding
Secondary outcomes	• Stroke • SE • Death • MI • PE • TIA • Hospitalization	• Stroke • SE • Death • MI	• Stroke • SE • Death • MI	• Stroke • SE • Death • MI

**Including bleeding leading to permanent disability*

Major bleeding definition

RE-LY	ROCKET	ARISTOTLE
1. Reduction in the hemoglobin level ≥20 g /L, 2. transfusion ≥2 u of blood, 3. or symptomatic bleeding in a critical area or organ. 4. Life-threatening: fatal bleeding, symptomatic intracranial bleeding, bleeding with a decrease in the hemoglobin level of at least 50 g per liter, or bleeding requiring transfusion of at least 4 units of blood or inotropic agents or necessitating surgery. All other bleeding was considered minor.	1. clinically overt bleeding associated with any of the following: fatal outcome, involving a critical site (ie, intracranial, intraspinal, intraocular, pericardial, intraarticular, intramuscular with compartment syndrome, or retroperitoneal), or 2. clinically overt bleeding associated with a fall in hemoglobin concentration of ≥2 g/dL, or leading to transfusion of ≥2 units of packed red blood cells or whole blood	1. a decrease in Hb level of ≥2 g/dL over a 24-hour period; 2. a transfusion of ≥2 U of packed red blood cells; 3. bleeding that is fatal or occurs in at least 1 of the following critical sites: intracranial, intraspinal, intraocular, pericardial, intraarticular, intramuscular with compartment syndrome, retroperitoneal

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.

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

Nearly 60% with some renal impairment

Demographics

	RELY	ROCKET	ARISTOTLE	AVERROES
Age, yr	71	73	70	70
Weight, kg	83	-	82	-
BMI, kg/m^2	-	28.2	-	28.5
SBP / DBP, mmHg	131/77 (mean)	130/80 (median)	130/- (median)	132/- (mean)
Male sex	64%	60%	65%	59%

Characteristics of AF

	RELY	ROCKET	ARISTOTLE	AVERROES
Type of AF				
Persistent/permanent	67.2%	81.0%	84.7%	73.0%
Paroxysmal	32.8%	17.6%	5.3%	27.0%
Newly diagnosed	-	1.4%	-	-
$CHADS_2$ score, mean	**2.1**	**3.5**	**2.1**	**2.1**
0 or 1	31.9%	**0**	34.0%	36.2%
2	35.6%	**13.0%**	35.8%	35.7%
3-6	32.4%	**86.9%**	30.2%	28.0%
Renal impairment (CrCl 30-50)	19 %	20,7 %	15 %	30 % (eGFR 30-59)

Risk Factors

	RELY	ROCKET	ARISTOTLE	AVERROES
Age ≥75 years	-	**43.2%**	31.2%	33.8%
Previous stroke/TIA	20.0%	**54.8%**	19.4%	13.6%
Prior MI	16.6%	**17.3%**	14.2%	-
Heart Failure	32.0%	**62.5%**	35.4%	38.8%
Diabetes mellitus	23.3%	**39.9%**	25.0%	19.6%
Hypertension	78.9%	**90.5%**	87.4%	86.4%
Periph. vasc. disease	-	**5.9%**	-	2.7%

Inclusion criteria

- Age ≥ 18 years
- Permanent or persistent atrial fibrillation or atrial flutter documented by ECG at the time of enrollment.
- Presence of <u>at least 1 risk factor for stroke</u>

One or more of the following risk factor(s) for stroke:

