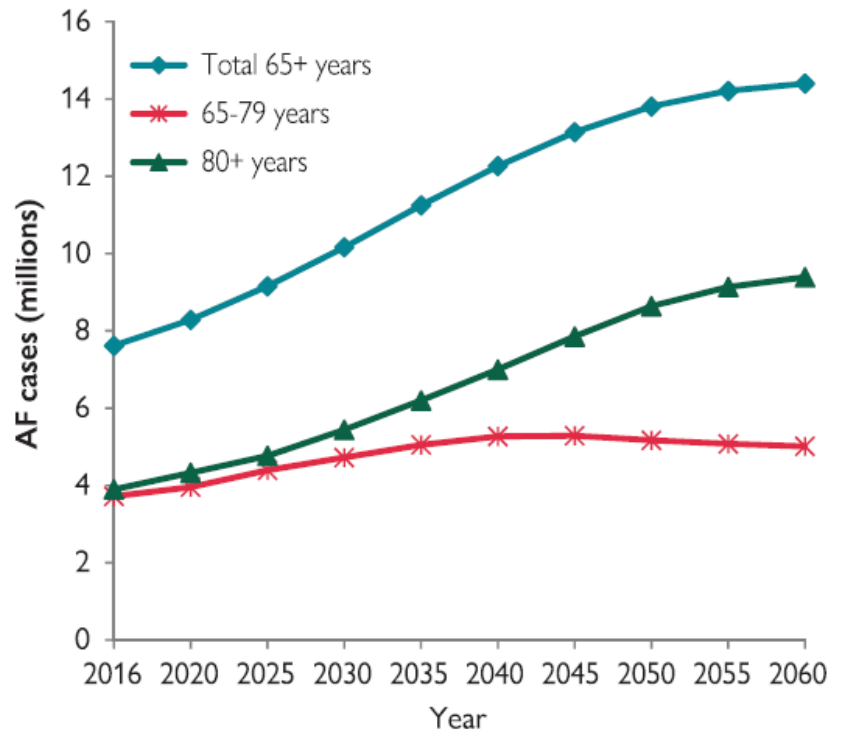


# Update on NOAC Management of Fragile Patient with AF : Focused on Rivaroxaban

**Youngjin Cho, MD, PhD**  
Division of Cardiology, Department of Internal Medicine  
Seoul National University Bundang Hospital

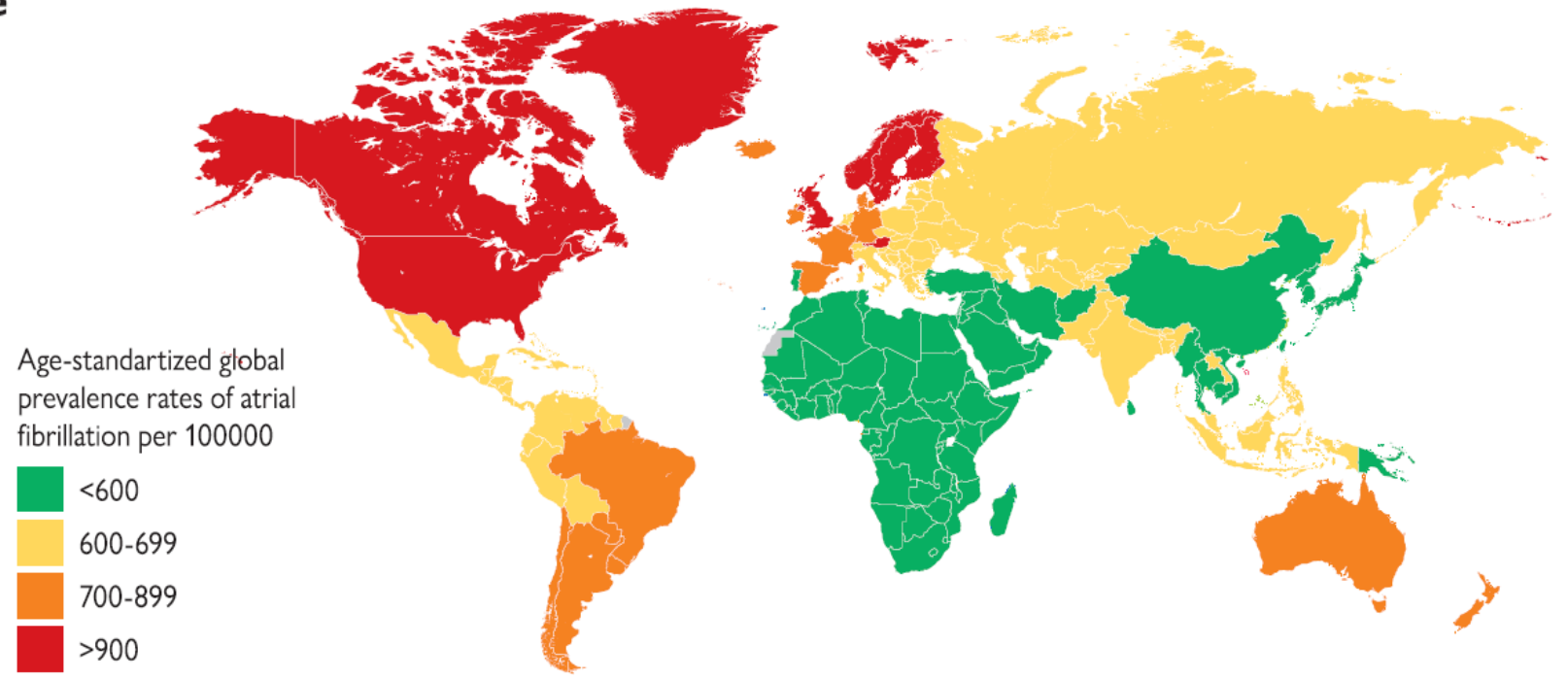
# Global Prevalence of Atrial Fibrillation

### Projected increase in AF prevalence among elderly in EU 2016-2060



### GLOBAL PREVALENCE OF AF

(globally, 43.6 million individuals had prevalent AF/AFL in 2016)

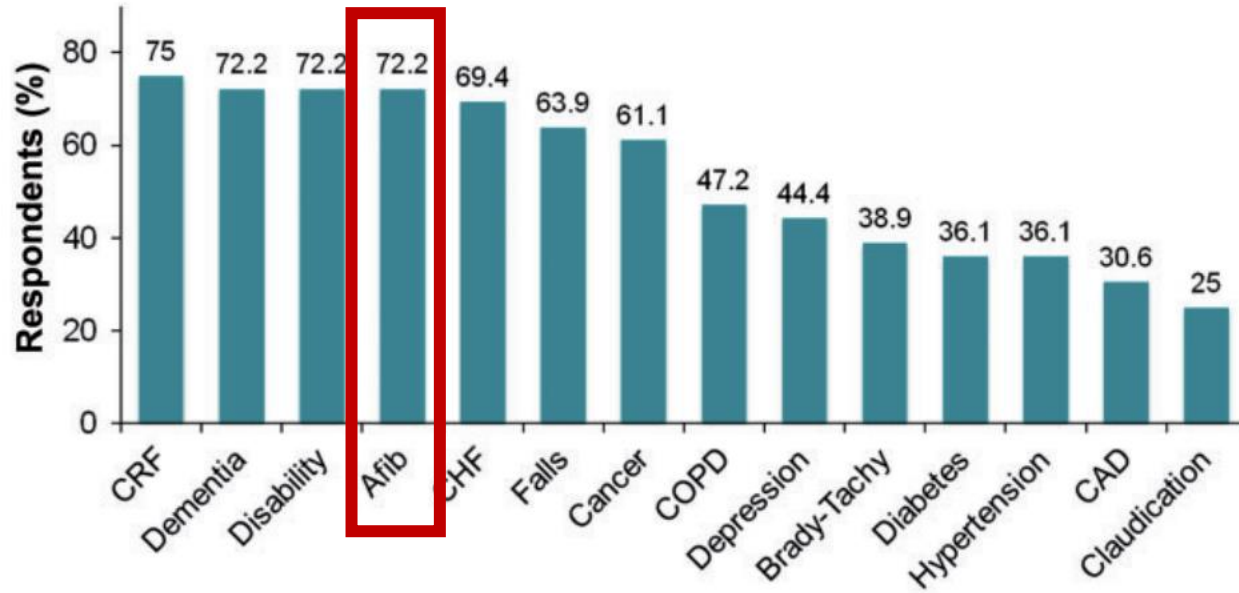


# NOAC use in Frail patients

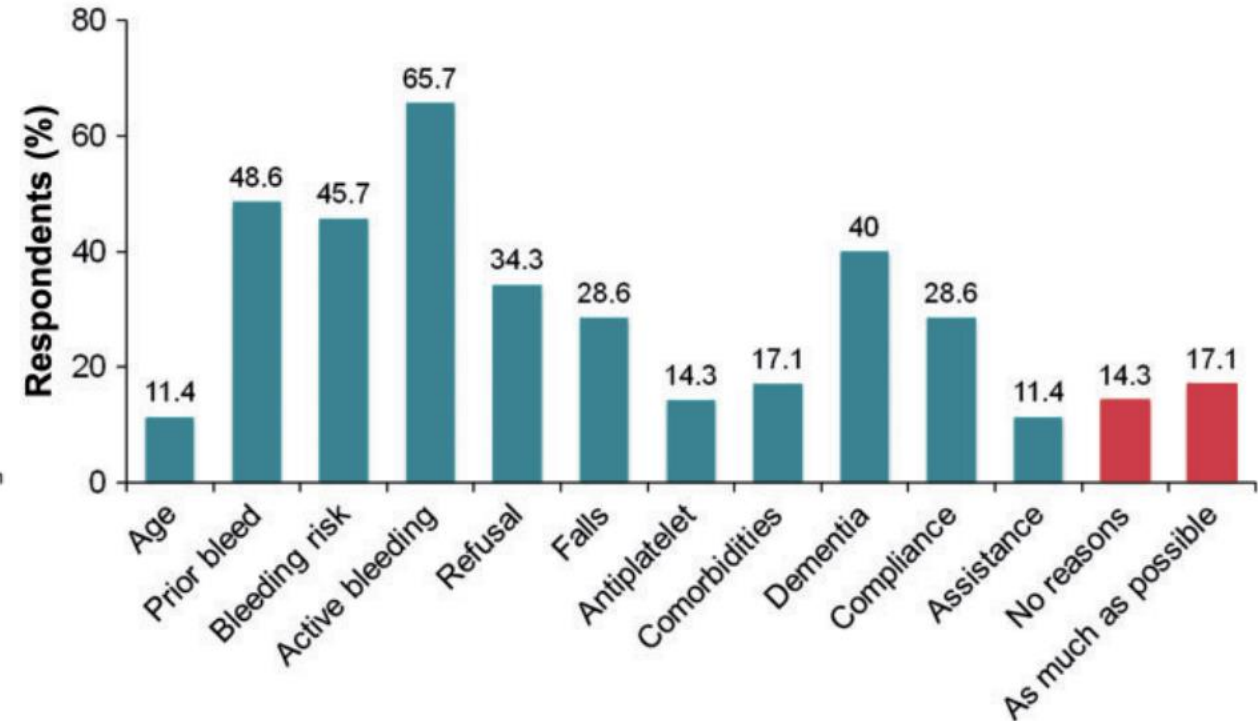
<b>Very Fit</b>	People who are robust, active, energetic and motivated. These people commonly exercise regularly. They are among the fittest for their age.
<b>Well</b>	People who have no active disease symptoms but are less fit than category 1. Often, they exercise or are very active occasionally, e.g. seasonally.
<b>Managing Well</b>	People whose medical problems are well controlled but are not regularly active beyond routine walking.
<b>Vulnerable</b>	While not dependent on others for daily help, often symptoms limit activities. A common complaint is being “slowed up”, and/or being tired during the day.
<b>Mildly Frail</b>	These people often have more evident slowing and need help in high order with ADLs (finances, transportation, heavy housework, medications). Typically, mild frailty progressively impairs shopping and walking outside alone, meal preparation and housework.
<b>Moderately Frail</b>	People need help with all outside activities and with keeping house. Inside, they often have problems with stairs and need help with bathing and might need minimal assistance (cuing, standby) with dressing.
<b>Severely Frail</b>	Completely dependent for personal care, from whatever cause (physical or cognitive). Even so, they seem stable and not at high risk of dying (within ~ 6 months).
<b>Very Severely Frail</b>	Completely dependent, approaching the end of life. Typically, they could not recover even from a minor illness.
<b>Terminally Ill</b>	Approaching the end of life. This category applies to people with a life expectancy <6 months, who are not otherwise evidently frail.

