



Simposio
I NUOVI ANTICOAGULANTI ORALI IN
GERIATRIA: L'ETÀ... DEL CAMBIAMENTO

Bologna 26-29 Novembre 2014

I NAO nel paziente anziano con fibrillazione atriale: analogie e differenze

Stefano Fumagalli

Cardiologia e Medicina Geriatrica, AOU Careggi e Università di Firenze



Bologna 26-29 Novembre 2014

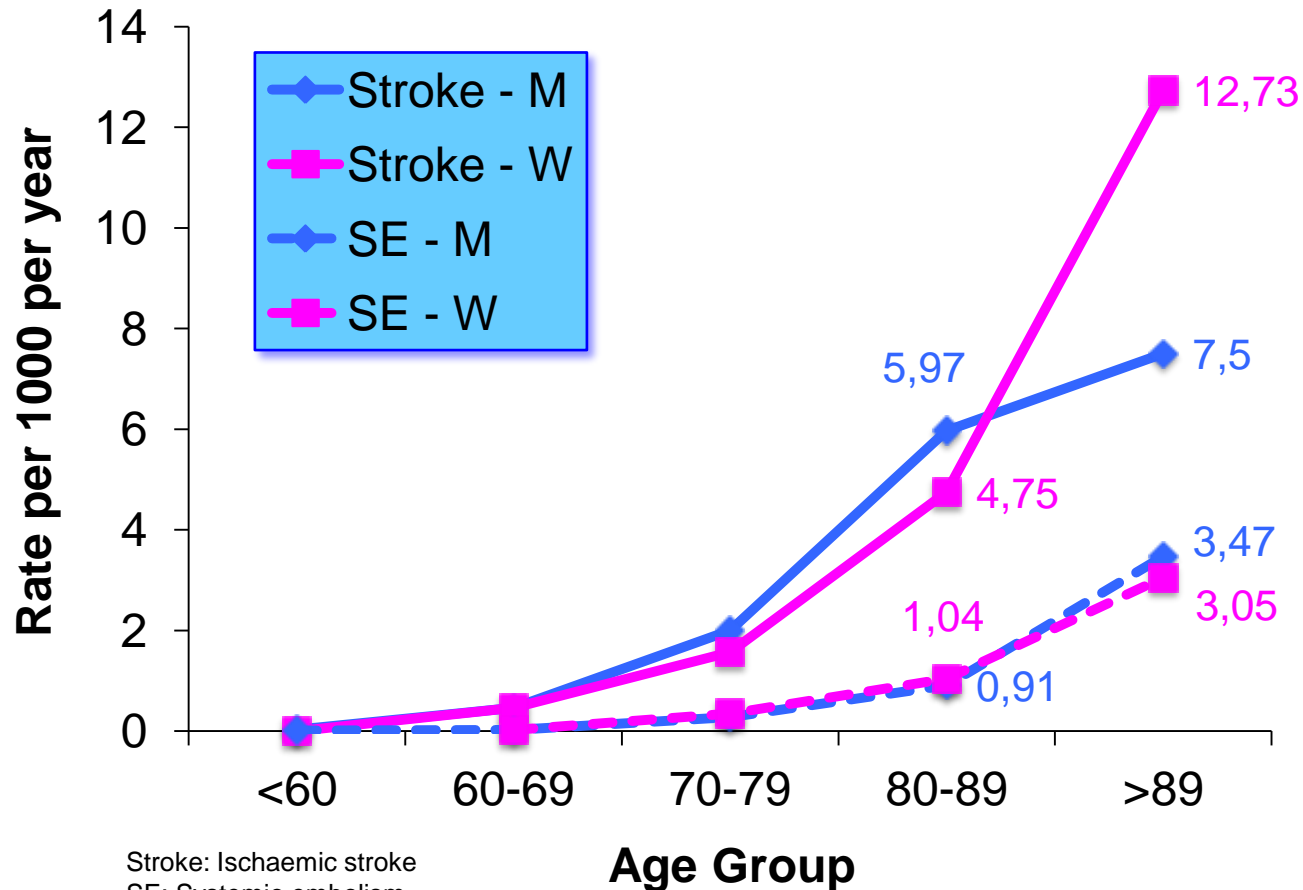
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Premesse

Age-Specific Incidence, Outcome, Cost and Projected Future Burden of Atrial Fibrillation-Related Embolic Vascular Events: A Population-Based Study

Age-specific rates of first ever AF-related incident ischaemic stroke and systemic embolism in the Oxford Vascular Study
(2002-2012; N=92728; 9 general practices - about 100 family doctors)

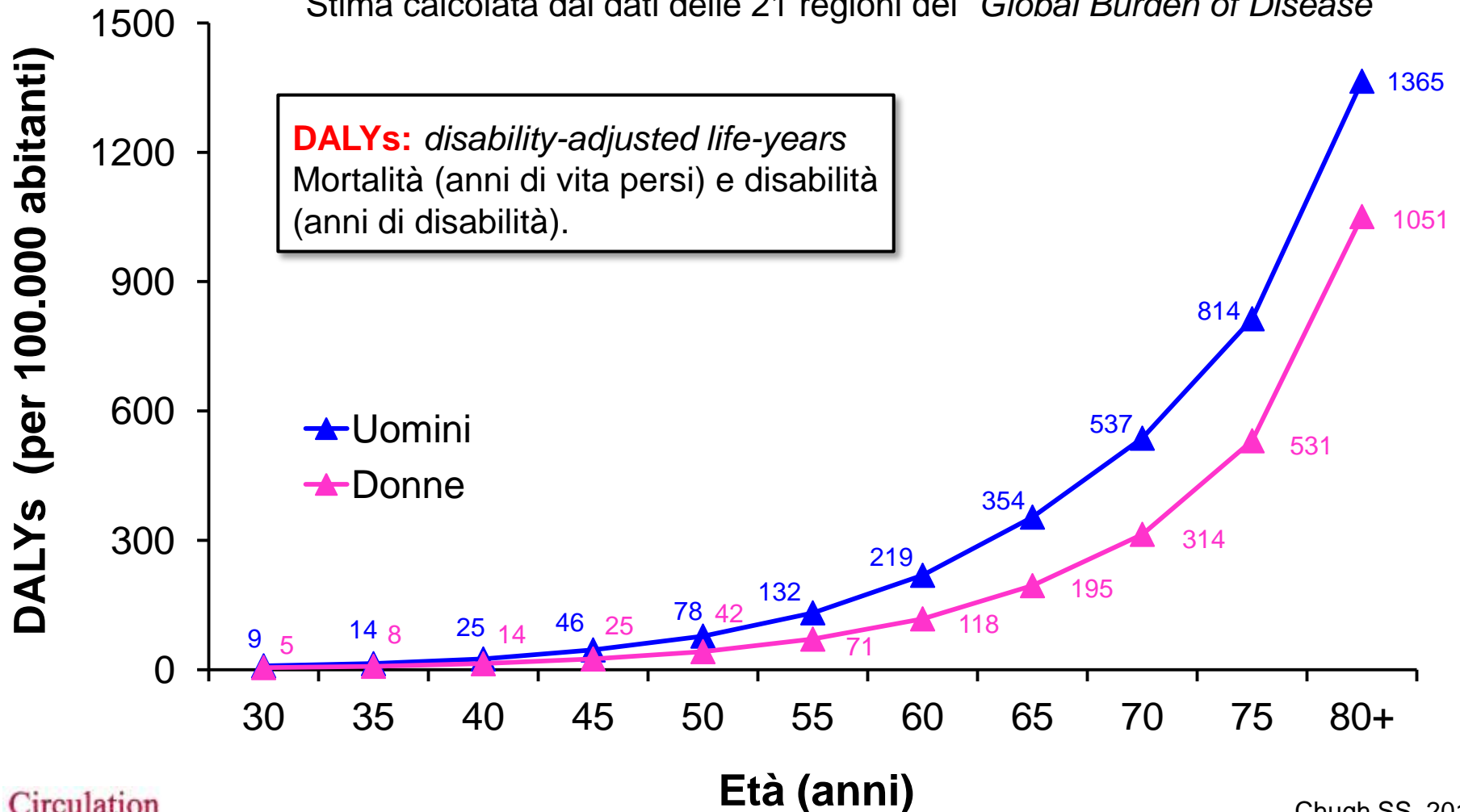


Worldwide Epidemiology of Atrial Fibrillation

A Global Burden of Disease 2010 Study

Disabilità per FA nel 2010, per genere ed età nei paesi industrializzati

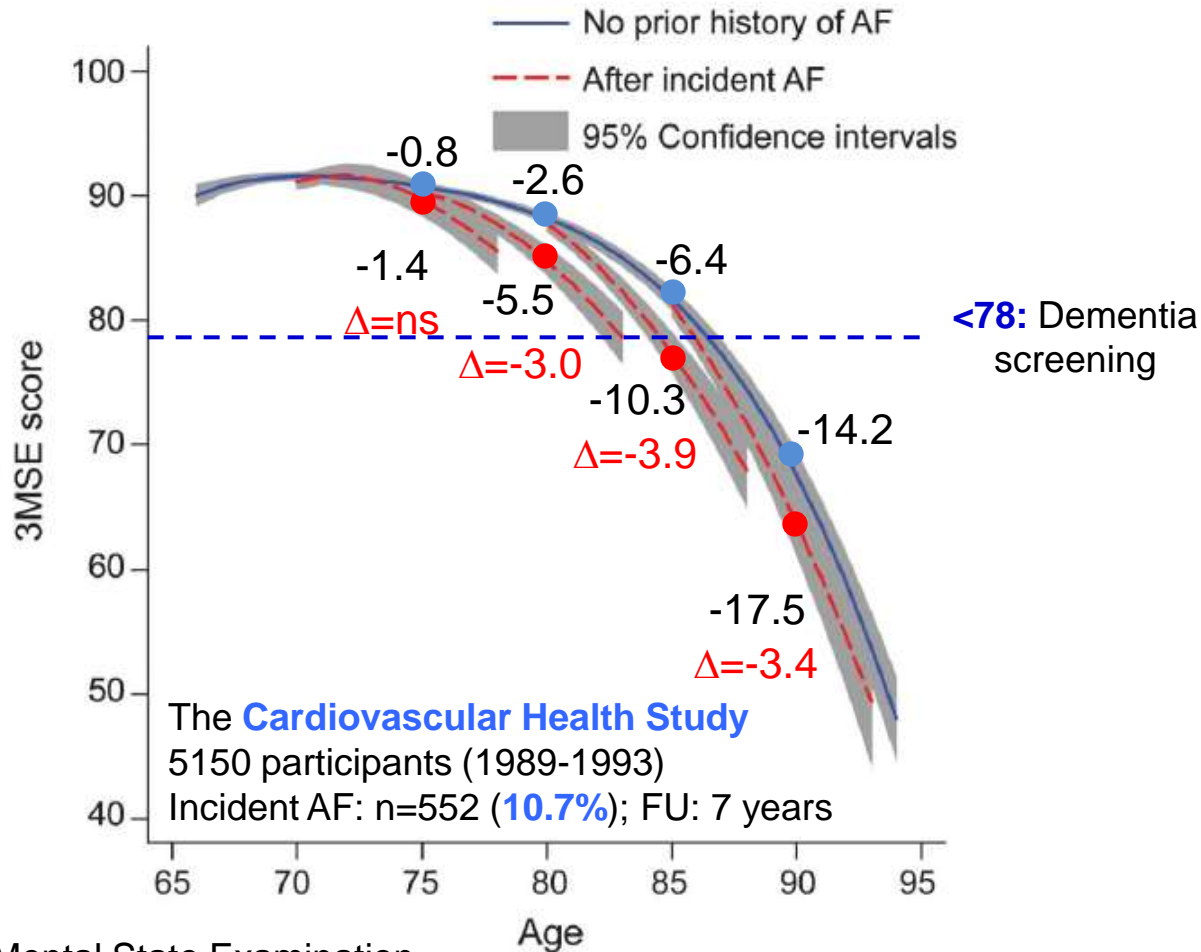
Stima calcolata dai dati delle 21 regioni del "Global Burden of Disease"



Atrial fibrillation and cognitive decline

A longitudinal cohort study

Model-predicted 3MSE score trajectories in CHS participants with and without incident AF (74.4 vs. 72.9 years)

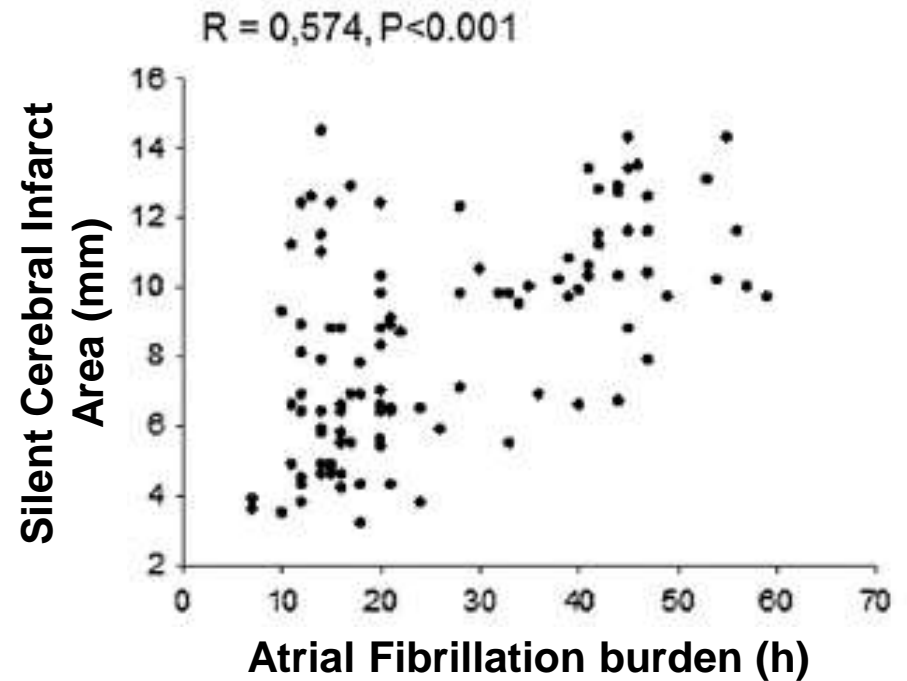
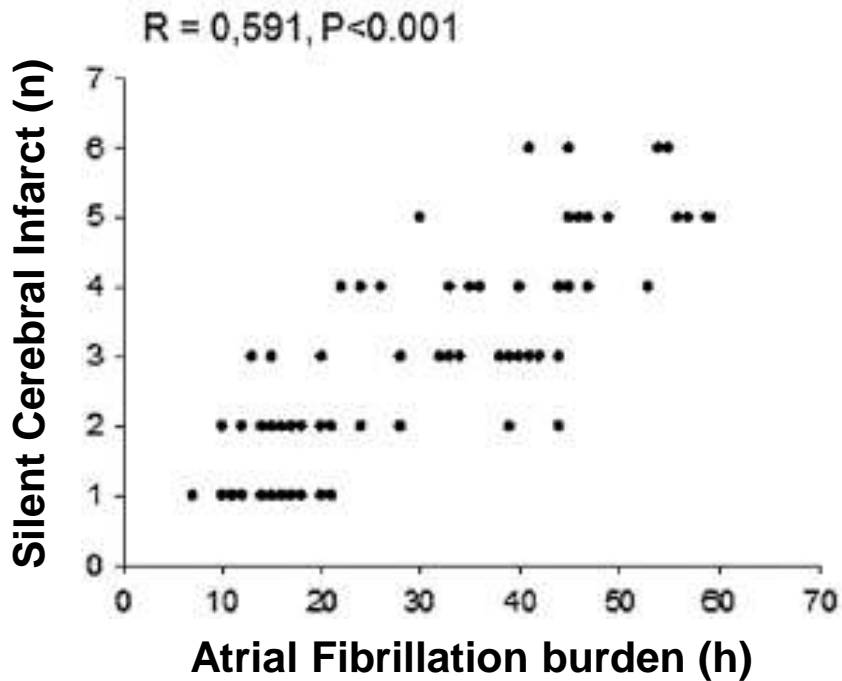


3MSE: Modified Mini-Mental State Examination - Scores range from 0 (worst) to 100 (best)

Brief Episodes of Silent Atrial Fibrillation Predict Clinical Vascular Brain Disease in Type 2 Diabetic Patients