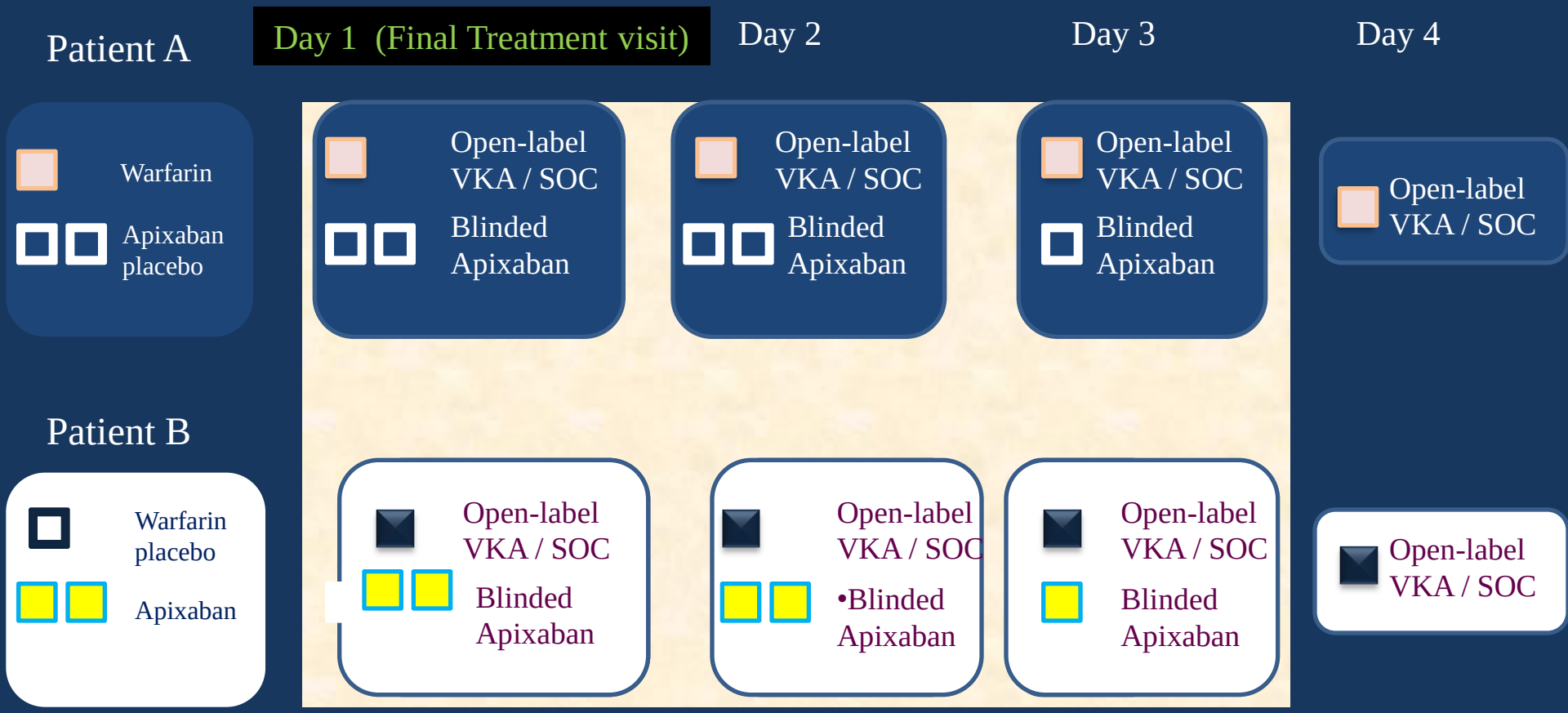
✓Age 75 years or older
✓Prior stroke, TIA or systemic embolus
✓Either symptomatic congestive heart failure within 3 months or left ventricular dysfunction with an LV ejection fraction (LVEF) ≤ 40% by echocardiography, radionuclide study or contrast angiography
✓Diabetes mellitus
✓Hypertension requiring pharmacological treatment

Trial Metrics

- Patients enrolled from December 2006 to Feb 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.*

« Apixaban bridging » end of the study: guidance for the transition to open-label warfarin (VKA / SOC)



ROCKET-AF Study Specific End of Treatment Transition

- To maintain study blind
  - Started VKA at expected maintenance dose
  - No overlap with blinded study drug
  - No INRs for 3 days
  - Heparin bridging therapy allowed but infrequently used