The 'Canadian Study of Health and Aging' (CHSA) Clinical Frailty Scale, based on comprehensive geriatric assessment including structured interview

# Fragile Patient with AF



Comorbidities most frequently associated to the frailty syndrome according to the participants' opinion



Most important reasons not to prescribe an anticoagulant drug to a frail patient with atrial fibrillation

# Fragile Patient with AF

---

- Elderly
- Low Body Weight
- Kidney Disease

# Prediction of Risk for AF

**TABLE 1 CHARGE-AF Scoring System for Prediction of Risk for AF**

	Coefficient × per Increment
Age	0.508 x (per 5 yrs)
Height	0.248 x (per 10 cm)
Weight	0.115 x (per 15 kg)
Systolic BP	0.197 x (per 20 mm Hg)
Diastolic BP	-0.101 x (per 10 mm Hg)
Current smoker	0.359
Antihypertensive medication	0.349
Diabetes	0.237
Congestive heart failure	0.701
Myocardial infarction	0.496
LVH by electrocardiogram	
PR interval (<120 vs. 120-199 ms)	
PR interval (>199 vs. 120-199 ms)	

**TABLE 2 HATCH Score for Prediction of Progression From Paroxysmal to More Persistent AF and Prediction of New AF After Atrial Flutter Ablation**

H	Hypertension	1
A	Age ≥75 yrs	1
T	Transient ischemic attack or stroke	2
C	Chronic obstructive pulmonary disease	1
H	Heart failure	2

# Prediction of Risk for AF

**TABLE 3 CHADS<sub>2</sub> Score for Prediction of Stroke in Atrial Fibrillation Patients**

C	Congestive heart failure	1
H	Hypertension (>140/90 mm Hg)	1
A	Age ≥75 yrs	1
D	Diabetes mellitus	1
S <sub>2</sub>	Prior TIA or stroke	2

**TABLE 4 CHA<sub>2</sub>DS<sub>2</sub>-VASc Score for Prediction of Stroke in Atrial Fibrillation Patients**

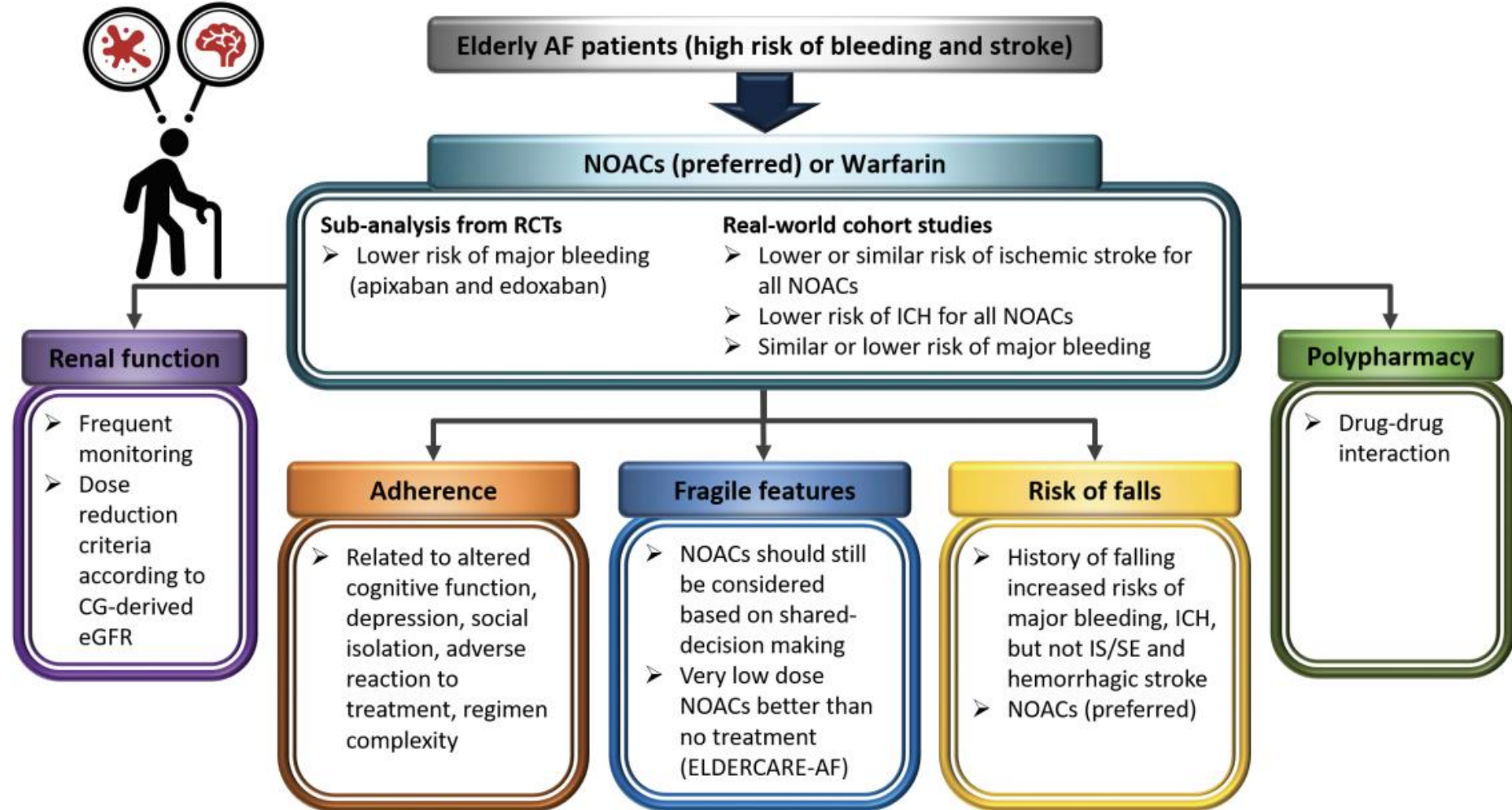
C	Congestive heart failure	1
H	Hypertension (>140/90 mm Hg)	1
A	Age ≥75 yrs	2
D	Diabetes mellitus	1
S <sub>2</sub>	Prior TIA or stroke	2
V	Vascular disease (MI, aortic plaque, and so on)	1
A	Age 65–74 yrs	1
Sc	Sex category (female = 1 point)	1

**TABLE 5 HAS-BLED Score for Prediction of Bleeding Risk**

H	Hypertension	1
A	Abnormal liver or renal function	1 point each
S	Stroke	1
B	Bleeding	1
L	Labile INRs	1
E	Elderly (>65)	1
D	Drugs or ETOH	1 point each

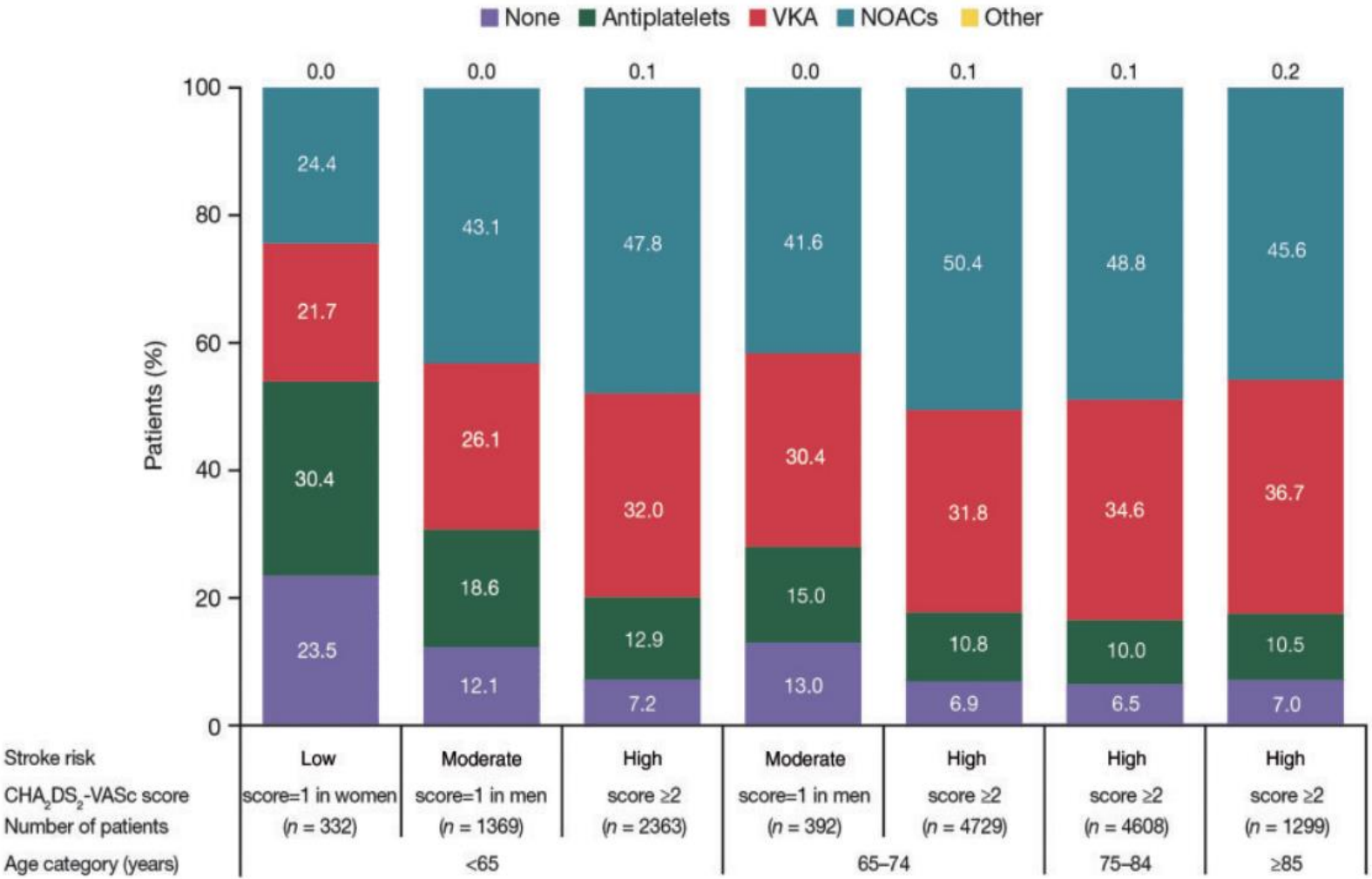
ETOH = ethyl alcohol; INR = international normalized ratio.