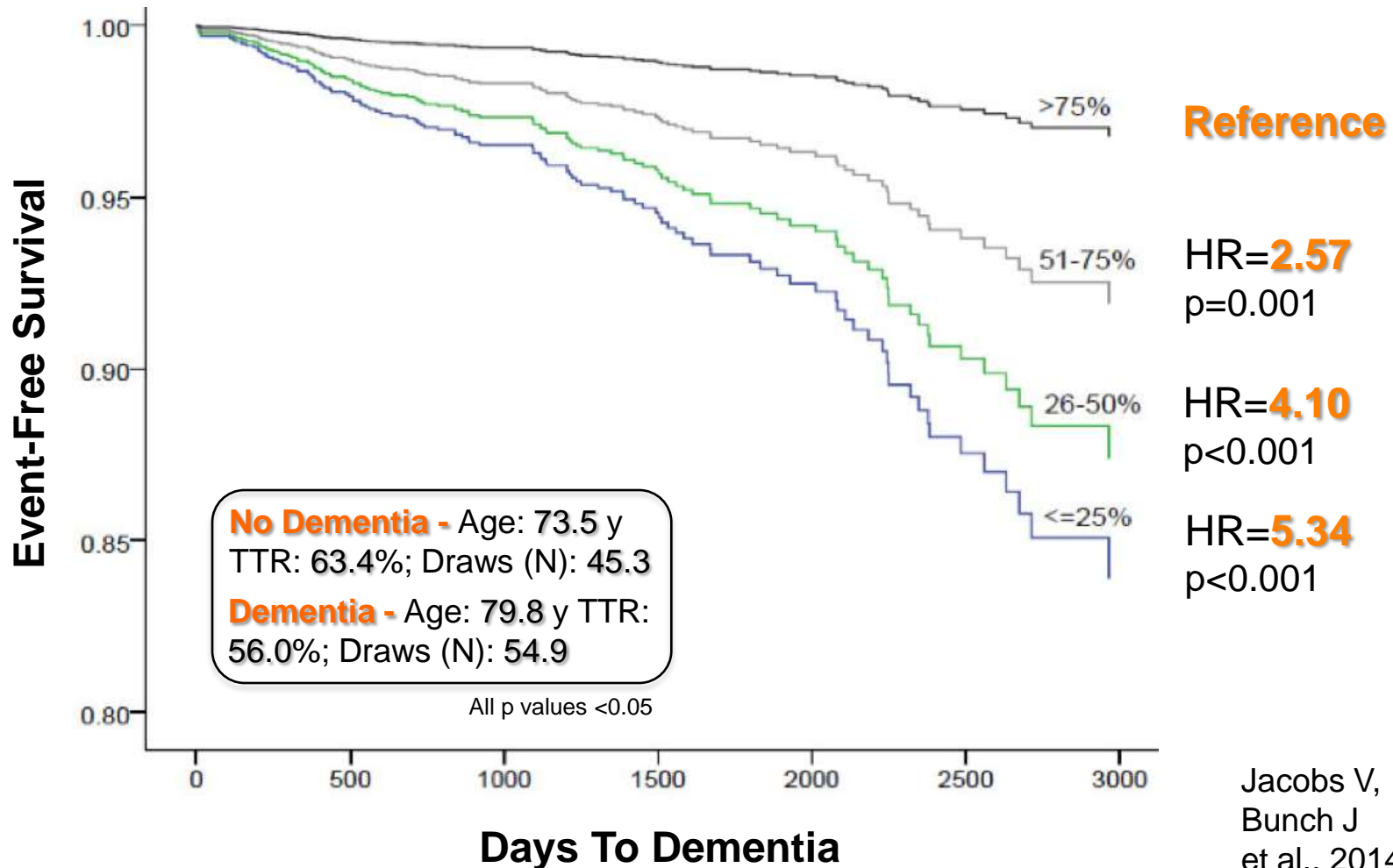


Relation Between silent cerebral infarct and episodes of atrial fibrillation



Time Outside of Therapeutic Range in Atrial Fibrillation Patients is Associated with Long-term Risk of Dementia

Event-free survival estimates for dementia incidence (4.2%) among categories of percent TTR (N=2605; median FU: 4 years)

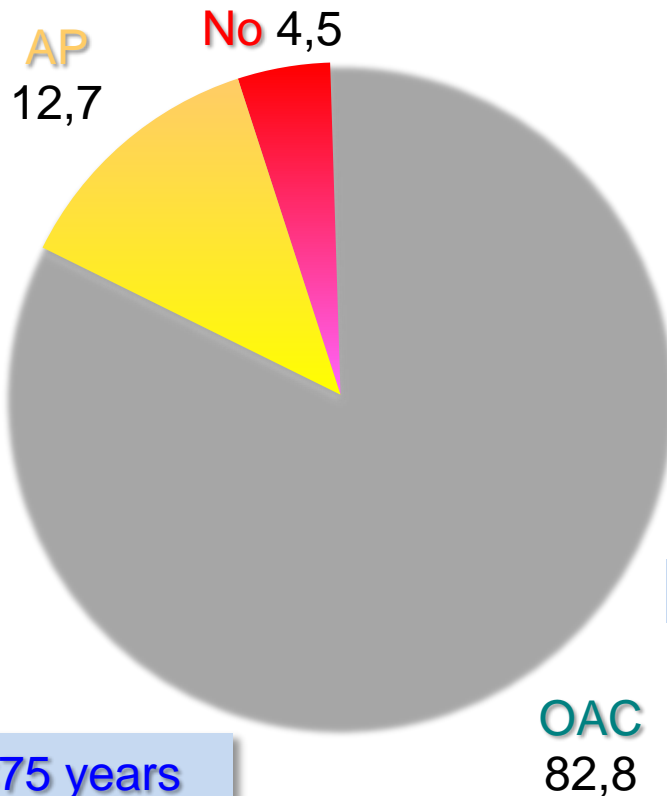


Jacobs V,
Bunch J
et al., 2014

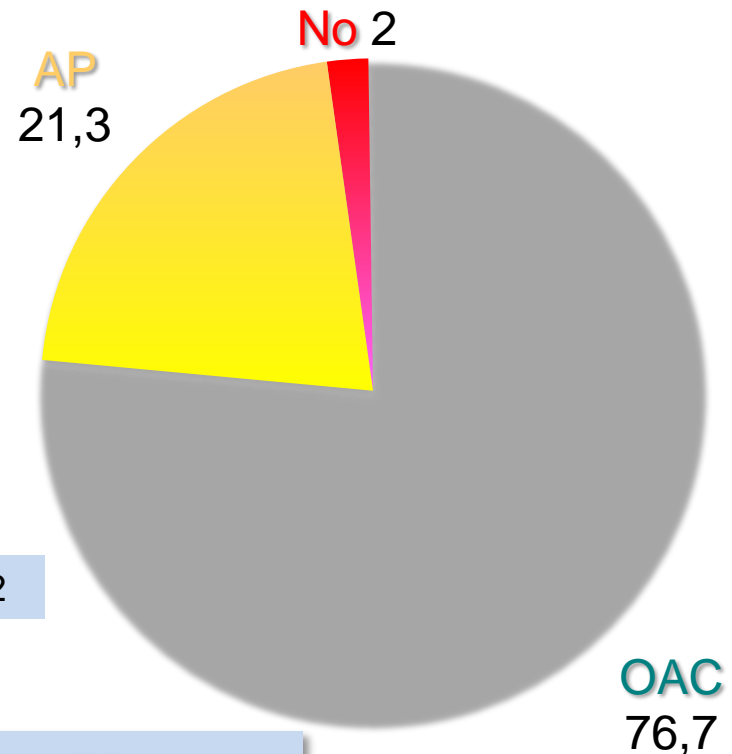


Age-Related Differences in Presentation, Treatment, and Outcome of Patients With Atrial Fibrillation in Europe: the EurObservational Research Programme – Atrial Fibrillation (EORP-AF) General Pilot Registry

Antithrombotic drugs at discharge by age-group



Age <75 years
N=2068



Age ≥75 years
N=1051

P=0.0012

Fumagalli S, Marchionni N,
Lip GYH (submitted)



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Le evidenze dei grandi trial

European Heart Rhythm Association Practical Guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation

Heidbuchel H,
2013



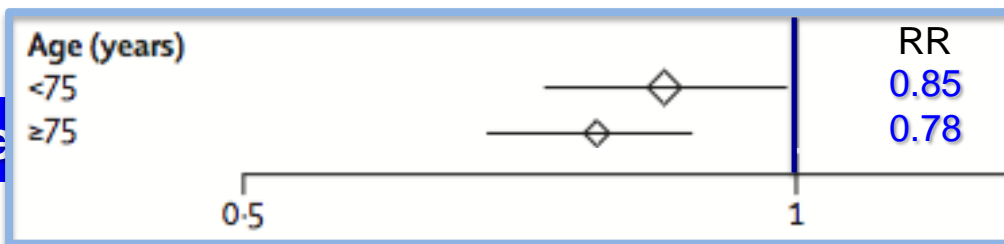
Assorbimento e metabolismo dei NAO

	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Biodisponibilità	3-7%	50%	62%	66% 100% pasti
Profarmaco	Si	No	No	No
Eliminazione renale	80%	27%	50%	35%
CYP3A4	No	Minore	Minima	Si
Interazione con cibo	No	No	+ 6-22%	+ 39%
Raccomandato ai pasti	No	No	/	Si
Anti-H2/PPI	- 12-30%	No	No	No
Emivita	12-17	12	9-11	5-9 Y 11-13 E

Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials

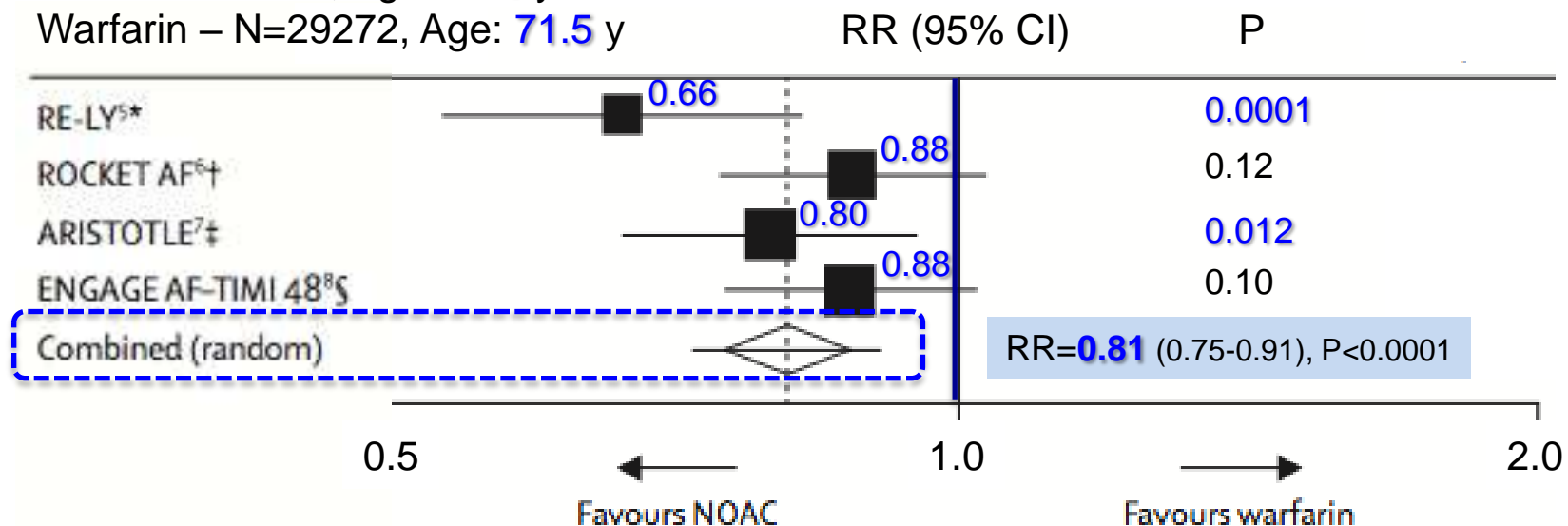
THE LANCET

Stroke or systemic embolism



NOA – N=42411, Age: 71.6 y

Warfarin – N=29272, Age: 71.5 y



Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials

THE LANCET

Secondary efficacy and safety

Efficacy

Ischaemic stroke

Haemorrhagic stroke

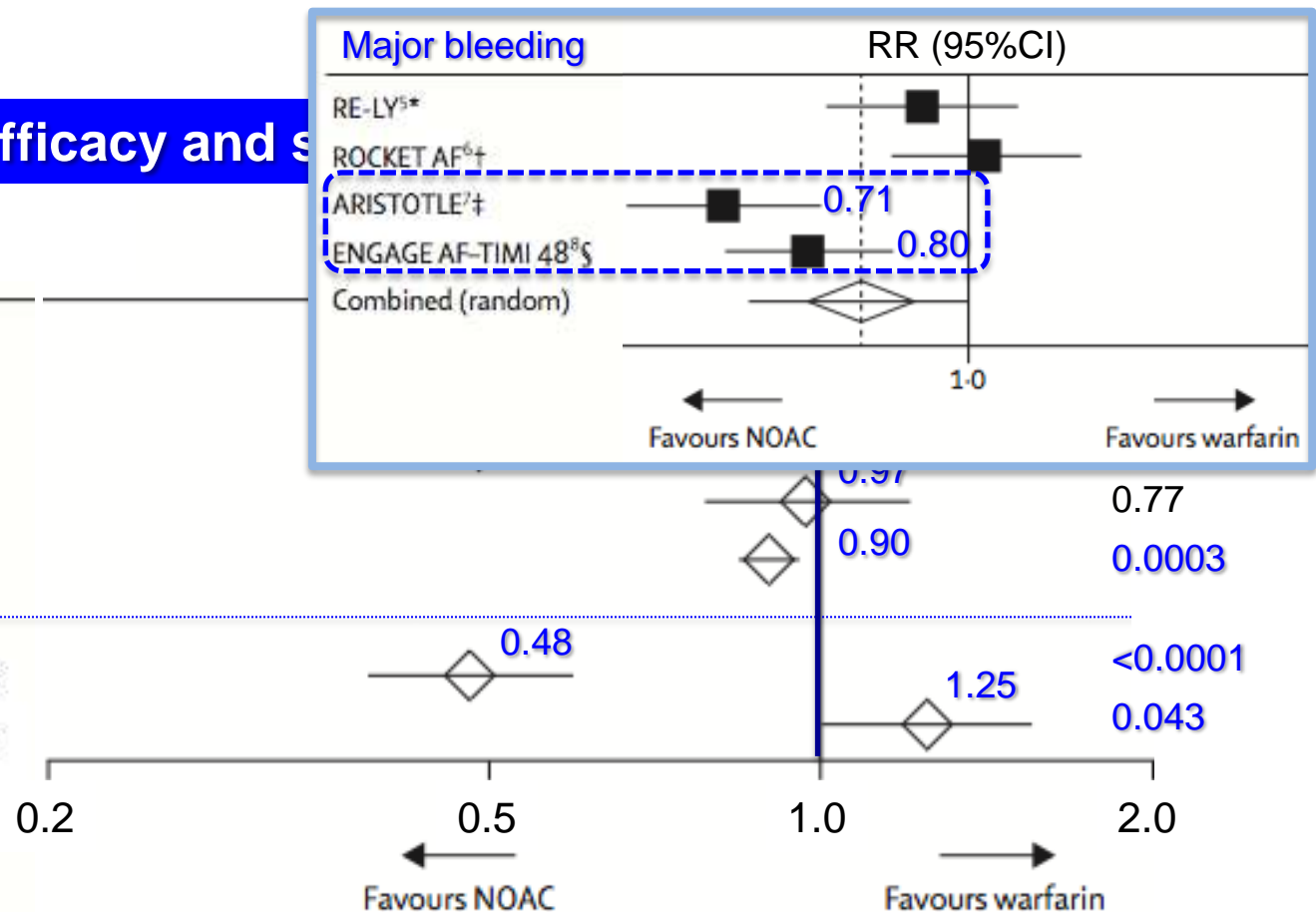
Myocardial infarction

All-cause mortality

Safety

Intracranial haemorrhage

Gastrointestinal bleeding





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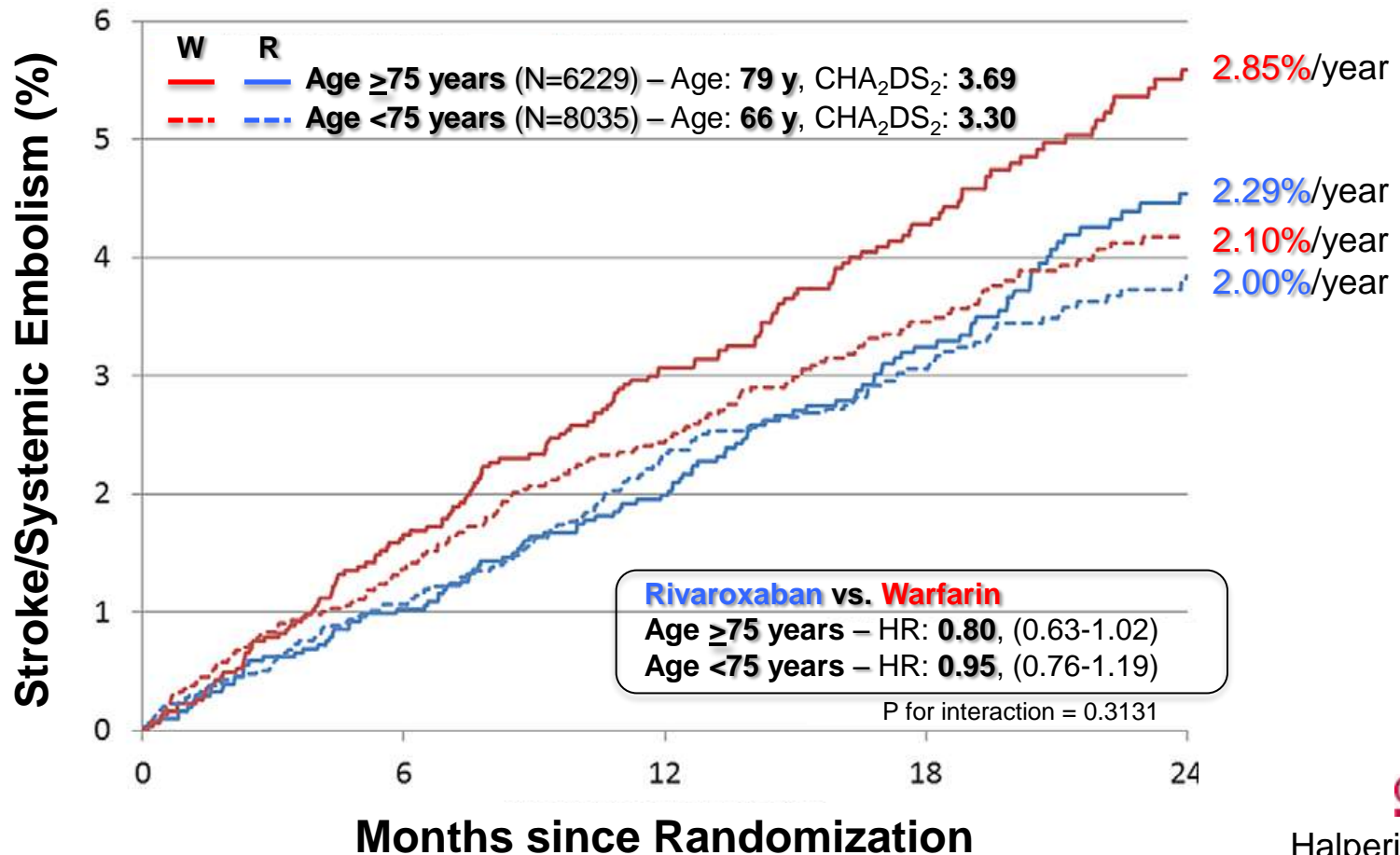
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Le evidenze dei grandi trial
in pazienti di età avanzata

Efficacy and Safety of Rivaroxaban Compared With Warfarin Among Elderly Patients With Nonvalvular Atrial Fibrillation in the Rivaroxaban Once Daily, Oral, Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF)

Cumulative proportion of patients experiencing primary end points over 24 months by age-group



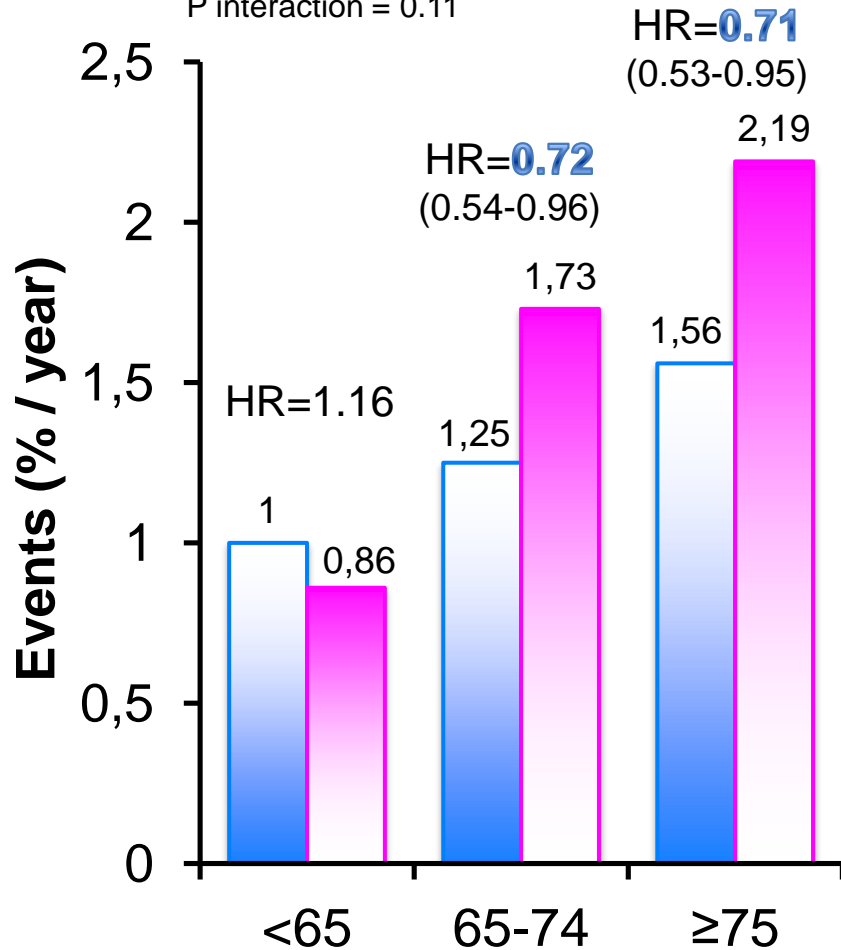
Efficacy and safety of apixaban compared with warfarin according to age for stroke prevention in atrial fibrillation: observations from the ARISTOTLE trial



The effect of apixaban vs. warfarin according to age (1)

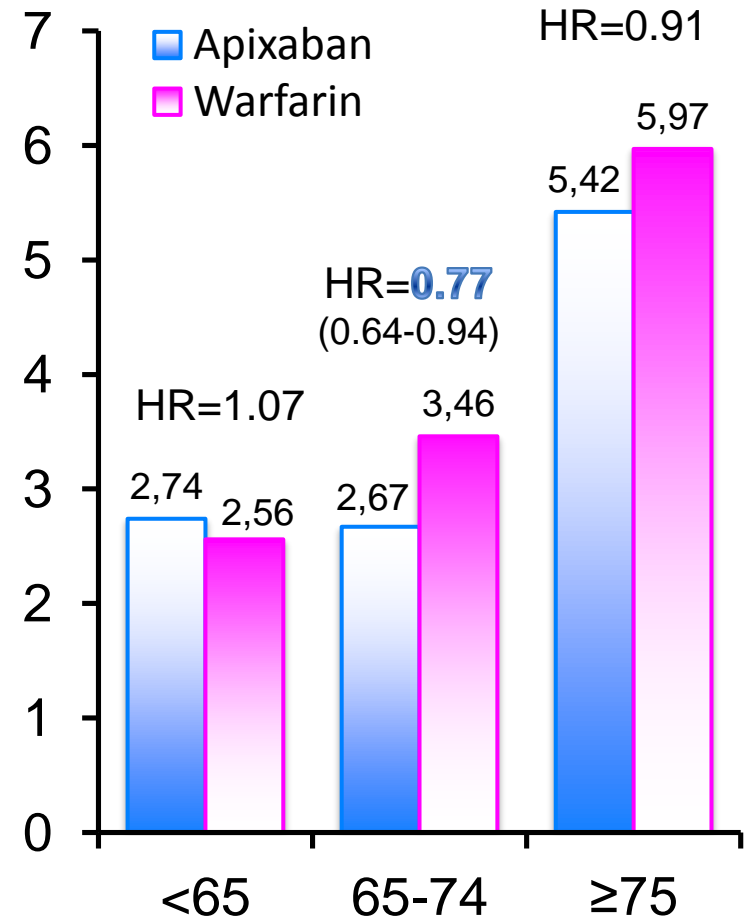
Stroke / Systemic embolism

P interaction = 0.11



All-cause mortality

P interaction = 0.43



<65 – N=5471; 65-74 – N=7052; ≥75 – N=5678

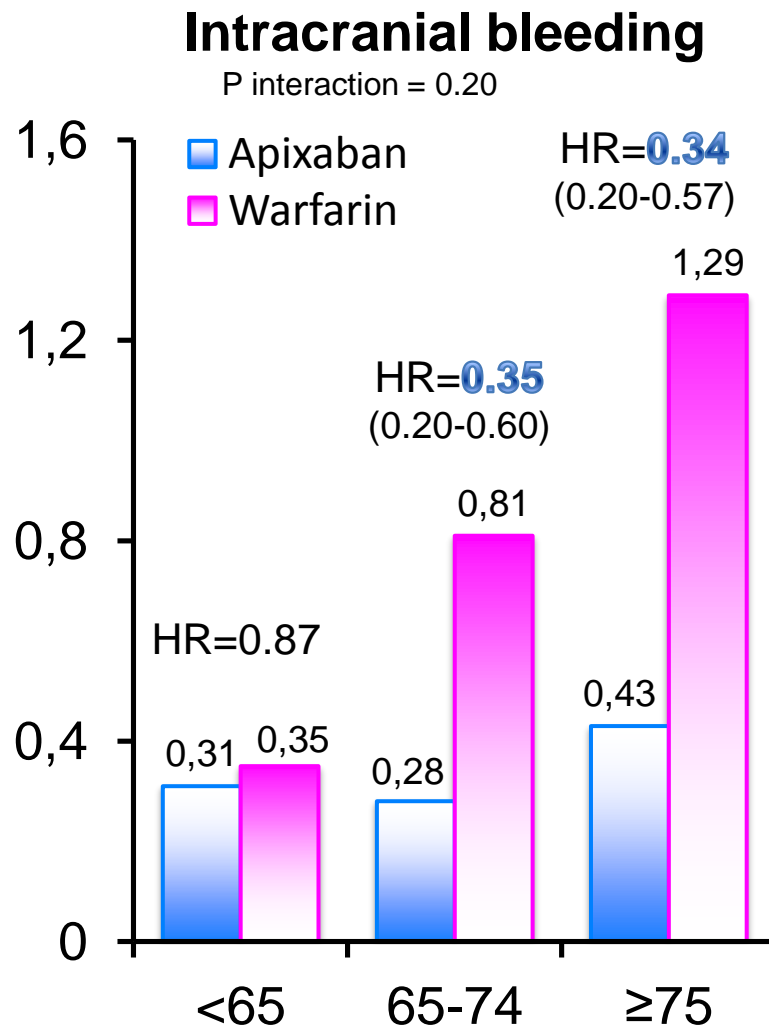
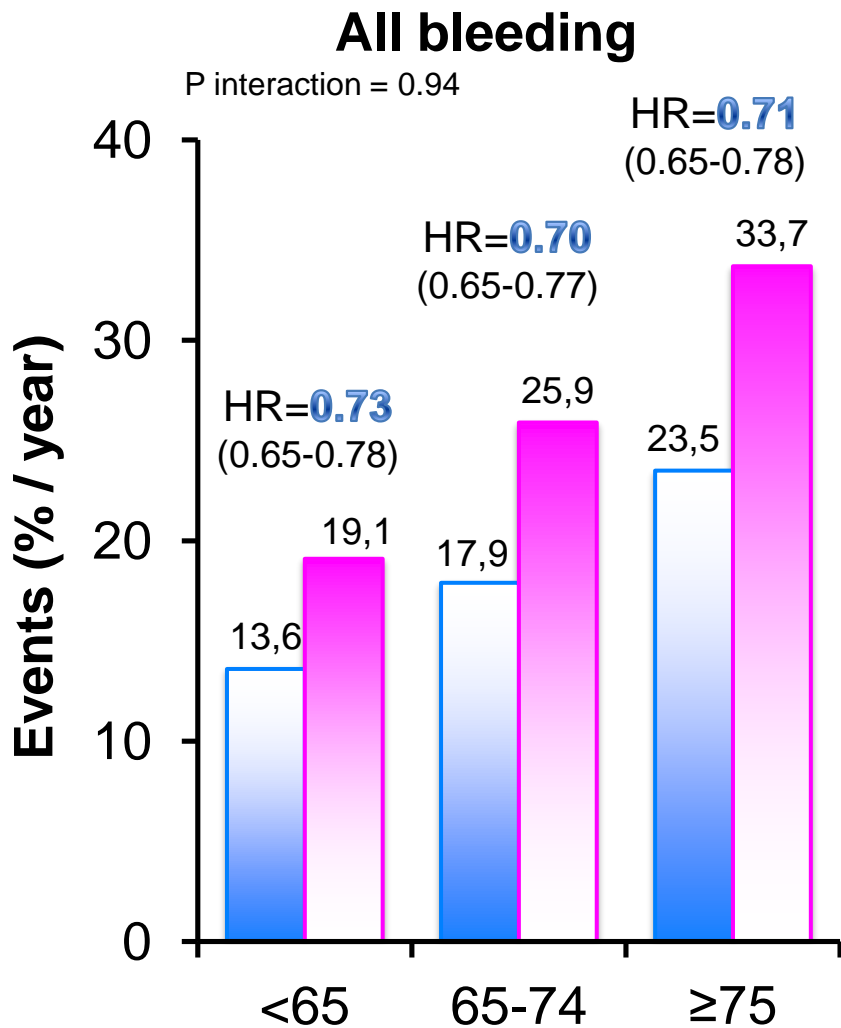
Age-groups (years)

Halvorsen S, 2014

Efficacy and safety of apixaban compared with warfarin according to age for stroke prevention in atrial fibrillation: observations from the ARISTOTLE trial



The effect of apixaban vs. warfarin according to age (2)



<65 – N=5471; 65-74 – N=7052; ≥75 – N=5678

Age-groups (years)

Halvorsen S,

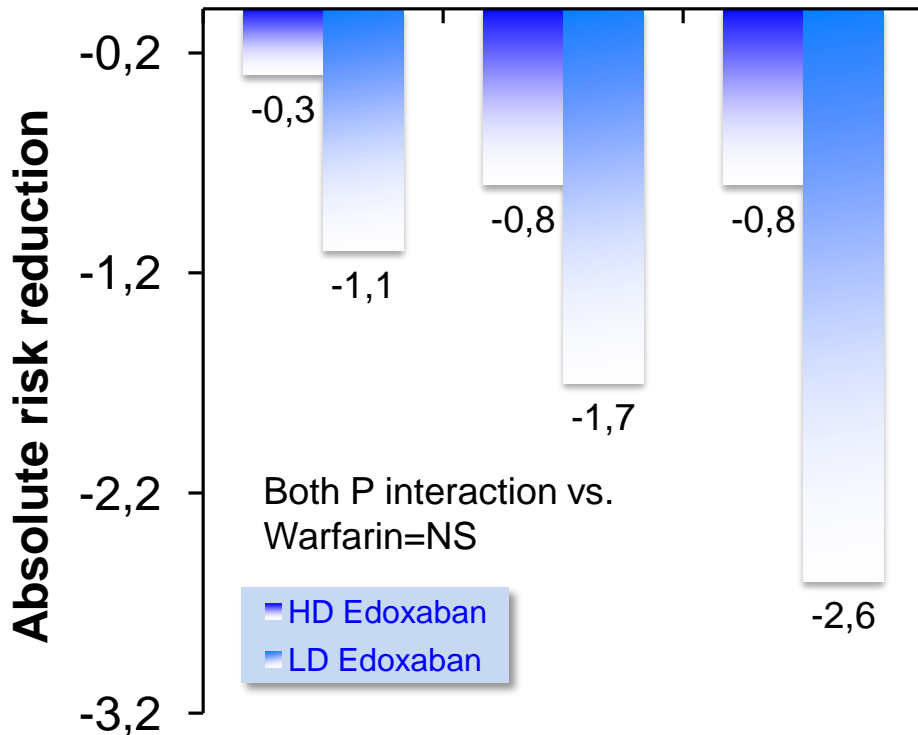
Efficacy and Safety of Edoxaban for the Management of Elderly Patients With Atrial Fibrillation: Engage AF-TIMI 48

Session Treatment of Arrhythmias: Pharmacological---Novel Anticoagulants

ISTH major bleeding

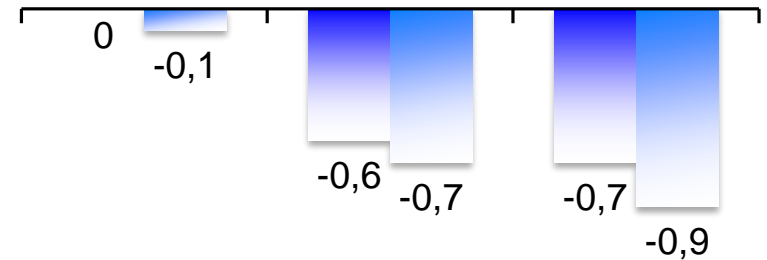
Warfarin
rate (%/y)

