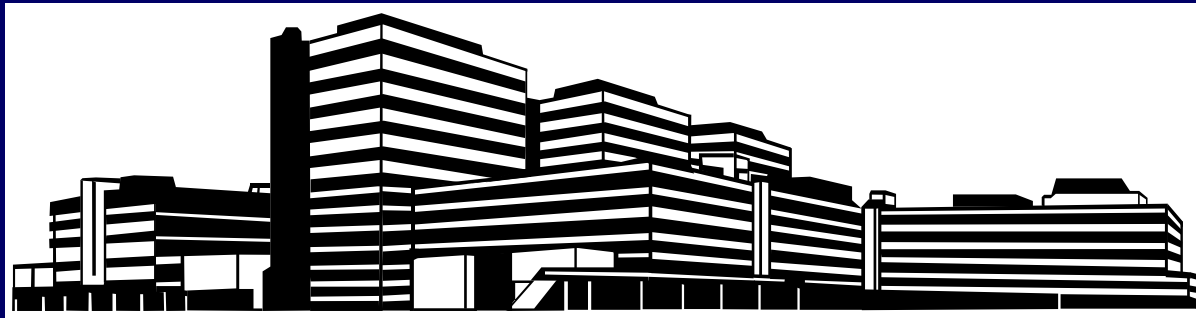
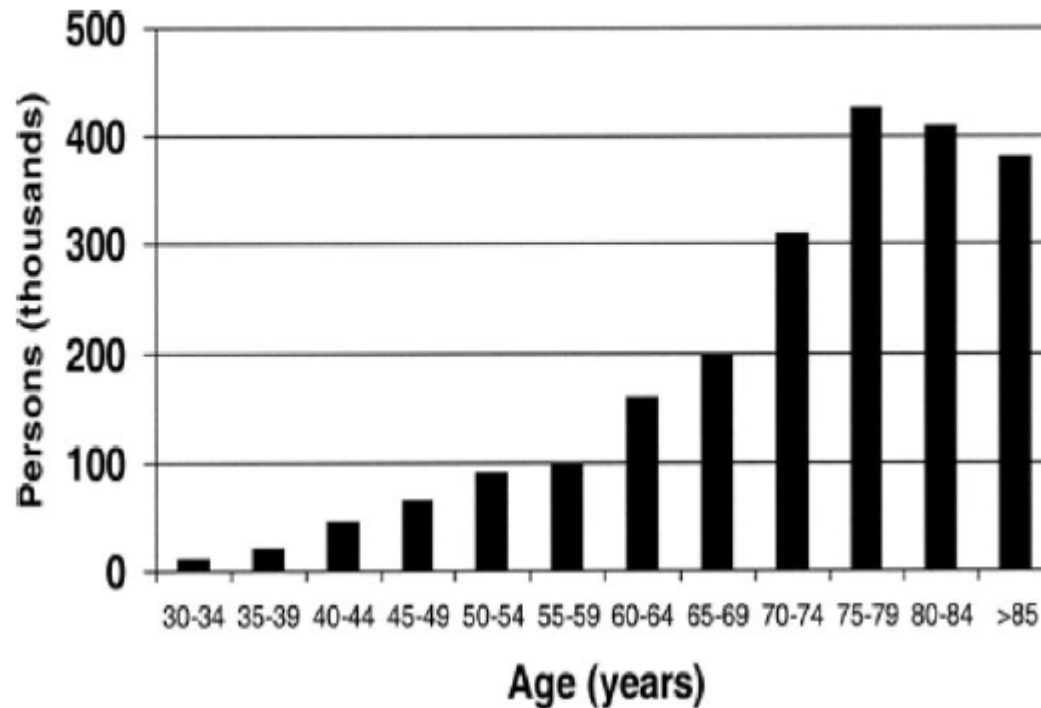


# Nieuwe antithrombotica bij boezemfibrilleren



Ron Peters  
Afdeling Cardiologie  
AMC  
2 december 2011



**Figure 4.** Estimated age-specific prevalence of atrial fibrillation (AF) based on 4 population-based surveys. Prevalence, age, distribution, and gender of patients with AF analysis and implications. Modified with permission from Feinberg WM, Blackshear JL, Laupacis A, et al. Prevalence, age distribution, and gender of patients with atrial fibrillation. Analysis and implications. *Arch Intern Med* 1995;155:469–73 (19). Copyright © 1995, American Medical Association. All rights reserved.

# AF Investigators' Collaborative Analysis: Risk Factors for Stroke in nonvalvular AF

<u>Risk Factor</u>	<u>Relative Risk</u>
<b>Congestive heart failure</b>	<b>1.4</b>
<b>Hypertension</b>	<b>1.6</b>
<b>Age (continuous)</b>	<b>1.4/10 years</b>
<b>Diabetes mellitus</b>	<b>1.7</b>
<b>Previous Stroke or TIA</b>	<b>2.5</b>

# CHADS<sub>2</sub> score

- Congestive heart failure
- Hypertension
- Age
- Diabetes
- History of Stroke (telt dubbel)

### Annual Stroke Risk<sup>[2]</sup>

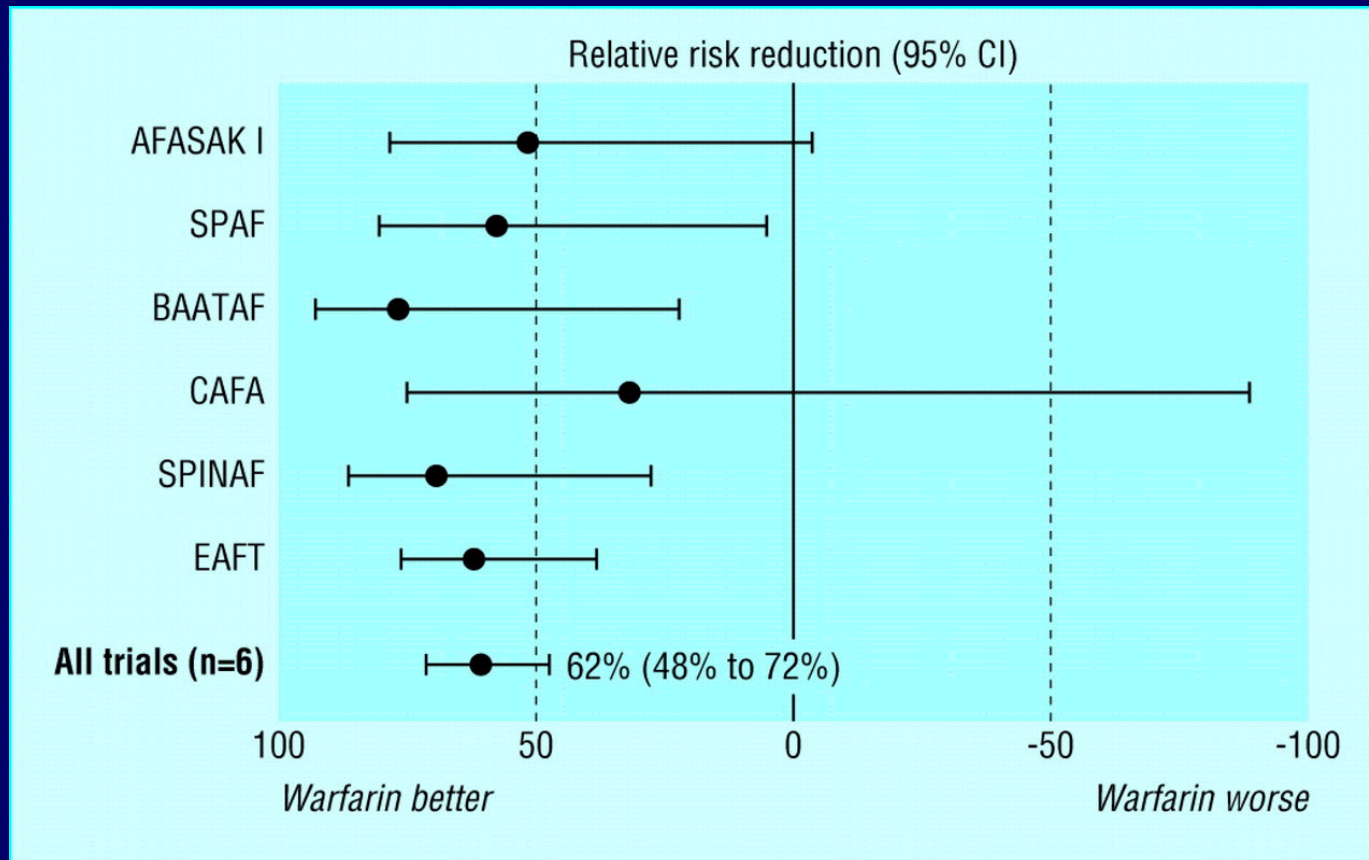
CHADS <sub>2</sub> Score	Stroke Risk %	95%CI
0	1.9	1.2–3.0
1	2.8	2.0–3.8
2	4.0	3.1–5.1
3	5.9	4.6–7.3
4	8.5	6.3–11.1
5	12.5	8.2–17.5
6	18.2	10.5–27.4

