



**ARISTOTLE**<sup>TM</sup>

# **Efficacy and Safety of Apixaban Compared with Warfarin at Different Levels of INR Control for Stroke Prevention in Atrial Fibrillation**

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for the ARISTOTLE investigators.

# Disclosures for Lars Wallentin



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# Background



- Warfarin effectively prevents stroke in atrial fibrillation.
- Warfarin has a narrow therapeutic range at INR 2.0–3.0 and needs regular laboratory guided dose adjustments as dose response is influenced by age, body weight, genetics, food, and other medications.
- Patient time in therapeutic range (TTR) varies widely between individuals, sites, and countries, and this affects outcomes.
- The quality of patients' INR control at the center or country level may interact with the treatment effects when comparing new antithrombotic treatments with warfarin.

# Atrial Fibrillation with at Least One Additional Risk Factor for Stroke



## Inclusion risk factors

- Age  $\geq$  75 years
- Prior stroke, TIA or SE
- HF or LVEF  $\leq$  40%
- Diabetes mellitus
- Hypertension

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

## Exclusion

- 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

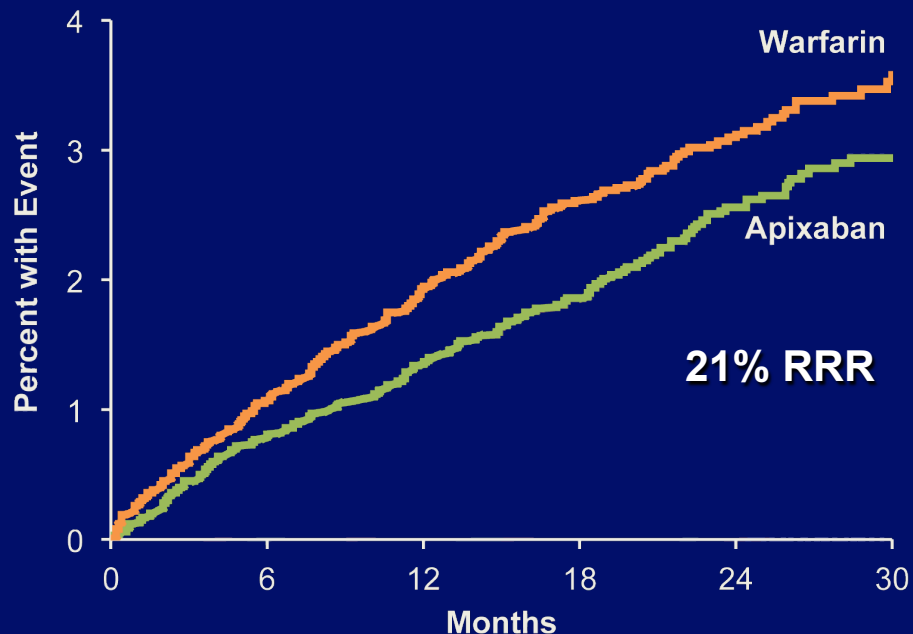
**Primary outcome: stroke or systemic embolism**