# Considerations in Elderly patients

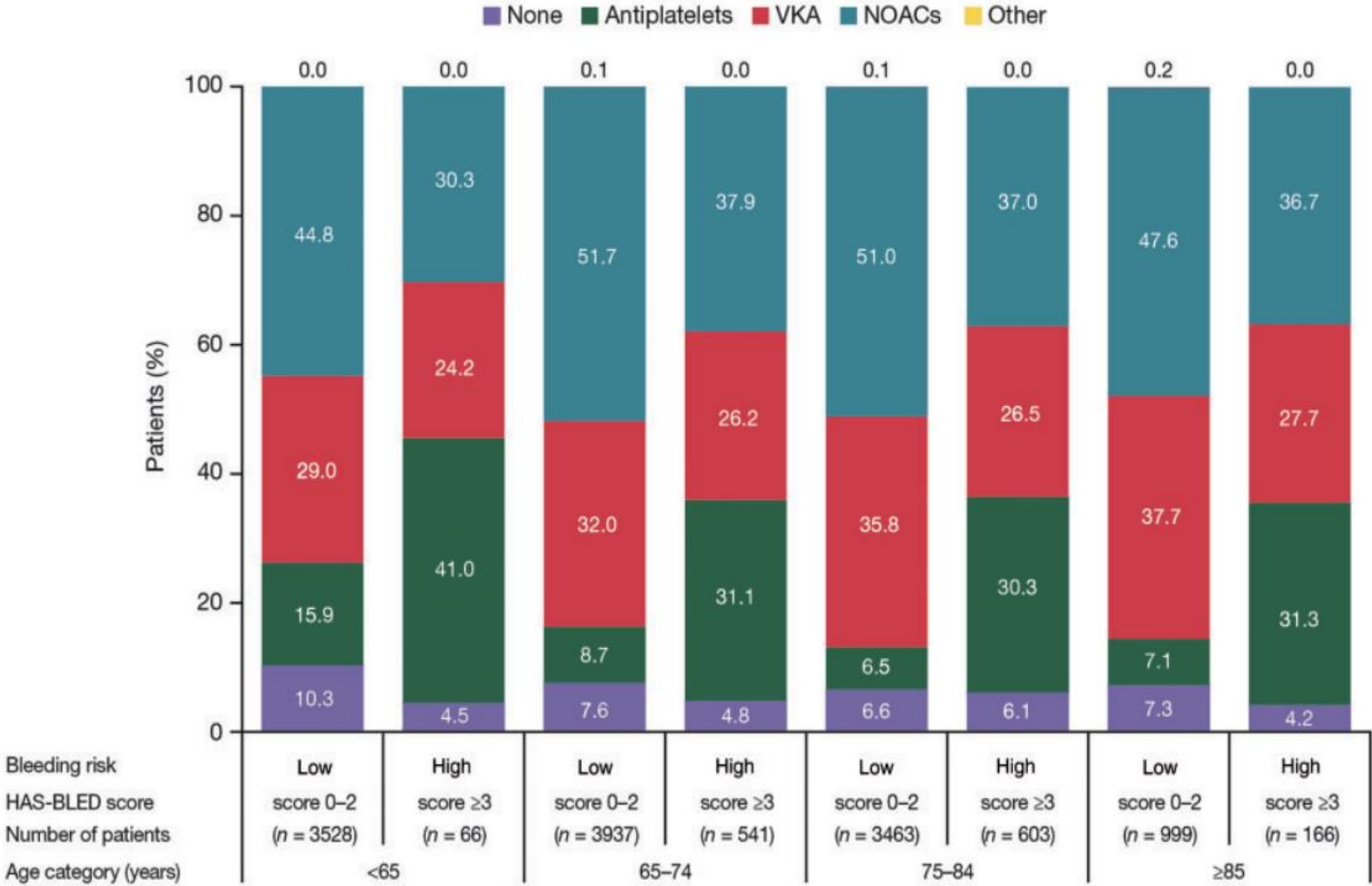




# Antithrombotic Treatment in relation to Age

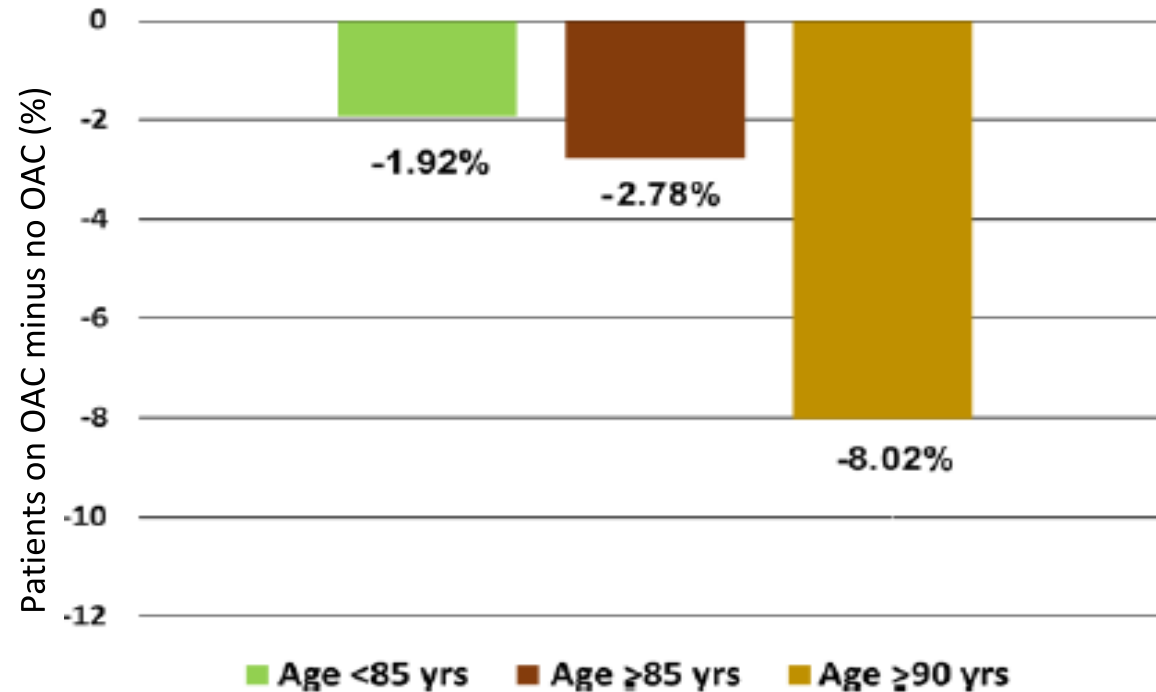


# Antithrombotic Treatment in relation to Age



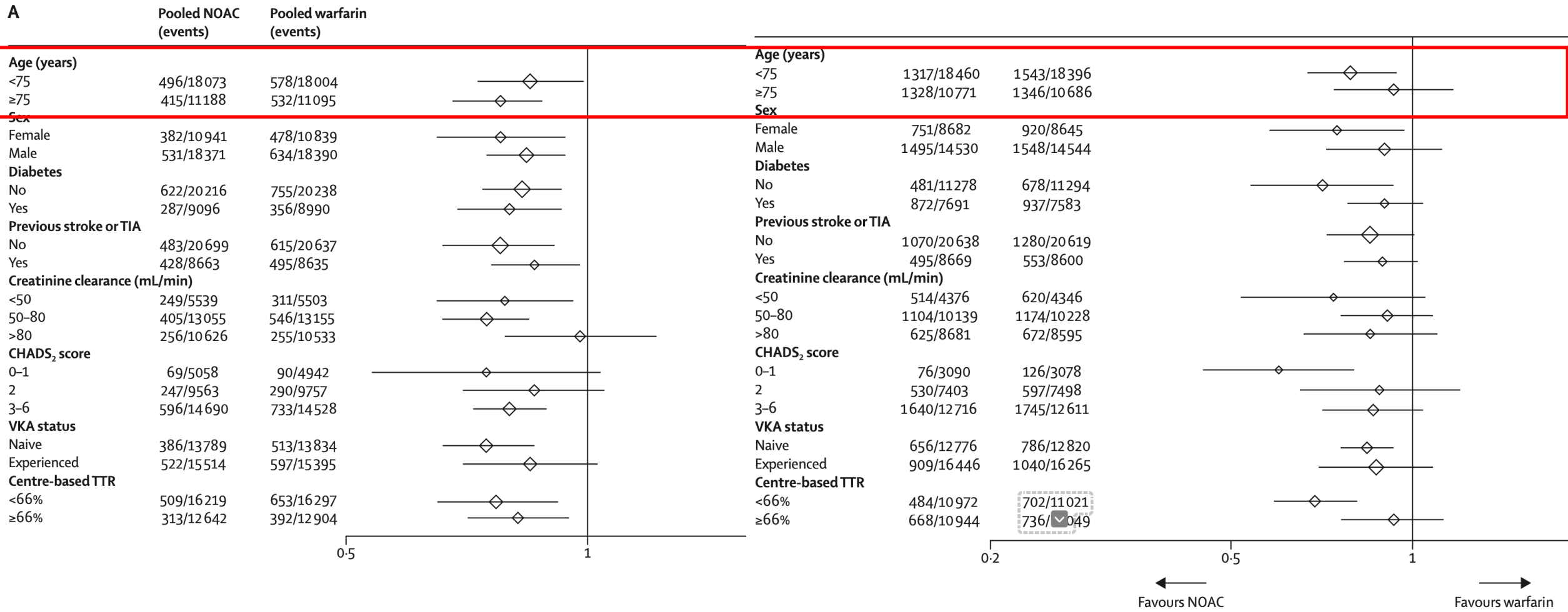
# PREFER (European registry) study – OAC in patients $\geq 85$

## Net clinical benefit of OAC vs no OAC according to different age strata



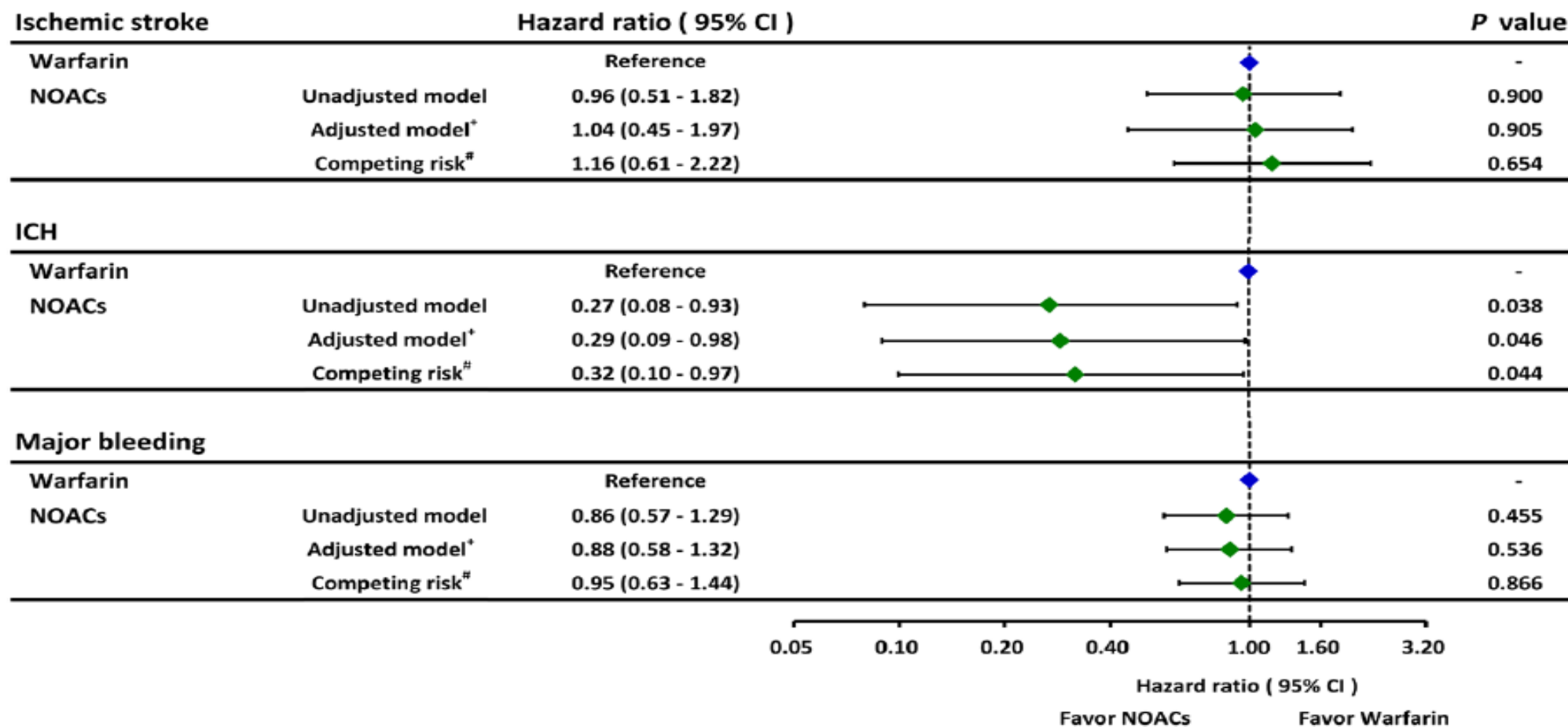
# NOAC vs VKA in elderly AF (≥75 years)

## Pooled analysis of RCTs



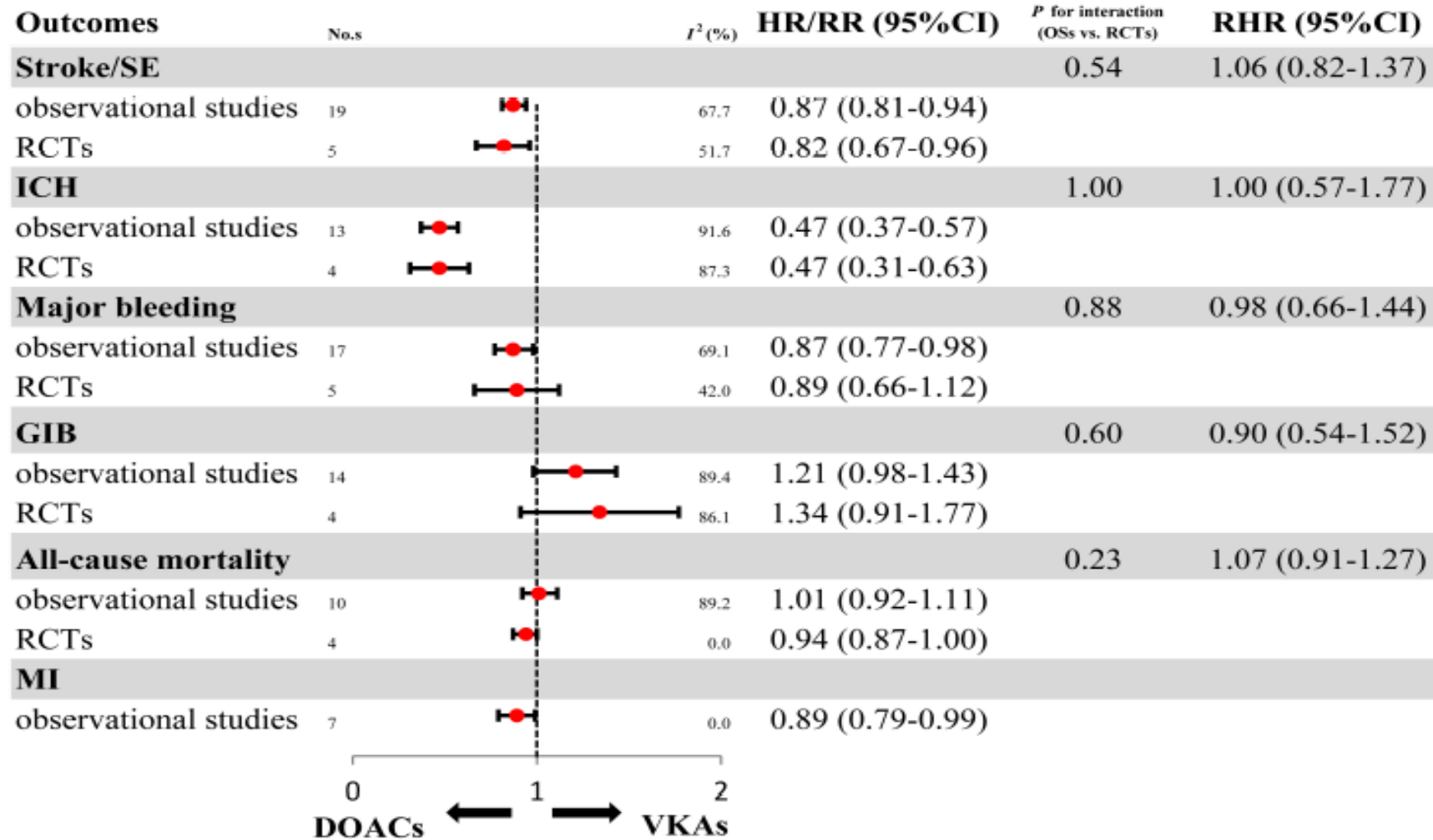
# Real World data : NOAC vs Warfarin in elderly AF( $\geq 90$ years)

Era with NOACs ( Year 2012 - 2015 )



# NOAC vs. VKA in elderly patients ( $\geq 75$ years)

Meta-analysis of 32 studies (5 RCTs)

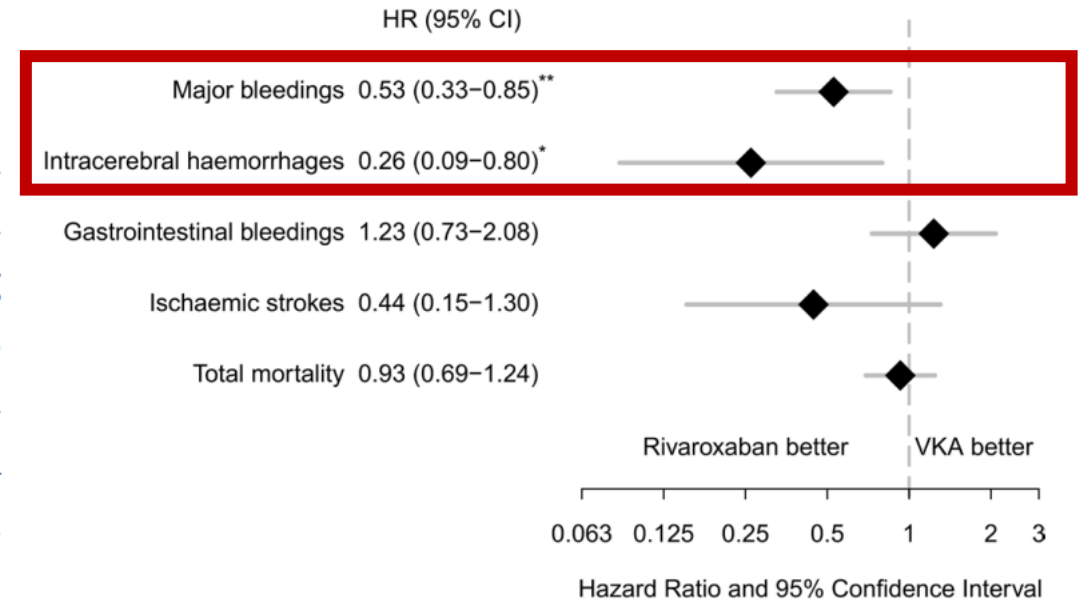


# Rivaroxaban in Elderly patients

ORIGINAL RESEARCH

## Bleeding risk with rivaroxaban compared with vitamin K antagonists in patients aged 80 years or older with atrial fibrillation

In the rivaroxaban cohort, 65% of patients were prescribed rivaroxaban as initial anticoagulant therapy, while 35% switched from VKA. Thirty-six per cent of patients were prescribed 20 mg of rivaroxaban once daily, 63% 15 mg and 1% 10 mg. In patients with a baseline eGFR 30–50 mL/min, 84.5% were prescribed rivaroxaban 15 mg once daily. In patients with a baseline eGFR  $\geq 50$  mL/min, rivaroxaban was prescribed 20 mg once daily in 54.6% and 15 mg once daily in 45.4% of patients.