**Table 8** CHA<sub>2</sub>DS<sub>2</sub>VASc score and stroke rate

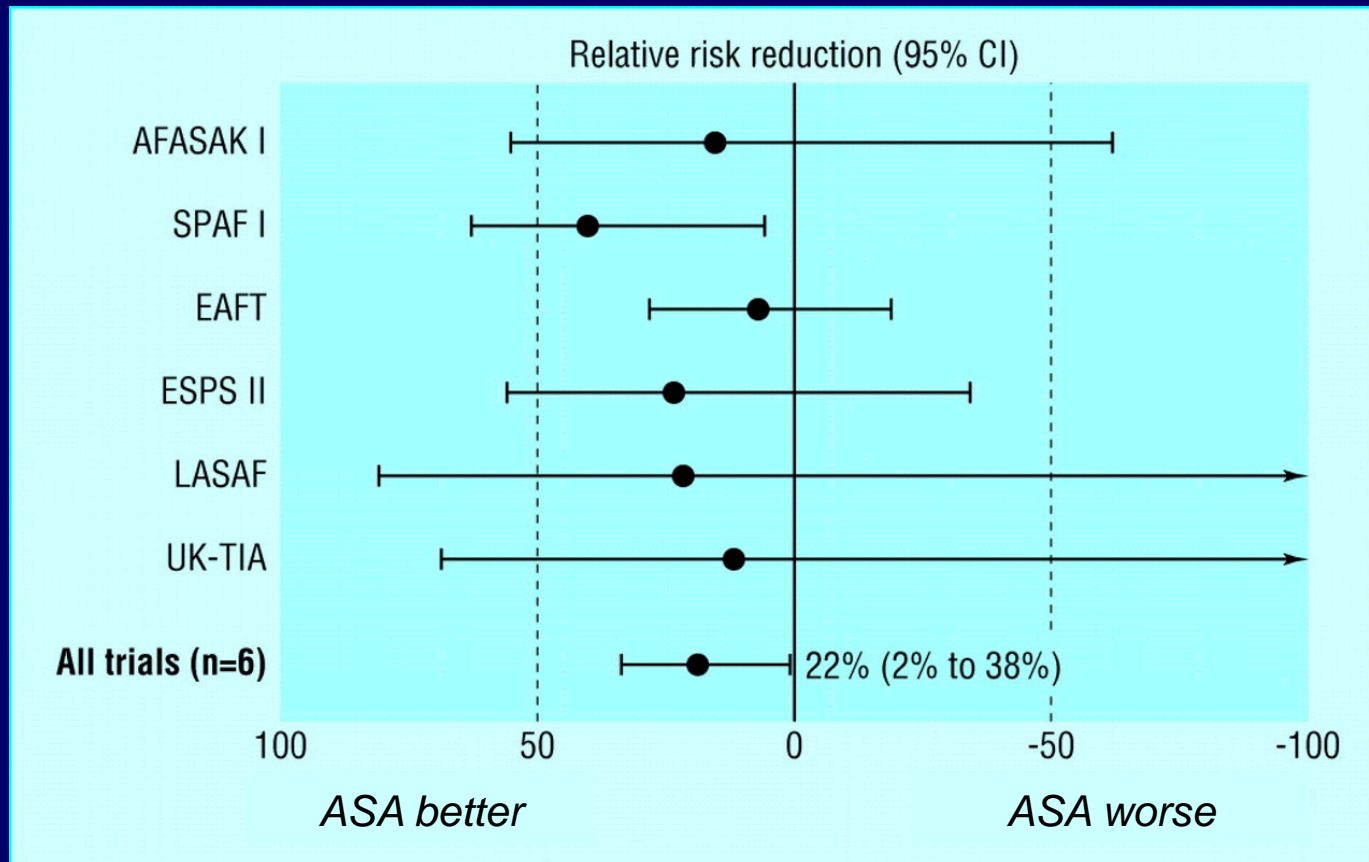
(a) Risk factors for stroke and thrombo-embolism in non-valvular AF	
‘Major’ risk factors	‘Clinically relevant non-major’ risk factors
Previous stroke, TIA, or systemic embolism Age $\geq 75$ years	Heart failure or moderate to severe LV systolic dysfunction (e.g. LV EF $\leq 40\%$ ) Hypertension - Diabetes mellitus Female sex - Age 65–74 years Vascular disease <sup>a</sup>
(b) Risk factor-based approach expressed as a point based scoring system, with the acronym CHA <sub>2</sub> DS <sub>2</sub> -VASc (Note: maximum score is 9 since age may contribute 0, 1, or 2 points)	
Risk factor	Score
Congestive heart failure/LV dysfunction	1
Hypertension	1
Age $\geq 75$	2
Diabetes mellitus	1
Stroke/TIA/thrombo-embolism	2
Vascular disease <sup>a</sup>	1
Age 65–74	1
Sex category (i.e. female sex)	1
<b>Maximum score</b>	<b>9</b>

<b>(c) Adjusted stroke rate according to CHA<sub>2</sub>DS<sub>2</sub>-VASc score</b>		
<b>CHA<sub>2</sub>DS<sub>2</sub>-VASc score</b>	<b>Patients (n=7329)</b>	<b>Adjusted stroke rate (%/year)<sup>b</sup></b>
0	1	0%
1	422	1.3%
2	1230	2.2%
3	1730	3.2%
4	1718	4.0%
5	1159	6.7%
6	679	9.8%
7	294	9.6%
8	82	6.7%
9	14	15.2%

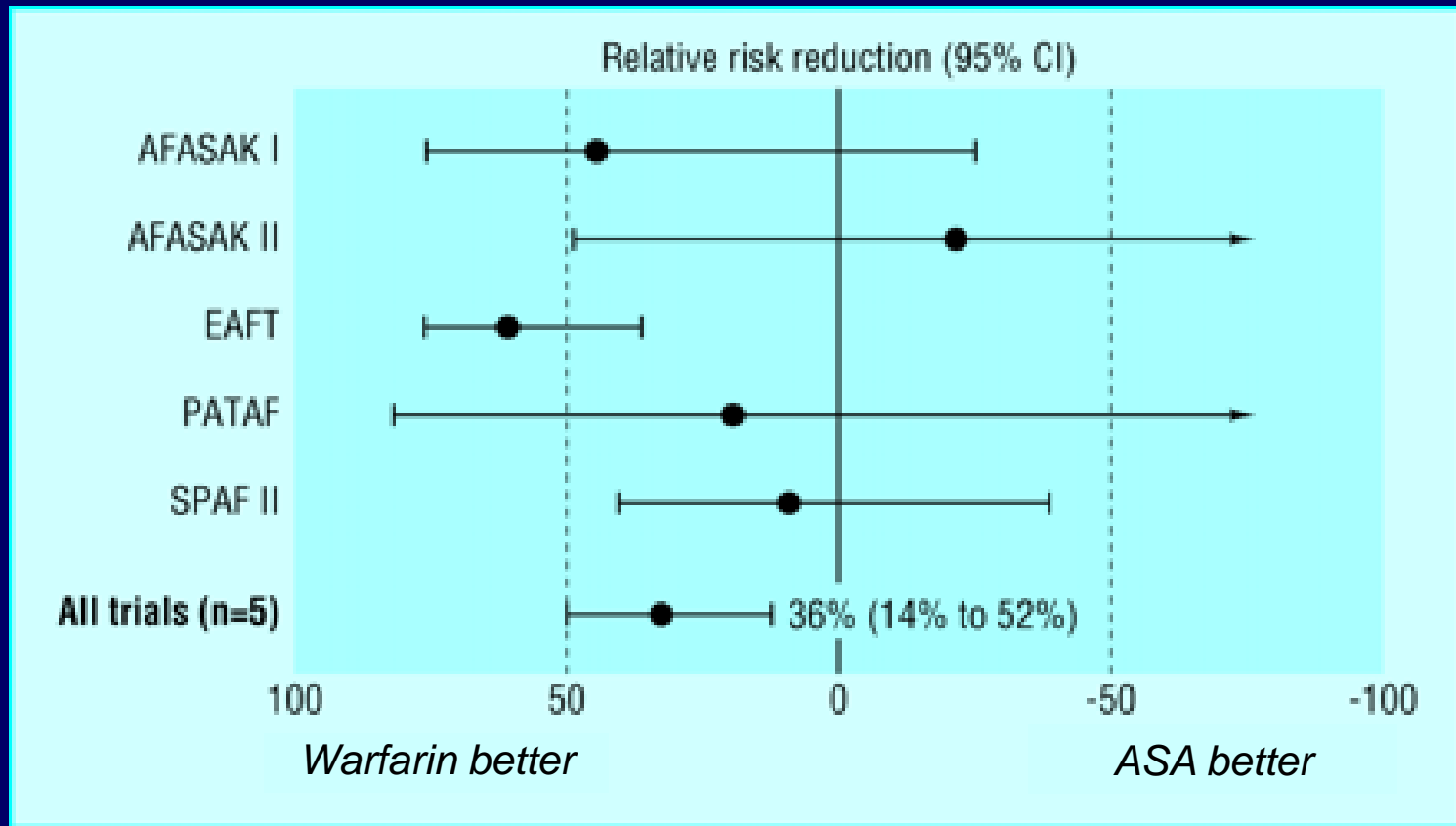
# Relative Risk Reduction of Stroke in Atrial Fibrillation Warfarin Compared with Placebo<sup>1</sup>