1.8 <65
3.3 65-74
4.8 >74



Intracranial hemorrhage

0.3 <65
0.9 65-74
1.2 >74

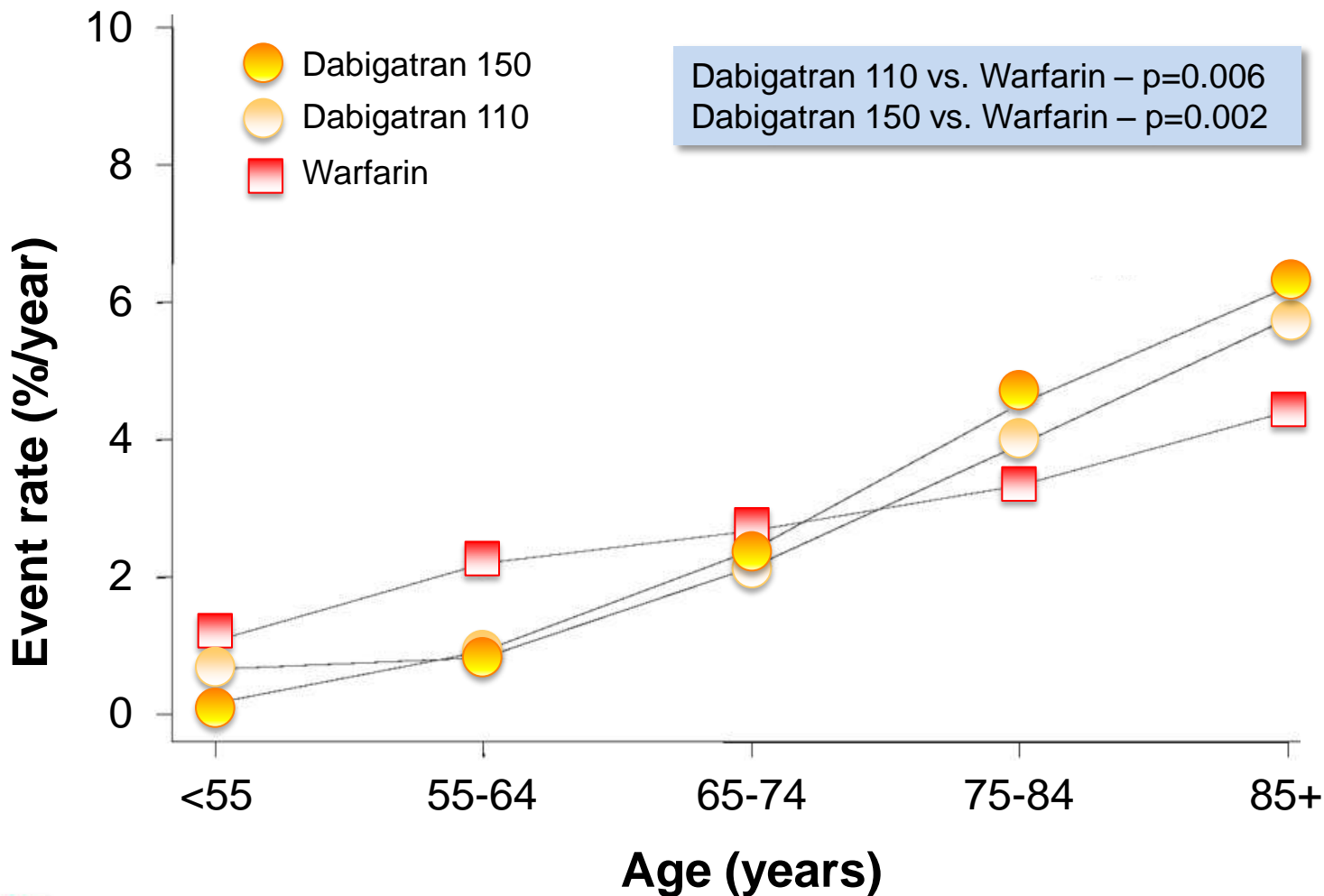


Both P interaction vs. Warfarin=NS

<65 years – N=5497
65-74 years – N=7134
>74 years – N=8474

Risk of Bleeding With 2 Doses of Dabigatran Compared With Warfarin in Older and Younger Patients With Atrial Fibrillation

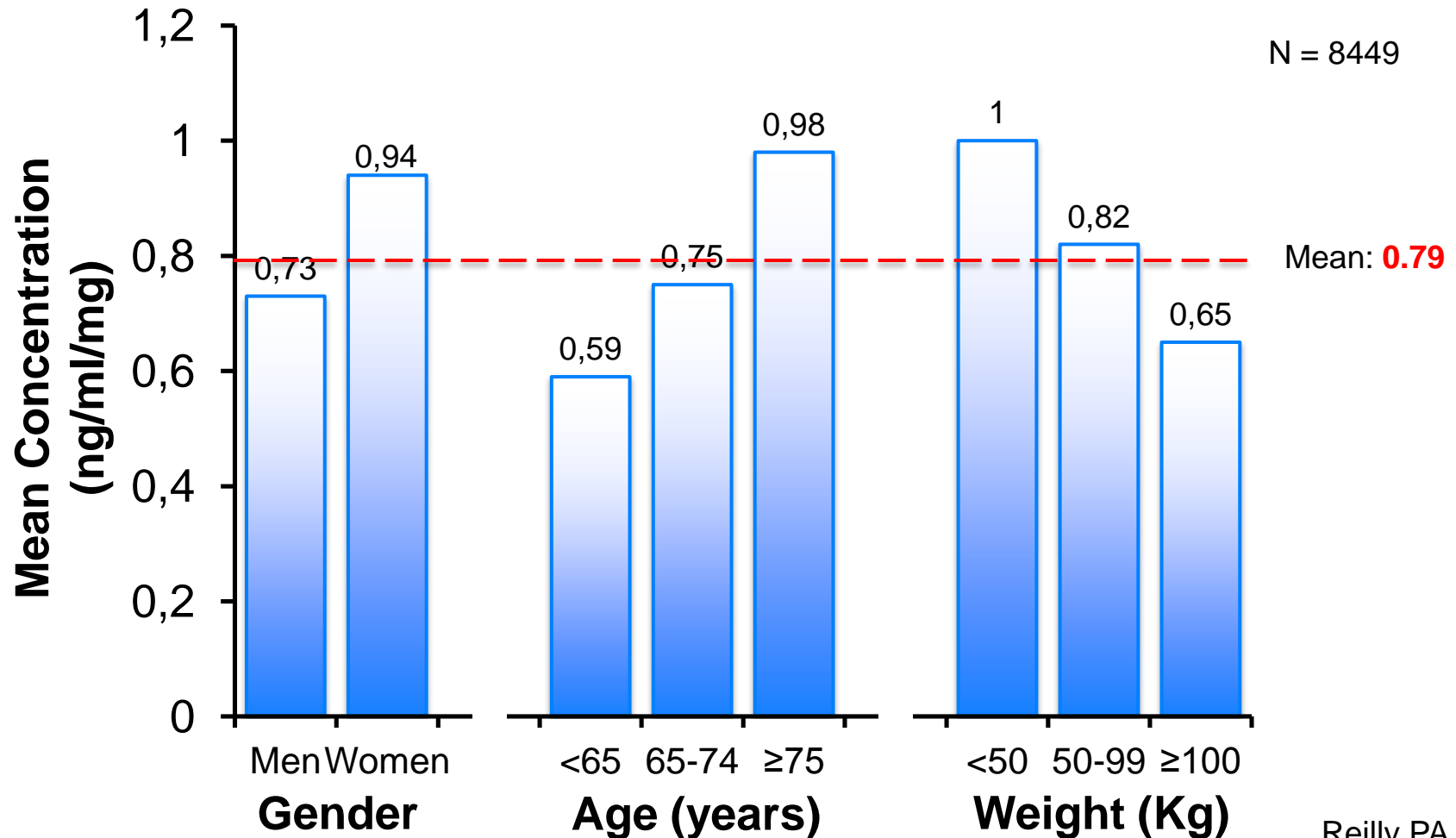
RELY – Extracranial Major Bleeding Rate, by Age-Group



The Effect of Dabigatran Plasma Concentrations and Patient Characteristics on the Frequency of Ischemic Stroke and Major Bleeding in Atrial Fibrillation Patients



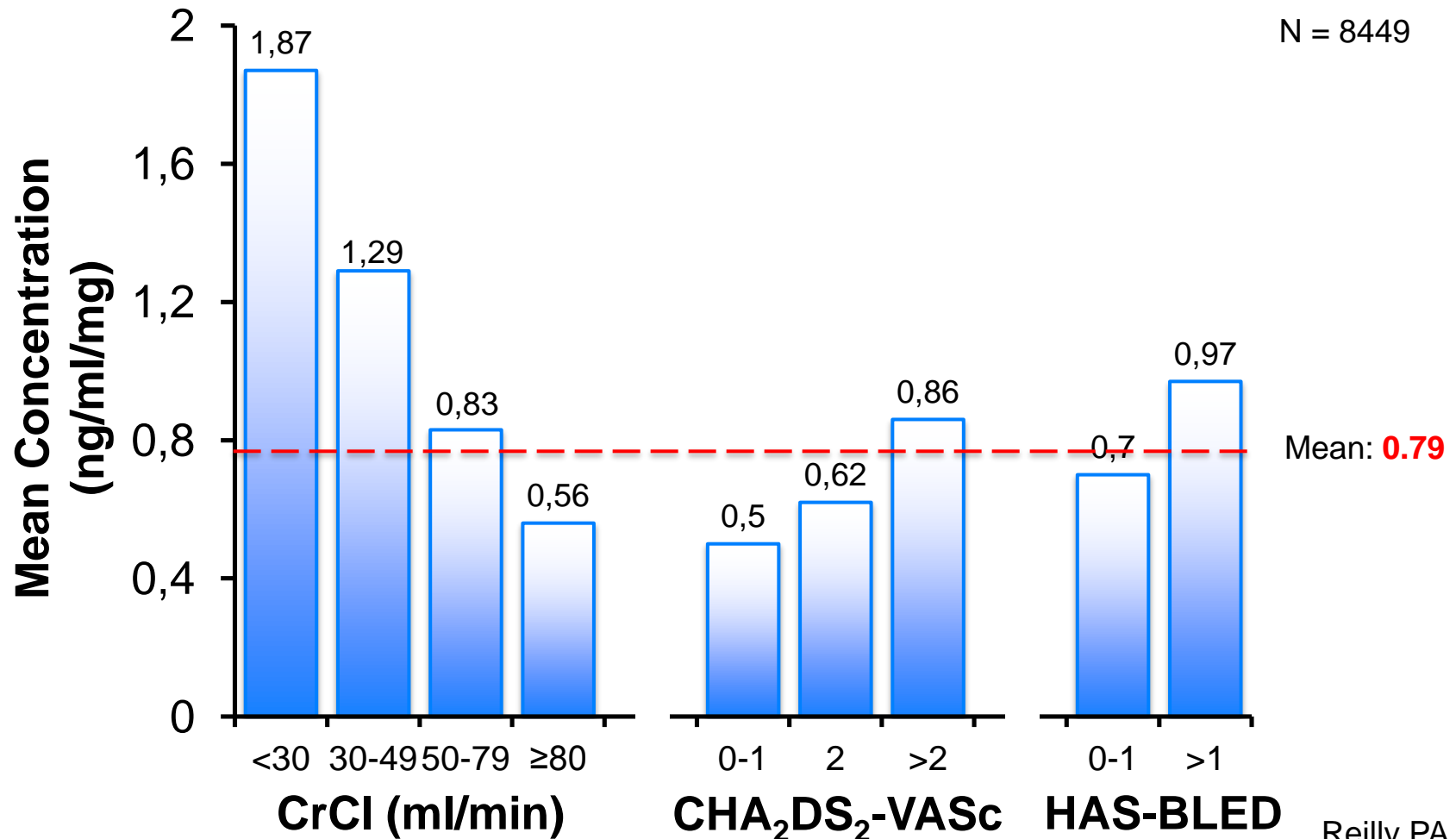
Dose-Normalized Plasma Through Concentrations of Dabigatran by Demographic Characteristics in the RE-LY Trial (1)



The Effect of Dabigatran Plasma Concentrations and Patient Characteristics on the Frequency of Ischemic Stroke and Major Bleeding in Atrial Fibrillation Patients

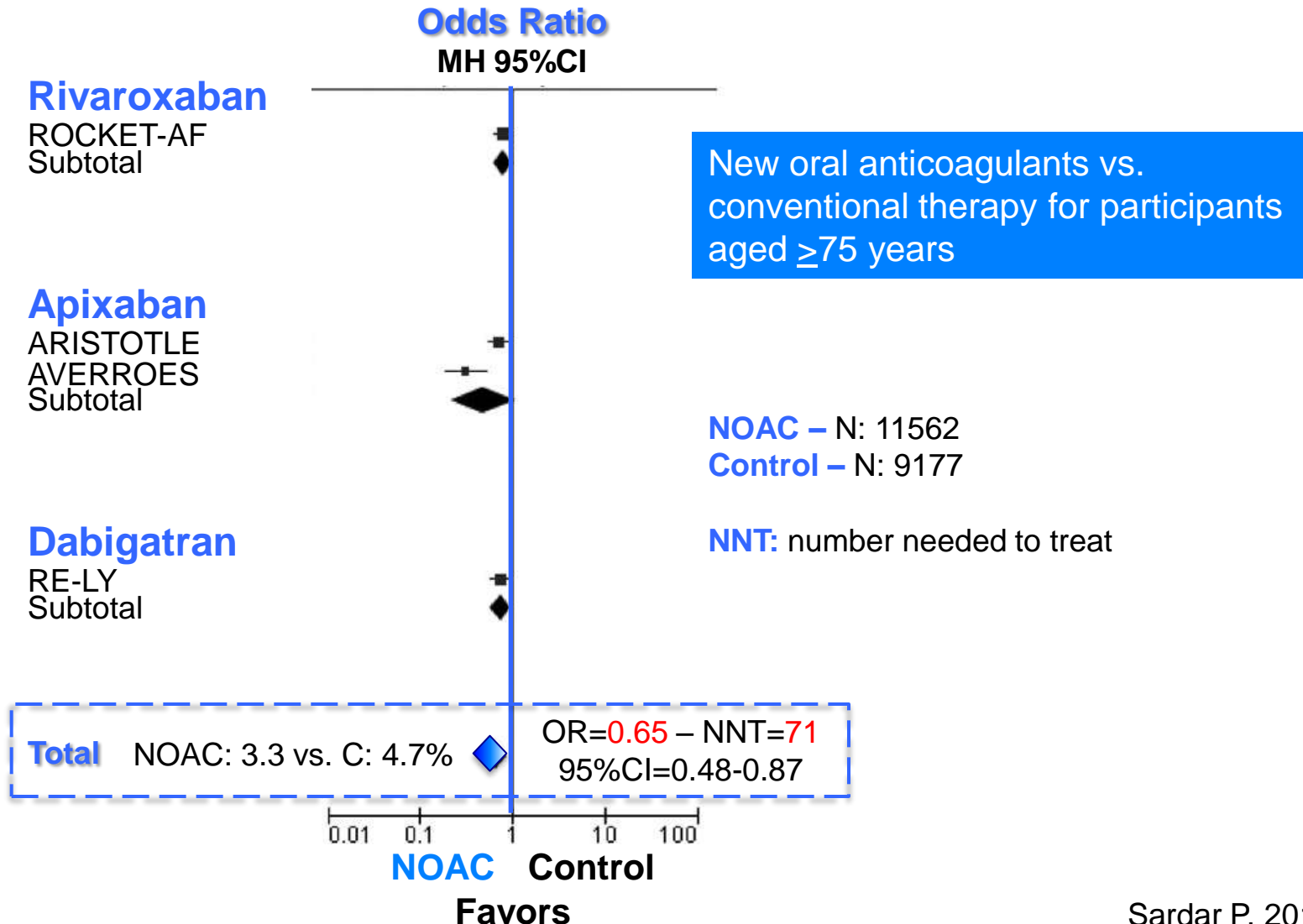


Dose-Normalized Plasma Through Concentrations of Dabigatran by Demographic Characteristics in the RE-LY Trial (2)