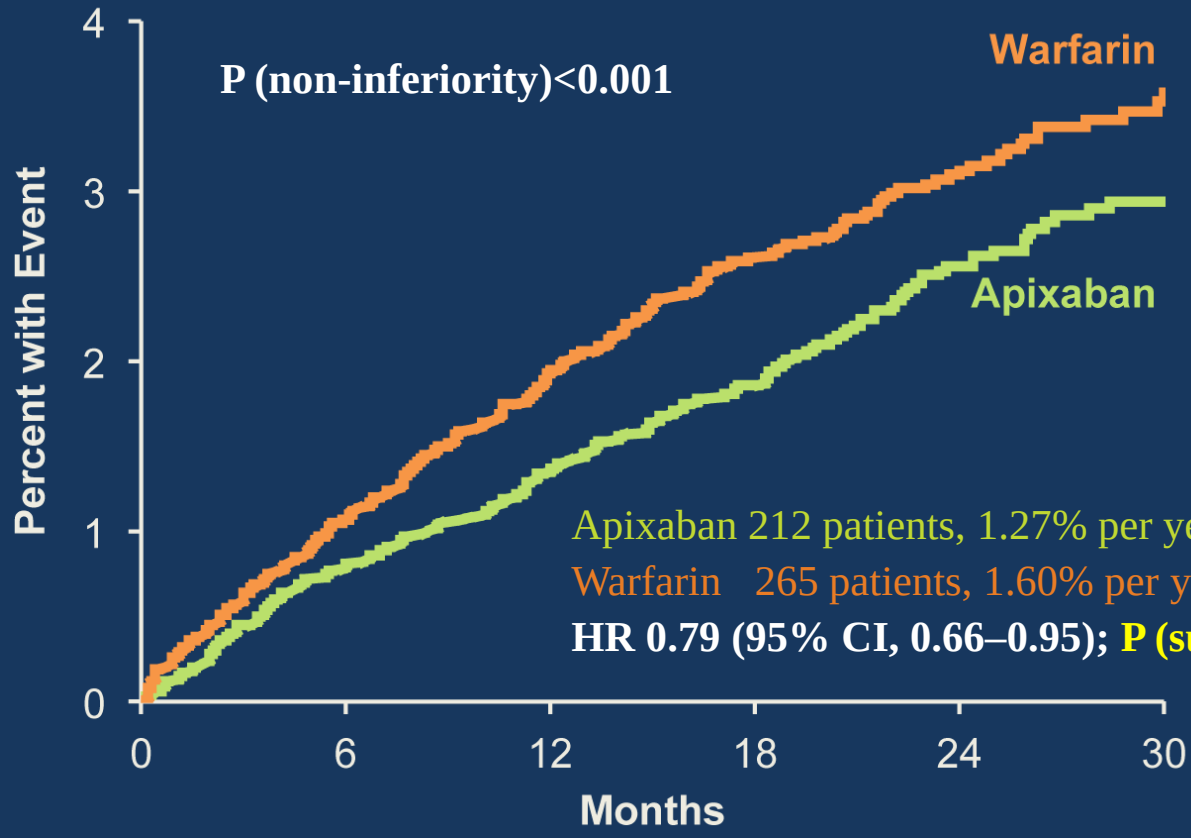
- Impact
  - Imbalance in anticoagulation between treatment groups

- Other options considered but not implemented based on feedback from IDMC review of early discontinuer event rates during the study

FDA adcom at http://www.fda.gov/AdvisoryCommittees/default.htm

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

Efficacy Outcomes

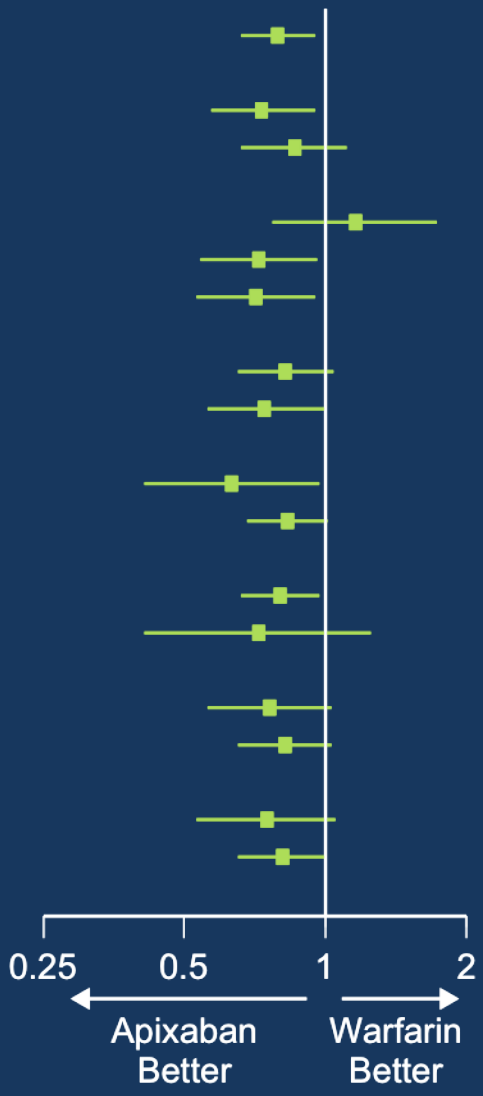
Outcome	Apixaban (N=9120) Event Rate (%/yr)	Warfarin (N=9081) Event Rate (%/yr)	HR (95% CI)	P Value
Stroke or systemic embolism*	1.27	1.60	0.79 (0.66, 0.95)	0.011
Stroke	1.19	1.51	0.79 (0.65, 0.95)	0.012
Ischemic or uncertain	0.97	1.05	0.92 (0.74, 1.13)	0.42
Hemorrhagic	0.24	0.47	0.51 (0.35, 0.75)	<0.001
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