# Relative Risk Reduction of Stroke in Atrial Fibrillation ASA Compared with Placebo<sup>1</sup>



# Relative Risk Reduction of Stroke in Atrial Fibrillation Warfarin Compared with ASA<sup>1</sup>



# Nieuwe antithrombotica bij boezemfibrilleren



Apixaban 2 maal 5 mg  
Eliquis®  
Pfizer

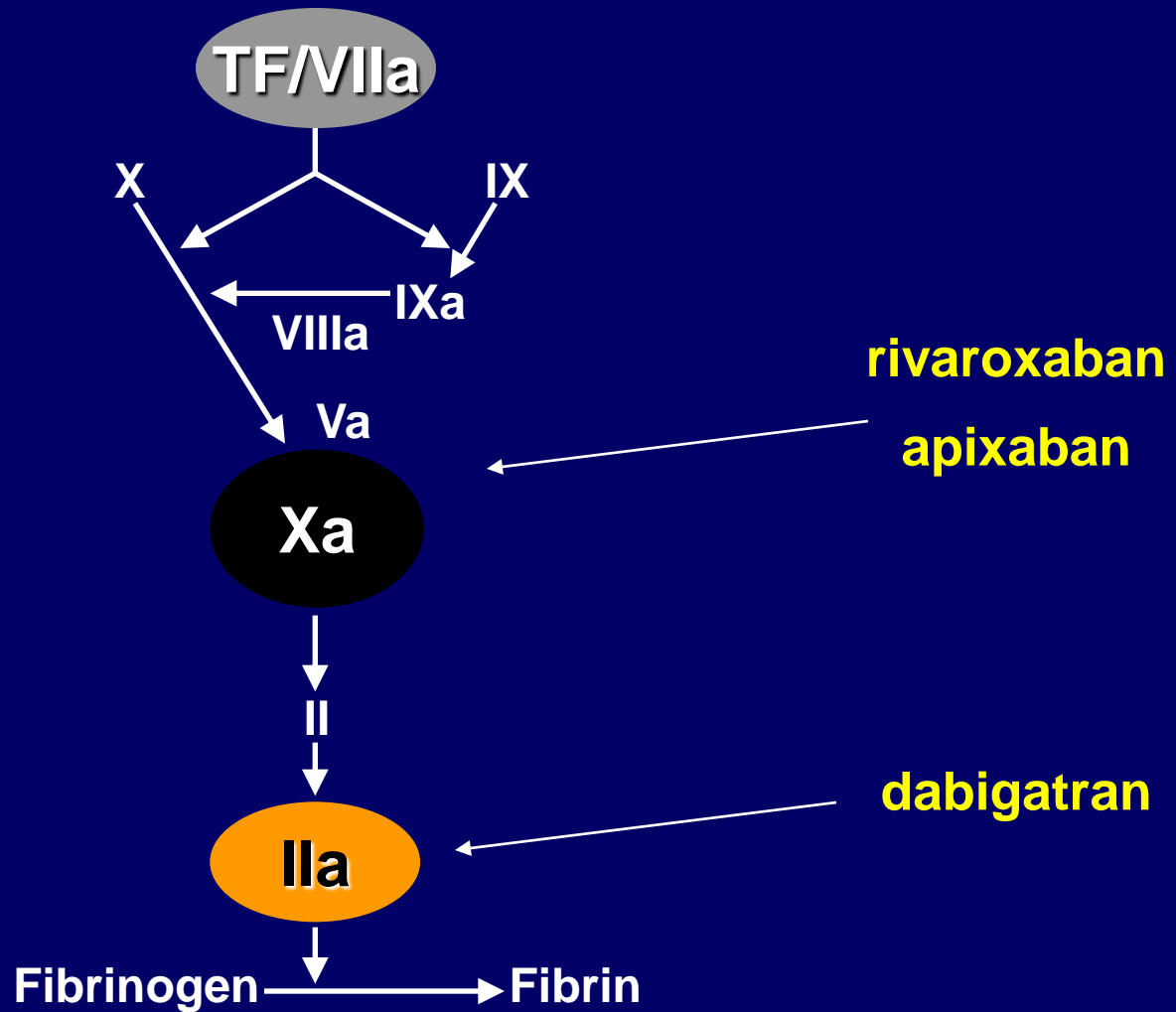


Dabigatran 2 maal 150 mg  
Pradaxa®  
Boehringer



Rivaroxaban 1 maal 20 mg  
Xarelto®  
Bayer

Vit K:  
II, VII, IX, X

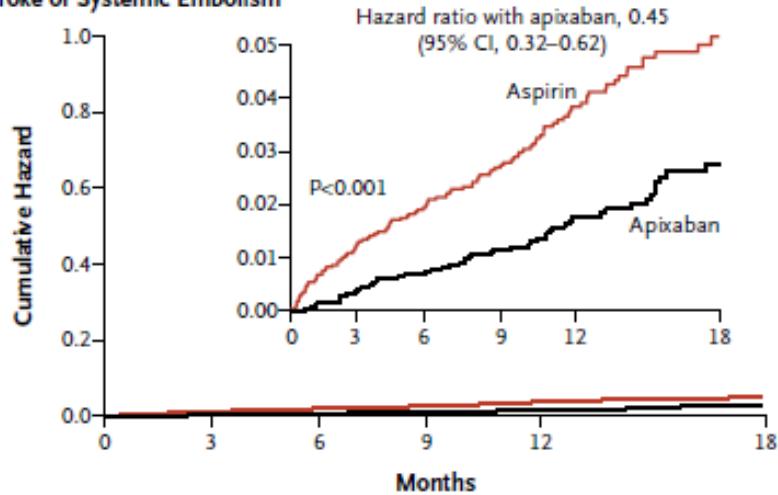


# farmacologie

	T1/2	klaring	dosering
dabigatran	12-17 uur	80% renaal	2 maal daags
rivaroxaban	7-11 uur	30% renaal	1 maal daags
apixaban	12 uur	25% renaal	2 maal daags

# AVERROES trial

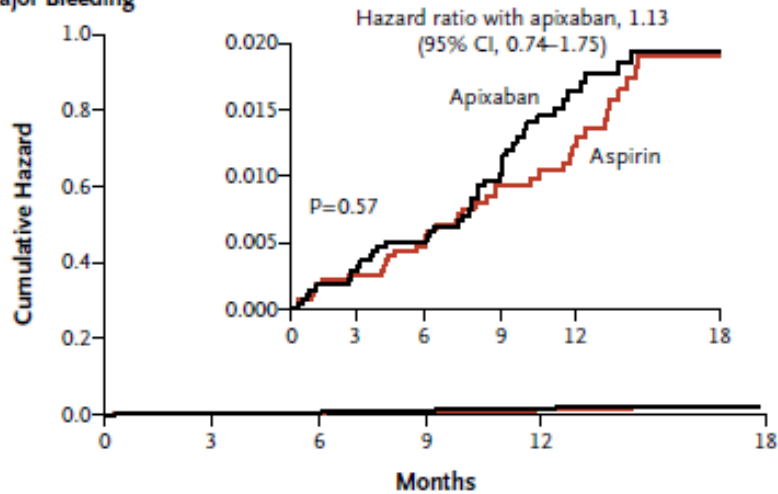
## A Stroke or Systemic Embolism



### No. at Risk

	0	3	6	9	12	18
Aspirin	2791	2716	2530	2112	1543	628
Apixaban	2808	2758	2566	2125	1522	615

## B Major Bleeding



### No. at Risk

	0	3	6	9	12	18
Aspirin	2791	2738	2557	2140	1571	642
Apixaban	2808	2759	2566	2120	1521	622



- Double blind
- 2 dd 5 mg apix. or warfarin
- 2 dd 2,5 in subset (age, renal function)
- Primary outcome stroke + syst. embolism
- Prim. Safety: major bleeding

# inclusion



- 2 or more episodes of a.fib
- At least 1 additional risk factor

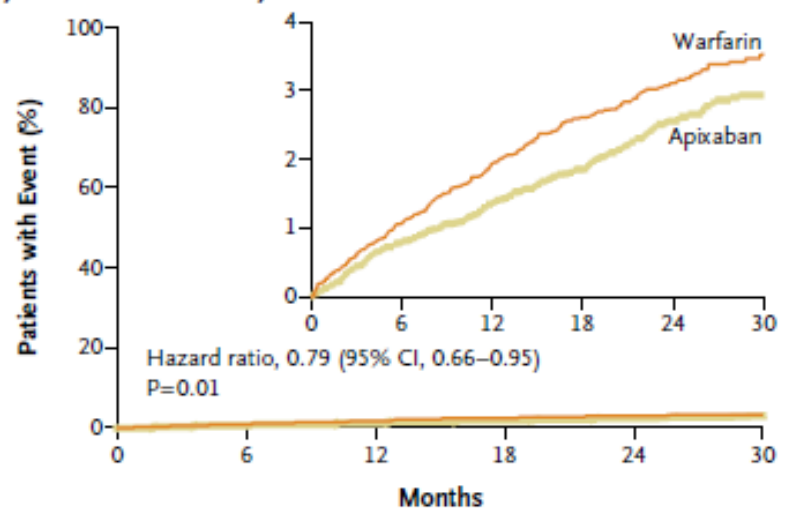
# exclusion



- Reversible cause of a.fib
- Valvular a.fib
- Other indication for VKA
- Aspirin > 165 mg or 2 antiplatelet drugs
- Severe renal failure



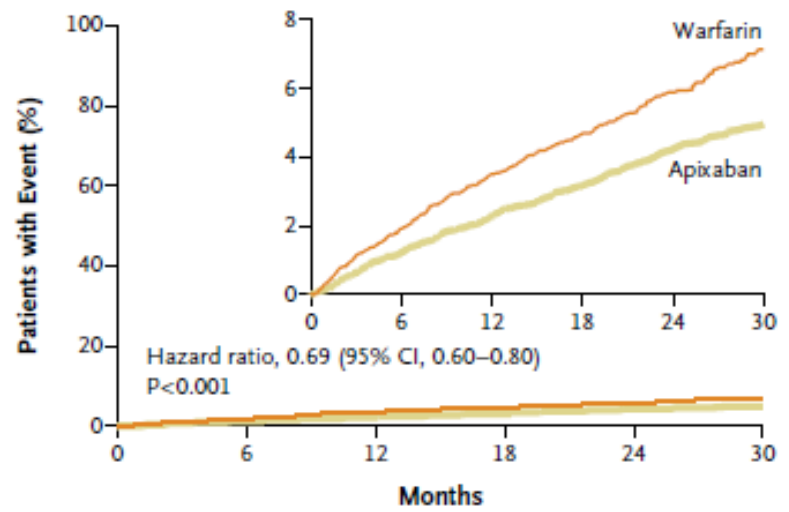
**A Primary Outcome: Stroke or Systemic Embolism**