Comparison of rate of events between rivaroxaban and VKA in the propensity score-matched sample

\* $p < 0.05$ , \*\* $p < 0.001$

# Rivaroxaban in Elderly patients

ORIGINAL RESEARCH

## Bleeding risk with rivaroxaban compared with vitamin K antagonists in patients aged 80 years or older with atrial fibrillation

**Table 2** Events during the follow-up period among rivaroxaban and VKA groups

Event	Rivaroxaban		VKA		HR (95% CI)
	n (%)	/100 person-years	n (%)	/100 person-years	
Major bleedings	63 (6.3)	7.4	102 (11.2)	14.6	0.49 (0.36 to 0.67)
Fatal bleedings	9 (0.9)	1.0	21 (3.3)	3.0	0.34 (0.16 to 0.76)
Intracerebral haemorrhages	11 (1.1)	1.3	28 (3.1)	4.0	0.65 (0.45 to 0.93)
Gastrointestinal haemorrhages	26 (3.0)	3.0	34 (3.7)	4.9	0.82 (0.53 to 1.28)
Ischaemic strokes	14 (1.4)	1.6	19 (2.1)	2.7	0.57 (0.29 to 1.14)
All-cause mortality	178 (17.9)	20.3	241 (26.5)	34.5	0.59 (0.49 to 0.72)

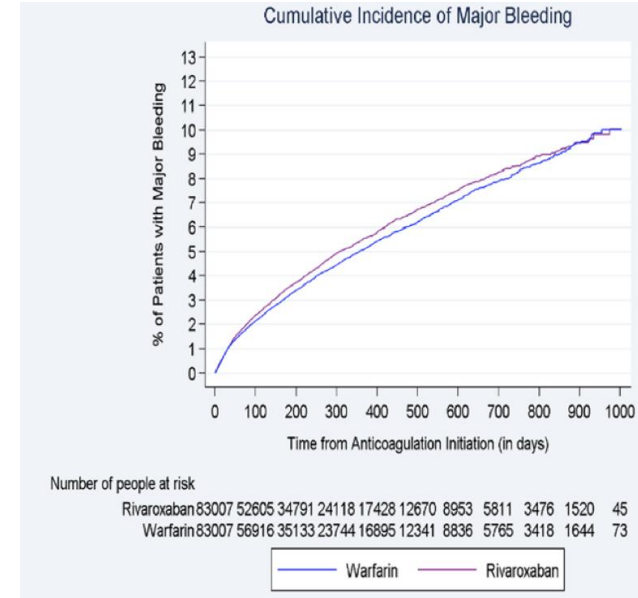
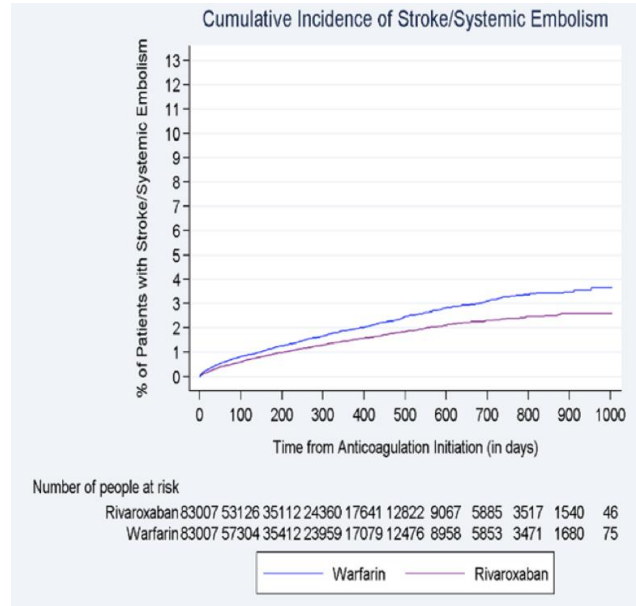
n (%), count (percentage); HR (95% CI), hazard ratio (95% confidence interval)



# Effectiveness and Safety of Oral Anticoagulants Among Nonvalvular Atrial Fibrillation Patients

## The ARISTOPHANES Study

Gregory Y.H. Lip, MD; Allison Keshishian, MPH; Xiaoyan Li, PhD; Melissa Hamilton, MPH; Cristina Masseria, PhD; Kiran Gupta, PhD; Xuemei Luo, PhD; Jack Mardekian, PhD; Keith Friend, MD; Anagha Nadkarni, PhD; Xianying Pan, MS; Onur Baser, PhD; Steven Deitelzweig, MD



Stroke/SE Subgroup	Apixaban vs. Warfarin			Dabigatran vs. Warfarin			Rivaroxaban vs. Warfarin		
	No. of events (incidence rate - per 100 person-years)	HR (95% CI)		No. of events (incidence rate - per 100 person-years)	HR (95% CI)		No. of events (incidence rate - per 100 person-years)	HR (95% CI)	
<b>Age, years</b>									
<65	50 (1.07) vs. 73 (1.35)	0.76 (0.53-1.08)*	+	30 (0.92) vs. 41 (1.22)	0.76 (0.47-1.22)	+	79 (1.18) vs. 98 (1.47)	0.81 (0.60-1.09)	+
65-74	121 (1.21) vs. 187 (1.47)	0.76 (0.61-0.96)*	+	62 (1.02) vs. 93 (1.44)	0.71 (0.51-0.98)	+	207 (1.05) vs. 283 (1.43)	0.74 (0.62-0.88)	+
75-79	69 (1.10) vs. 157 (2.02)	0.51 (0.38-0.68)*	+	62 (1.79) vs. 67 (1.84)	0.98 (0.69-1.38)	+	158 (1.33) vs. 216 (1.80)	0.74 (0.61-0.91)	+
≥80	198 (1.77) vs. 403 (2.98)	0.55 (0.47-0.65)*	+	105 (2.22) vs. 137 (2.89)	0.77 (0.60-0.99)	+	405 (2.20) vs. 548 (2.91)	0.76 (0.66-0.86)	+

# Non-vitamin K antagonist oral anticoagulants in very elderly east Asians with atrial fibrillation: A nationwide population-based study



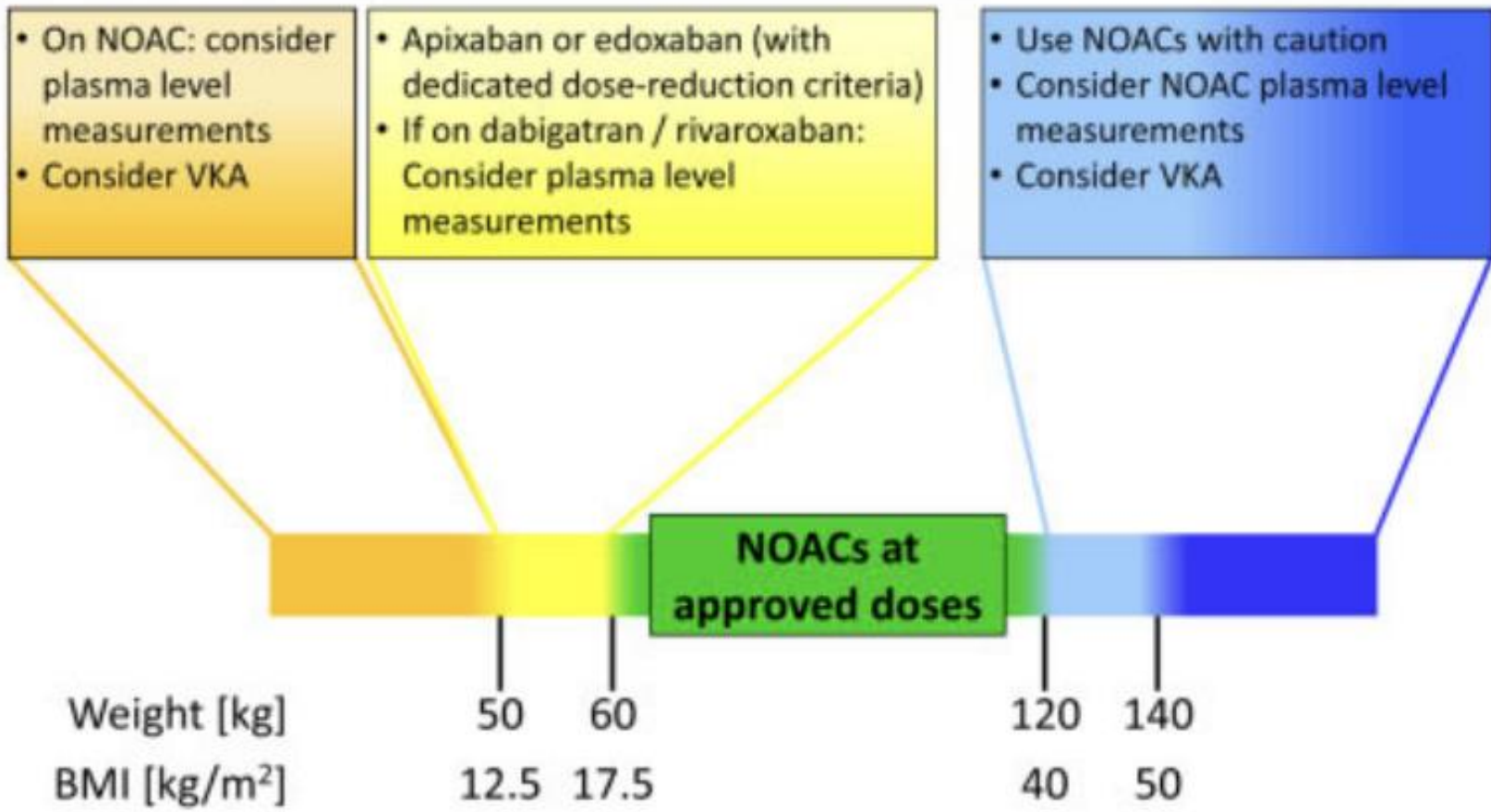
Soonil Kwon, MD,<sup>a,1</sup> So-Ryoung Lee, MD,<sup>a,1</sup> Eue-Keun Choi, MD, PhD,<sup>a,b</sup> Won-Seok Choe, MD,<sup>c</sup> Euijae Lee, MD,<sup>c</sup> Jin-Hyung Jung, MS,<sup>d</sup> Kyung-Do Han, PhD,<sup>e</sup> Seil Oh, MD, PhD,<sup>a,b</sup> and Gregory Y. H. Lip, MD<sup>b,f,g</sup> *Seoul, Bucheon, Republic of Korea; Liverpool, United Kingdom; and Aalborg, Denmark*

Patients aged ≥80 years (n=24,659)

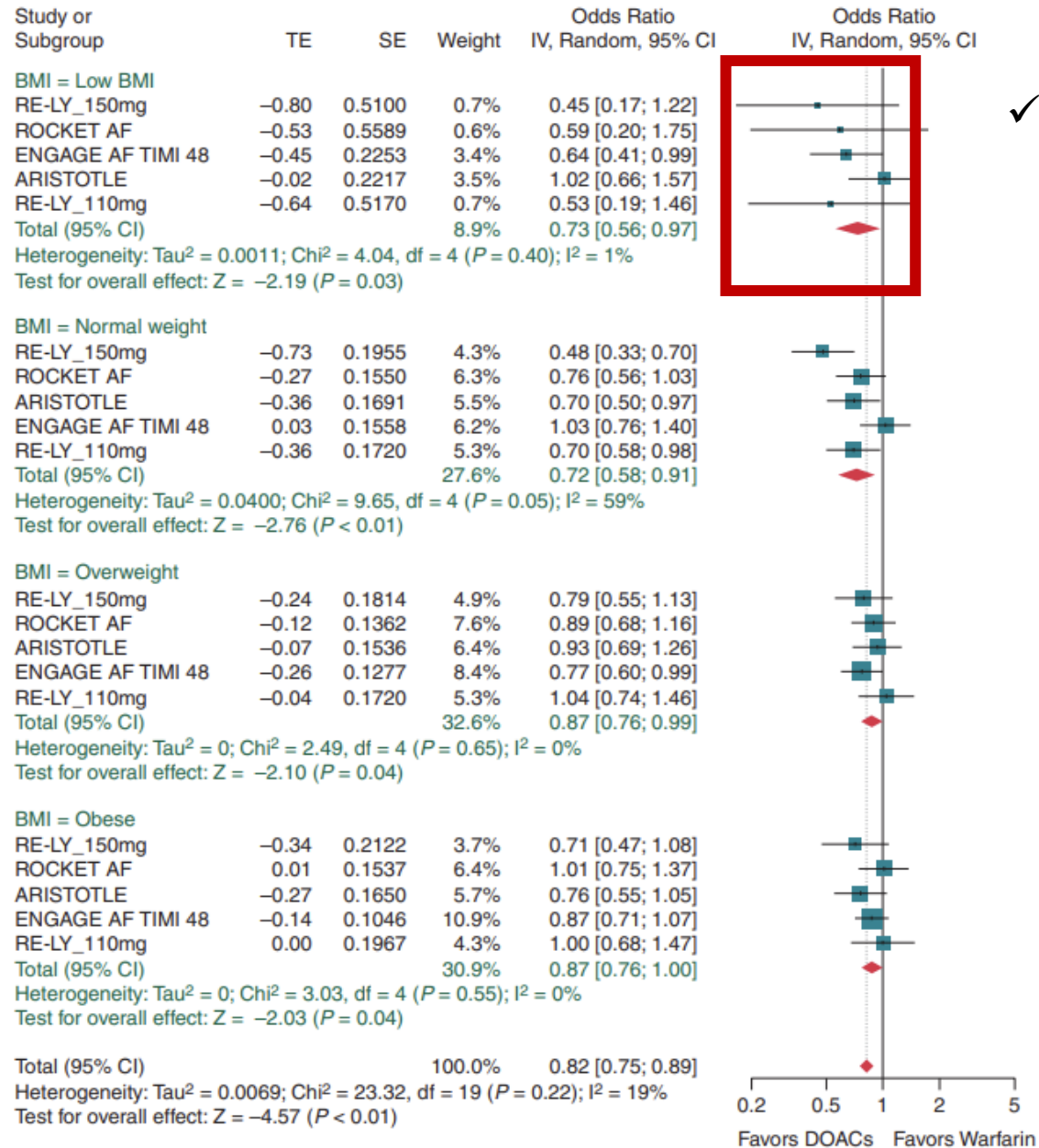
	Weighted IR per 100 PY		HR (95% CI)	P value	
	Warfarin (n=4,086)	NOAC (n=20,573)			
Ischemic stroke	5.3	4.0	0.74 (0.62-0.89)	0.001	
Intracranial hemorrhage	1.0	0.9	0.87 (0.59-1.33)	0.491	
GI bleeding	3.7	3.1	0.82 (0.66-1.02)	0.063	
Major bleeding	4.7	4.0	0.83 (0.69-1.01)	0.060	
Composite clinical outcome	9.7	7.8	0.78 (0.69-0.90)	0.004	