Subgroups for Stroke and Systemic Embolism

(1 of 2)

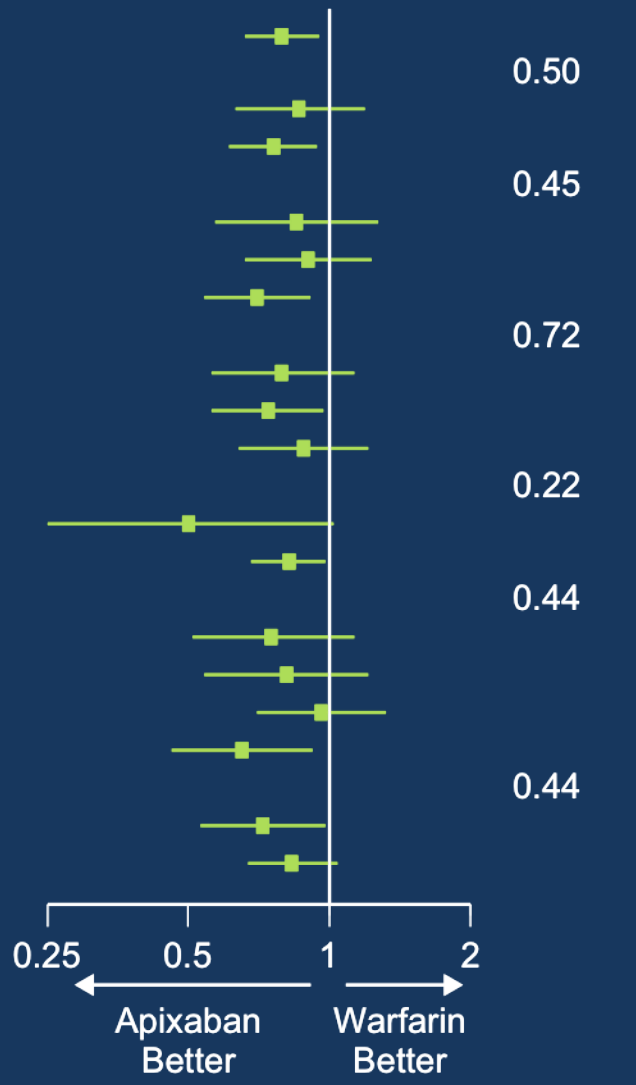
Characteristics	No. of Patients	Apixaban no. of events (%/yr)	Warfarin no. of events (%/yr)	P-value for Interaction
All Patients	18201	212 (1.27)	265 (1.60)	
Prior Warfarin/VKA Status				0.39
Experienced	10401	102 (1.1)	138 (1.5)	
Naïve	7800	110 (1.5)	127 (1.8)	
Age				0.12
<65 yrs	5471	51 (1.0)	44 (0.9)	
≥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)	