**No. at Risk**

Apixaban	9120	8726	8440	6051	3464	1754
Warfarin	9081	8620	8301	5972	3405	1768

**B Major Bleeding**



**No. at Risk**

Apixaban	9088	8103	7564	5365	3048	1515
Warfarin	9052	7910	7335	5196	2956	1491

**Figure 1. Kaplan–Meier Curves for the Primary Efficacy and Safety Outcomes.**

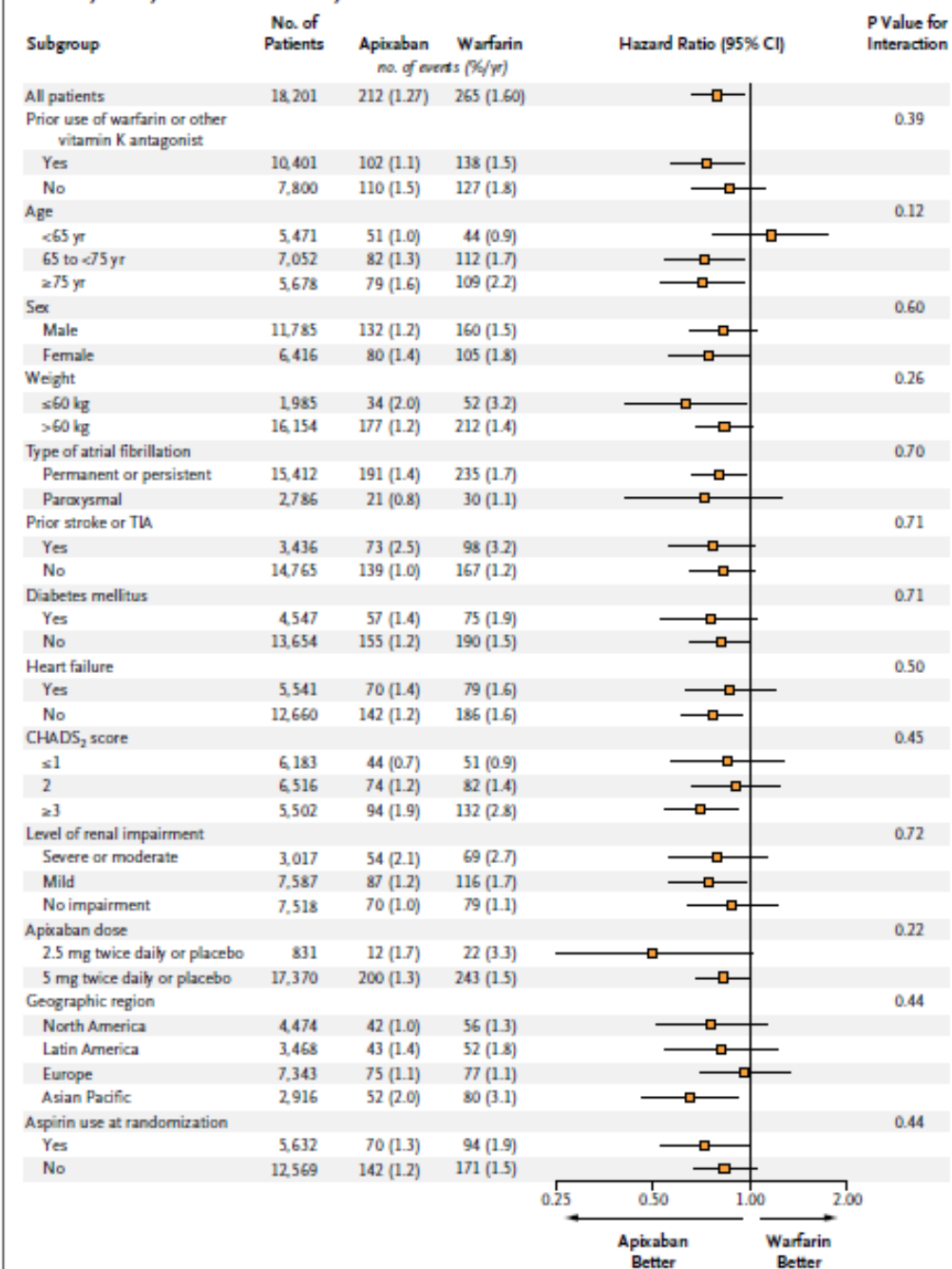
**Table 2. Efficacy Outcomes.\***

Outcome	Apixaban Group (N=9120)		Warfarin Group (N=9081)		Hazard Ratio (95% CI)	P Value
	Patients with Event	Event Rate	Patients with Event	Event Rate		
	<i>no.</i>	<i>%/yr</i>	<i>no.</i>	<i>%/yr</i>		
Primary outcome: stroke or systemic embolism	212	1.27	265	1.60	0.79 (0.66–0.95)	0.01
Stroke	199	1.19	250	1.51	0.79 (0.65–0.95)	0.01
Ischemic or uncertain type of stroke	162	0.97	175	1.05	0.92 (0.74–1.13)	0.42
Hemorrhagic stroke	40	0.24	78	0.47	0.51 (0.35–0.75)	<0.001
Systemic embolism	15	0.09	17	0.10	0.87 (0.44–1.75)	0.70
Key secondary efficacy outcome: death from any cause	603	3.52	669	3.94	0.89 (0.80–0.998)	0.047
Other secondary outcomes						
Stroke, systemic embolism, or death from any cause	752	4.49	837	5.04	0.89 (0.81–0.98)	0.02
Myocardial infarction	90	0.53	102	0.61	0.88 (0.66–1.17)	0.37
Stroke, systemic embolism, myocardial infarction, or death from any cause	810	4.85	906	5.49	0.88 (0.80–0.97)	0.01
Pulmonary embolism or deep-vein thrombosis	7	0.04	9	0.05	0.78 (0.29–2.10)	0.63

**Table 3. Bleeding Outcomes and Net Clinical Outcomes.\***

Outcome	Apixaban Group (N= 9088)		Warfarin Group (N= 9052)		Hazard Ratio (95% CI)	P Value
	Patients with Event	Event Rate	Patients with Event	Event Rate		
	no.	%/yr	no.	%/yr		
Primary safety outcome: ISTH major bleeding†	327	2.13	462	3.09	0.69 (0.60–0.80)	<0.001
Intracranial	52	0.33	122	0.80	0.42 (0.30–0.58)	<0.001
Other location	275	1.79	340	2.27	0.79 (0.68–0.93)	0.004
Gastrointestinal	105	0.76	119	0.86	0.89 (0.70–1.15)	0.37
Major or clinically relevant nonmajor bleeding	613	4.07	877	6.01	0.68 (0.61–0.75)	<0.001
GUSTO severe bleeding	80	0.52	172	1.13	0.46 (0.35–0.60)	<0.001
GUSTO moderate or severe bleeding	199	1.29	328	2.18	0.60 (0.50–0.71)	<0.001
TIMI major bleeding	148	0.96	256	1.69	0.57 (0.46–0.70)	<0.001
TIMI major or minor bleeding	239	1.55	370	2.46	0.63 (0.54–0.75)	<0.001
Any bleeding	2356	18.1	3060	25.8	0.71 (0.68–0.75)	<0.001
Net clinical outcomes						
Stroke, systemic embolism, or major bleeding	521	3.17	666	4.11	0.77 (0.69–0.86)	<0.001
Stroke, systemic embolism, major bleeding, or death from any cause	1009	6.13	1168	7.20	0.85 (0.78–0.92)	<0.001

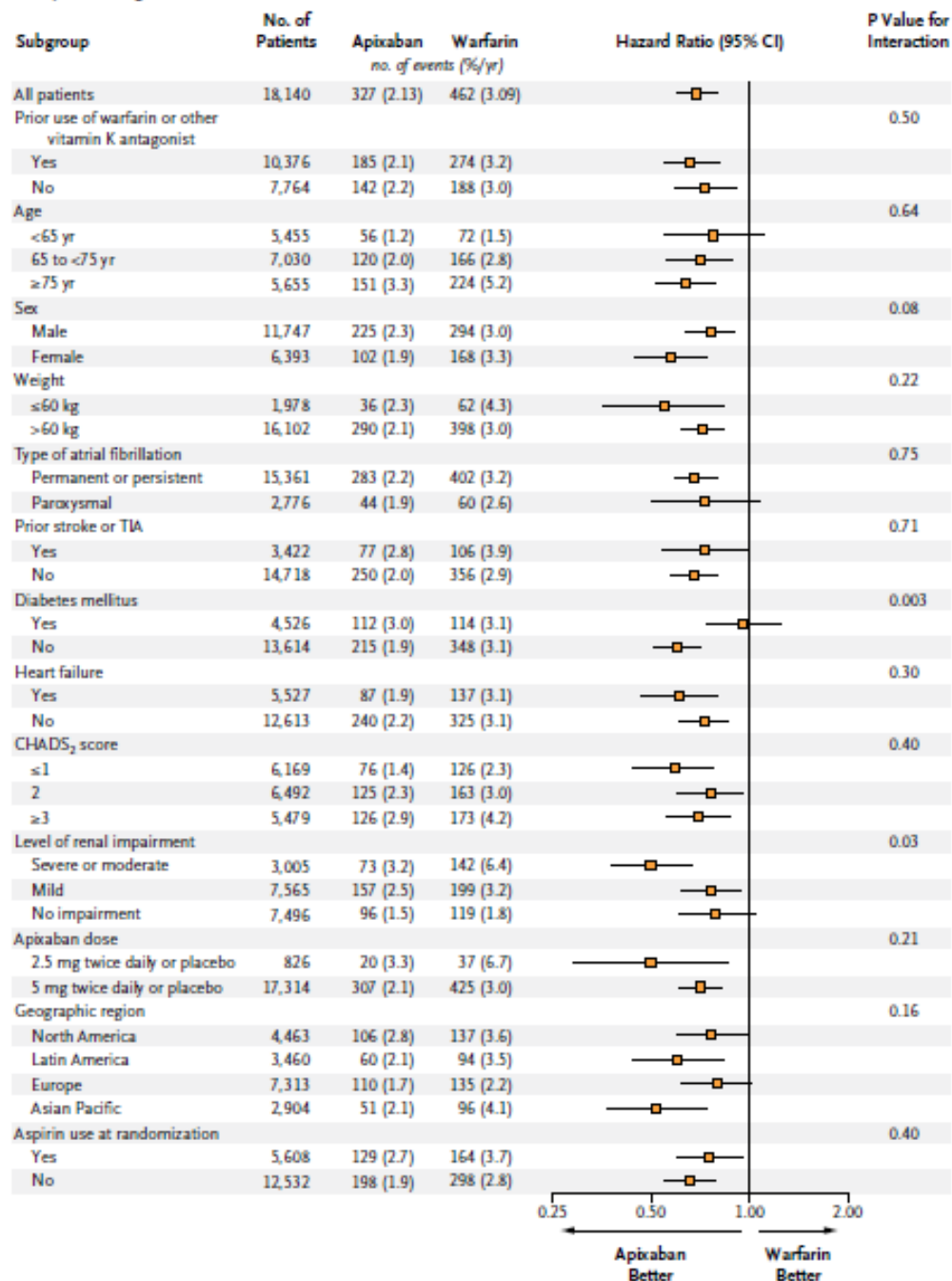
**A Primary Efficacy Outcome: Stroke and Systemic Embolism**