0.1      1.0      10  
 Favor NOAC      Favor WFR

# NOACs in Low & Overweight patient

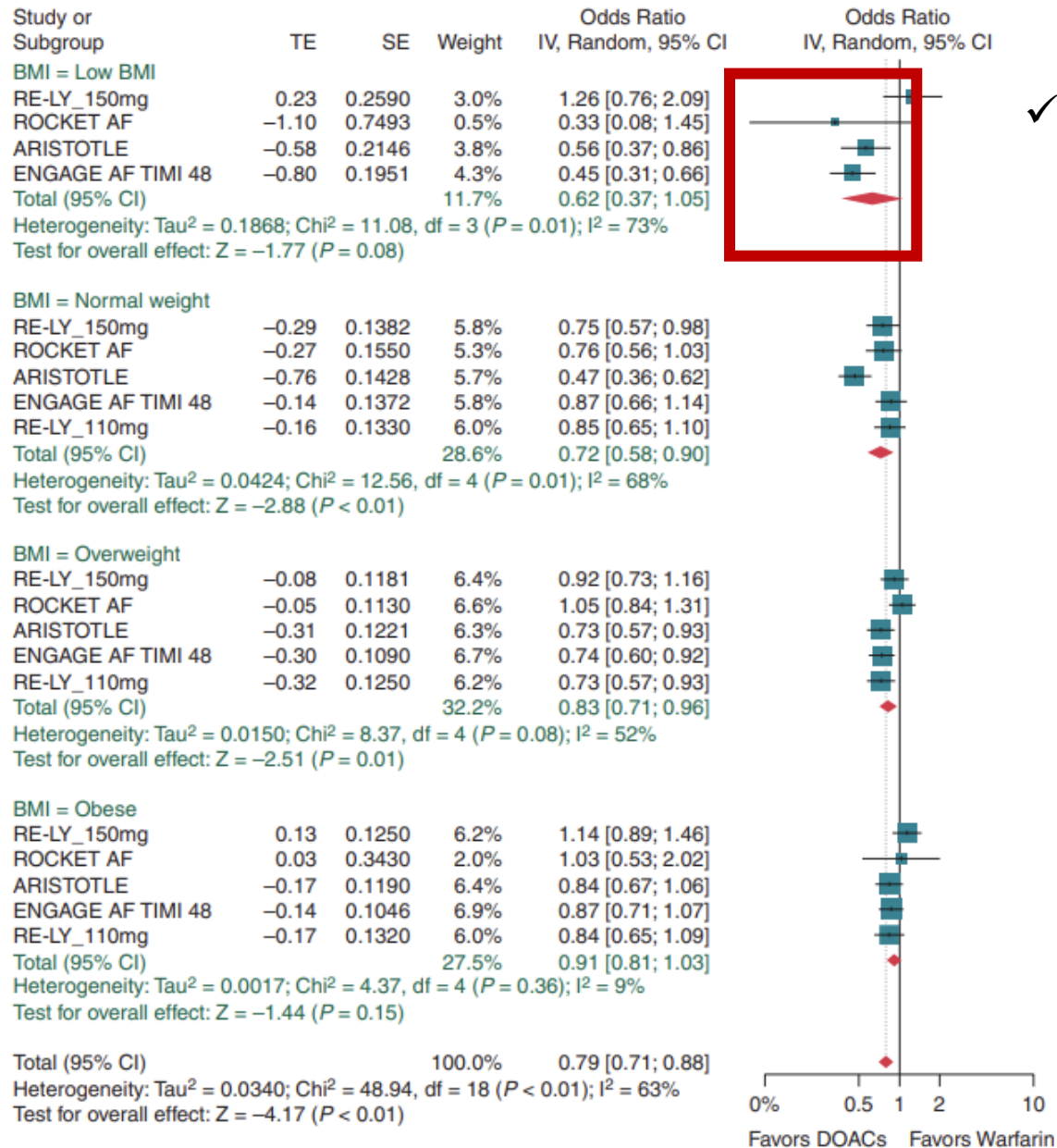


# NOACs in Low Body Weight



- ✓ Stroke or systemic embolization with NOACs vs. warfarin in patients with atrial fibrillation according to body mass index

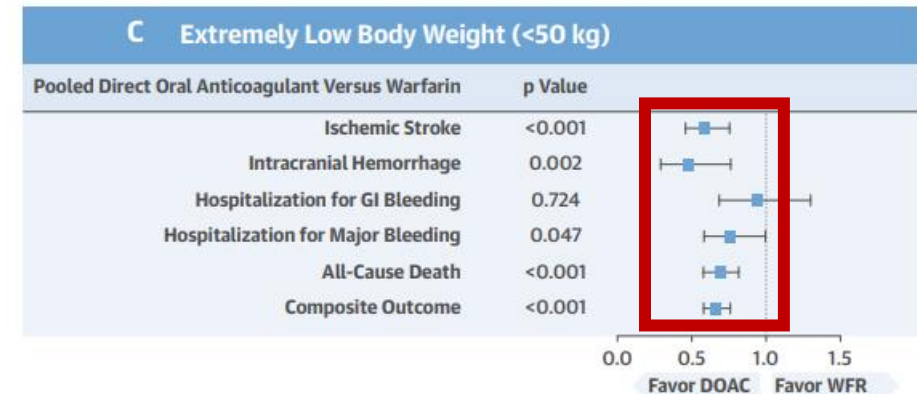
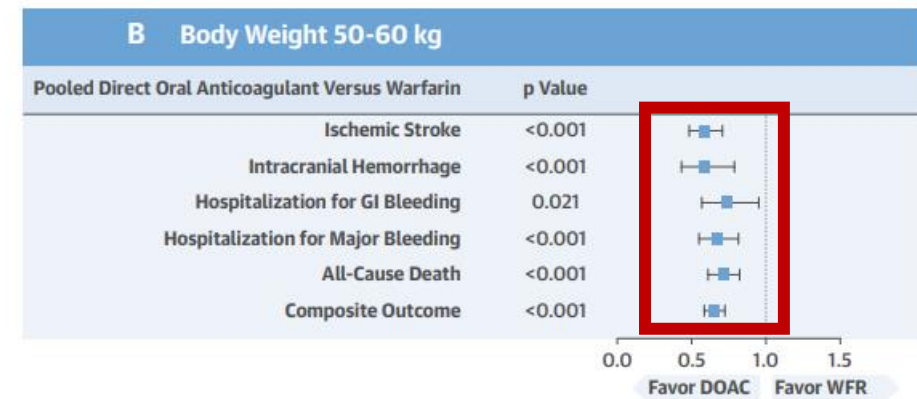
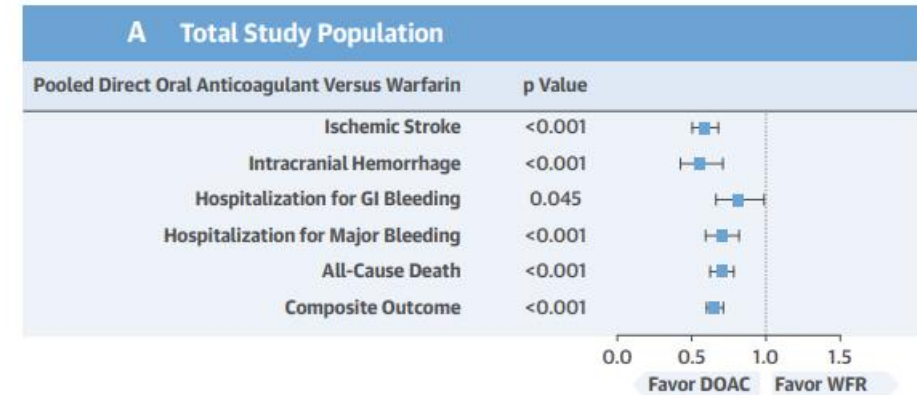
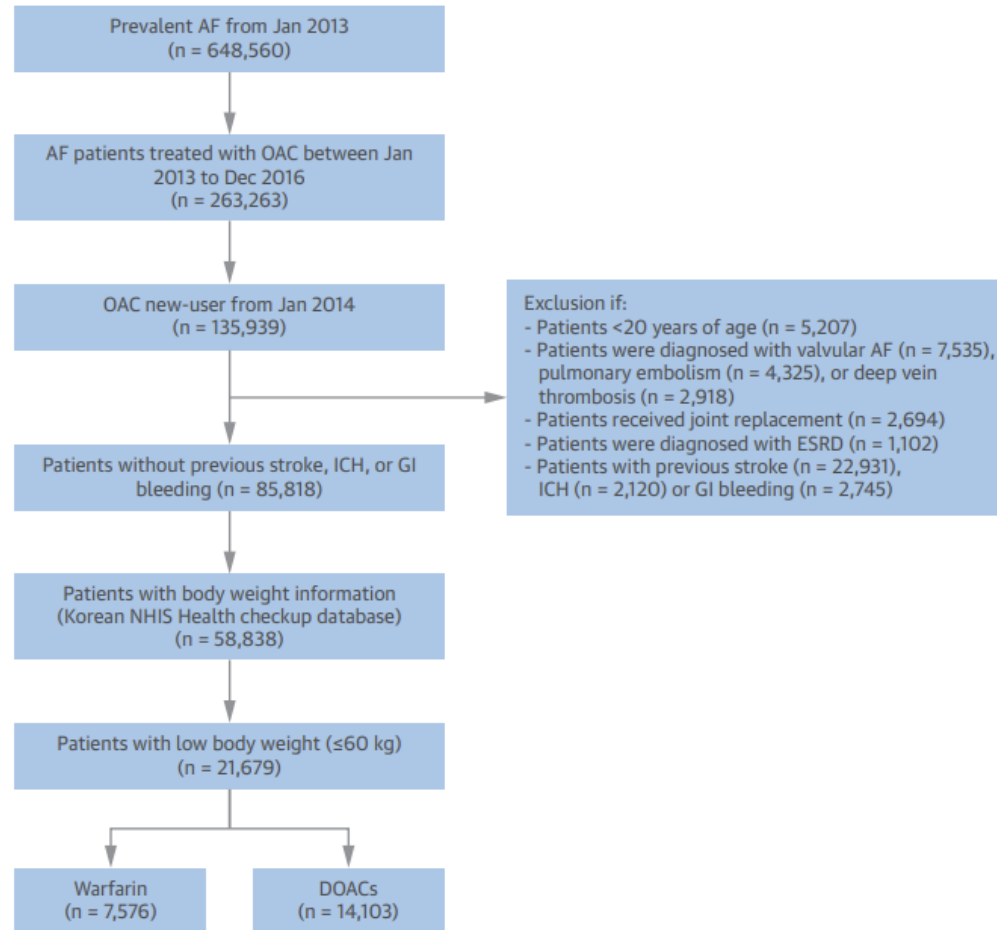
# NOACs in Low Body Weight



✓ Major bleeding with NOACs vs. warfarin in patients with atrial fibrillation according to BMI