Subgroups for Stroke and Systemic Embolism

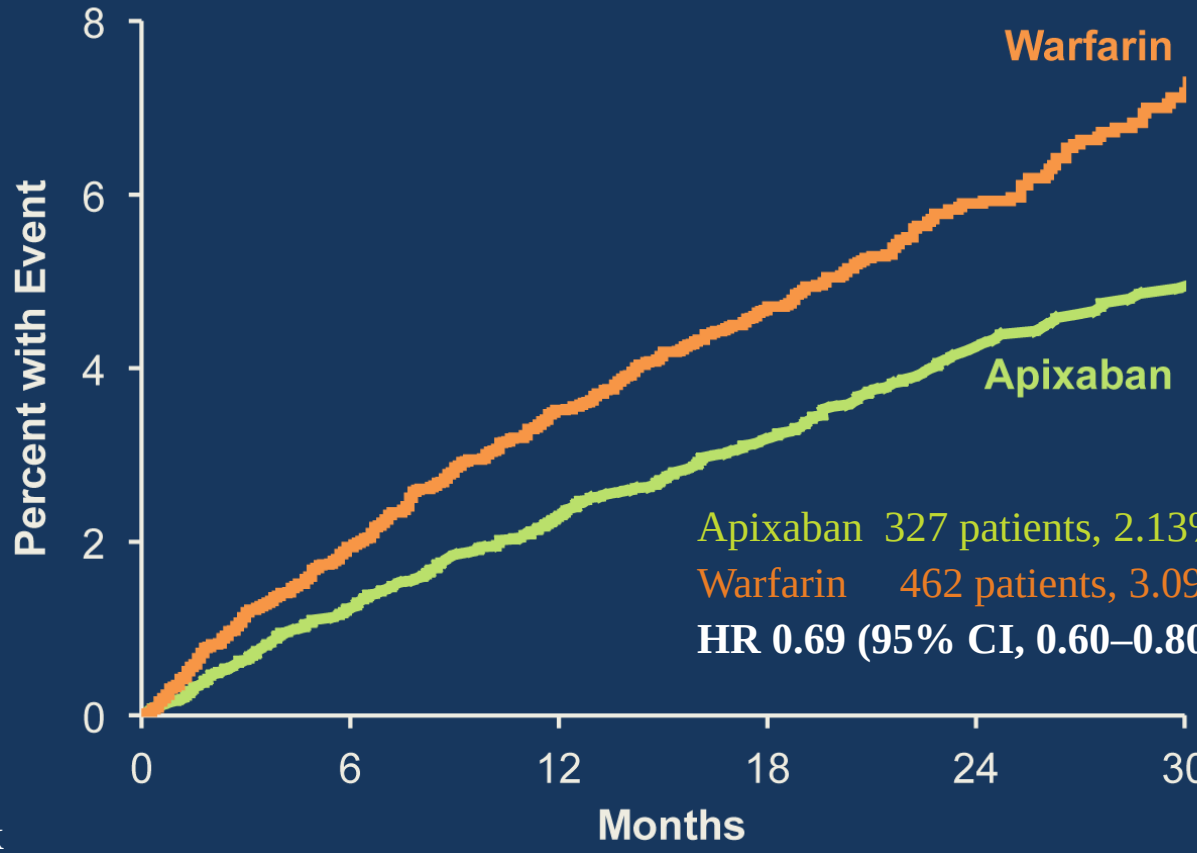
(2 of 2)

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)	



Major Bleeding

ISTH definition



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

Bleeding Comparison in ARISTOTLE

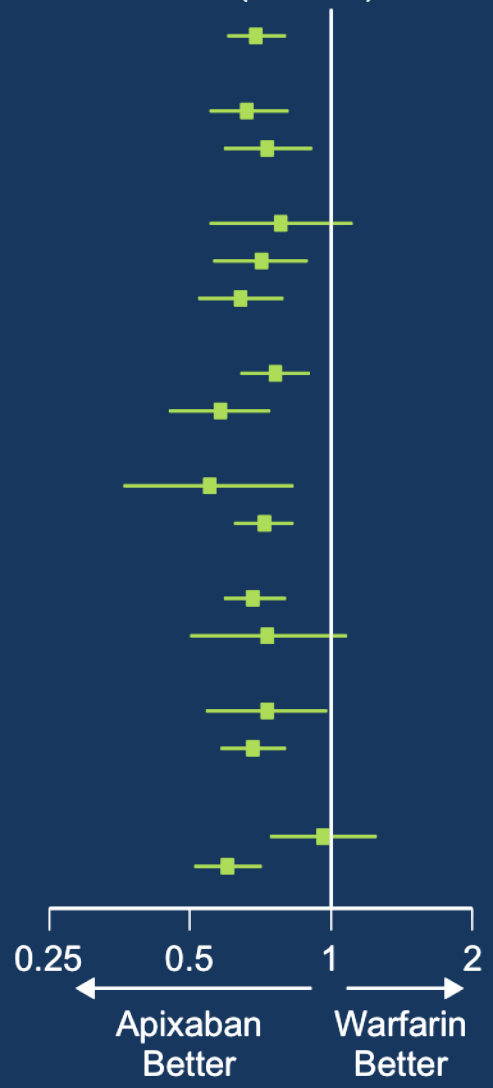
- The more severe the bleeding, the bigger the RRR with apaixaban

