

# NOAs for stroke prevention in Atrial Fibrillation: potential advantages in the elderly patients

**Giancarlo Agnelli**

Internal & Cardiovascular Medicine - Stroke Unit  
University of Perugia, Italy



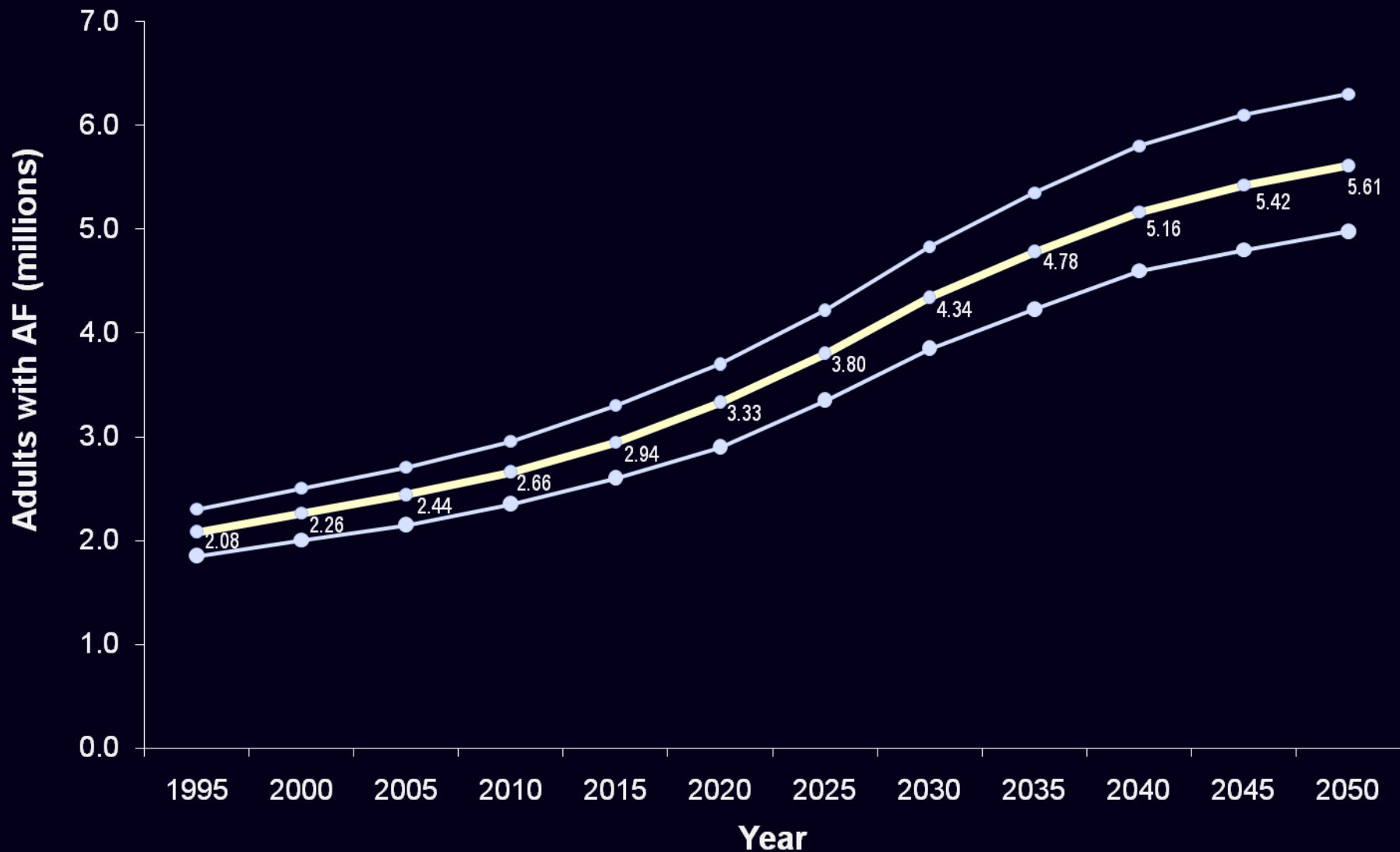
# My talk today

- Age as a risk factor for Afib (and related stroke)
- Age in the risk stratification scores
- Aspirin vs. VKA in the elderly patients
- Recent Afib trials with NOAs for stroke prevention
- Elderly patients in the NOAs trials: prevalence & outcome

# My talk today

- Age as a risk factor for Afib (and related stroke)
- Age in the risk stratification scores
- Aspirin vs. VKA in the elderly patients
- Recent Afib trials with NOAs for stroke prevention
- Elderly patients in the NOAs trials: prevalence & outcome

# Prevalence of AF in US or Europe



50-60% patients over 80% years

Go et al., JAMA 2001

# Age and VKA treatment for Afib

## Perugia University Anticoagulation Clinic II

- Patients: **1676**

### Gender

- Males 868 (51.8%)
- Females 808 (48.2%)

### Age\*

Range: 20-97

Classe età	N	%
< 65 years	142/1675**	<b>8.5</b>
65-75 years	434/1675	<b>25.9</b>
76-79 years	307/1675	<b>18.3</b>
> 80 years	674/1765	<b>40.2</b>
> 90 years	118/1765	7.0

} 981  
patients  
(58.5%)

# My talk today

- Age as a risk factor for Afib (and related stroke)
- Age in the risk stratification scores
- Aspirin vs. VKA in the elderly patients
- Recent Afib trials with NOAs for stroke prevention
- Elderly patients in the NOAs trials: prevalence & outcome

## CHADS<sub>2</sub> Score

Risk Factor	
CHF / LV dysfunction	1
Hypertension	1
Age > 75 years	1
Diabetes mellitus	1
Stroke / TIA	2