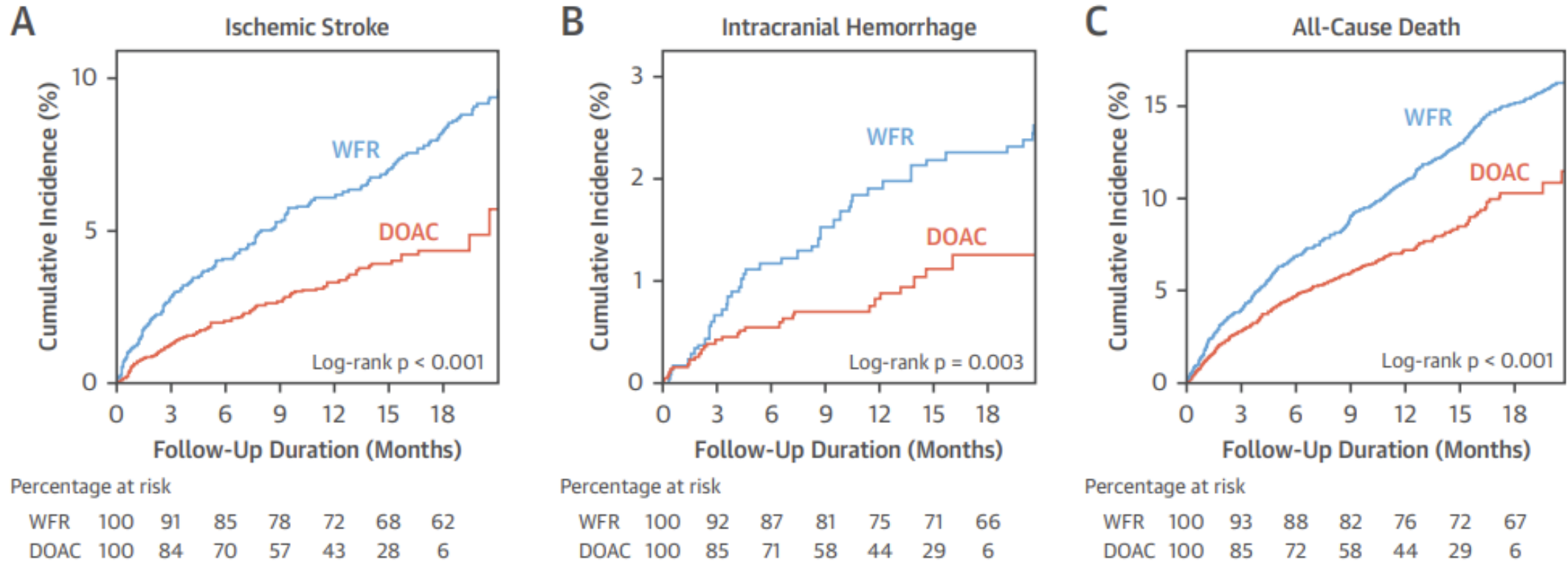
# NOACs in Low Body Weight

## Direct Oral Anticoagulants in Patients With Nonvalvular Atrial Fibrillation and Low Body Weight



# NOACs in Low Body Weight

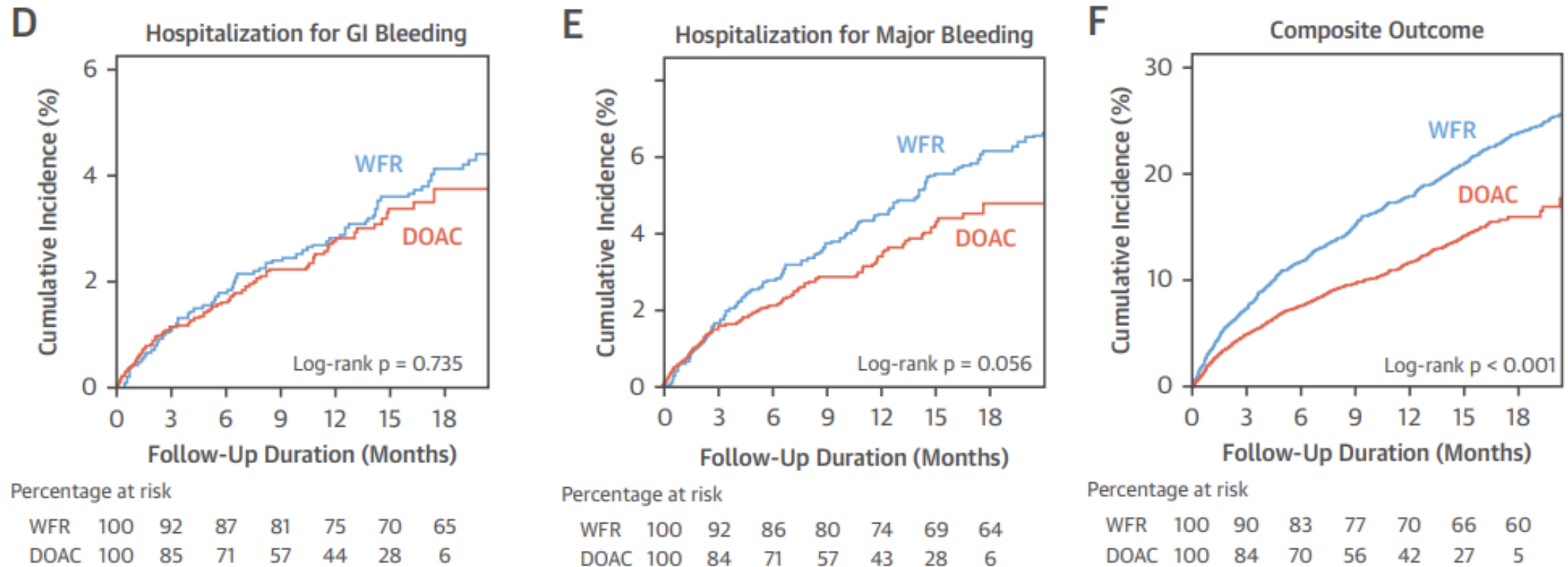
**FIGURE 3** Cumulative Incidence Curves of 6 Clinical Outcomes in Pooled DOAC Versus WFR in Patients With Extremely Low Body Weight (<50 kg)



- ✓ In this real-world Asian population with nonvalvular AF and low body weight ( $\leq 60$  kg), DOACs showed better effectiveness and safety than warfarin.
- ✓ This result remained consistent in patients with extremely low body weight (<50 kg)

# NOACs in Low Body Weight

**FIGURE 3** Cumulative Incidence Curves of 6 Clinical Outcomes in Pooled DOAC Versus WFR in Patients With Extremely Low Body Weight (<50 kg)



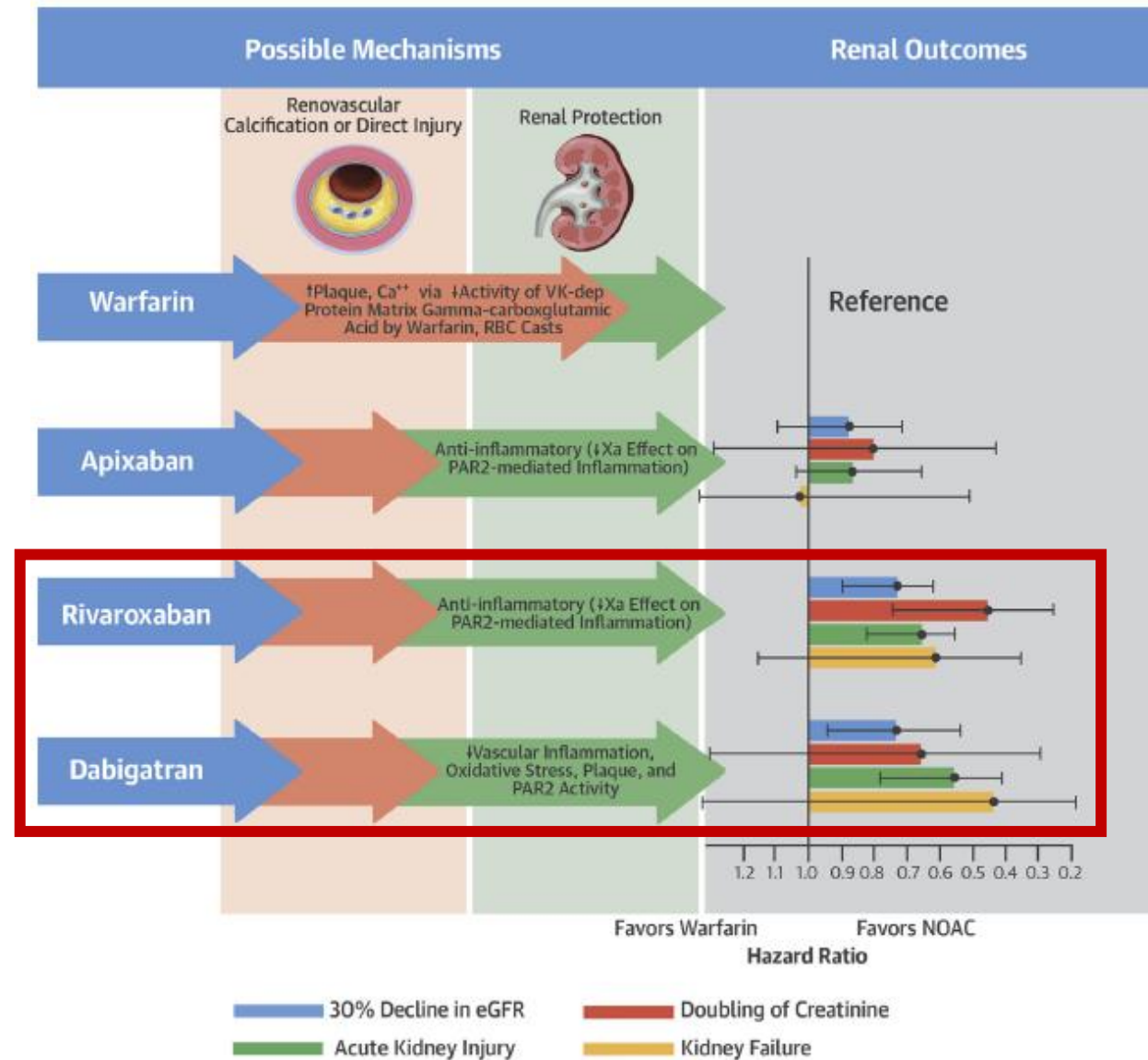
- ✓ In this real-world Asian population with nonvalvular AF and low body weight ( $\leq 60$  kg), DOACs showed better effectiveness and safety than warfarin.
- ✓ This result remained consistent in patients with extremely low body weight (<50 kg)



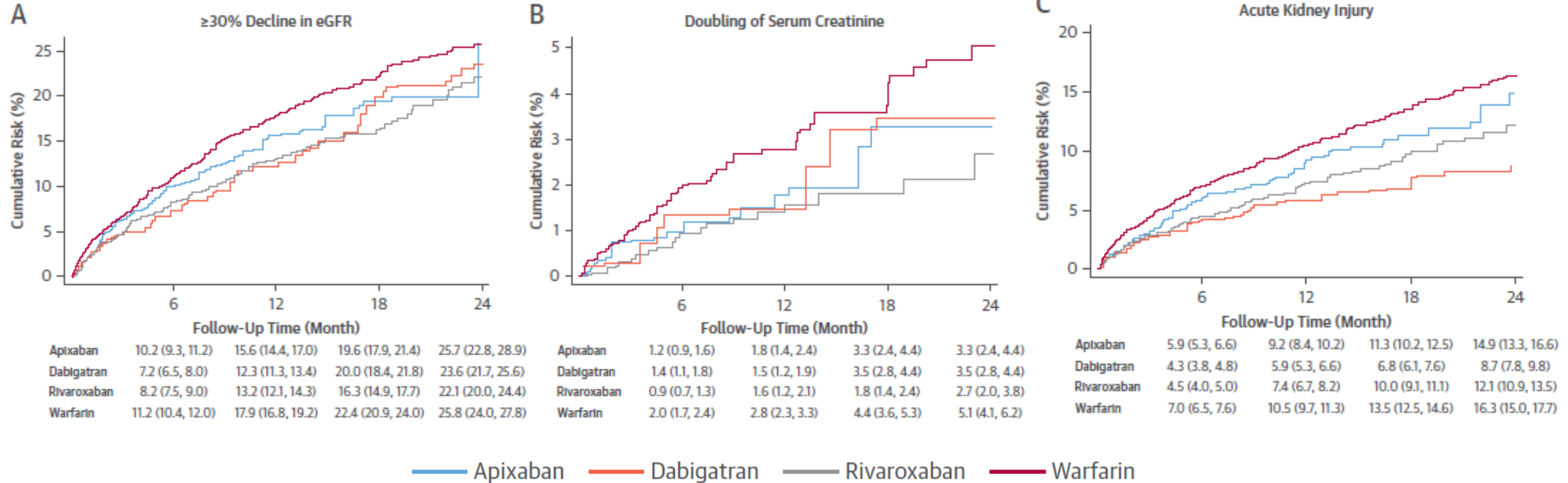
# Dose-Reduction Criteria for NOACs

RE-LY <sup>[a]</sup> Dabigatran*	ROCKET-AF <sup>[b]</sup> Rivaroxaban	ARISTOTLE <sup>[c]</sup> Apixaban	ENGAGE-AF <sup>[d]</sup> Edoxaban*
<ul style="list-style-type: none"><li>• No dose reduction criteria but 2 doses evaluated<ul style="list-style-type: none"><li>– 150 mg bid</li><li>– 110 mg bid</li></ul></li></ul>	<ul style="list-style-type: none"><li>• 20 → 15 mg qd for<ul style="list-style-type: none"><li>– CrCl 30 to 49 mL/min</li></ul></li></ul>	<ul style="list-style-type: none"><li>• 5 → 2.5 mg bid for ANY 2 of<ul style="list-style-type: none"><li>– Age ≥ 80</li><li>– Body weight ≤ 60 kg</li><li>– Serum creatinine ≥ 1.5 mg/dL</li></ul></li></ul>	<ul style="list-style-type: none"><li>• 60 → 30 mg qd or 30 → 15 mg qd for<ul style="list-style-type: none"><li>– CrCl 30 to 50 mL/min</li><li>– Body weight ≤ 60 kg</li><li>– Use of quinidine, verapamil, or dronedarone</li></ul></li></ul>

# Renal Outcome of NOACs vs VKA



# Renal Outcome of NOACs vs VKA



# Optimal Rivaroxaban Dose in Asian Patients With Atrial Fibrillation and Normal or Mildly Impaired Renal Function

So-Ryoung Lee, MD; Eue-Keun Choi, MD, PhD; Kyung-Do Han, PhD; Jin-Hyung Jung, BSc;  
Seil Oh, MD, PhD; Gregory Y.H. Lip, MD

**Background and Purpose**—Although rivaroxaban 15 mg (R15) was only given to patients with creatinine clearance (CrCl)  $\leq 50$  mL/min in the pivotal clinical trial, this dose has been commonly prescribed in Asian patients with nonvalvular atrial fibrillation regardless of renal function. There is a paucity of information on the clinical outcomes of R15 compared with rivaroxaban 20 mg (R20) in patients with CrCl  $\geq 50$  mL/min. This study aimed to examine the effectiveness and safety of 2 doses of rivaroxaban in Asian patients with atrial fibrillation and CrCl  $\geq 50$  mL/min.