**Figure 2. Relative Risks of the Primary Efficacy and Safety Outcomes. According to Major Prespecified Subgroups.**



## B Major Bleeding



# conclusions



- Apixaban superior to warfarin
- Caused less bleeding
- Reduced mortality

# Study Design

# ROCKET

## Atrial Fibrillation

### Risk Factors

- CHF
- Hypertension
- Age  $\geq$  75
- Diabetes

At least 2 or 3 required\*

### OR

- Stroke, TIA or Systemic embolus

### Rivaroxaban

20 mg daily  
15 mg for Cr Cl 30-49 ml/min

*Randomize  
Double Blind /  
Double Dummy  
(n ~ 14,000)*

### Warfarin

INR target - 2.5  
(2.0-3.0 inclusive)

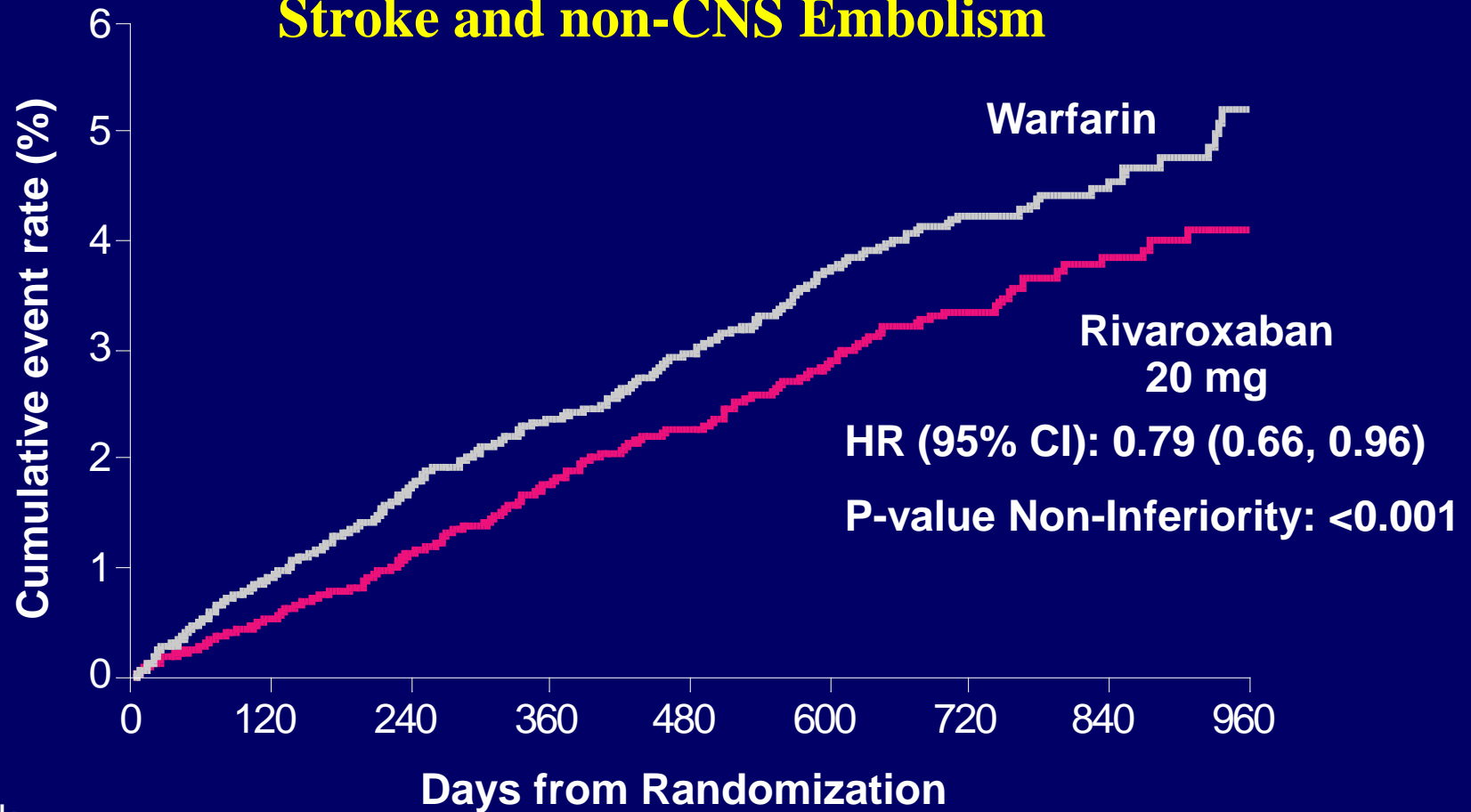
Monthly Monitoring  
Adherence to standard of care guidelines

**Primary Endpoint: Stroke or non-CNS Systemic Embolism**

\* Enrollment of patients without prior Stroke, TIA or systemic embolism and only 2 factors capped at 10%

# ROCKET

## Primary Efficacy Outcome Stroke and non-CNS Embolism



No. at risk:

Rivaroxaban	6958	6211	5786	5468	4406	3407	2472	1496	634
Warfarin	7004	6327	5911	5542	4461	3478	2539	1538	655

Event Rates are per 100 patient-years  
Based on Protocol Compliant on Treatment Population

# Primary Safety Outcomes

# ROCKET

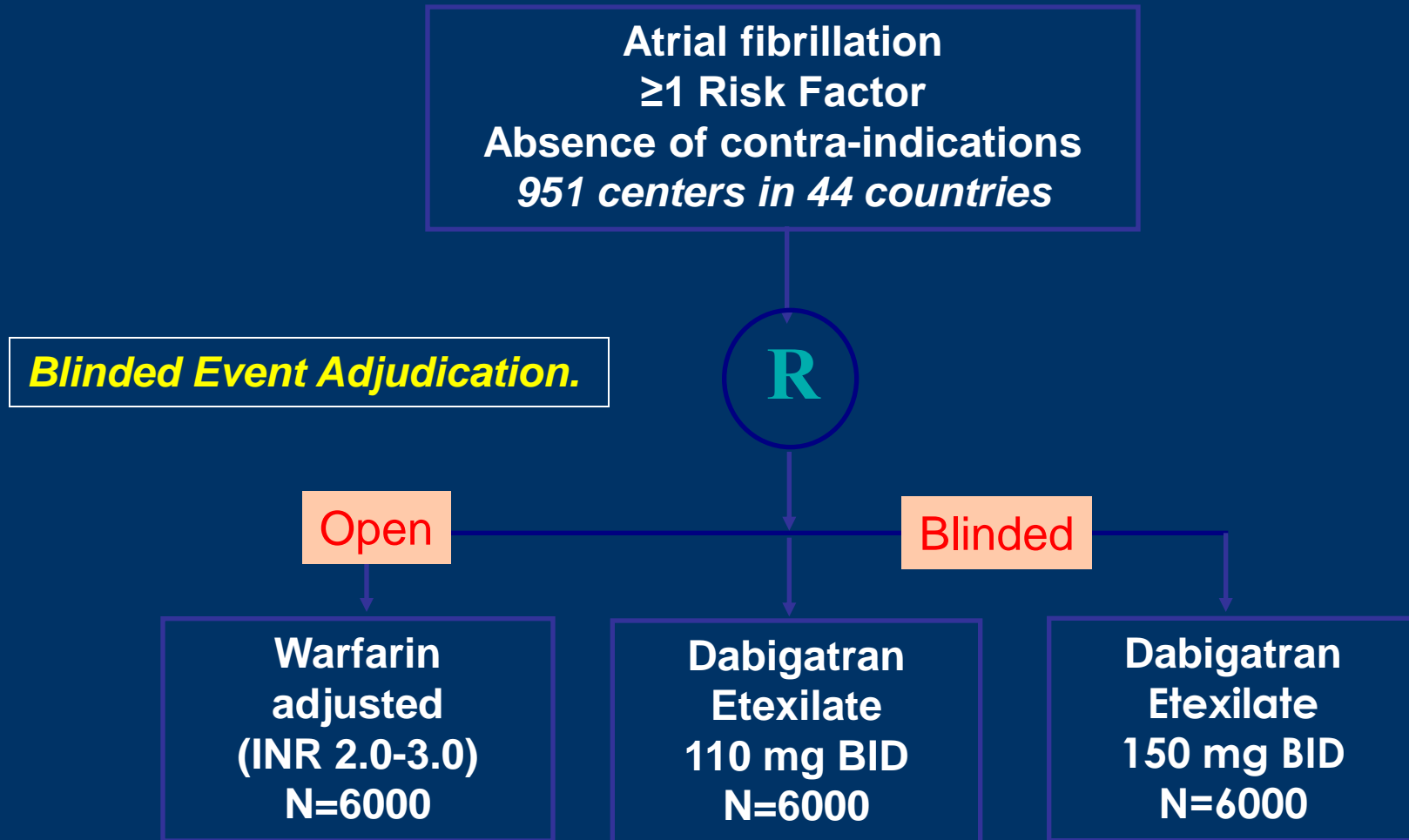
	Rivaroxaban	Warfarin		
	Event Rate	Event Rate	HR (95% CI)	P- value
Major and non-major Clinically Relevant	14.91	14.52	1.03 (0.96, 1.11)	0.442
Major	3.60	3.45	1.04 (0.90, 1.20)	0.576
Non-major Clinically Relevant	11.80	11.37	1.04 (0.96, 1.13)	0.345