Derived from risk factors identified in datasets in non-VKA treated patients

# CHA<sub>2</sub>DS<sub>2</sub>-VASc Score

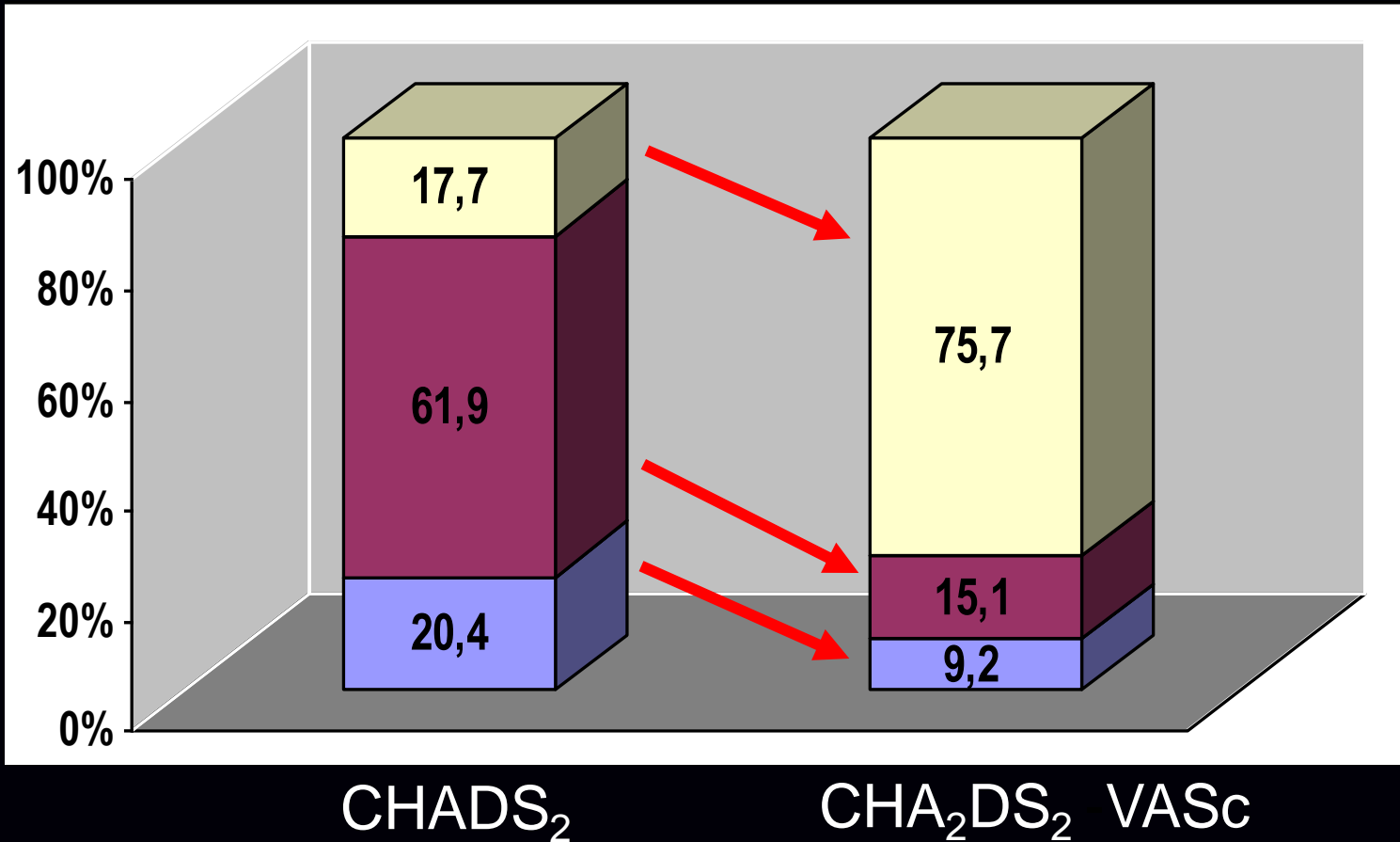
Risk Factor	Score
<u>C</u> ongestive heart failure / LV dysfunction	1
<u>H</u> ypertension	1
<u>A</u> ge ≥ 75 y	2
<u>D</u> iabetes mellitus	1
<u>S</u> troke / TIA / systemic embolism	2
<u>V</u> ascular disease (prior myocardial infarction, peripheral artery disease or aortic plaque)	1
<u>A</u> ge 65 - 74 y	1
<u>S</u> ex category (i.e. female gender)	1

To identify: truly low-risk patients by being more inclusive



# CHADS<sub>2</sub> & CHA<sub>2</sub>DS<sub>2</sub> VASc Score

% in Risk of Thromboembolism Category



- High Risk (score  $\geq 2$ )
- Intermediate Risk (score 1)
- Low Risk (score 0)

# HAS-BLED bleeding risk score

<b>H</b>	1 point	Hypertension
<b>A</b>	1 or 2 points	Abnormal renal and liver function
<b>S</b>	1	Stroke
<b>B</b>	1	Bleeding
<b>L</b>	1	Labile INRs
<b>E</b>	1	Age (e.g. age > 65 years)
<b>D</b>	1 or 2 points	Drugs or alcohol