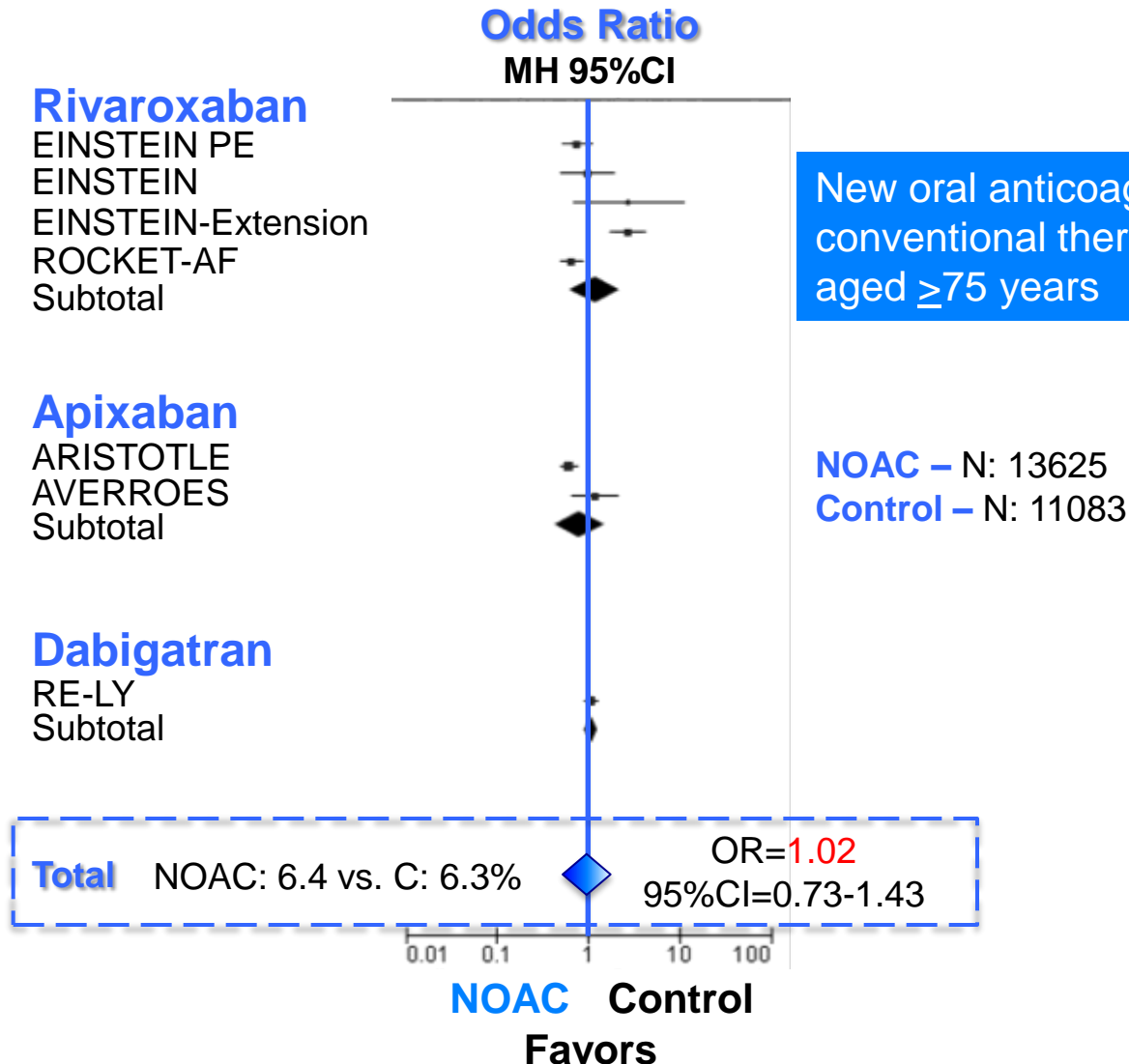
New Oral Anticoagulants in Elderly Adults: Evidence from a Meta-Analysis of Randomized Trials

Patients aged more than 75 years: Stroke or systemic embolism



New Oral Anticoagulants in Elderly Adults: Evidence from a Meta-Analysis of Randomized Trials

Patients aged more than 75 years: Major or clinically relevant bleeding





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Alcune situazioni particolari ...

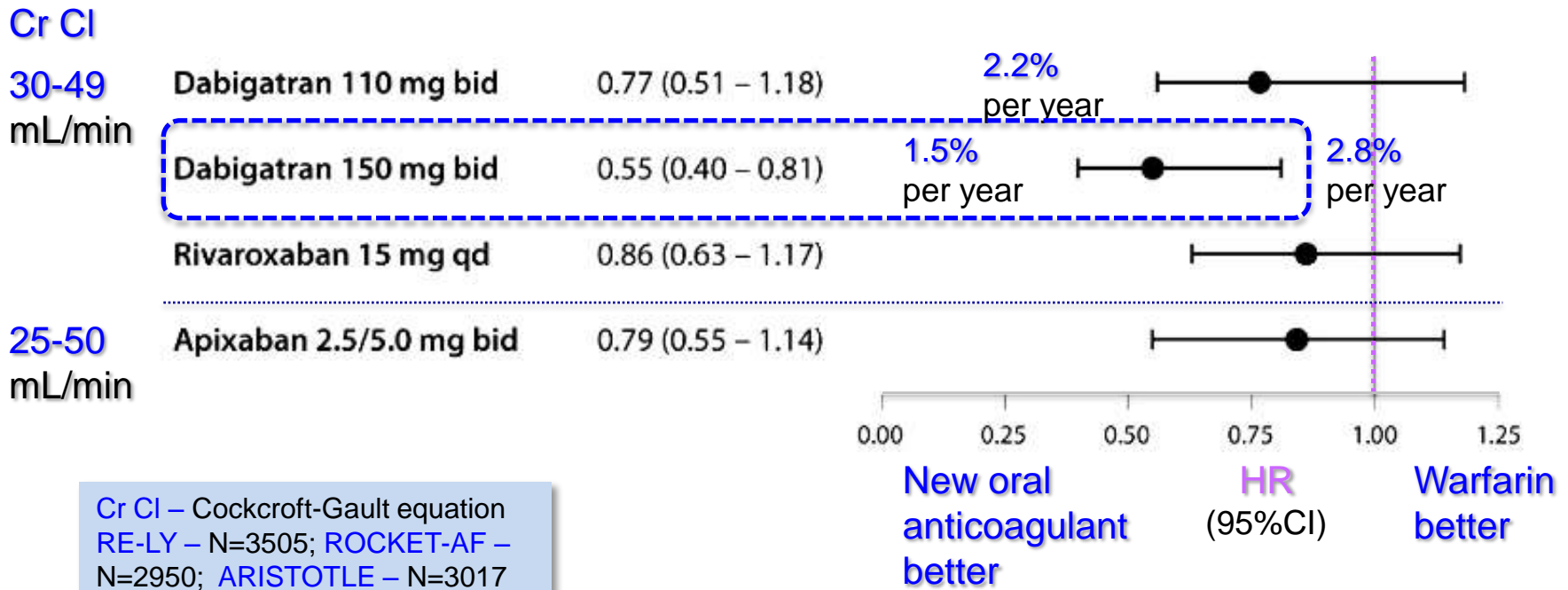


Review

Stroke Prevention in Atrial Fibrillation Patients With Chronic Kidney Disease



HRs for patients with stage III CKD from randomized trials comparing NOAs with warfarin for stroke and systemic embolism



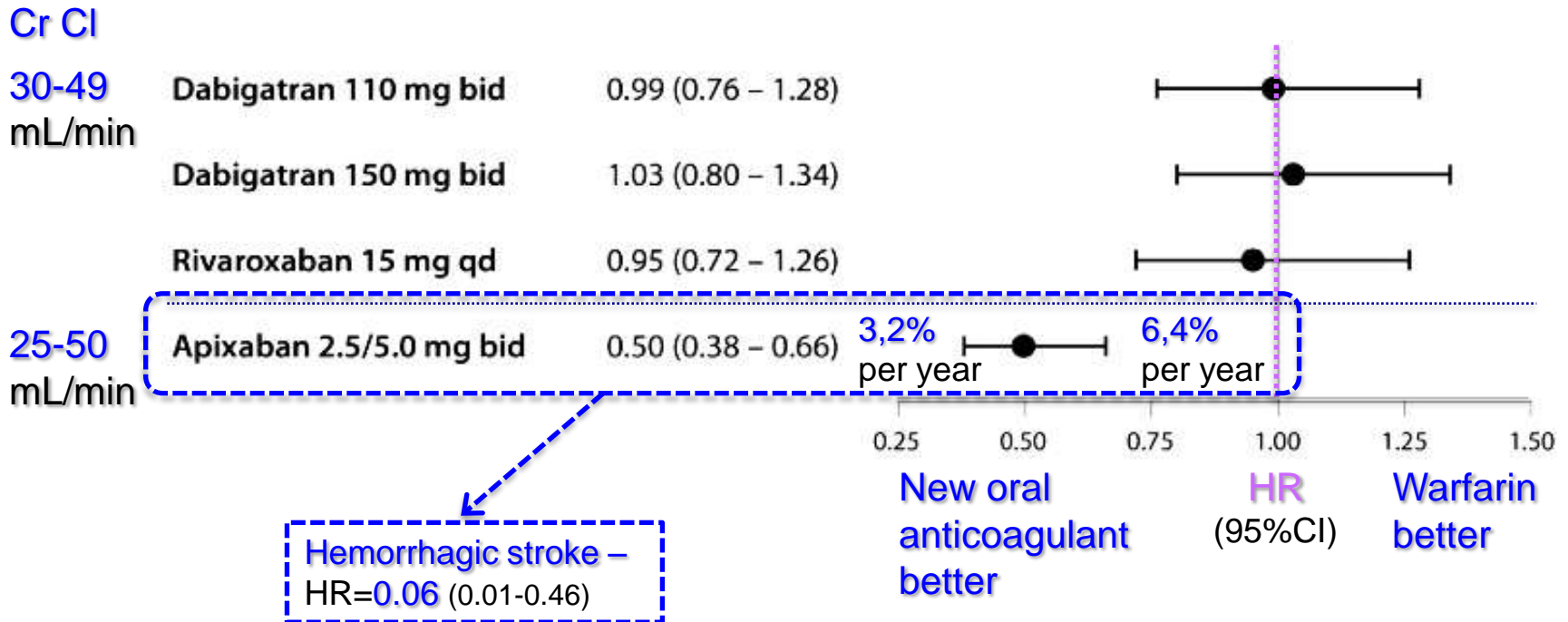


Review

Stroke Prevention in Atrial Fibrillation Patients With Chronic Kidney Disease

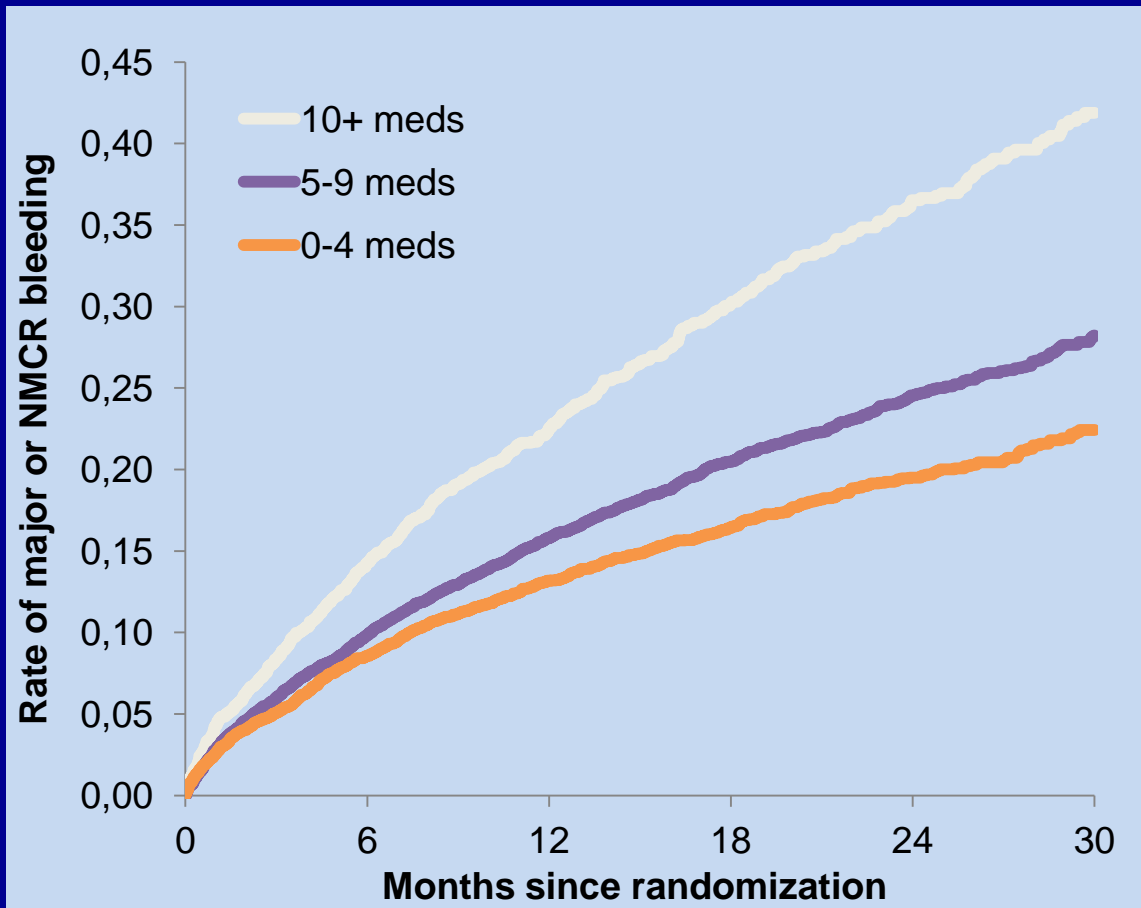


HRs for patients with stage III CKD from randomized trials comparing NOAs with warfarin for major bleeding



Polypharmacy and the Efficacy and Safety of Rivaroxaban versus Warfarin in the Prevention of Stroke

Cumulative Incidence of Major or NMCR Bleeding According to #Medications



Piccini JP, 2014



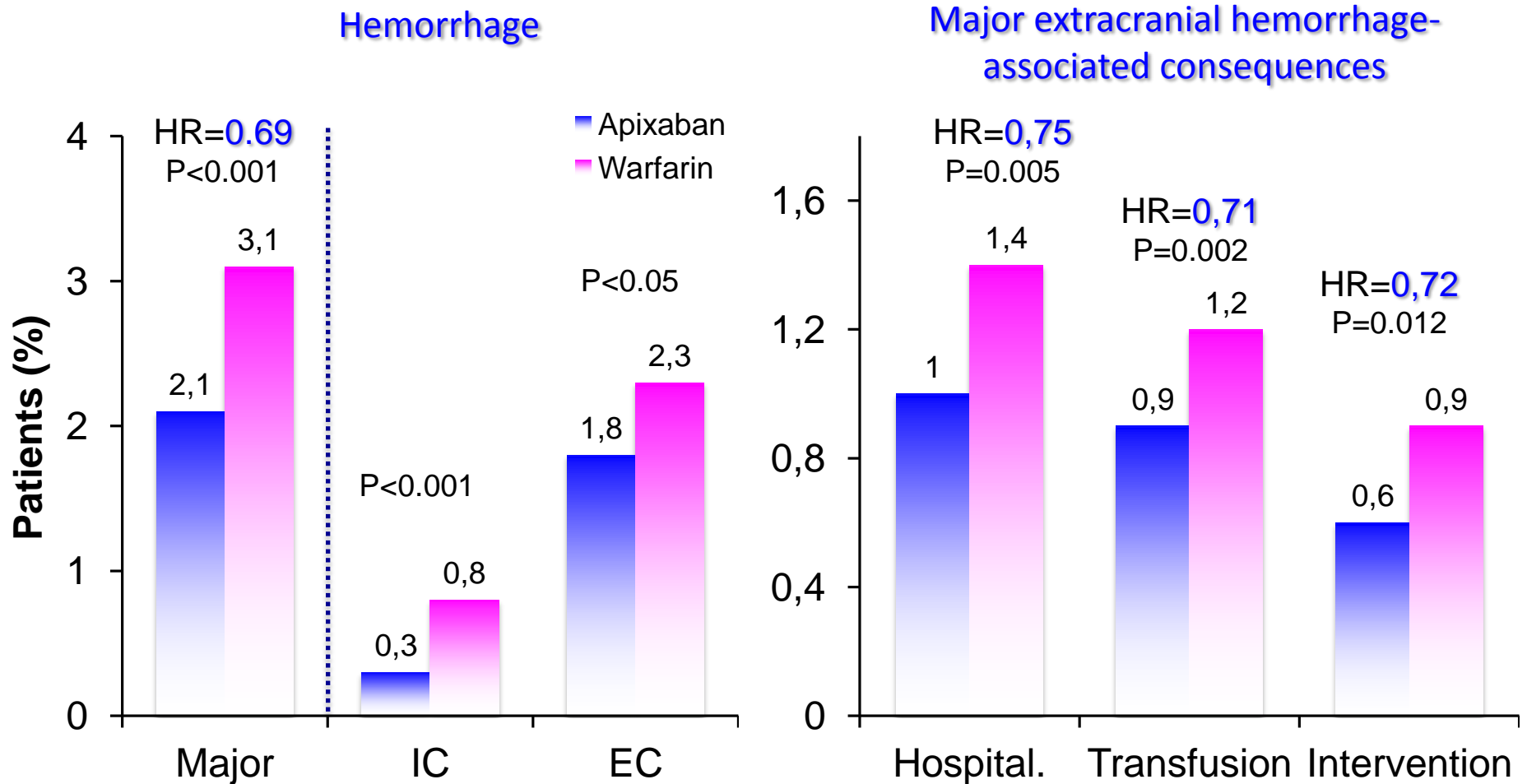
Major Bleeding in Patients With Atrial Fibrillation Receiving Apixaban or Warfarin