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

# ARISTOTLE Main Trial Results

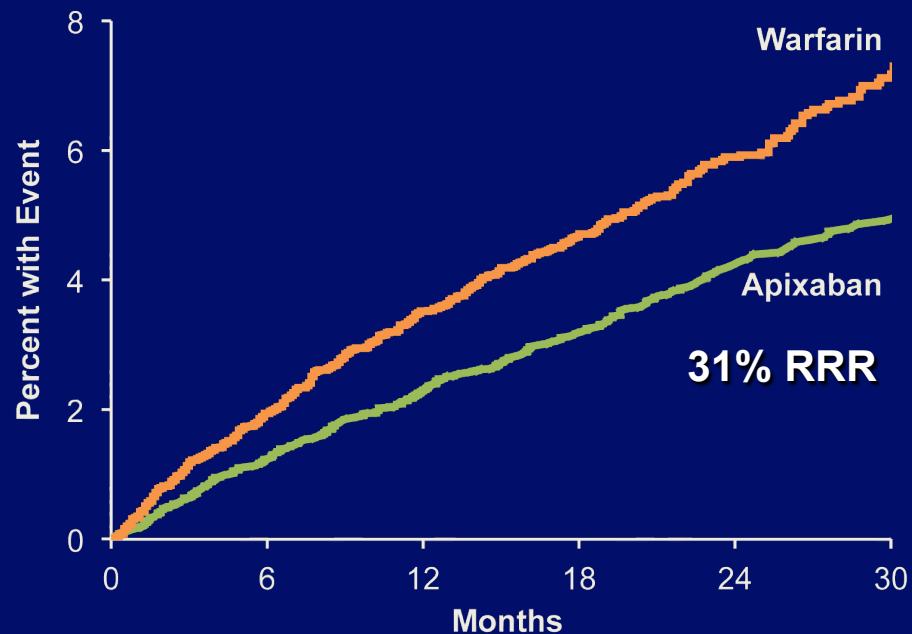


## Stroke or systemic embolism



Apixaban 212 patients, 1.27% per year  
Warfarin 265 patients, 1.60% per year  
HR 0.79 (95% CI, 0.66–0.95); P=0.011