**3 points: 3.5%/years**

# My talk today

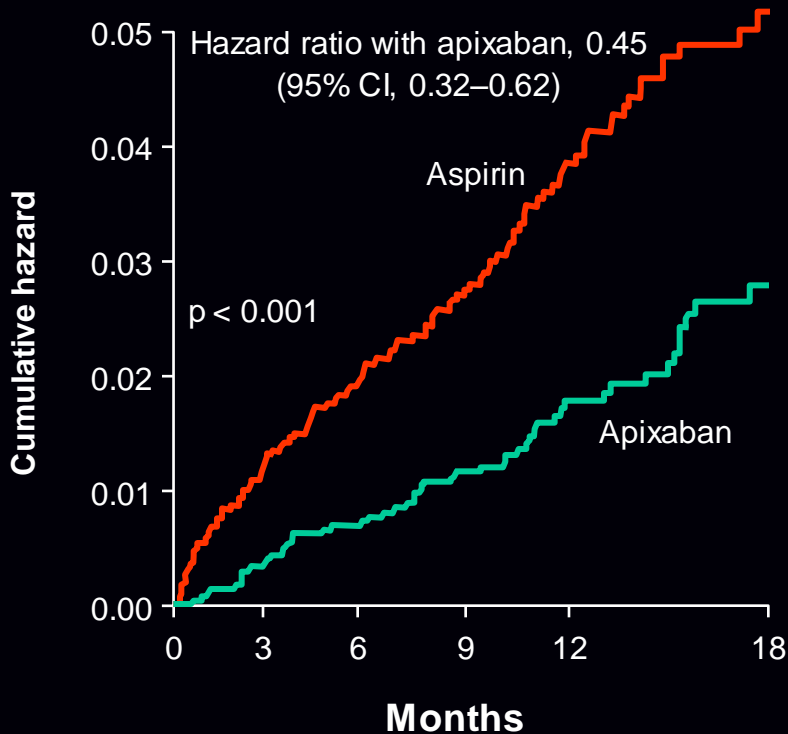
- Age as a risk factor for Afib (and related stroke)
- Age in the risk stratification scores
- Aspirin vs. VKA in the elderly patients
- Recent Afib trials with NOAs for stroke prevention
- Elderly patients in the NOAs trials: prevalence & outcome

# BAFTA

- 973 people aged  $\geq 75$  in AF (mean age 81)
- Aspirin 75mg vs. Warfarin target INR 2.5
- Mean follow up 2.7 years
- Primary outcome measure:
  - Fatal or disabling stroke (ischemic or haemorrhagic) or other intra-cranial haemorrhage or systemic embolus
  
- Warfarin 1.8% v aspirin 3.8%
- RR 0.48 (0.28-0.80)
- NNT: 50 for 1 year
- $p = 0.0027$

# AVERROES: efficacy & safety

## Stroke/systemic embolism



## Bleeding events

	Apixaban	Aspirin	p value
No. of events (%/yr)			
Patients (n)	2,808	2,791	
Major bleeding	44 (1.4%)	39 (1.2%)	0.57
Minor bleeding	188	153	0.05

# My talk today

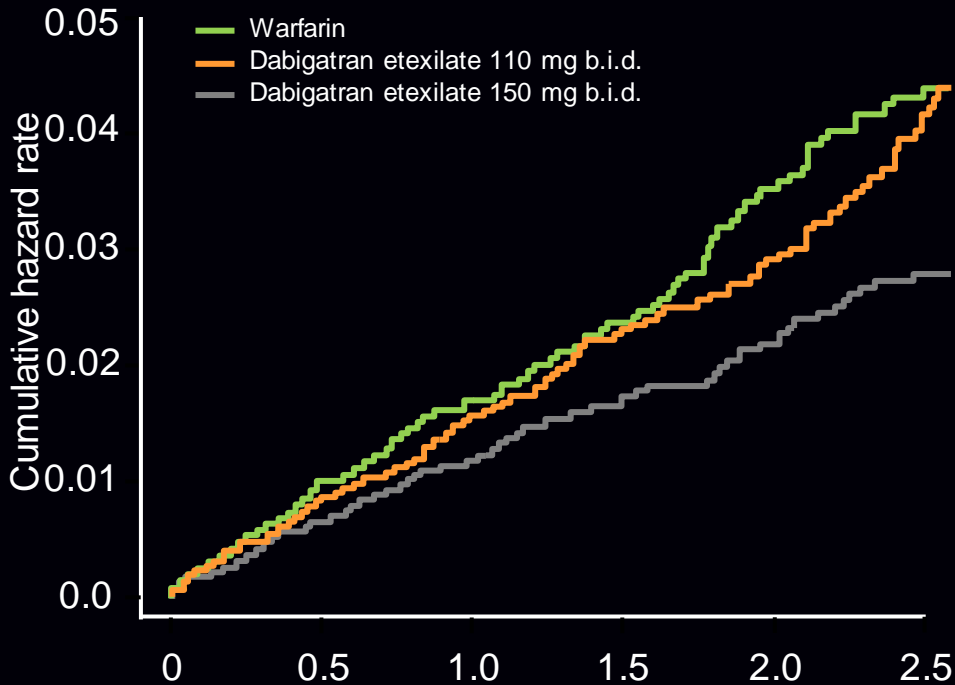
- Age as a risk factor for Afib (and related stroke)
- Age in the risk stratification scores
- Aspirin vs. VKA in the elderly patients
- **Recent Afib trials with NOAs for stroke prevention**
- Elderly patients in the NOAs trials: prevalence & outcome