Event Rates are per 100 patient-years  
Based on Safety on Treatment Population

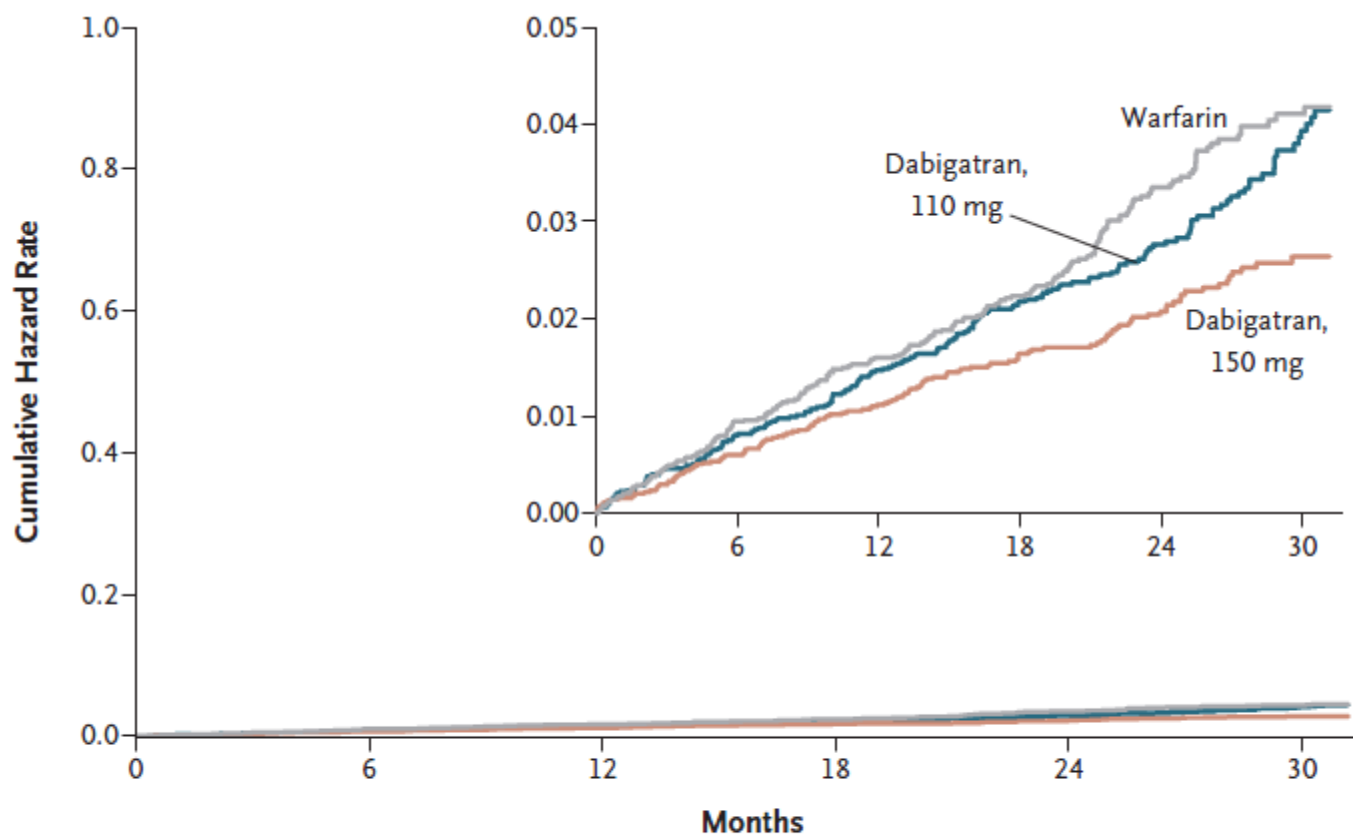
# ROCKET Summary

- **Efficacy:**
  - Rivaroxaban was non-inferior to warfarin for prevention of stroke and non-CNS embolism.
  - Rivaroxaban was superior to warfarin while patients were taking study drug.
  - By intention-to-treat, rivaroxaban was non-inferior to warfarin but did not achieve superiority.
- **Safety:**
  - Similar rates of bleeding and adverse events.
  - Less ICH and fatal bleeding with rivaroxaban.

# RE-LY: A Non-inferiority Trial



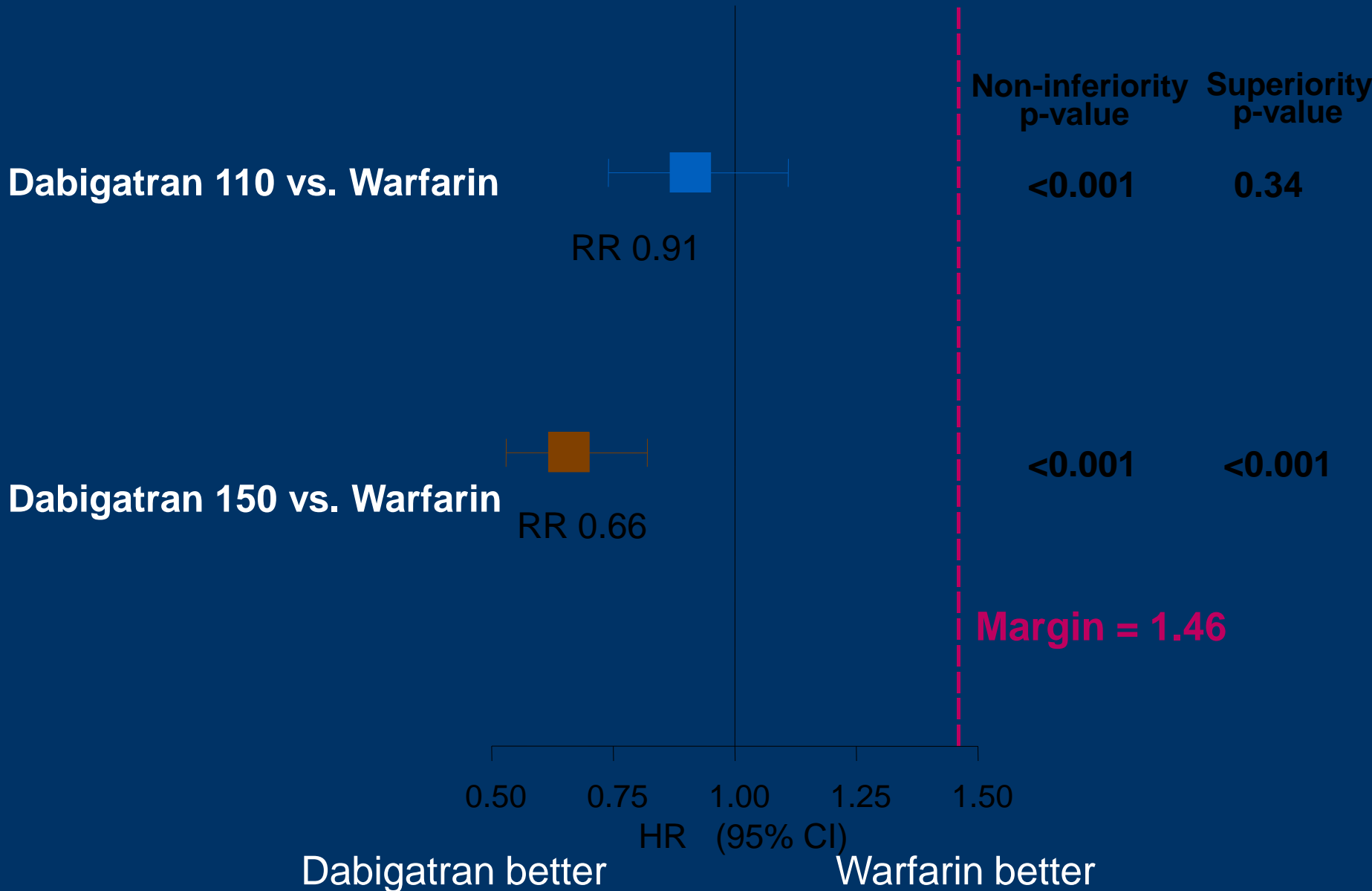
# RE-LY primary outcome: stroke or systemic embolism



## No. at Risk

Warfarin	6022	5862	5718	4593	2890	1322
Dabigatran, 110 mg	6015	5862	5710	4593	2945	1385
Dabigatran, 150 mg	6076	5939	5779	4682	3044	1429

# Stroke or Systemic Embolism



# RELY: dabigatran

	<b>Dabigatran</b> 2 x 110 n=6015	<b>Dabigatran</b> 2 x 150 n=6076	<b>Warfarin</b> N=6022 TTR 64%	<b>Hazard ratio</b> (95% CI) 2 x 110 vs warfarin	<b>Hazard ratio</b> (95% CI) 2 x 150 vs warfarin
<b>Stroke and non-CNS embolism</b>	1,53%/yr  n=182	1,11%/yr  n=134	1,69%/yr  n=199	<b>0.91</b> (0.74–1.11)	<b>0.66</b> (0.53–0.82)
<b>Major bleeding</b>	2.71%/yr  n=322	3.11%/yr  n=375	3.36%/yr  n=397	<b>0.80</b> (0.69–0.93) p=0.003	<b>0.93</b> (0.81–1.07) p=0.31