Type of Bleeding	Apixaban Event Rate (%/yr)	Warfarin Event Rate (%/yr)	Hazard Ratio (Apixaban/ Warfarin)	95% CI	p-value
ISTH Major	2.13	3.09	0.69	(0.60, 0.80)	<0.0001
ISTH Major/CRNM	4.07	6.01	0.68	(0.61, 0.75)	<0.0001
TIMI Major	0.96	1.69	0.57	(0.46, 0.70)	<0.0001
GUSTO Severe	0.52	1.13	0.46	(0.35, 0.60)	<0.0001
Intracranial	0.33	0.80	0.42	(0.30, 0.58)	<0.0001

Subgroups for Major Bleeding

(1 of 2)

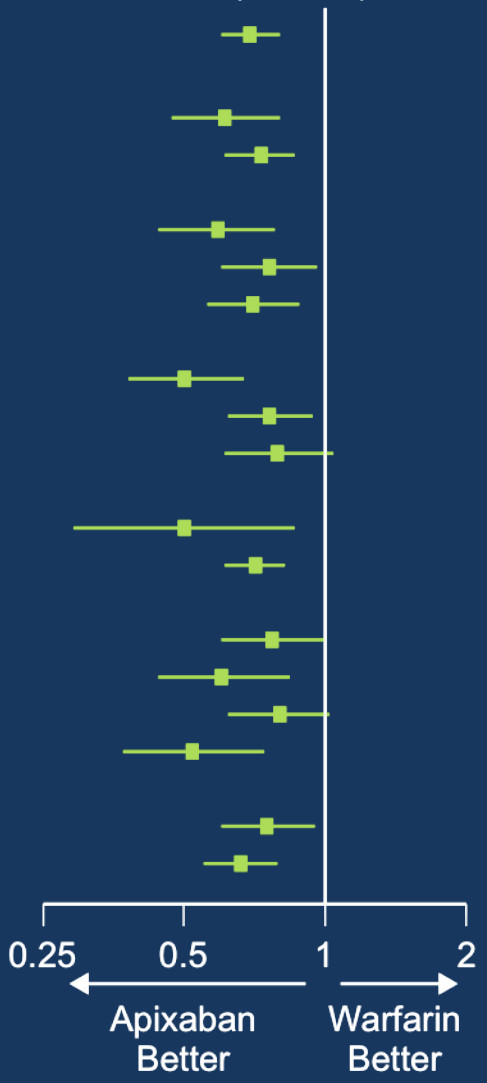
Characteristics	No. of Patients	Apixaban no. of events (%/yr)	Warfarin no. of events (%/yr)	P-value for Interaction
All Patients	18140	327 (2.13)	462 (3.09)	
Prior Warfarin/VKA Status				0.50
Experienced	10376	185 (2.1)	274 (3.2)	
Naïve	7764	142 (2.2)	188 (3.0)	
Age				0.64
<65 yrs	5455	56 (1.2)	72 (1.5)	
≥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)	



Subgroups for Major Bleeding

(2 of 2)