# NOACs: prevention of stroke in AFib

- Rely
- Rocket-AF
- Aristotle
- Engage
- Averro

# RELY (dabigatran)

## Stroke/systemic embolism



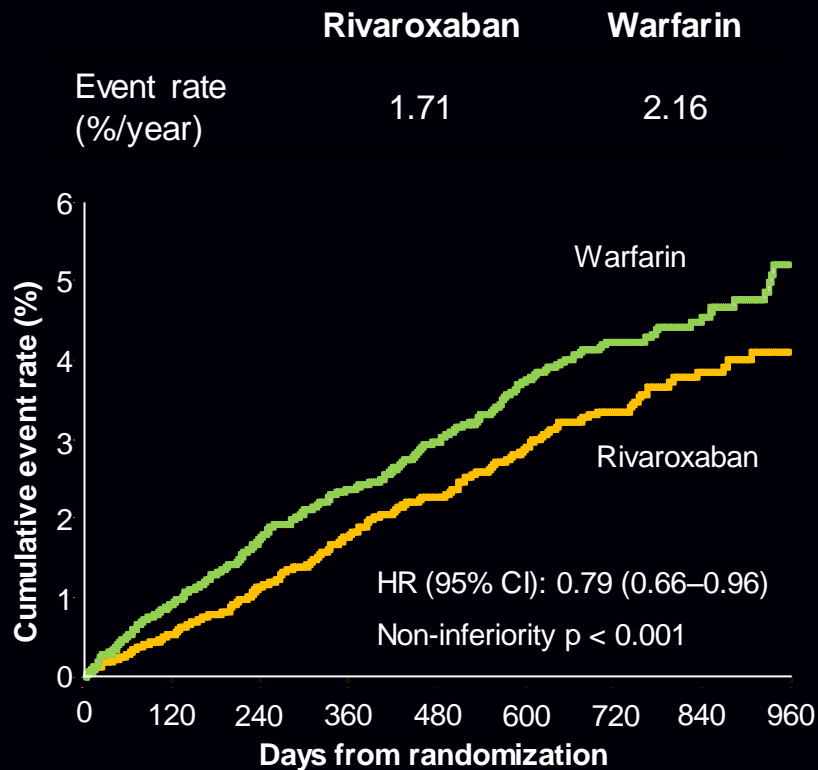
## Bleeding events

	Dabi. 110 mg (%/y)	Dabi. 150 mg (%/y)	Warf. (%/y)	p, dabi. 110 m mg vs. warf.	p, dabi. 150 mg vs warf.
Patients (n)	6,015	6,076	6,022		
Severe bleeds	2.71	3.11	3.36	0.003	0.31
life-threatening	1.22	1.45	1.80	< 0.001	0.037
non-life threatening	1.66	1.88	1.76	0.56	0.47
gastro-intestinal	1.12	1.51	1.02	0.43	< 0.001



# ROCKET- AF (rivaroxaban)

## Stroke and non-CNS embolism\*



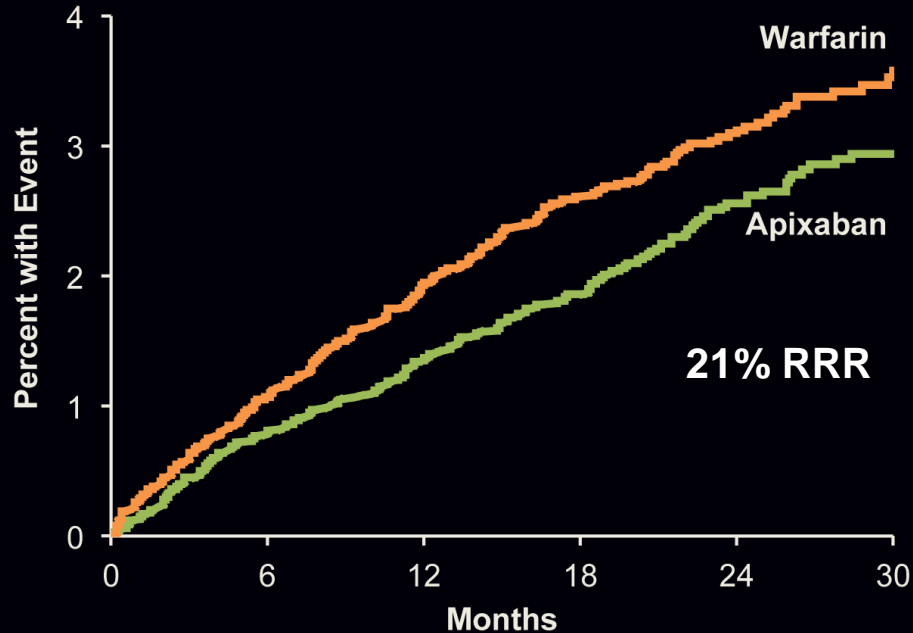
## Bleeding events

	Rivaroxaban	Warfarin	p value
Major and clinically relevant non-major	Rate (%/year) 14.91	Rate (%/year) 14.52	0.442
major	3.60	3.45	0.576
clinically relevant non-major	11.80	11.37	0.345

\* Based on protocol-compliant, on-treatment population.

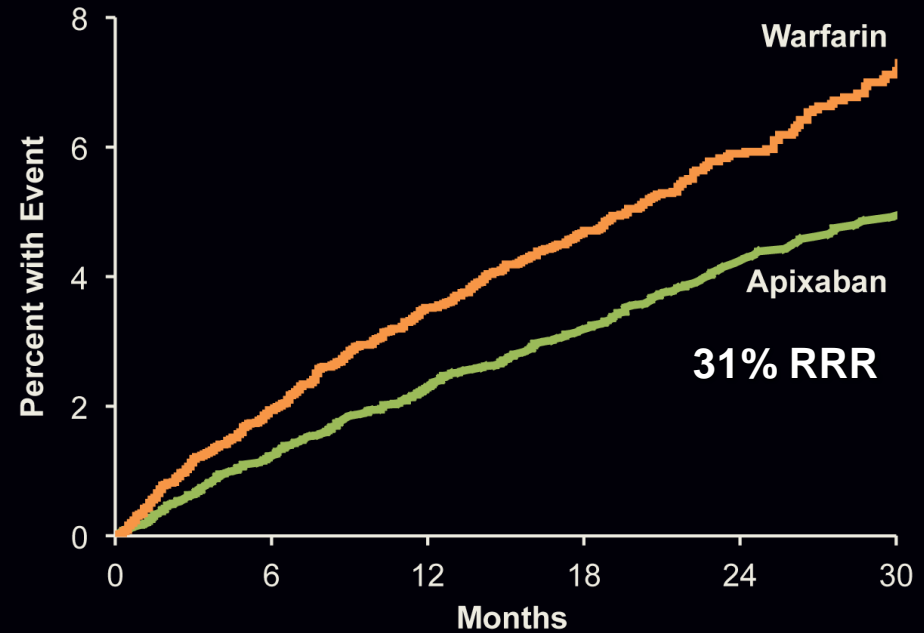
# ARISTOTLE: (apixaban)