Hylek EM, 2014



The ARISTOTLE Trial (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation): Predictors, Characteristics, and Clinical Outcomes

Characteristics of Hemorrhage by Treatment (Age – Yes: 74 vs. No: 70 years)



IC / EC: Intracranial / Extracranial

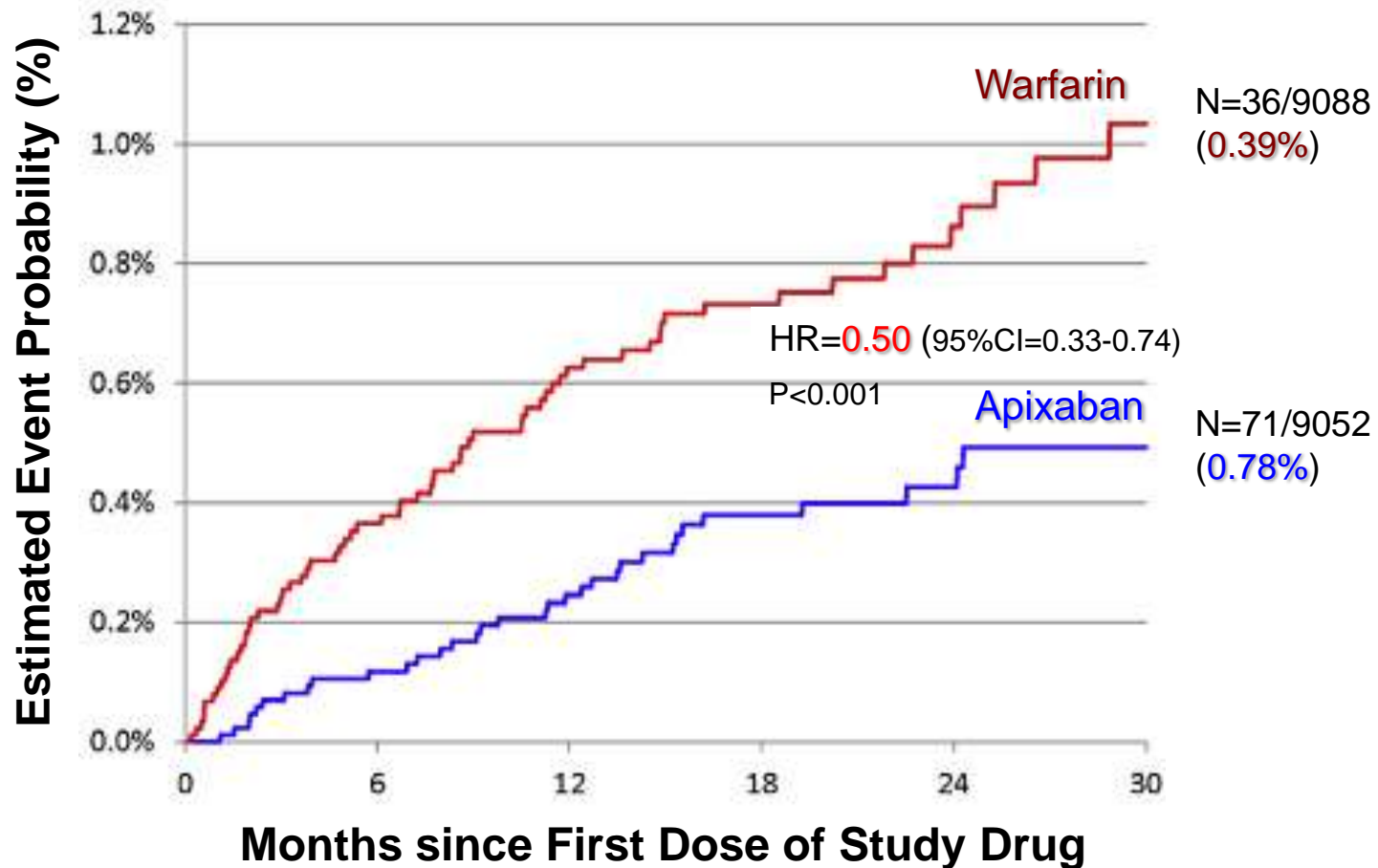
Hospital: Hospitalization; Intevntion: Medical / Surgical intervention

Major Bleeding in Patients With Atrial Fibrillation Receiving Apixaban or Warfarin



The ARISTOTLE Trial (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation): Predictors, Characteristics, and Clinical Outcomes

Major Bleeding Following by Death Within 30 Days (median follow-up time: 20.5 months)

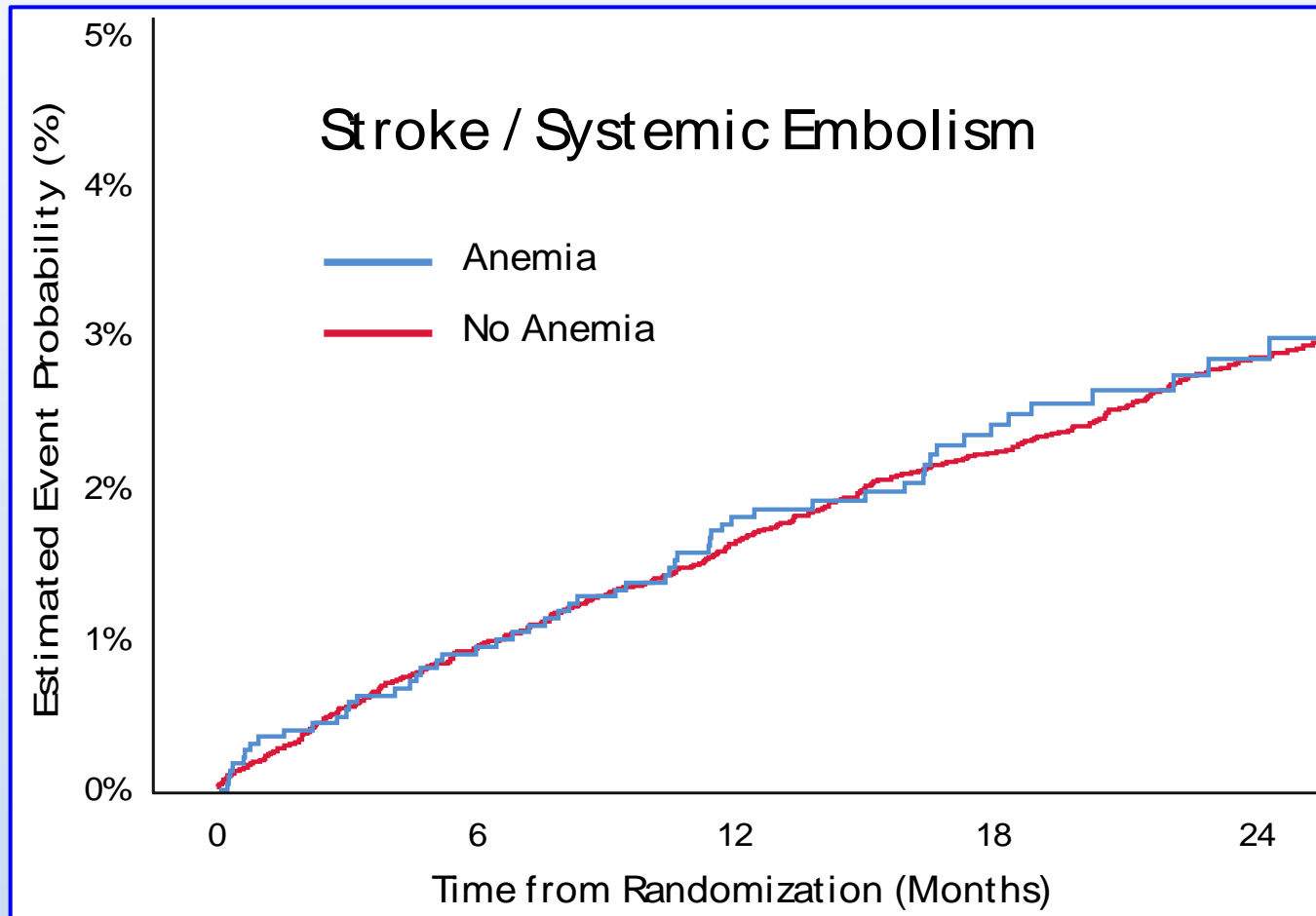


Anemia Predicts Bleeding and Mortality, But Not Stroke, in Patients with Atrial Fibrillation: Insights from ARISTOTLE

Westenbrink BD,
2014



Incidence of stroke and systemic embolism by presence of anemia

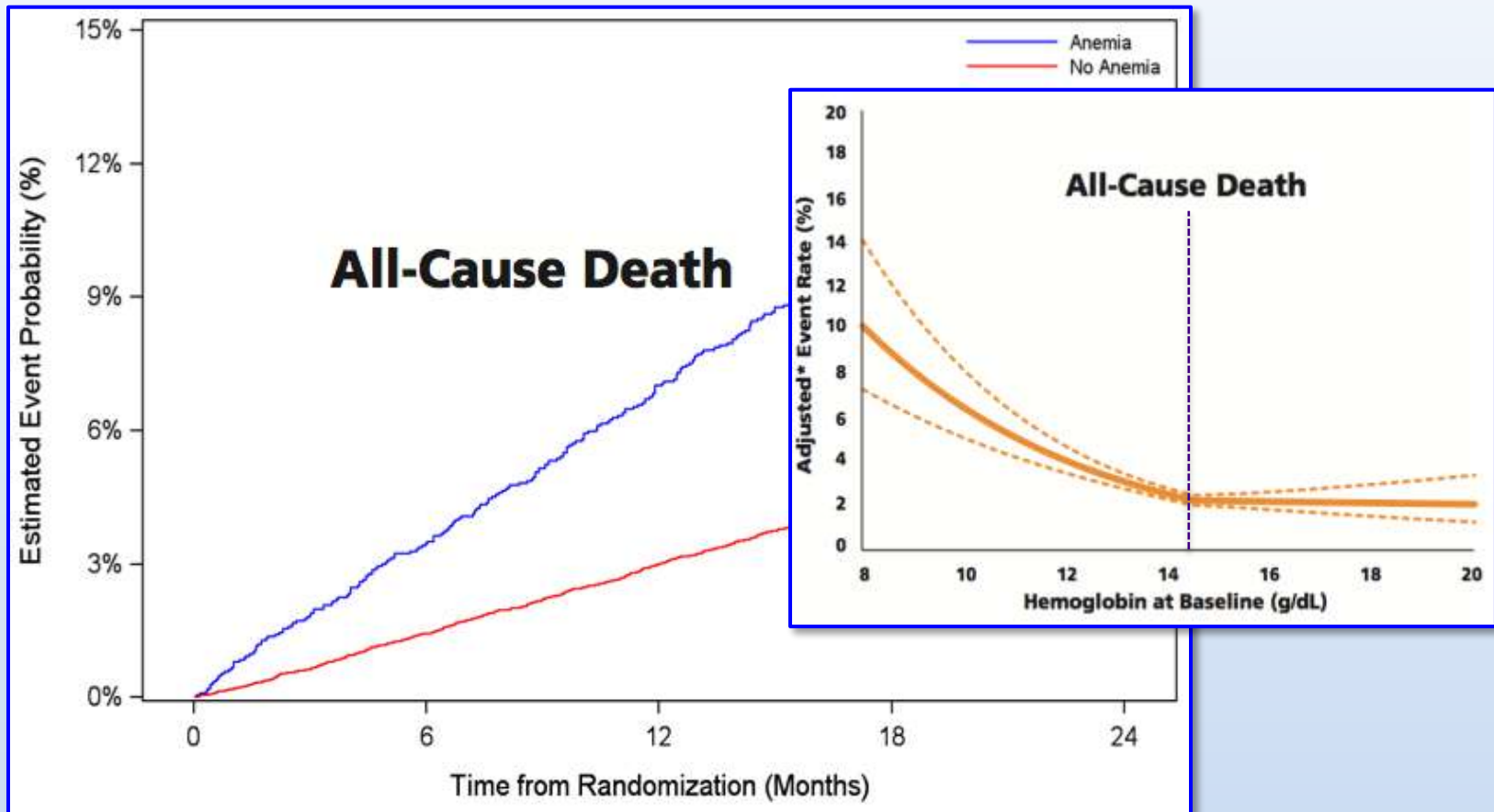


Anemia Predicts Bleeding and Mortality, But Not Stroke, in Patients with Atrial Fibrillation: Insights from ARISTOTLE

Westenbrink BD,
2014



All-cause mortality by presence of anemia

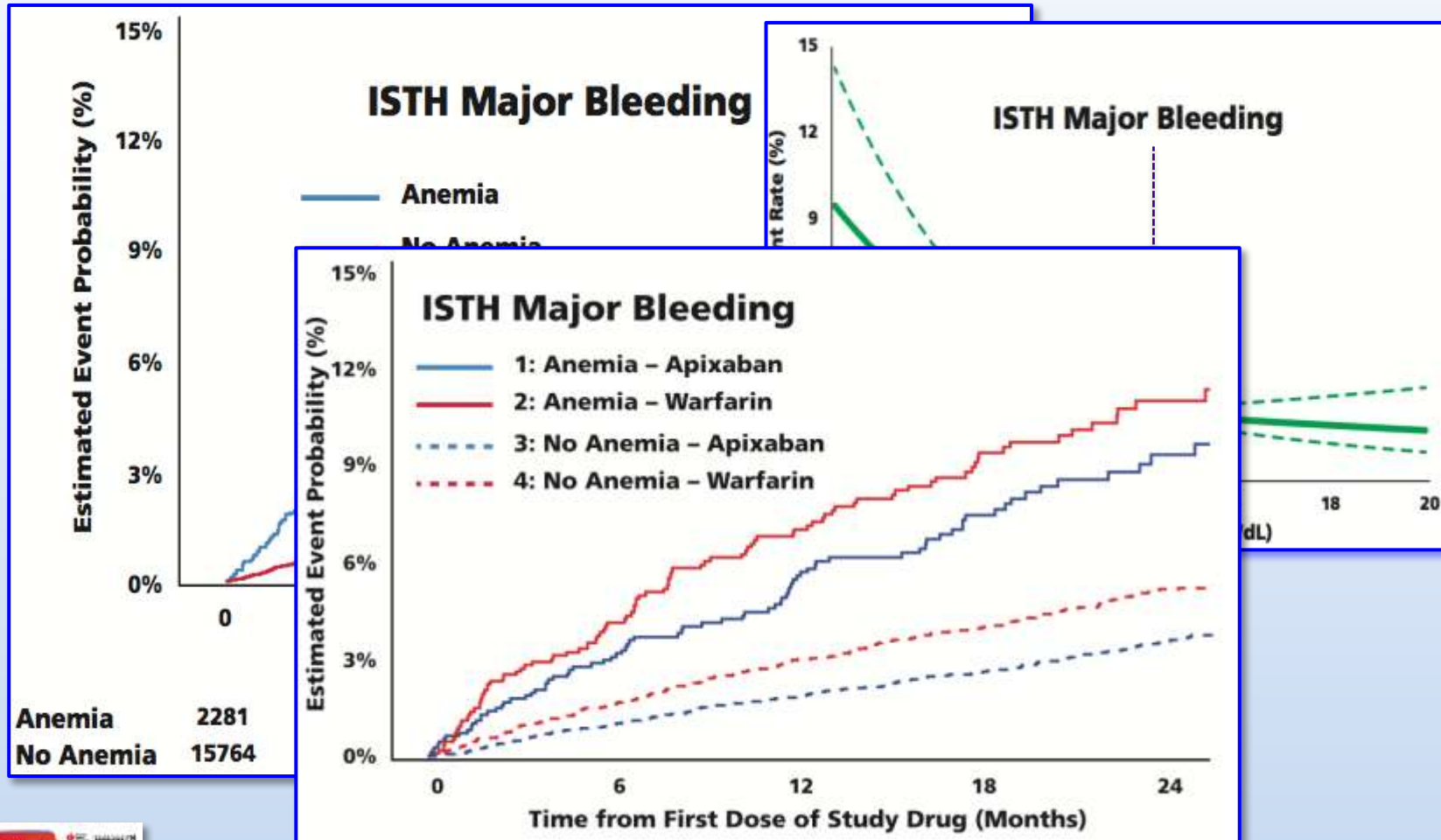


Anemia Predicts Bleeding and Mortality, But Not Stroke, in Patients with Atrial Fibrillation: Insights from ARISTOTLE