## ISTH major bleeding

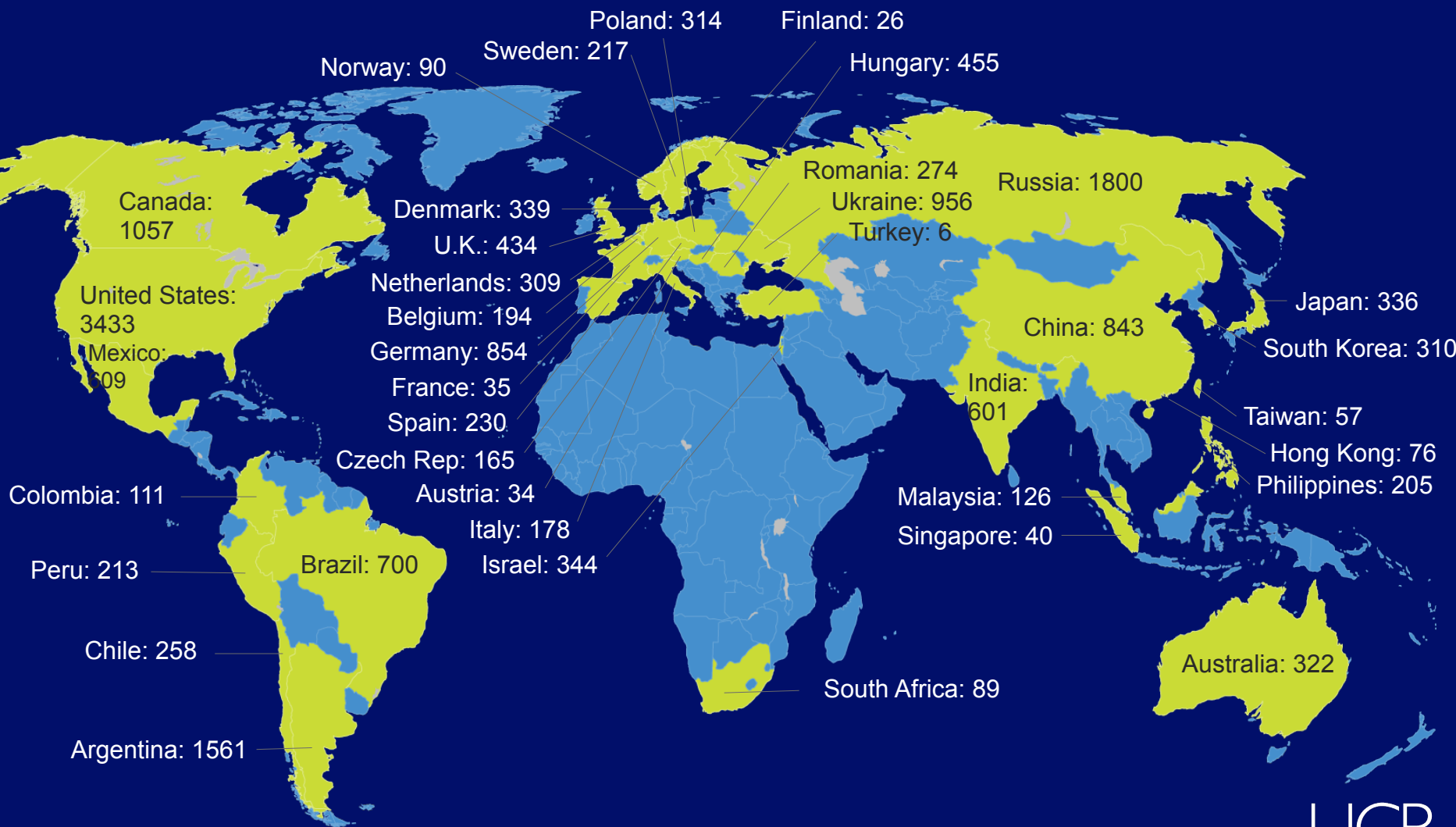


Apixaban 327 patients, 2.13% per year  
Warfarin 462 patients, 3.09% per year  
HR 0.69 (95% CI, 0.60–0.80); P<0.001

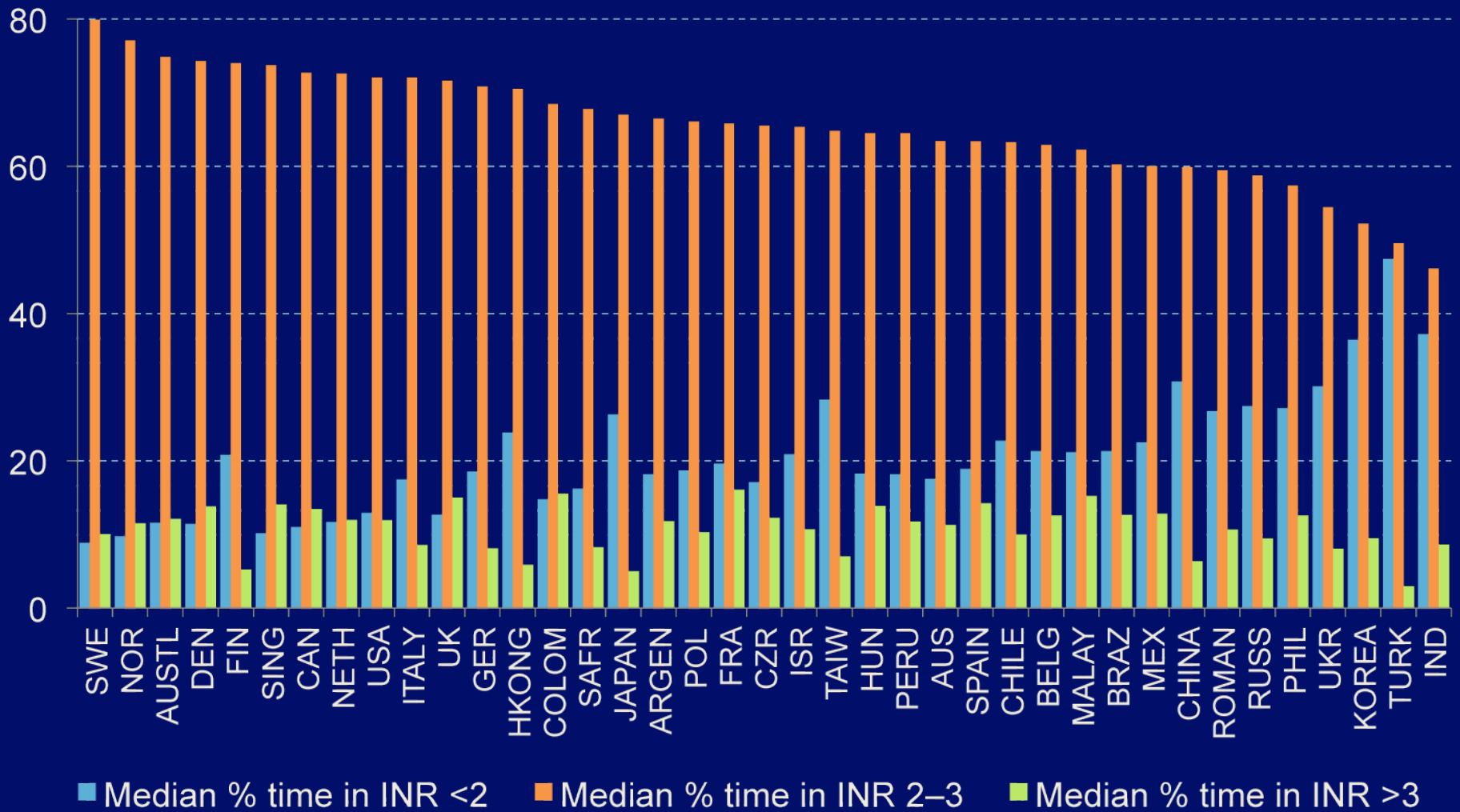
Median TTR 66%

# Enrollment

39 countries, 1034 sites, 18,201 patients



# Median of Patients TTR in Different Countries



# Objectives



What is the influence of centers' quality of INR control, as estimated in their warfarin-treated patients, on the effects of apixaban compared with warfarin on major outcome events (pre-specified analysis)