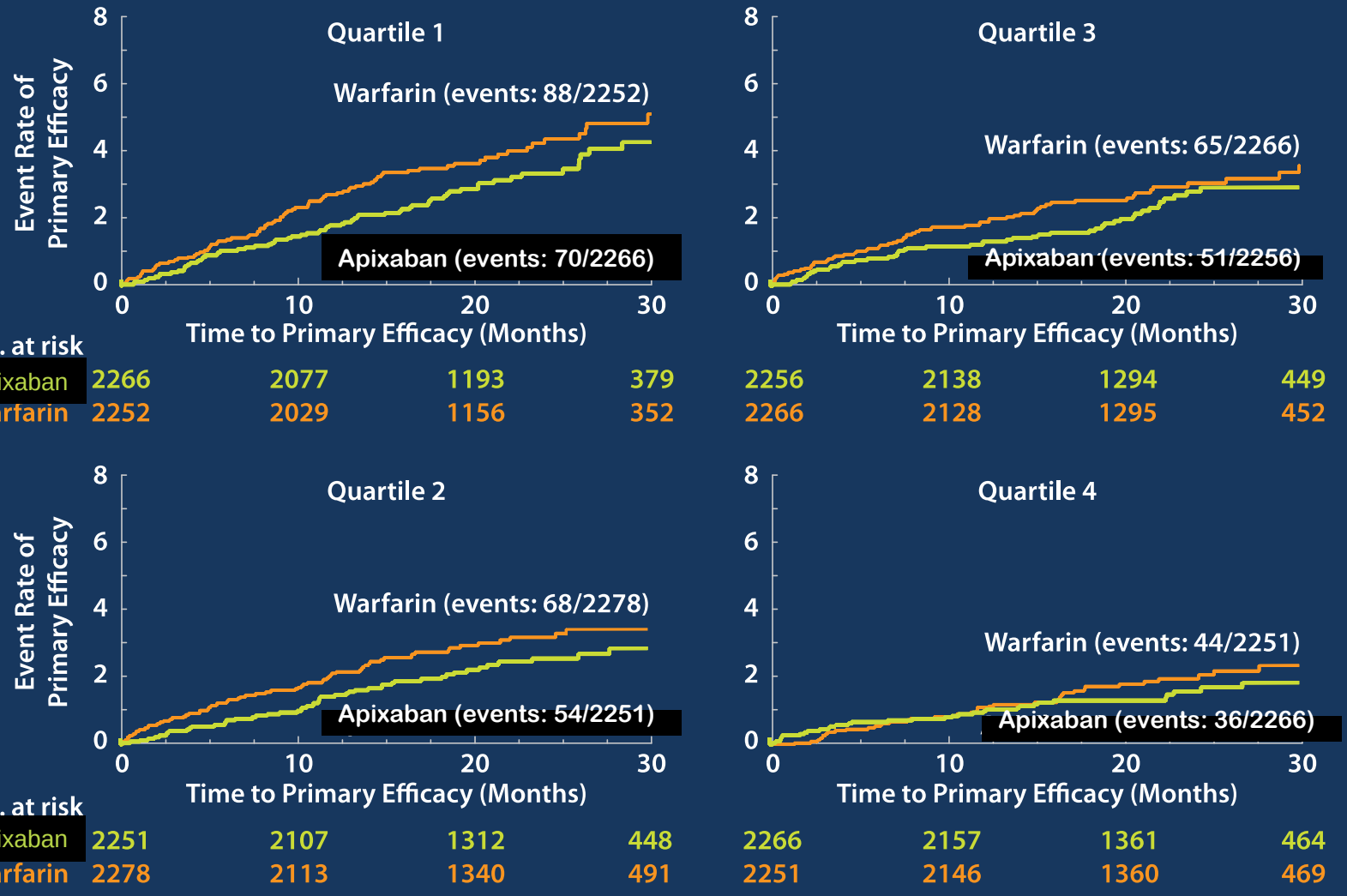
Characteristics	No. of Patients	Apixaban no. of events (%/yr)	Warfarin no. of events (%/yr)	P-value for Interaction
All Patients	18140	327 (2.13)	462 (3.09)	
Heart Failure				0.30
Yes	5527	87 (1.9)	137 (3.1)	
No	12613	240 (2.2)	325 (3.1)	
CHADs Score				0.40
≤ 1	6169	76 (1.4)	126 (2.3)	
=2	6492	125 (2.3)	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)	