Westenbrink BD, 2014



Incidence of ISTH major bleeding by presence of anemia





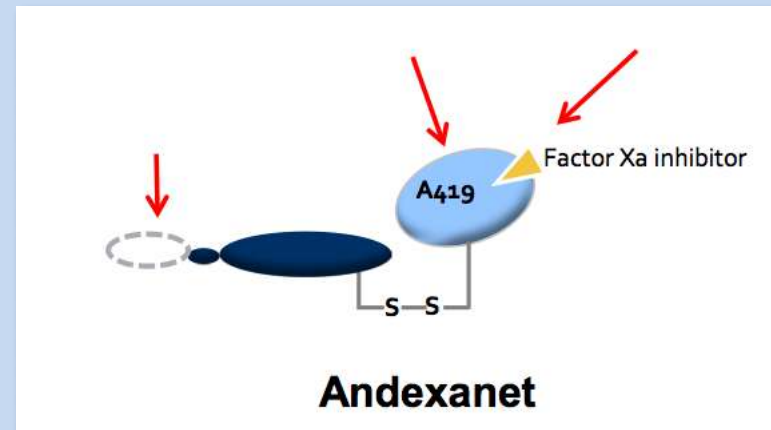
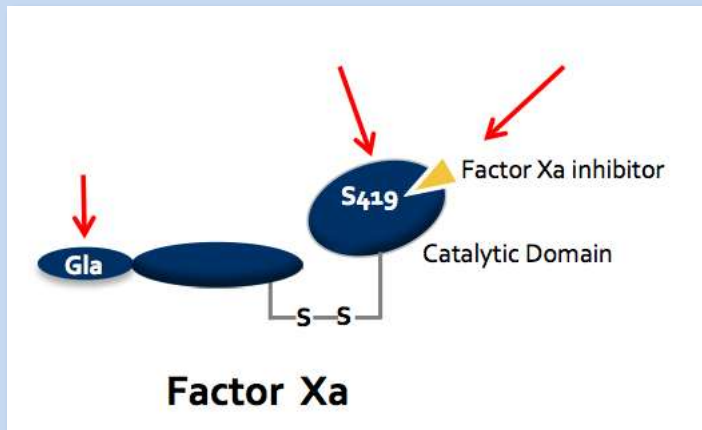
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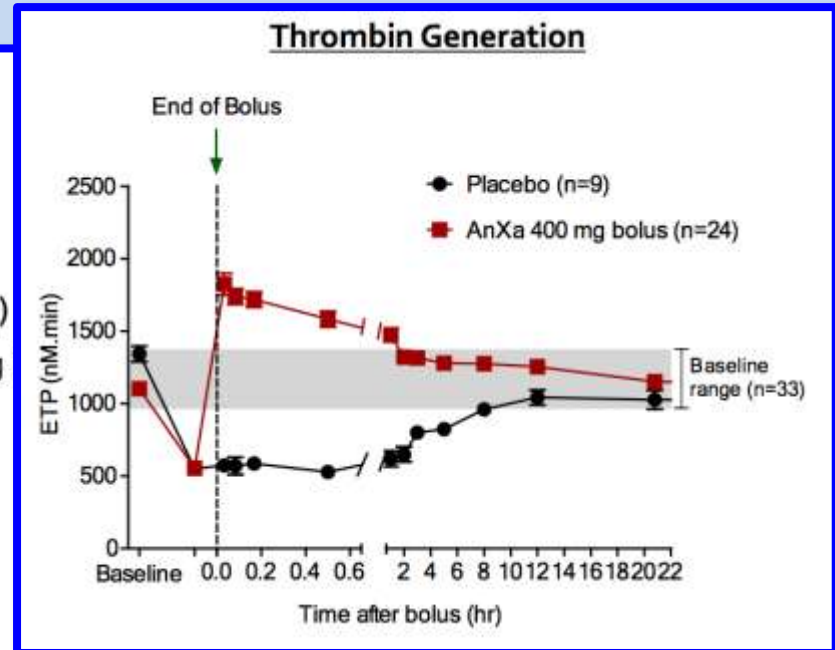
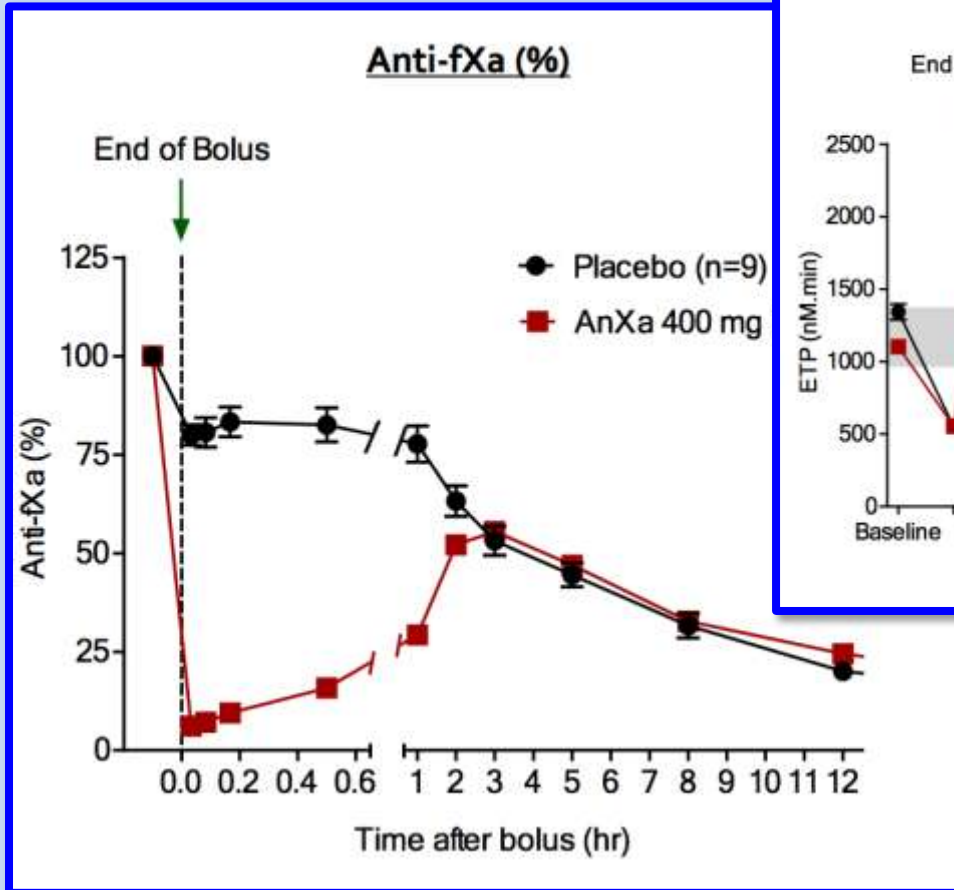
L'antidoto

ANNEXA™-A: A Phase 3 Randomized, Double-Blind, Placebo-Controlled Trial, Demonstrating Reversal of Apixaban-Induced Anticoagulation in Older Subjects by Andexanet alfa (PRT064445), a Universal Antidote for Factor Xa (fXa) Inhibitors



- Acts as a fXa decoy and retains high affinity for all fXa inhibitors
- Change of Serine to Alanine to eliminate catalytic activity and prevent prothrombin cleavage
- GLA domain removed to prevent anticoagulant effect

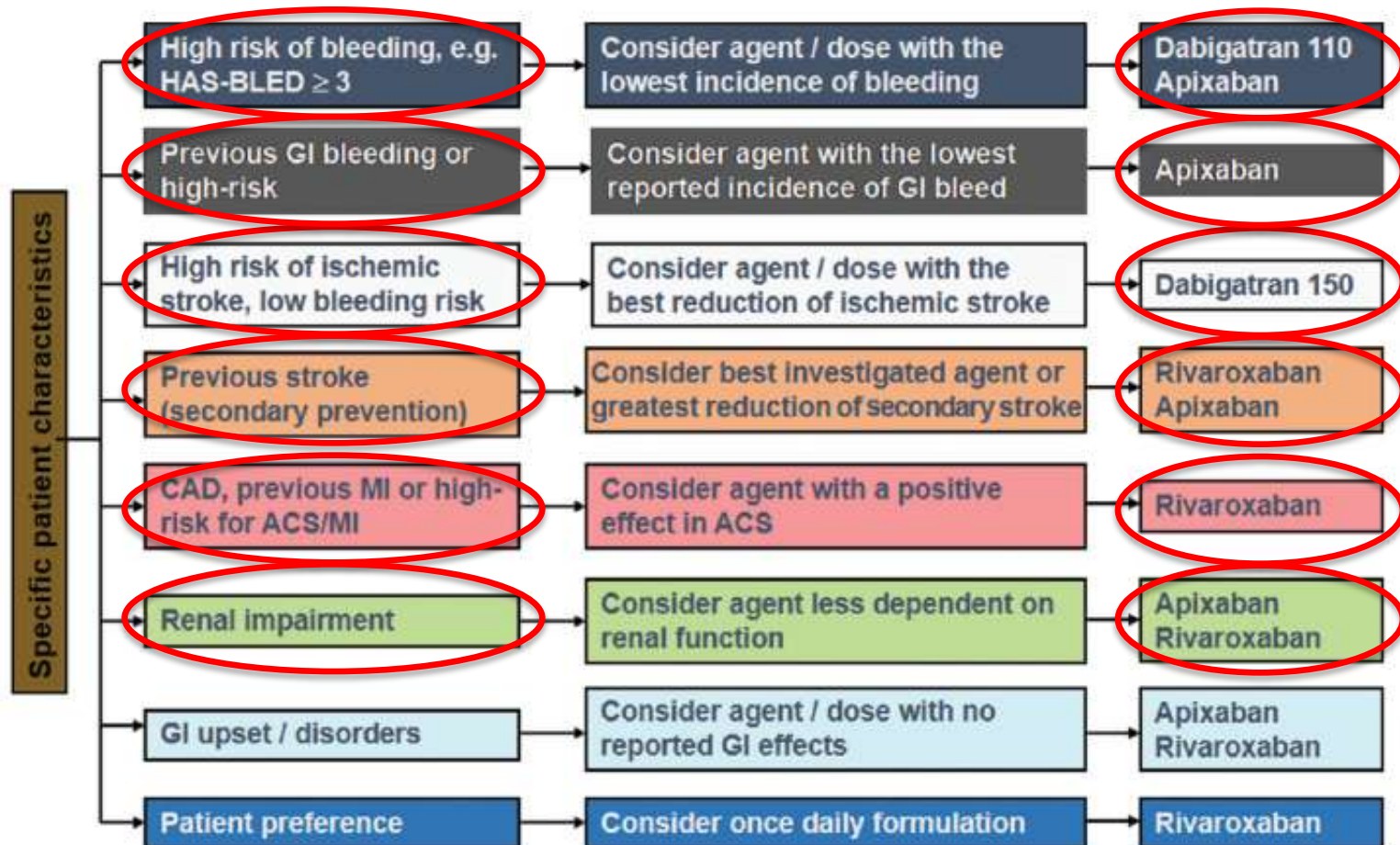
ANNEXA™-A: A Phase 3 Randomized, Double-Blind, Placebo-Controlled Trial, Demonstrating Reversal of Apixaban-Induced Anticoagulation in Older Subjects by Andexanet alfa (PRT064445), a Universal Antidote for Factor Xa (fXa) Inhibitors



Practical Considerations for Using Novel Oral Anticoagulants in Patients With Atrial Fibrillation



Possible considerations for selecting between NOA based on patient characteristics



ARE GERIATRIC SYNDROMES ASSOCIATED WITH RELUCTANCE TO INITIATE ORAL ANTICOAGULATION THERAPY IN ELDERLY ADULTS WITH NONVALVULAR ATRIAL FIBRILLATION?



Multivariate Predictors of the Absence of Oral Anticoagulation Therapy (N=137; Age: **82 years**; Permanent AF: **70%**; **Not** anticoagulated: **51%**; High risk – CHA₂DS₂VASc: **99%**; HAS-BLED: **39%**)

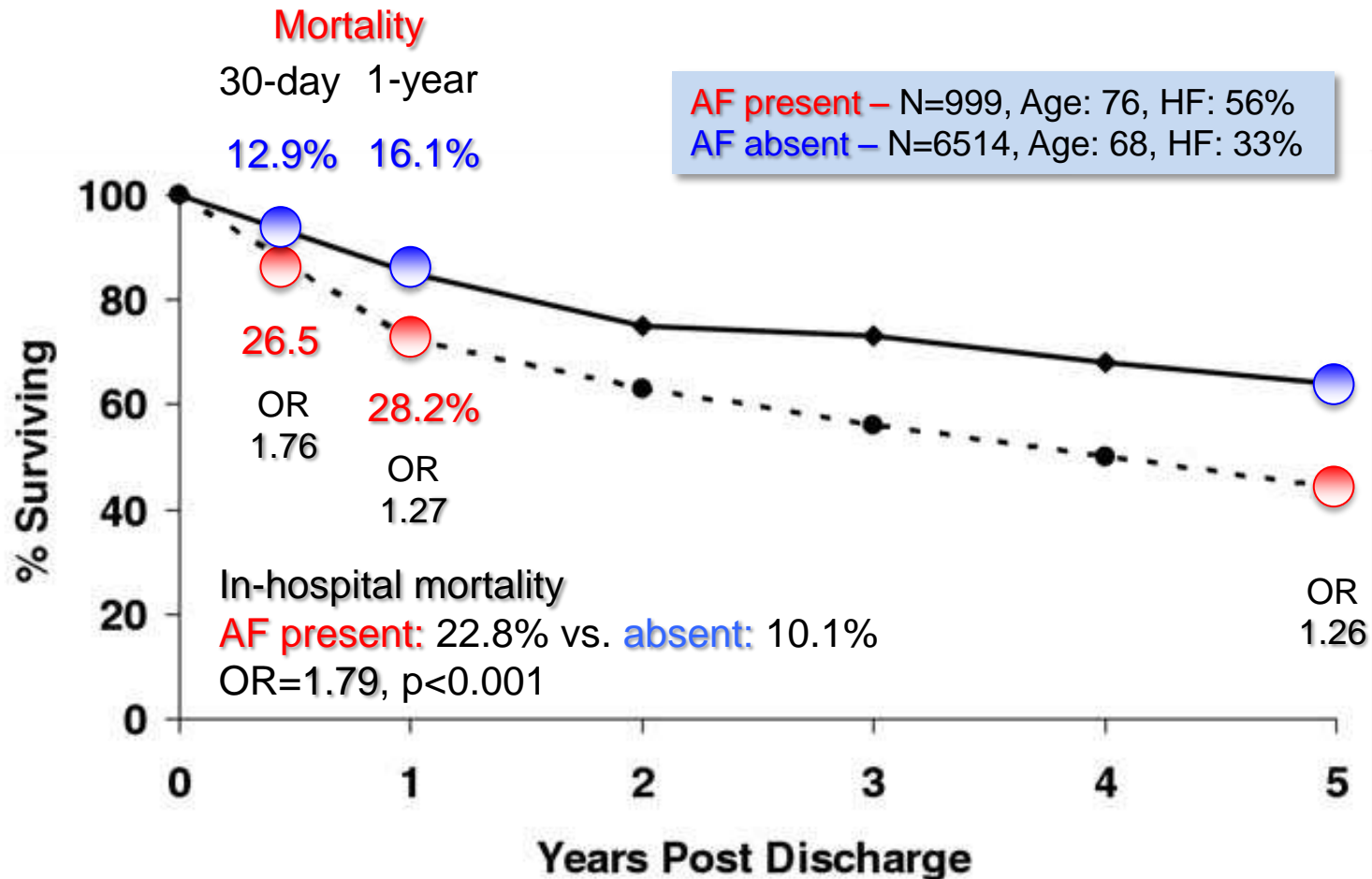
	OR	95%CI	p
Age	/	/	NS
Female	/	/	NS
Lives alone	/	/	NS
Education Years	/	/	NS
Depressive Symptoms	5.14	1.84-14.34	<0.05
Cognitive impairment	6.27	2.54-15.36	0.001
CHA ₂ DS ₂ VASc score	/	/	NS
HAS-BLED score	2.52	1.03-6.16	<0.05

Depressive Symptoms: Geriatric Depression Scale >5; **Cognitive impairment:** Mini-Mental State Examination ≤ 23