## Pre-specified outcomes:

- Stroke or systemic embolism (primary efficacy outcome)
- Mortality
- Composite of stroke, systemic embolism and myocardial infarction
- Major bleeding (primary safety outcome)
- Composite of major and clinically relevant non-major bleeding

## Post-hoc explored outcomes:

- Hemorrhagic stroke
- Net clinical benefit, i.e. the composite of stroke, systemic embolism, myocardial infarction, death and major bleeding.

# Methods



- Individual TTR during the trial was calculated for each warfarin treated patient by the Rosendaal method excluding the first 7 days after randomization and warfarin treatment interruptions until 2 days after the last dose of warfarin (patients with less than two INR levels were excluded, n=xx).
- The center's TTR was calculated as the median of individual TTRs during the whole study among its warfarin patients.
- The center's TTR was assigned as a proxy for centers' quality of INR control for all its patients (assigned to either warfarin or apixaban).
- The interquartile cut-off limits for centers' TTR were identified to keep the patient numbers within each quartile approximately balanced.

- Outcomes were compared across the four groups defined by the quartiles of centers' TTR as pre-specified
- Hazard ratios and their 95% confidence intervals are presented
- Tests for interactions between centers' TTR and randomized treatment effects were evaluated by multivariable Cox regression analyses using the patients' assigned center TTR value as a continuous variable.
- Interactions were adjusted for baseline variables potentially influencing both TTR and outcome: age, sex, body weight, CHADS2 score, prior stroke, diabetes mellitus, hypertension, heart failure, baseline medications (aspirin, digoxin, amiodarone, lipid lowering drug), and warfarin naïve/experienced status.

# Baseline Characteristics and Centers' TTR



Center TTR	<58.0	58.0–65.7	65.7–72.2	≥72.2	P-value
Number of patients	4538	4535	4533	4538	
TTR with warfarin	50.7	62.5	69.3	76.7	
Warfarin naive	57.4%	50.3%	35.4%	28.4%	<0.0001
Age (years, median)	68.0	69.0	71.0	72.0	<0.0001
Male	61.8%	61.8%	65.4%	70.1%	<0.0001
Weight (kg, median )	76.3	81.0	83.3	87.0	<0.0001
CHADS2 Score Mean	2.2	2.2	2.1	2.0	<0.0001
CHADS2 Score 3-6	32.6%	31.1%	30.0%	27.0%	<0.0001
Age > 75 yr	24.0%	28.1%	33.1%	39.5%	<0.0001
Prior stroke	13.4%	12.0%	11.5%	9.8%	<0.0001
Heart failure	41.8%	36.5%	27.2%	16.4%	<0.0001
Diabetes mellitus	23.8%	23.9%	25.1%	27.0%	0.0011
Hypertension	86.2%	89.8%	88.1%	85.7%	<0.0001
Prior MI	12.6%	15.3%	13.0%	15.9%	<0.0001

# Baseline Co-medication in Relation to Centers' TTR



Center TTR	<58.0	58.0–65.7	65.7–72.2	≥72.2	P-value
Randomized	4538	4535	4533	4538	
Aspirin	31.2%	35.2%	29.3%	28.2%	<0.0001
ARB	24.0%	21.5%	23.6%	26.5%	<0.0001
ACE I/ARB	70.6%	74.7%	70.2%	69.3%	<0.0001
Beta-blocker	60.3%	63.9%	64.5%	65.9%	<0.0001
Amiodarone	14.7%	13.9%	11.1%	5.8%	<0.0001
Digoxin	36.5%	33.9%	30.9%	28.1%	<0.0001
Lipid Lowering	34.0%	41.2%	47.2%	59.2%	<0.0001