## 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

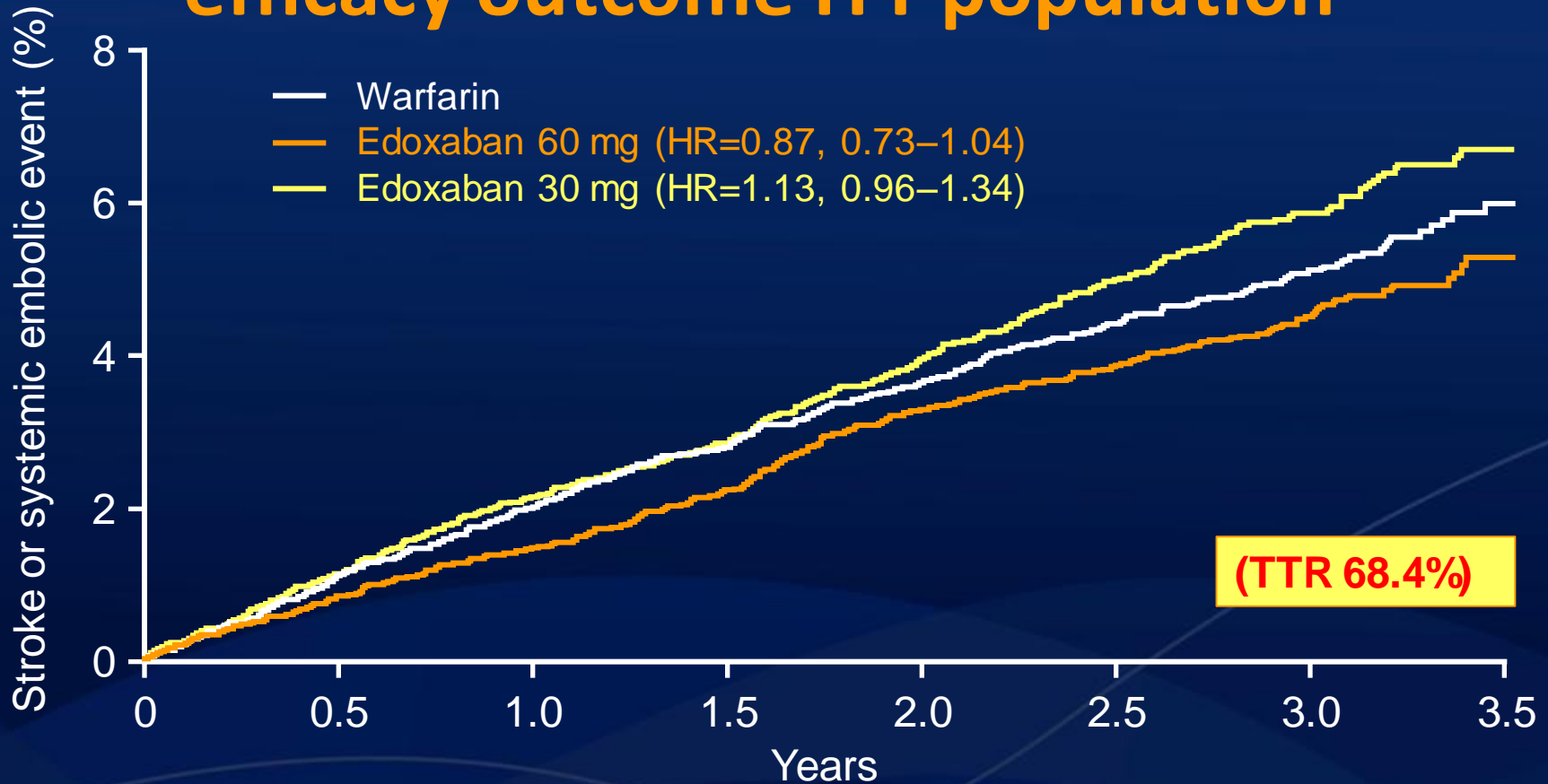
## ISTH major bleeding



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

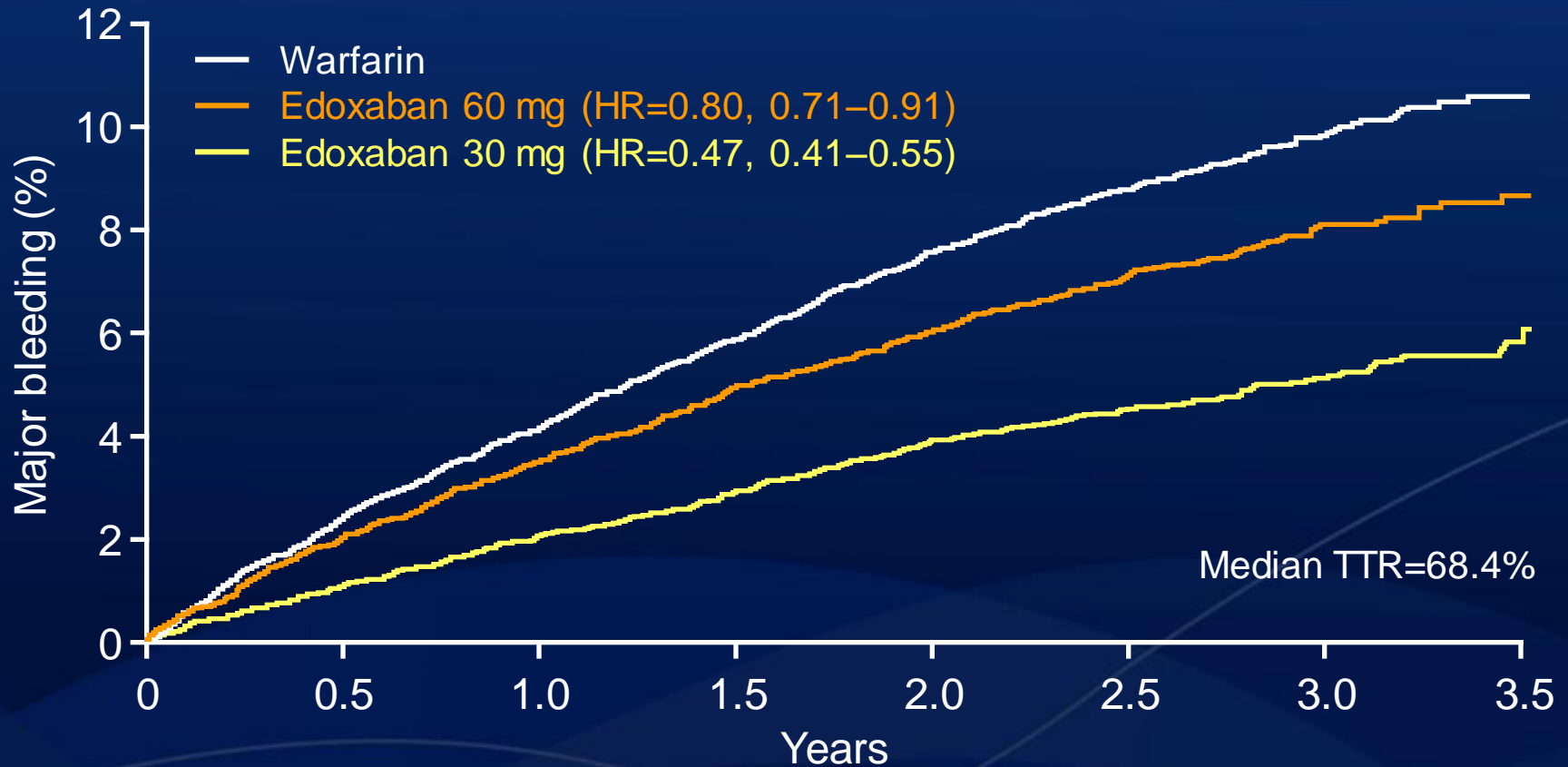
Median TTR 66%

# Kaplan-Meier of primary efficacy outcome ITT population



No.at risk	0	0.5	1.0	1.5	2.0	2.5	3.0	3.5
Warfarin	7036	6798	6615	6406	6225	4593	2333	536
Edoxaban (60)	7035	6816	6650	6480	6283	4659	2401	551
Edoxaban (30)	7034	6815	6631	6461	6277	4608	2358	534

# Kaplan-Meier of principal safety outcome



No. at risk	0	0.5	1.0	1.5	2.0	2.5	3.0	3.5
Warfarin	7012	6166	5630	5278	4941	3446	1687	370
Edoxaban (60)	7012	6039	5594	5232	4910	3471	1706	345
Edoxaban (30)	7002	6218	5791	5437	5110	3635	1793	386

# My talk today

- Age as a risk factor for Afib (and related stroke)
- Age in the risk stratification scores
- Aspirin vs. VKA in the elderly patients
- Recent Afib trials with NOAs for stroke prevention
- Elderly patients in the NOAs trials: prevalence & outcome

## NOACs: prevention of stroke in AFib

- **Rely:**
  - 41% older than 75 years
  - 17% older than 80 years
- **Rocket-AF**
  - 43% older than 75 years
  - 25% older than 80 years
- **Aristotle**
- 31% older than 75 years

# RELY

- 3016 (17%) people aged  $\geq 80$  years
  - 720 (4%) people aged  $\geq 85$  years
  - 79 (0.45) aged  $\geq 90$  years
- 
- **Stroke & SSE  $\geq 80$  years**
  - Dabigatran 110 bid vs. warfarin: HR 0.68
  - Dabigatran 150 bid vs. warfarin: HR 0.65
- 
- **ICH  $\geq 80$  years**
  - Dabigatran 110 bid vs. warfarin: HR 0.24
  - Dabigatran 150 bid vs. warfarin: HR 0.53