Subgroup	Patients total no.	Dabigatran		Warfarin	Hazard Ratio with Dabigatran, 110 mg (95% CI)	P Value for Interaction	Hazard Ratio with Dabigatran, 150 mg (95% CI)	P Value for Interaction
		110 mg	150 mg % per yr					
All patients	18,113	1.53	1.11	1.69				
Long-term VKA therapy						0.72		0.81
No	9,123	1.57	1.07	1.67				
Yes	8,989	1.49	1.15	1.70				
Sex						0.96		0.24
Male	11,514	1.35	1.10	1.49				
Female	6,598	1.86	1.14	2.03				
Body-mass index						0.71		0.21
<28	9,131	1.78	1.17	2.01				
≥28	8,962	1.28	1.04	1.34				
Weight						0.48		0.42
<50 kg	376	2.58	2.24	5.04				
50-99 kg	14,629	1.66	1.14	1.77				
≥100 kg	3,099	0.80	0.87	0.94				
Ethnic group						0.22		0.10
European or Arab	12,679	1.35	1.03	1.35				
Other	5,433	1.97	1.32	2.52				
Creatinine clearance						0.60		0.54
<50 ml/min	3,505	2.15	1.52	2.78				
50-79 ml/min	8,766	1.70	1.20	1.76				
≥80 ml/min	5,826	0.94	0.75	0.98				
CHADS <sub>2</sub> score						0.44		0.82
0 or 1	5,775	1.06	0.65	1.05				
2	6,455	1.43	0.84	1.38				
≥3	5,882	2.12	1.88	2.68				
Symptomatic heart failure						0.42		0.33
Yes	4,904	1.90	1.44	1.85				
No	13,203	1.40	1.00	1.63				
Hypertension						0.06		0.58
Yes	14,283	1.46	1.20	1.78				
No	3,829	1.79	0.78	1.36				
Diabetes						0.25		0.76
Yes	4,221	1.76	1.46	2.32				
No	13,891	1.46	1.01	1.50				
Stroke or TIA						0.65		0.34
Yes	3,623	2.32	2.07	2.74				
No	14,489	1.33	0.87	1.43				
Region						0.91		0.11
North America	6,533	1.19	1.11	1.51				

	<b>RELY</b>	<b>ROCKET</b>	<b>ARISTOTLE</b>
Leeftijd gemiddeld	72 jaar	73 jaar	70
CVA voorgesch.	20%	55%	19.5
Hypertensie	79%	91%	87
Hartfalen	32%	62%	35
diabetes	23%	39%	25
CHADS <sub>2</sub>	2,1	3,5	2.1
Follow-up	24 maanden	40 maanden	18 maanden

# Event rates in VKA group (% per year)

	RELY	ROCKET AF	ARISTOTLE
Hem. stroke	0.38	0.7	0.47
Stroke+embol	1.7	2.4	1.6
Maj bleed	3.1	3.4	3.1
Mortality	4.1	4.9	3.9
TTR (%)	64	55	52

## A comparison of risk reductions: point estimates and CI's

		Primary outcome Stroke + systemic embolism	Safety outcome Major bleeding
<b>Rocket</b>	Rivaroxaban 1x20	0.79 (0.66-0.96)	1.04 (0.90-1.20)
<b>Rely</b>	Dabigatran 2x150	0.66 (0.53-0.83)	0.93 (0.81-1.07)
<b>Aristotle</b>	Apixaban 2x20	0.79 (0.66-0.95)	0.69 (0.60-0.80)

# conclusies

- Alle 3 beter dan VKA
- Dabigatran 2x110 veiliger maar niet beter
- Dabigatran 2x150 beter maar niet veiliger
- Rivaroxaban 1 dd beter en veiliger
- Apixaban 2 dd beter en veiliger





# HAS-BLED: estimation of bleeding risk

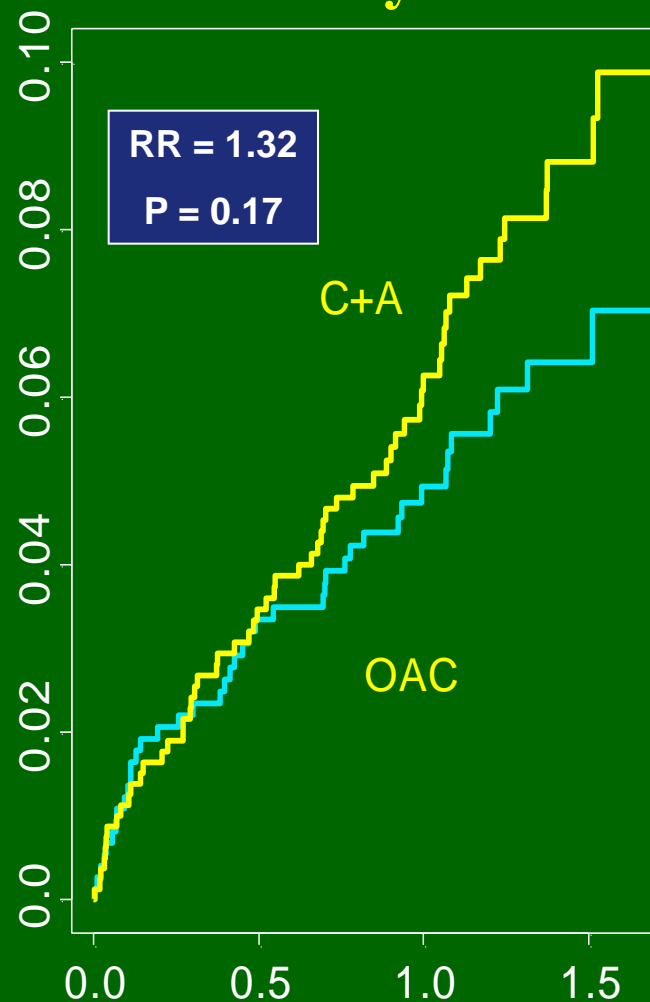
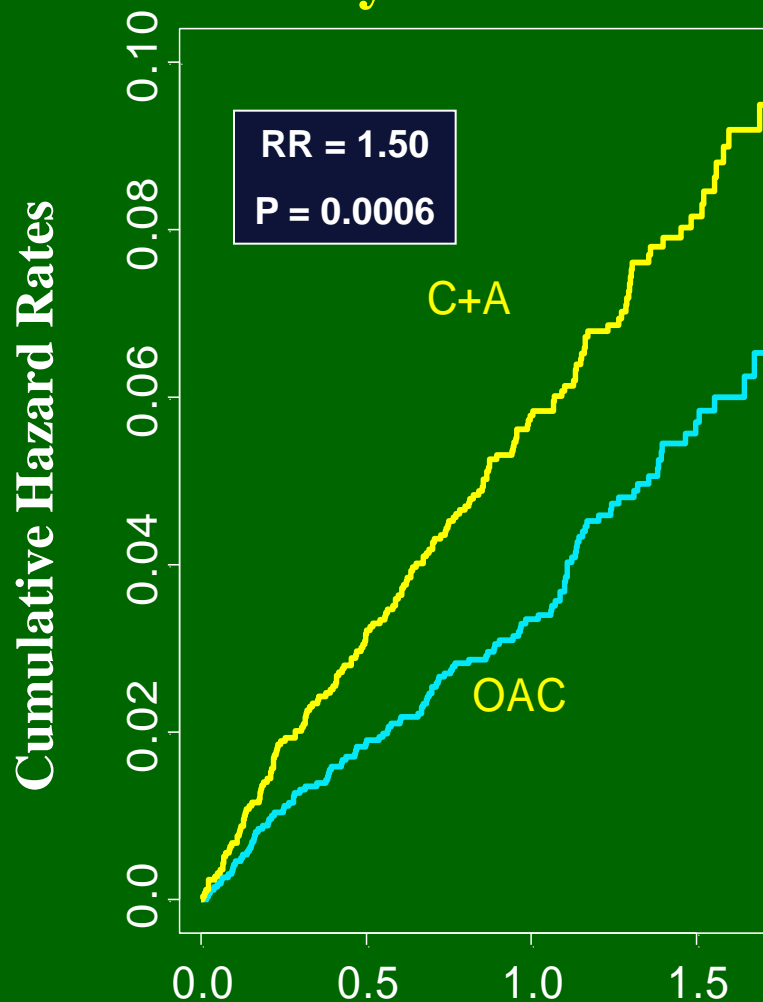
- Hypertension (uncontrolled)
- Abnormal liver/renal function
- Stroke
- Bleeding history or predisposition
- Labile INR (TTR < 60%)
- Elderly ('age e.g. >65')
- Drug/alcohol use (antiplatelet, NSAIDs)