# Stroke and Systemic Embolism (primary outcome) in Relation to Centers' TTR



Center TTR (%)	Apixaban		Warfarin		HR (95% CI)	Adjusted Interaction
	Events	Rate/100 person yrs	Events	Rate/100 person yrs		
< 58.0	70	1.75	88	2.28	0.77 (0.56, 1.06)	0.29
58.0–65.7	54	1.30	68	1.61	0.80 (0.56, 1.15)	
65.7–72.2	51	1.21	65	1.55	0.79 (0.54, 1.13)	
> 72.2	36	0.83	44	1.02	0.81 (0.52, 1.26)	

# Death and Composite Efficacy in Relation to Centers' TTR



Center cTTR	Apixaban		Warfarin		HR (95% CI)	Adjusted Interaction P
	Events	Rate/100 person yrs	Events	Rate/100 person yrs		
<b>Mortality</b>						<b>0.39</b>
< 58.0	163	3.95	191	4.75	0.83 (0.68, 1.03)	
58.0–65.7	158	3.71	177	4.10	0.91 (0.73, 1.12)	
65.7–72.2	147	3.44	174	4.07	0.84 (0.68, 1.05)	
> 72.2	133	3.03	127	2.91	1.04 (0.82, 1.33)	
<b>Composite Efficacy*</b>						<b>0.27</b>
< 58.0	212	5.31	254	6.57	0.81 (0.67, 0.97)	
58.0–65.7	212	5.12	231	5.50	0.93 (0.77, 1.12)	
65.7–72.2	202	4.83	236	5.66	0.85 (0.71, 1.03)	
> 72.2	180	4.18	185	4.33	0.96 (0.79, 1.18)	

\* Composite Efficacy is a composite of stroke, systemic embolism, death and myocardial infarction.

# Bleeding in Relation to Centers' TTR



Center TTR	Apixaban		Warfarin		HR (95% CI)	Adjusted Interaction P
	Events	Rate/100 person yrs	Events	Rate/100 person yrs		
Major bleeding						0.10
< 58.0	64	1.75	115	3.34	0.53 (0.39, 0.72)	
58.0–65.7	61	1.60	102	2.68	0.60 (0.43, 0.82)	
65.7–72.2	103	2.68	109	2.89	0.93 (0.71, 1.21)	
> 72.2	98	2.49	136	3.46	0.72 (0.55, 0.93)	
Major and clinically relevant bleeding						0.005
< 58.0	115	3.19	207	6.13	0.53 (0.42, 0.66)	
58.0–65.7	125	3.32	195	5.24	0.64 (0.51, 0.80)	
65.7–72.2	179	4.75	220	5.99	0.79 (0.65, 0.97)	
> 72.2	191	4.96	255	6.68	0.74 (0.62, 0.90)	

# Hemorrhagic Stroke and Net Clinical Benefit in Relation to Quartiles of Centers' TTR



Center TTR	Apixaban		Warfarin		HR (95% CI)	Adjusted Interaction P
	E	Rate/100 person yrs	E	Rate/100 person yrs		
<b>Hemorrhagic stroke</b>						<b>0.5058</b>
< 58.0	14	0.35	26	0.66	0.52 (0.27, 1.00)	
58.0–65.7	9	0.22	26	0.61	0.35 (0.16, 0.75)	
65.7–72.2	13	0.31	18	0.43	0.72 (0.35, 1.47)	
> 72.2	4	0.09	8	0.18	0.50 (0.15, 1.66)	
<b>Net clinical benefit *</b>						<b>0.1060</b>
< 58.0	250	7.00	326	9.74	0.73 (0.61, 0.86)	
58.0–65.7	255	6.86	294	7.95	0.86 (0.73, 1.02)	
65.7–72.2	278	7.44	308	8.40	0.89 (0.75, 1.04)	
> 72.2	255	6.58	285	7.41	0.89 (0.75, 1.05)	

\* Net clinical benefit is Stroke, Systemic embolism, Myocardial infarction, Total death, Major bleeding.

# Conclusion



- The benefits of apixaban over warfarin in preventing stroke, reducing bleeding and improving survival appear consistent regardless of centers' quality of INR control.
- Therefore, in patients with atrial fibrillation, apixaban is a more effective and safer treatment than warfarin across a wide range of warfarin management.

# THANKS to all Investigators and Patients



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