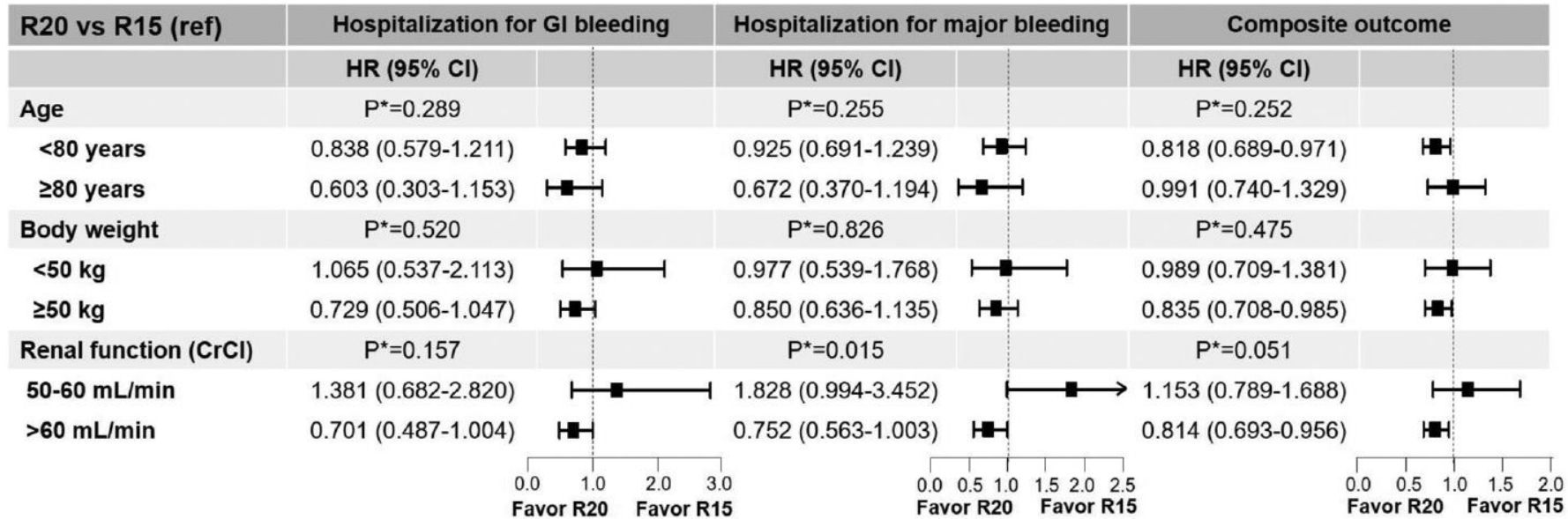
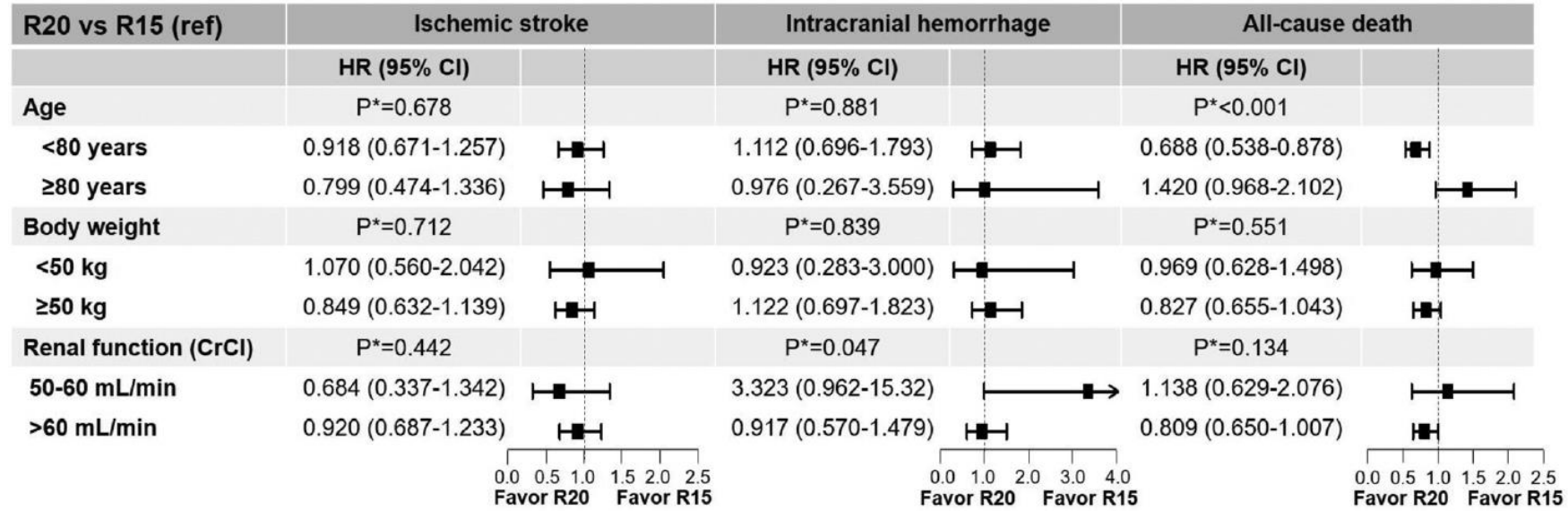
**Methods**—Using the Korean National Health Insurance Service database, patients with atrial fibrillation and normal or mildly impaired renal function (CrCl  $\geq 50$  mL/min) and naive to rivaroxaban or warfarin were included from January 2014 to December 2016. Three separate 1:1 propensity score–matched cohorts were conducted: R20 versus warfarin (n=15 584), R15 versus warfarin (n=11 554), and R20 versus R15 (n=10 392). Hazard ratios for ischemic stroke, intracranial hemorrhage, gastrointestinal bleeding, major bleeding, all-cause death, and composite clinical outcome were analyzed.

# Rivaroxaban 15mg in CrCl $\geq$ 50mL/min

Rivaroxaban 15mg vs Warfarin



# Rivaroxaban 15mg vs 20mg



# Rivaroxaban in Kidney Disease

## Evidence for warfarin and NOACs in AF by CKD stage

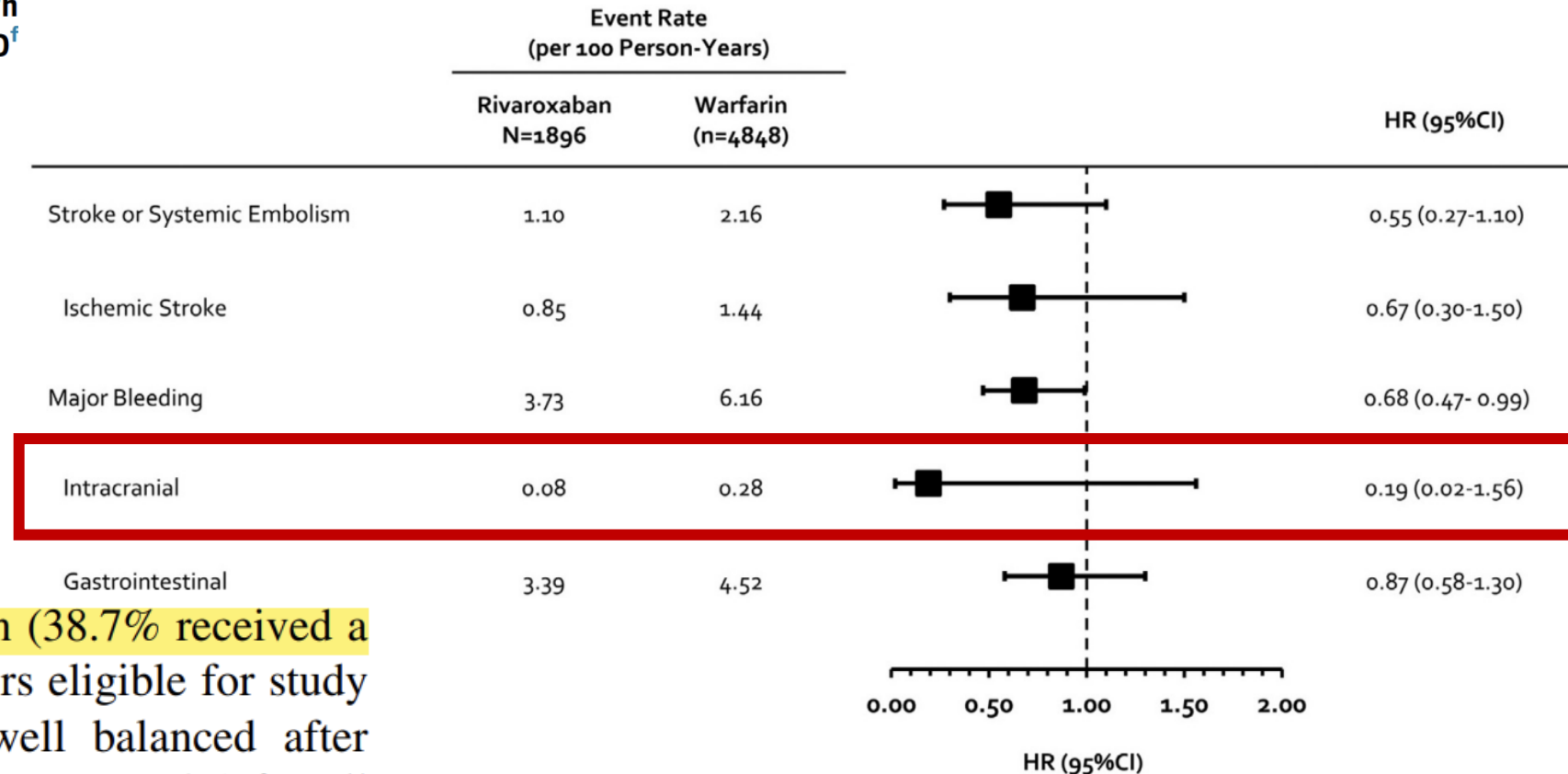
CKD stage	Warfarin	DOACs
Mild to moderate Stages 2-3 (eGFR 30-90 mL/min/1.73 m <sup>2</sup> )	Primarily observational data supporting use	High quality data support use, may be superior to warfarin
Severe Stage 4 (eGFR 15-29 mL/min/1.73 m <sup>2</sup> )	Limited data supports use	Pharmacologic studies allow for use with dose reductions, lack patient data
End stage renal disease Stage 5 (eGFR <15 mL/min/1.73 m <sup>2</sup> or on hemodialysis)	Majority of studies suggest lack of benefit and possible harm	<i>Dabigatran</i> removed by dialysis <i>Rivaroxaban</i> has safe drug levels based on modeling, but lacks patient data <i>Apixaban</i> safe and effective based on modeling and retrospective data, prospective data needed

# Rivaroxaban in Chronic Hemodialysis



## Rivaroxaban Versus Warfarin in Patients With Nonvalvular Atrial Fibrillation and Severe Kidney Disease or Undergoing Hemodialysis

Craig I. Coleman, PharmD<sup>a,b</sup>, Reinhold Kreutz, MD, Ph  
Daniel Eriksson, MS<sup>f</sup>, Anna-Katharina Meinecke, PhD<sup>f</sup>

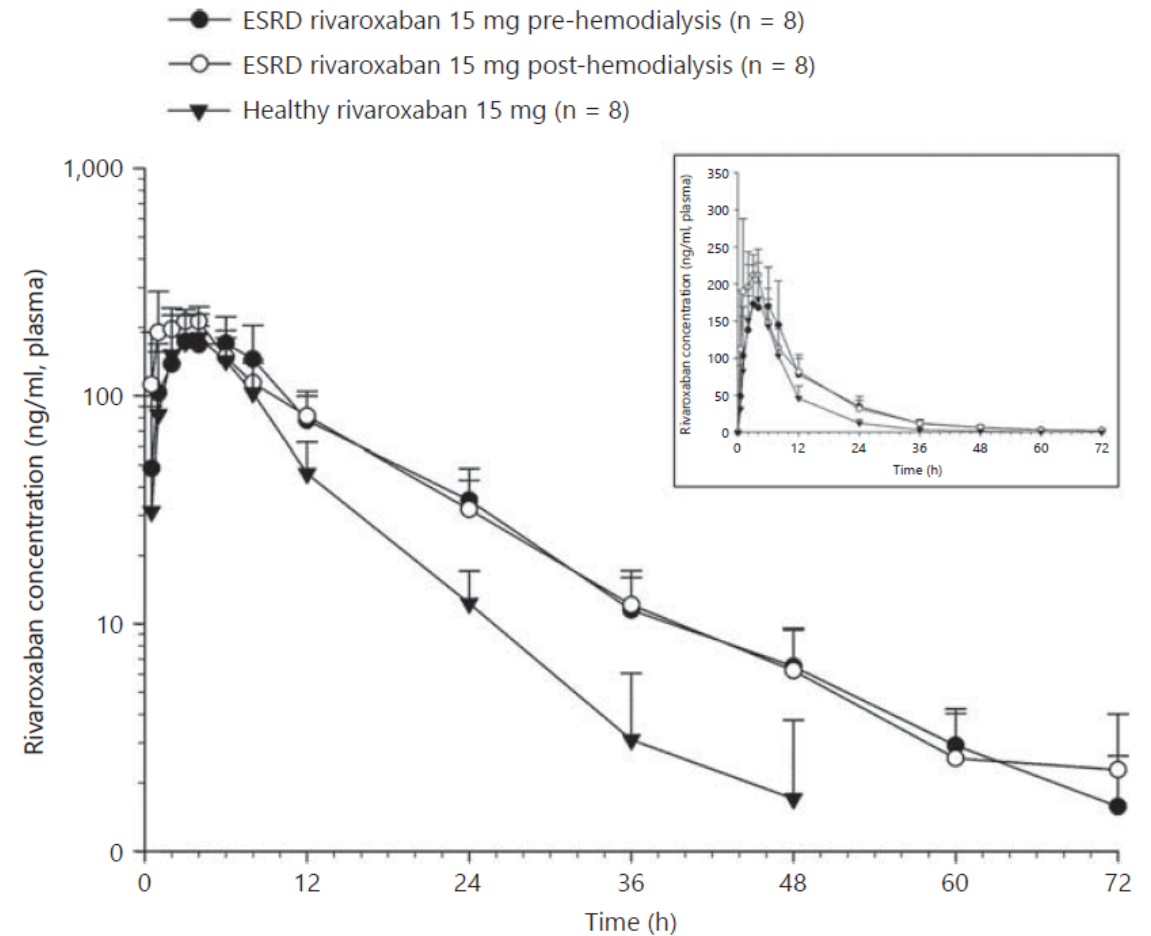
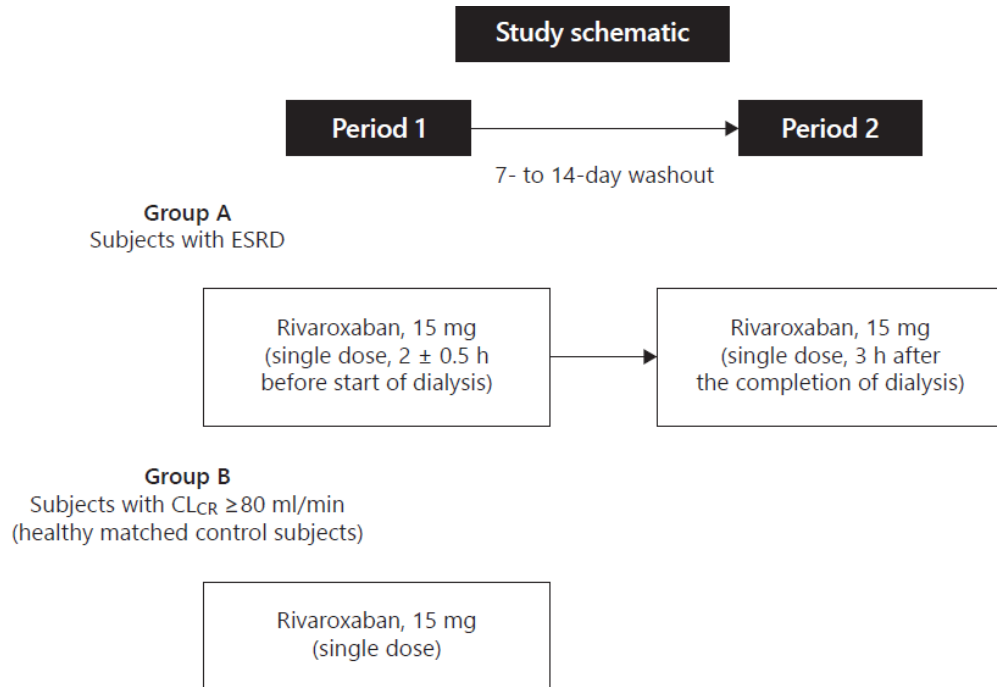