# ROCKET- AF

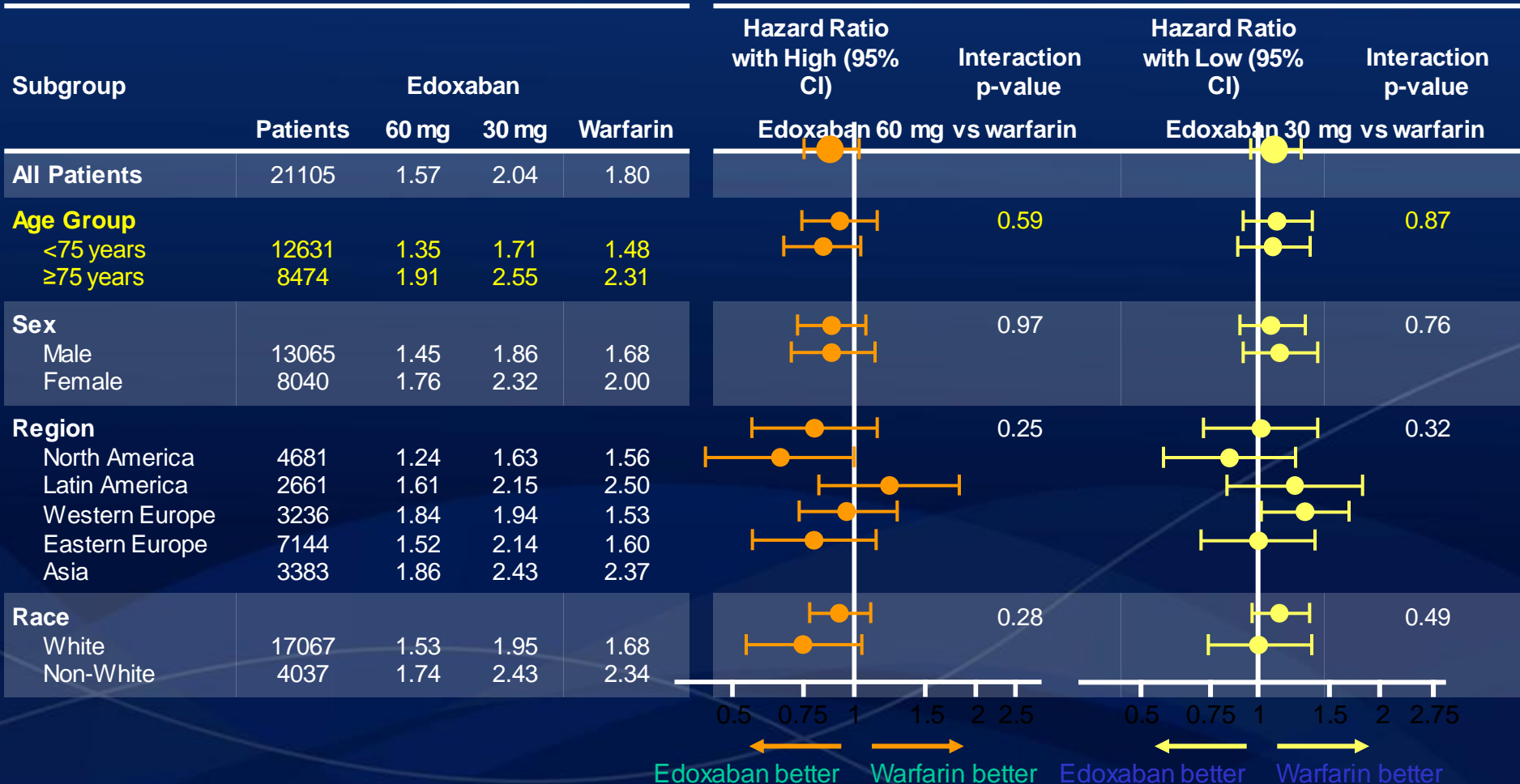
%/ <b>year</b>	<b>Age ≥ 75 years</b>		<b>HR (95% CI)</b>	<b>Age &lt; 75 years</b>		<b>HR (95% CI)</b>	<b>p-value*</b>
	<b>R</b> N=3082	<b>W</b> N=3082		<b>R</b> N=3999	<b>W</b> N=4088		
Stroke/SE <sup>1</sup>	2.29	2.85	0.80 (0.63-1.02)	2.00	2.10	0.95 (0.76-1.19)	0.31
Fatal/disabling stroke <sup>1</sup>	1.14	1.50	0.76 (0.55-1.06)	0.90	1.09	0.83 (0.60-1.15)	0.72
Mortality <sup>2</sup>	2.08	2.49	0.84 (0.64-1.07)	1.71	2.01	0.85 (0.66-1.09)	0.93
Major bleeding <sup>3</sup>	4.86	4.40	1.11 (0.92-1.34)	2.69	2.79	0.964 (0.78-1.19)	0.34
ICH <sup>3</sup>	0.66	0.83	0.80 (0.499-1.282)	0.37	0.68	0.54 (0.33-0.89)	0.27
CRNMB <sup>3</sup>	15.61	13.54	1.15 (1.03-1.23)	9.22	9.87	0.94 (0.83-1.05)	0.01

R=rivaroxaban; W=warfarin; \*p-value for interaction; ICH=intracerebral haemorrhage; CRNMB=clinically relevant non-major bleeding

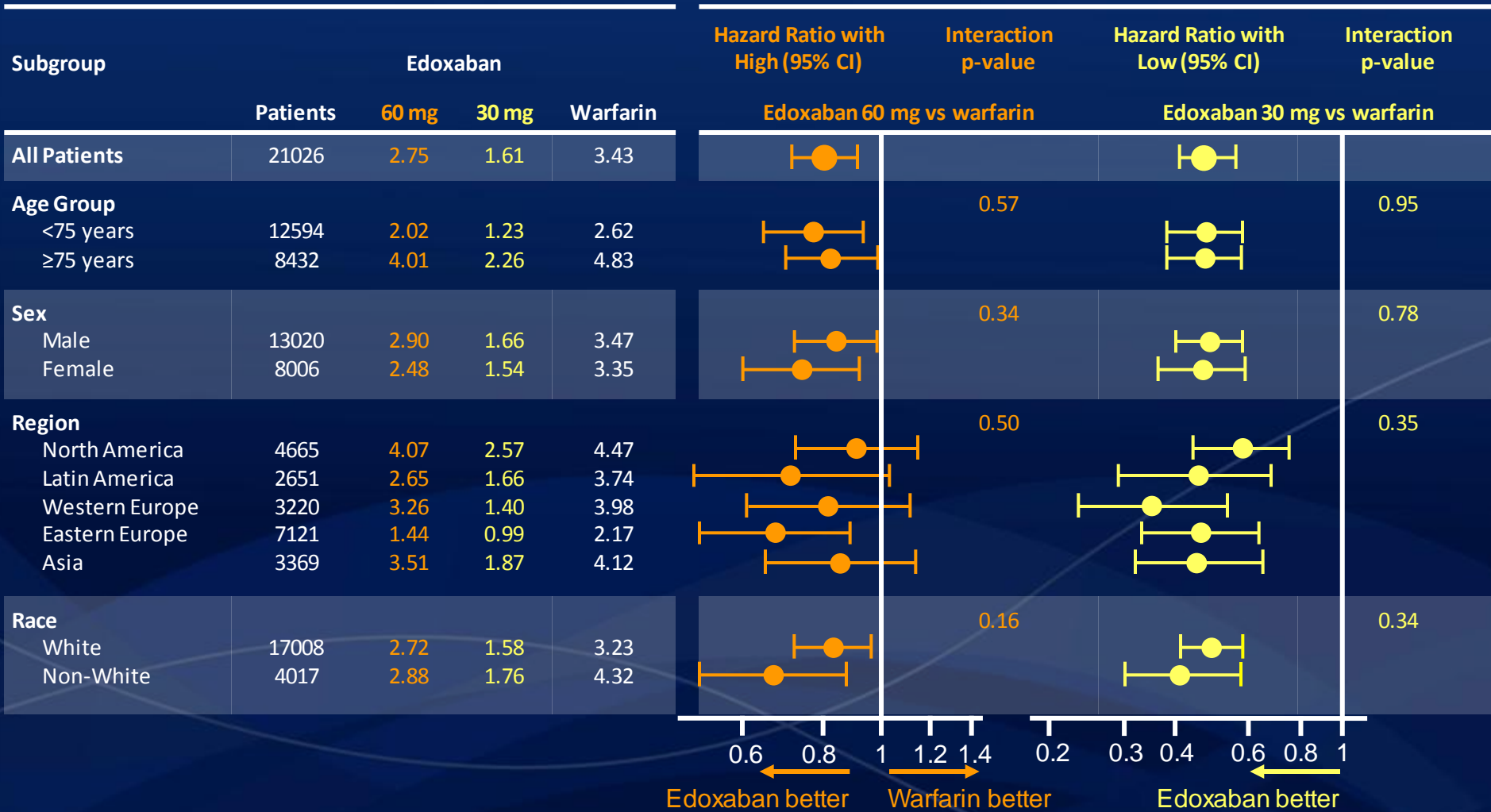
<sup>1</sup>ITT population, <sup>2</sup> safety population excluding a GCP violating site, <sup>3</sup>safety population