Adverse Events and Liver Function Tests

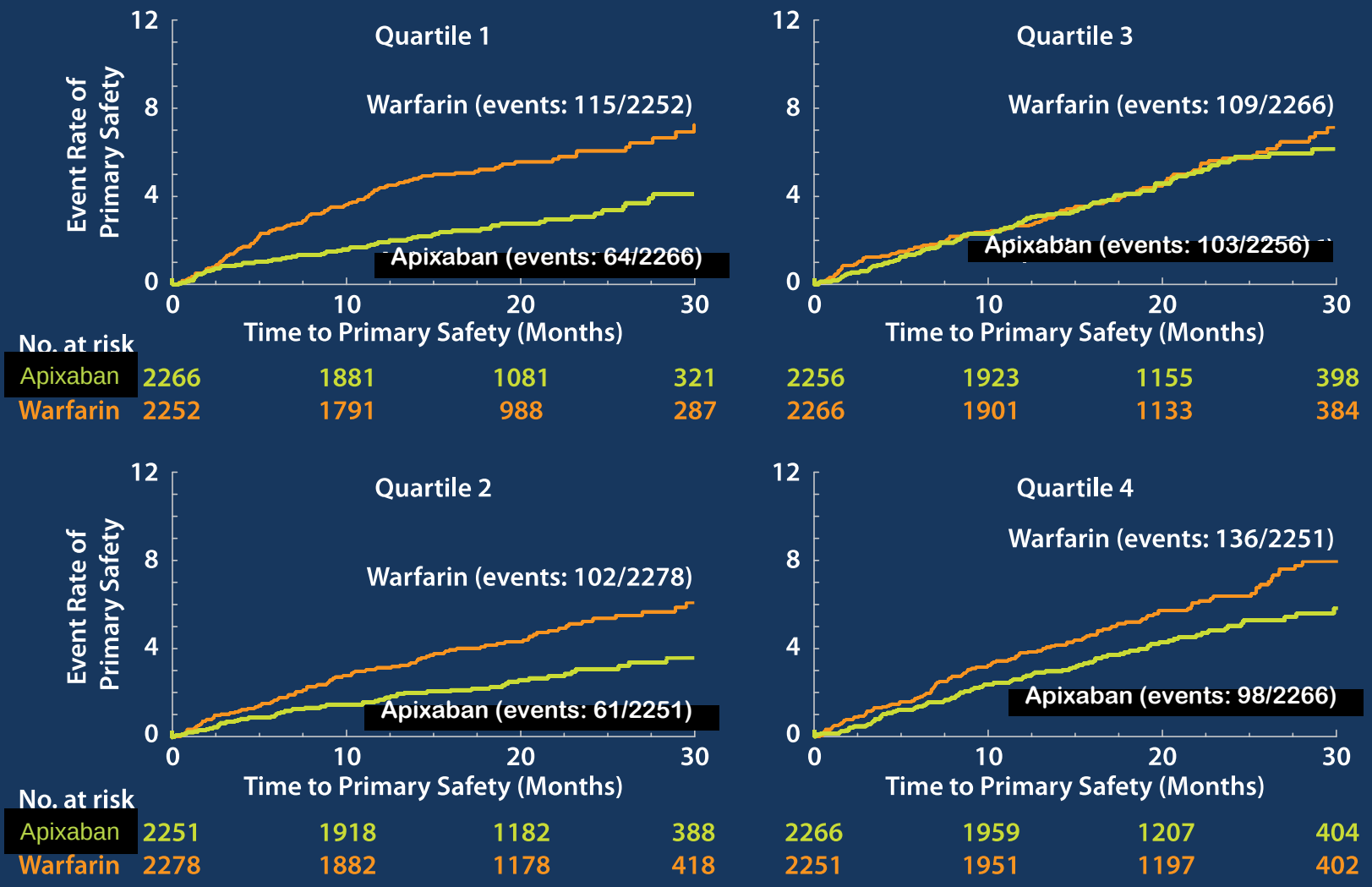
N (%)	Apixaban (N=9088)	Warfarin (N=9052)
Total patients with an adverse event	7406 (81.5)	7521 (83.1)
Total patients with a serious adverse event	3182 (35.0)	3302 (36.5)
Serious adverse events reported in ≥ 1% of patients in either treatment group		
Atrial fibrillation	301 (3.3)	287 (3.2)
Pneumonia	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)

Stroke and Systemic Embolism in Relation to Quartiles of Centers' TTR



Wallentin L. European Society of Cardiology Congress, Paris, France, 28 August 2011.
Available at: http://www.escardio.org/congresses/esc-2011/congress-reports/Documents/28-8-CTU/ARISTOTLE-presenter-Wallentin-slides.pdf

Major Bleeding in Relation to Quartiles of Centers' TTR



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Conclusion

- The benefits of apixaban over warfarin in preventing stroke, reducing bleeding and improving survival appear consistent regardless of centers' quality of INR control

Adapted from Wallentin L. European Society of Cardiology Congress, Paris, France, 28 August 2011.
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