# Stroke, Non-CNS Systemic Embolism, MI, Vascular Death

Entry OAC

Interaction P = 0.55

No Entry OAC



ACTIVE W

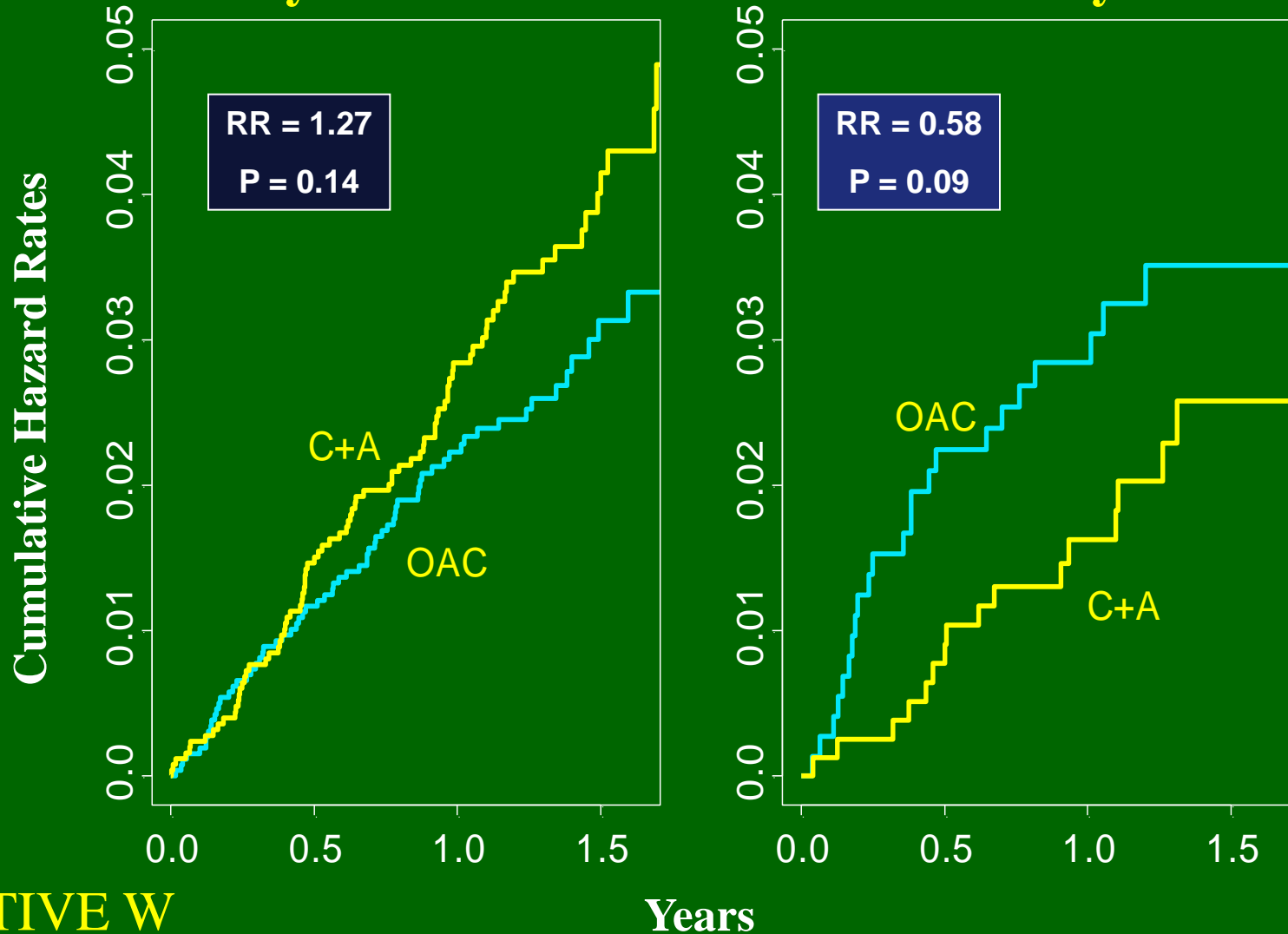
Years

# Major Bleeding

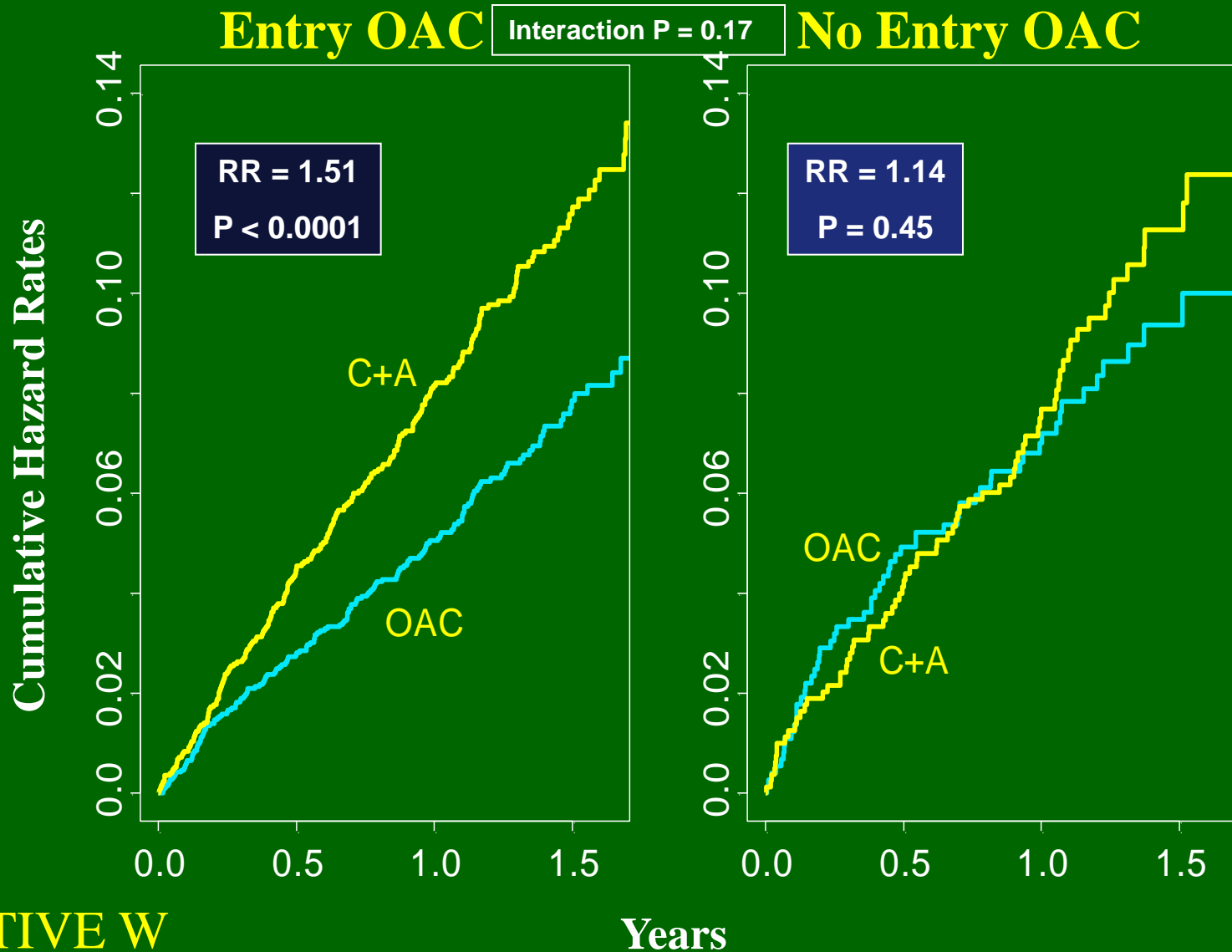
**Entry OAC**

Interaction P = 0.032

**No Entry OAC**

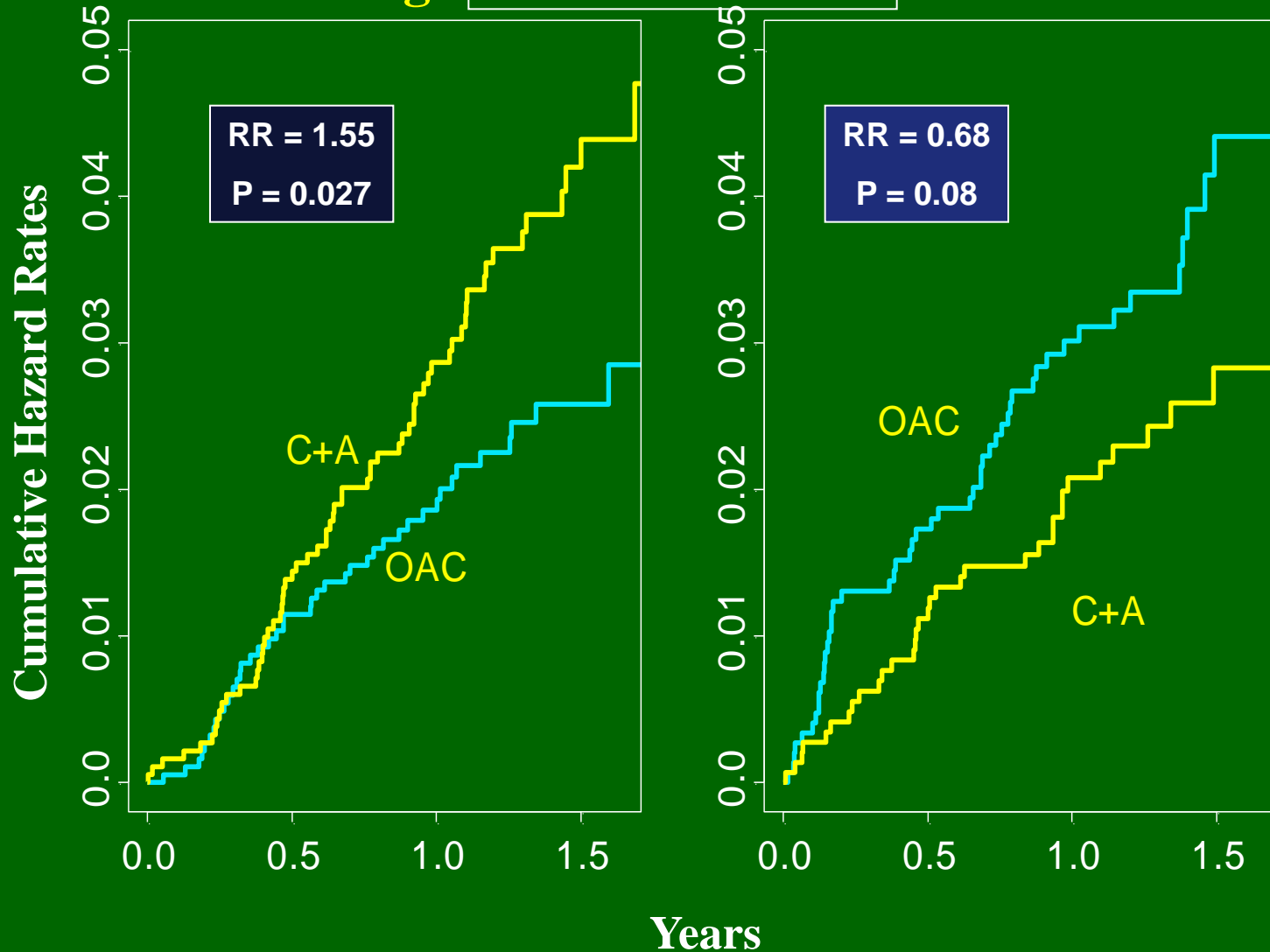


# Primary Outcome + Major Bleeding



# Major Bleeding by Center INR Control

$\geq 65\%$  INR in Range    Interaction P = 0.0006     $<65\%$  INR in Range



# Primary+Major Bleed by Centre INR Control

$\geq 65\%$  INR in Range   Interaction P = 0.002    $<65\%$  INR in Range