In total, we identified 1896 rivaroxaban (38.7% received a dose <20 mg/d) and 4848 warfarin users eligible for study inclusion. Baseline covariates were well balanced after adjustment (absolute standardized differences <0.1 for all



# Rivaroxaban 15mg in Chronic Hemodialysis

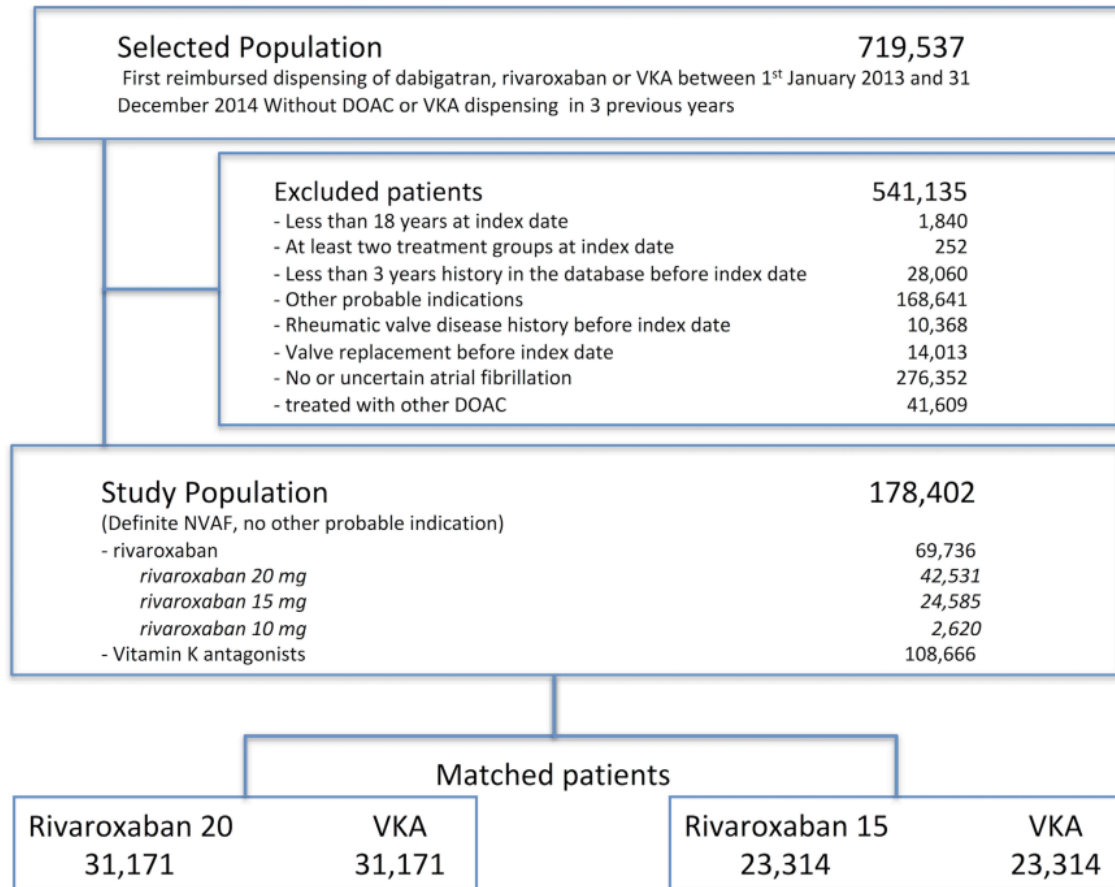
## Pharmacokinetics, Pharmacodynamics, and Safety of Single-Dose Rivaroxaban in Chronic Hemodialysis



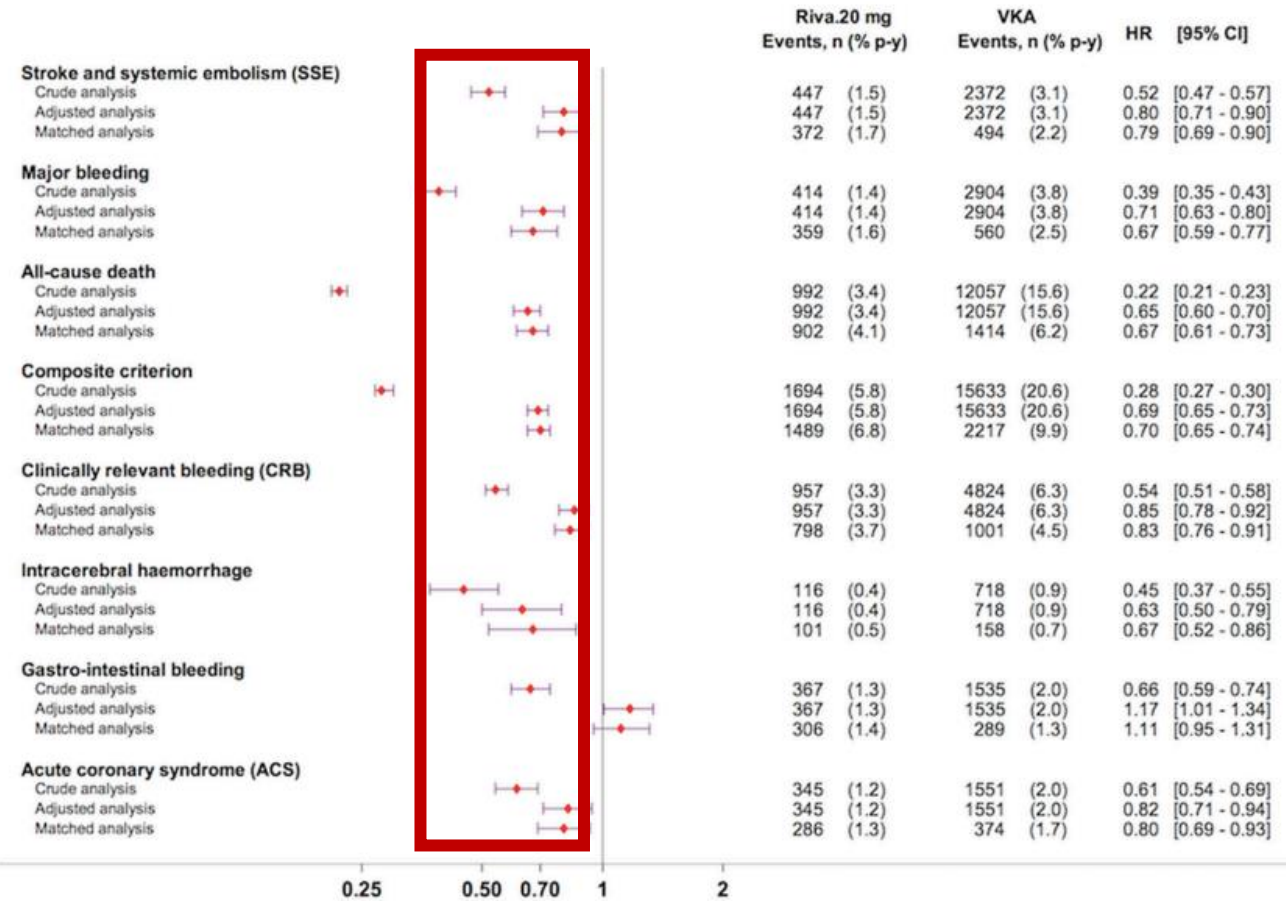
- ✓ Changes in PK and PD parameters in chronic dialysis patients were generally comparable to changes observed previously in patients with moderate-to-severe renal impairment who were not undergoing dialysis, and support use of a 15mg dose in this patient population

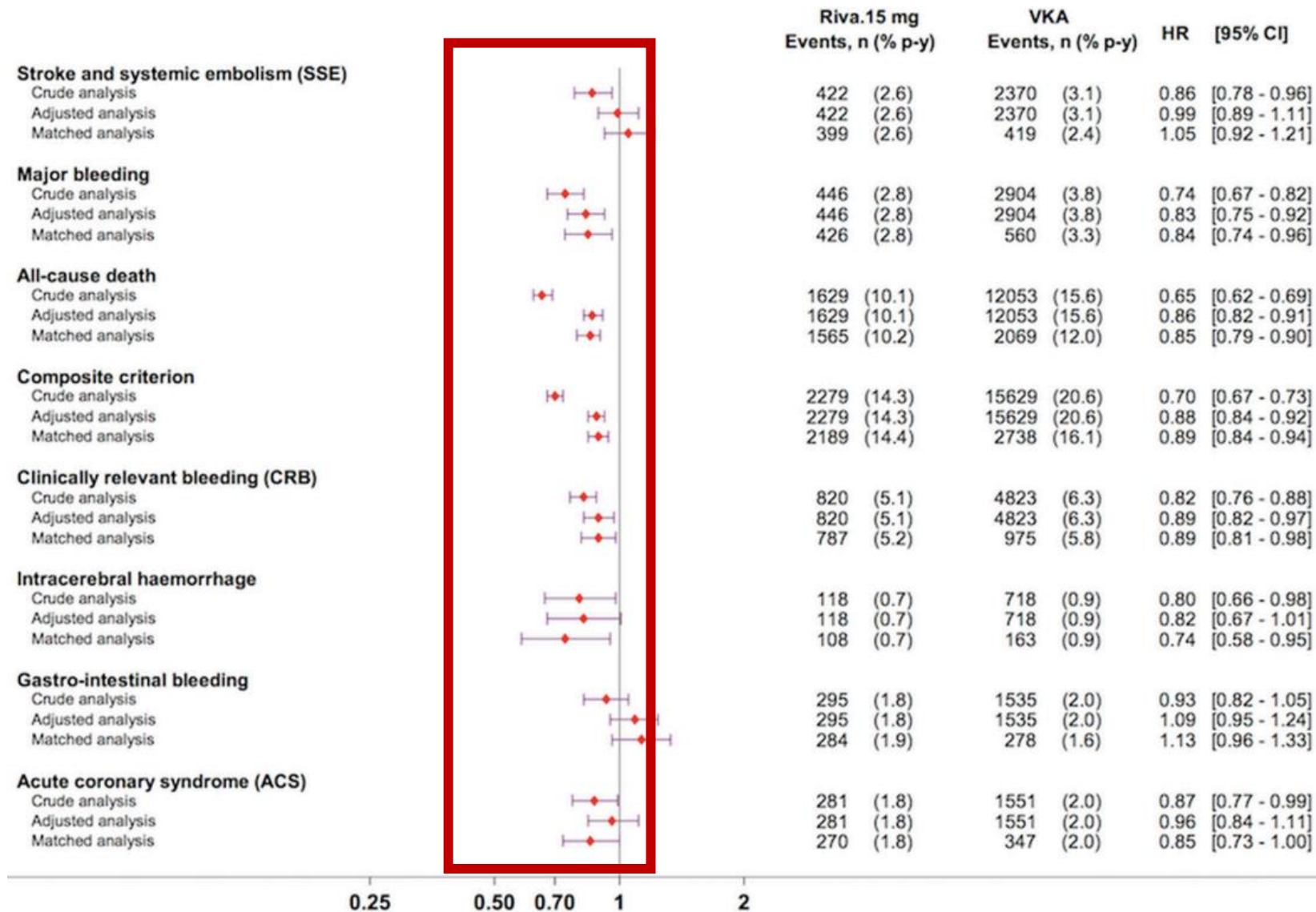
# Effectiveness and Safety of Rivaroxaban 15 or 20 mg Versus Vitamin K Antagonists in Nonvalvular Atrial Fibrillation

## A Population-Based New Users High-Dimensional Propensity Score Matched Cohorts Study



### Rivaroxaban 20mg vs VKA





✓ Rivaroxaban 15mg appears to be at least as effective and safer than VKA for the prevention of thromboembolic events in NVAf

# Conclusion

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## Fragile Patient with AF: focused on Rivaroxaban

### [Elderly]

- ✓ Bleeding risk is lower with rivaroxaban than with VKA in stroke prevention in patients  $\geq 80$  years old with non-valvular AF

### [High Fall Risk]

- ✓ Rivaroxaban reduced patients' risk of intracranial hemorrhage and were at least as effective in preventing stroke or systemic embolism as warfarin in NVAF patients at high-risk for falls

### [Low Body Weight]

- ✓ Major bleeding with NOACs vs. warfarin in patients with atrial fibrillation according to BMI
- ✓ No specific outcome data was available for patients with  $< 60$  kg or  $< 50$  kg in patients the full AF dose of rivaroxaban

### [Kidney Disease]

- ✓ Rivaroxaban is associated with lower risks of adverse renal outcomes than warfarin
- ✓ Rivaroxaban 20mg showed better results for the composite clinical outcome in  $\text{CrCl} \geq 50 \text{ mL/min}$  than rivaroxaban 15mg
- ✓ Rivaroxaban 20mg was associated with higher risk of major bleeding than Rivaroxaban 15mg in patients with  $\text{CrCl} 50\text{--}60 \text{ mL/min}$
- ✓ Rivaroxaban has safe drug levels based on modeling, but lacks patient data in CKD stage 5

# 리복사반 정

성분함량: 1정 중 Rivaroxaban 2.5mg / 10mg / 15mg / 20mg

제품성상: 2.5 mg: 노란색의 양면이 볼록한 원형의 필름코팅정



10 mg: 분홍색의 양면이 볼록한 원형의 필름코팅정



15 mg: 갈색의 양면이 볼록한 원형의 필름코팅정



20 mg: 어두운 빨간색의 양면이 볼록한 원형의 필름코팅정



약가: 2.5 mg: 640원

10 mg: 770원

15 mg: 950원

20 mg: 1,188원