# Subgroups: efficacy

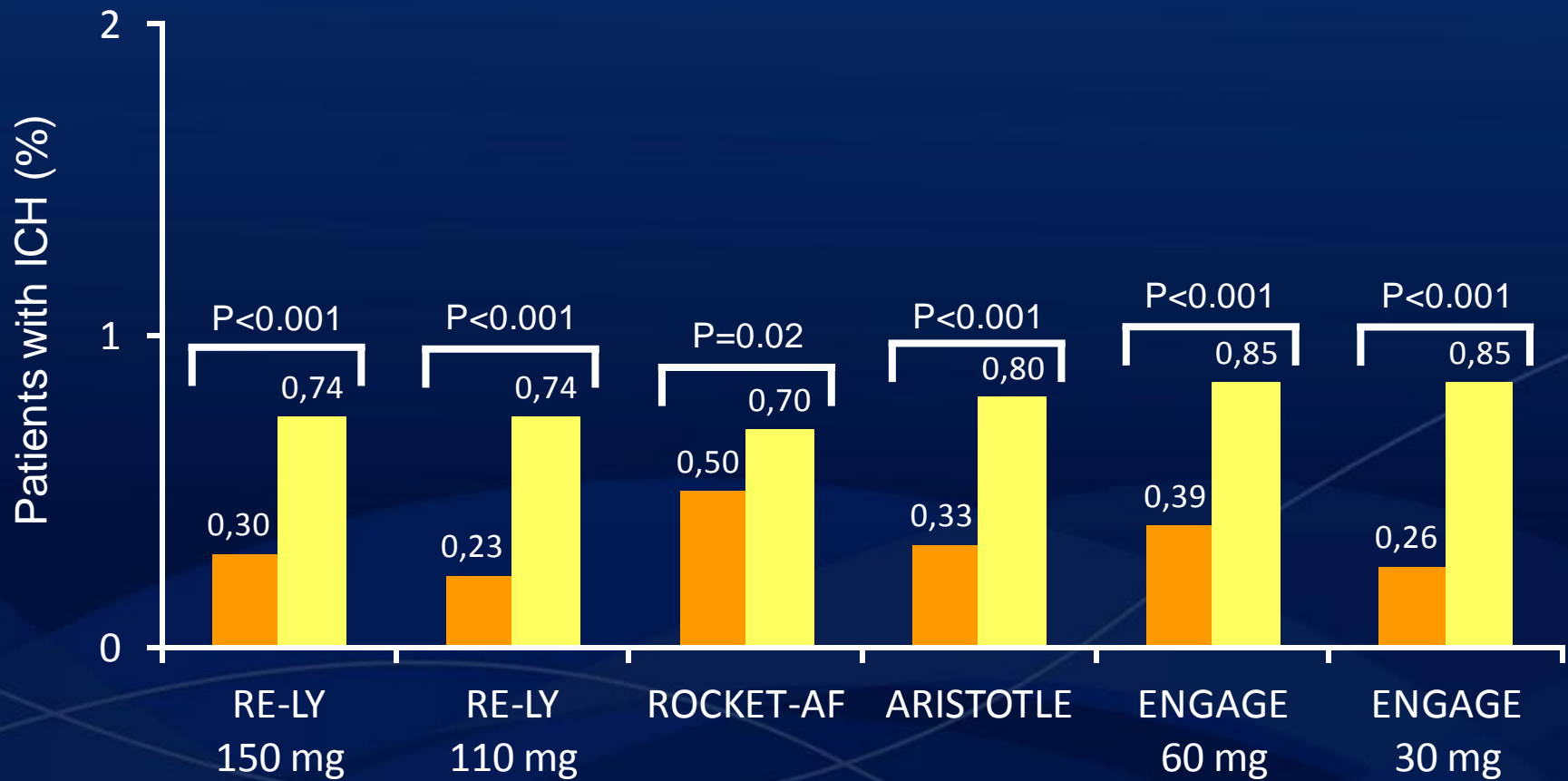


# Subgroups: safety



# Phase III AF trials: intracranial hemorrhage

■ NOAC ■ Warfarin



## Responsible use of NOAs

- Although safer than VKA, NOAs hold the risk of bleeding
- NOAs should be given for approved indications at validated doses (assessing the potential benefit in the individual patient)
- Patients should receive a complete information about the NOAs treatment at the start-up visit
- An adherence to treatment plan as well as a follow-up plan with regular visits should be set-up
- A hospital police to deal with bleeding complications and emergency surgery should be set-up and spread-out