Trends in Atrial Fibrillation Complicating Acute Myocardial Infarction

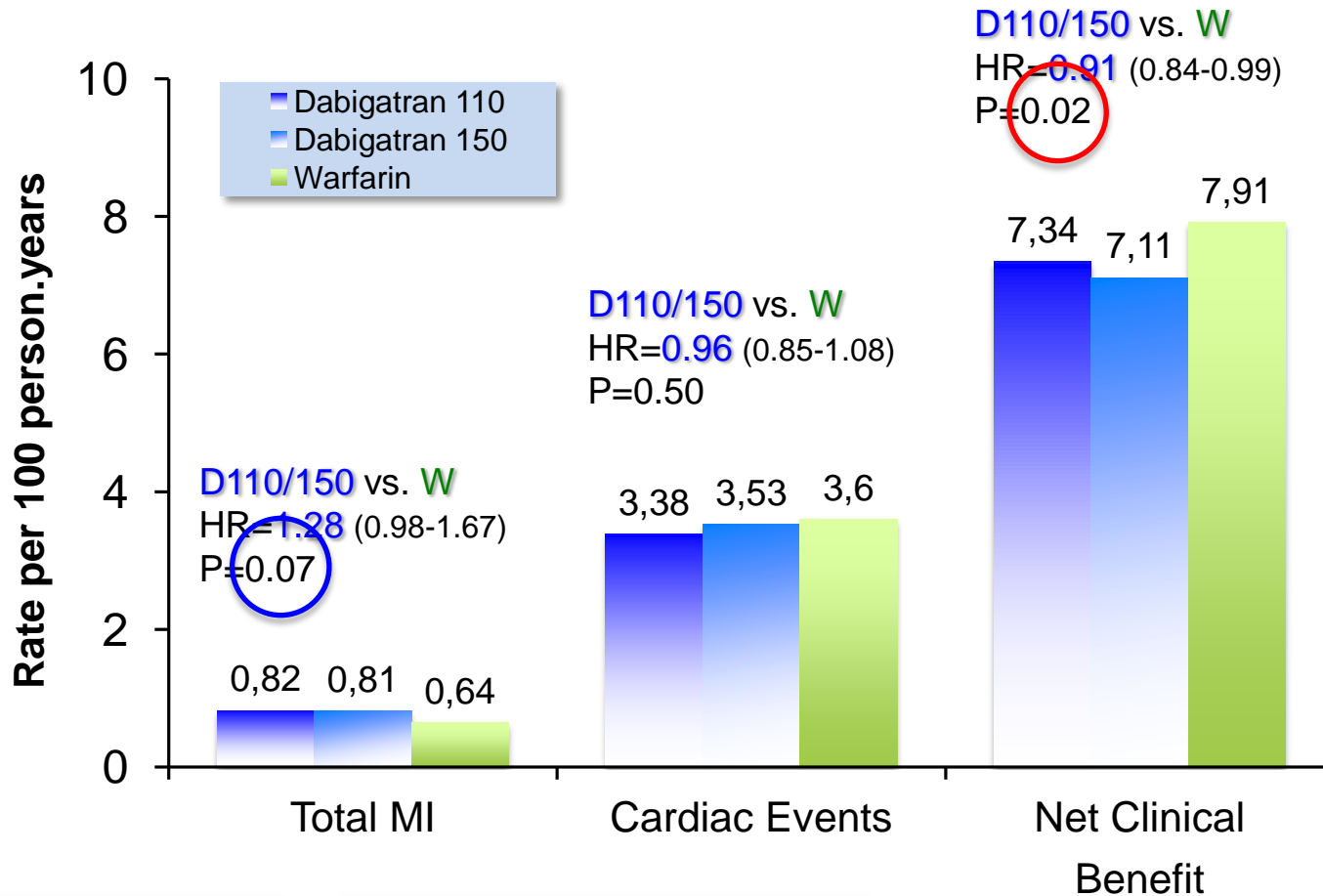


Long-term survival according to presence of AF during hospitalization for AMI in the Worcester Heart Attack Study



Myocardial Ischemic Events in Patients With Atrial Fibrillation Treated With Dabigatran or Warfarin in the RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) Trial

Cardiac Events During RE-LY by Treatment Group (Dabigatran 110/150 mg – N=6015/6076, Warfarin – N=6022)

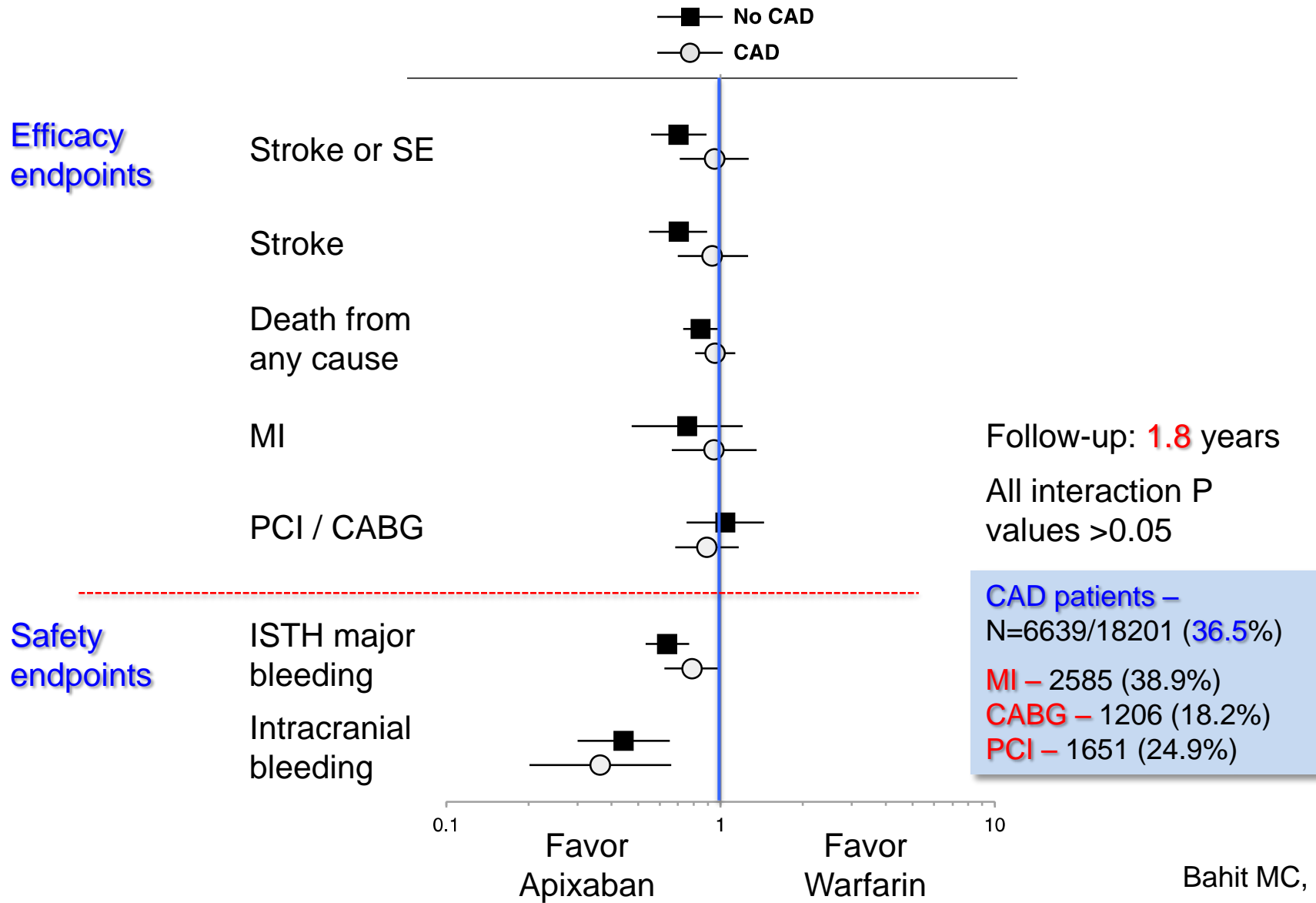


Cardiac events: MI, UA, CABG, PCI, SCD, Cardiac Death

Net Clinical Benefit: Stroke, MI, CV Death, TEP, SEE, Major Bleeding



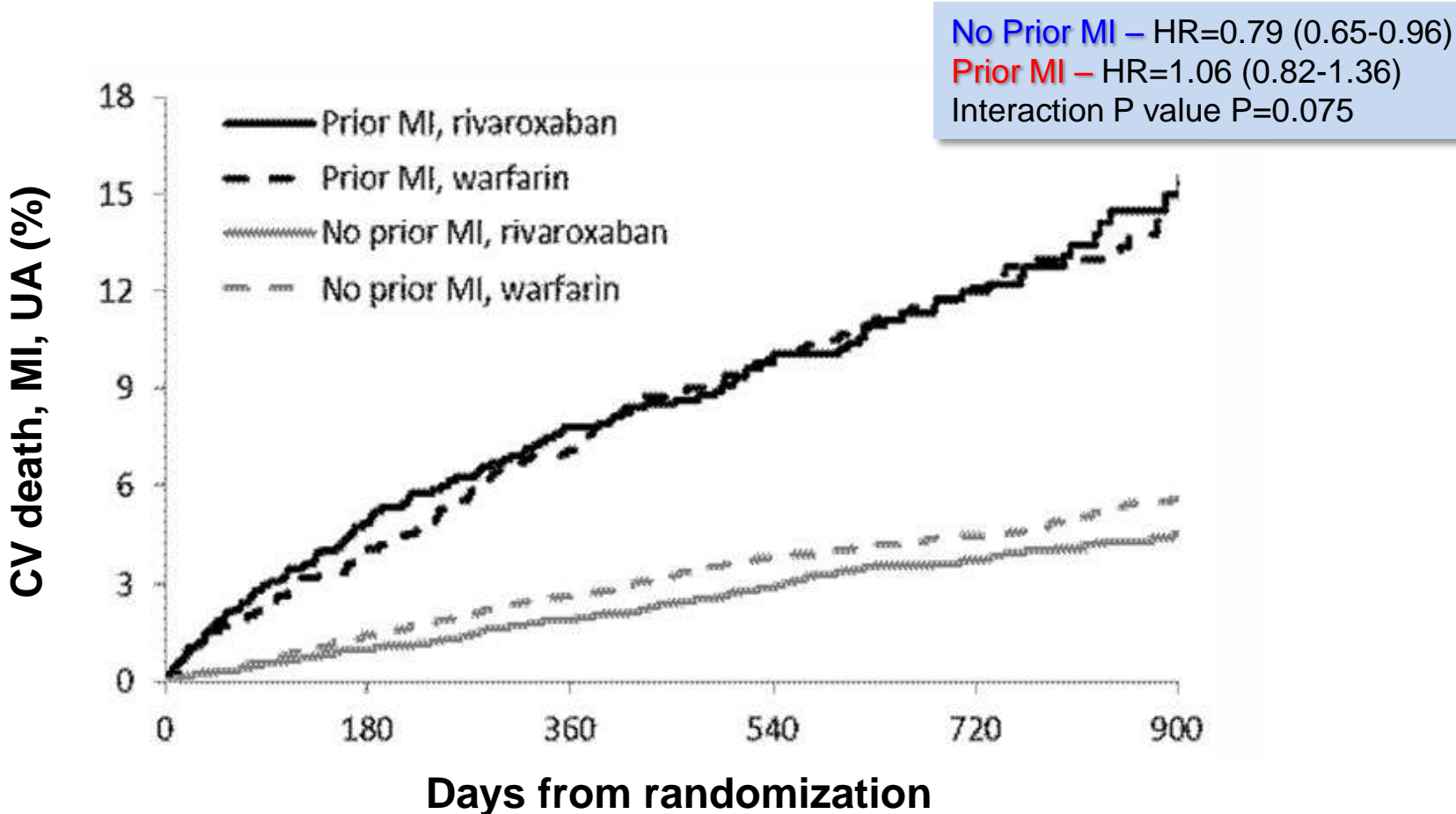
Apixaban vs. warfarin efficacy and safety according to CAD status



Ischaemic cardiac outcomes in patients with atrial fibrillation treated with vitamin K antagonism or factor Xa inhibition: results from the ROCKET AF trial



Cardiovascular death, myocardial infarction, and unstable angina in patients with and without prior MI by treatment assignment

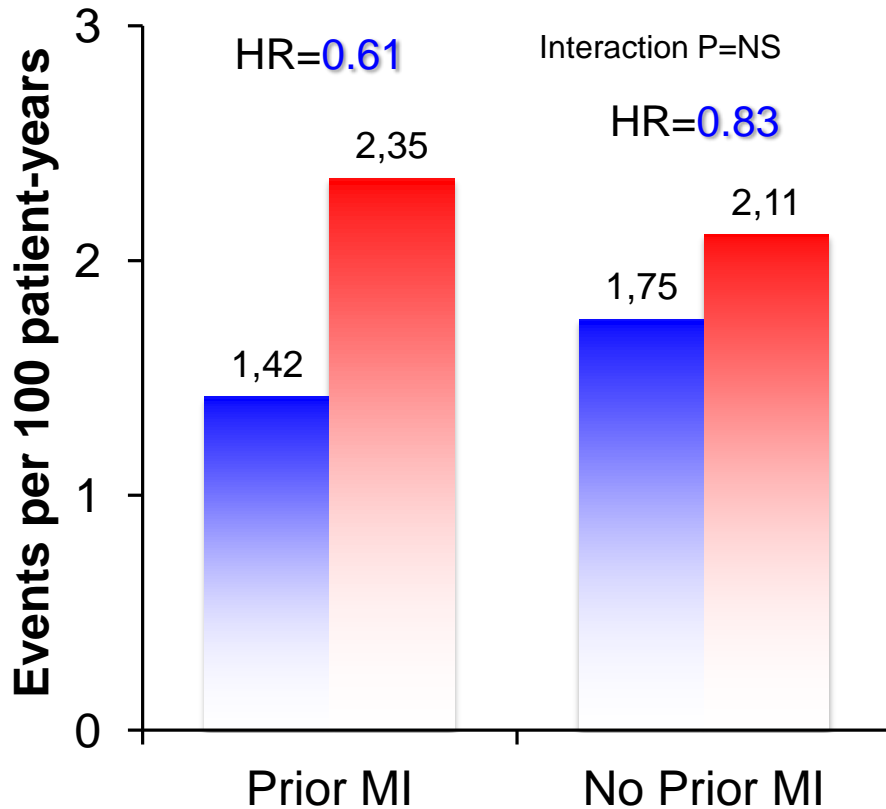


Ischaemic cardiac outcomes in patients with atrial fibrillation treated with vitamin K antagonism or factor Xa inhibition: results from the ROCKET AF trial

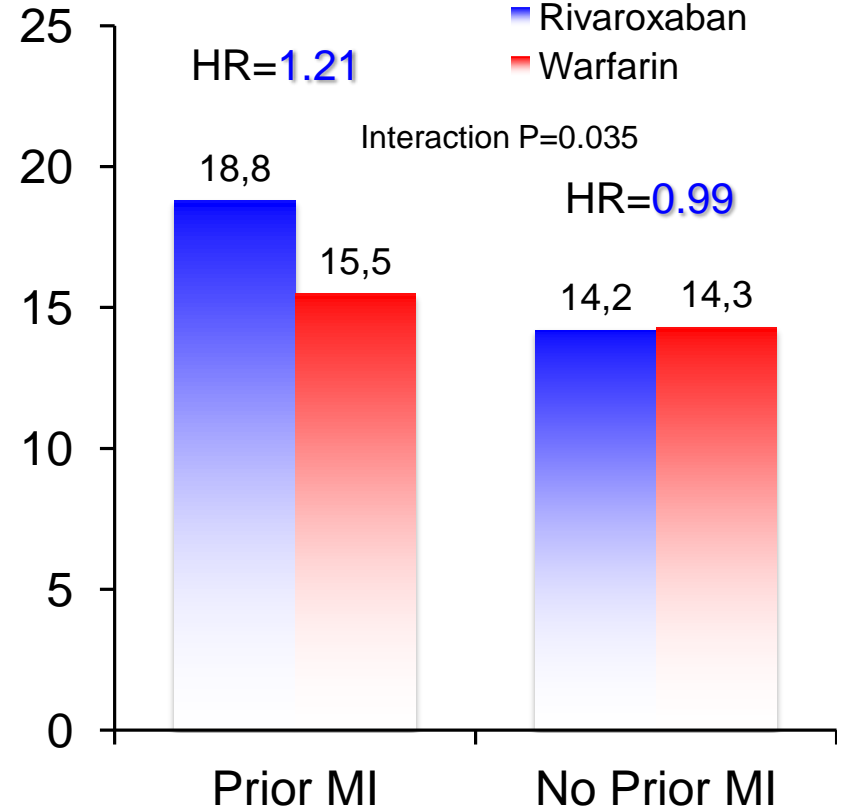


Efficacy and safety outcomes by treatment and prior MI condition (prior MI – N=2468/14264, 17.3%)

Stroke or non-CNS SE



Major and NMCR bleeding events



NMCR: non major clinically relevant bleeding

Myocardial Ischemic Events in 'Real World' Patients with Atrial Fibrillation Treated with Dabigatran or Warfarin

Cumulative incidence of MI according to treatment history and current treatment (the Danish Registries; FU: 16 months)

