

실제 임상 현장에서의 NOAC 사용 전략

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Agenda

- **Status of AF in Korea & Guidelines for AF**
- **Optimal Anticoagulation therapies**
- **Clinical Evidence of Rivaroxaban in AF**
- **Rivaroxaban in patients with Coronary Artery Disease**
- **Preserving Kidney Function with Rivaroxaban**

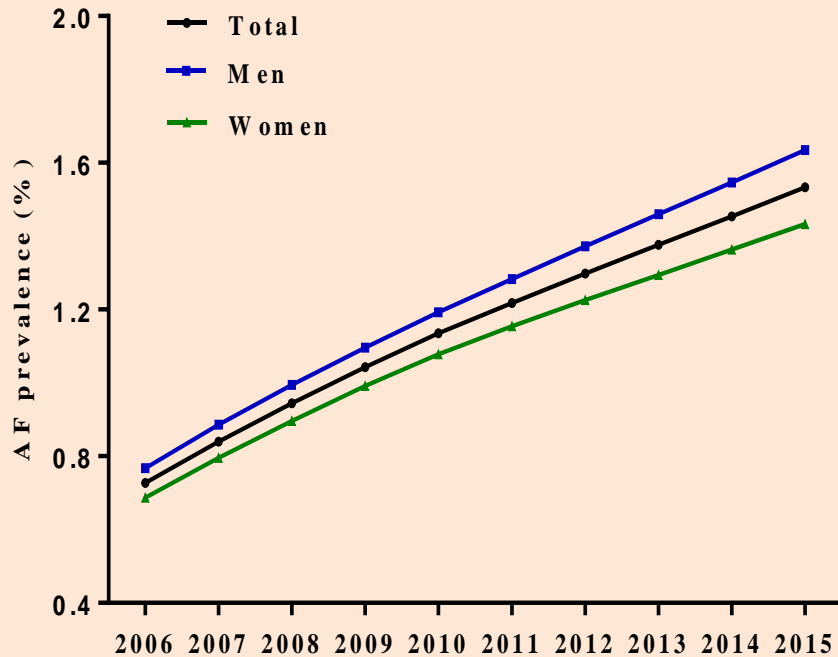
Status of AF in Korea & Guidelines for AF

01

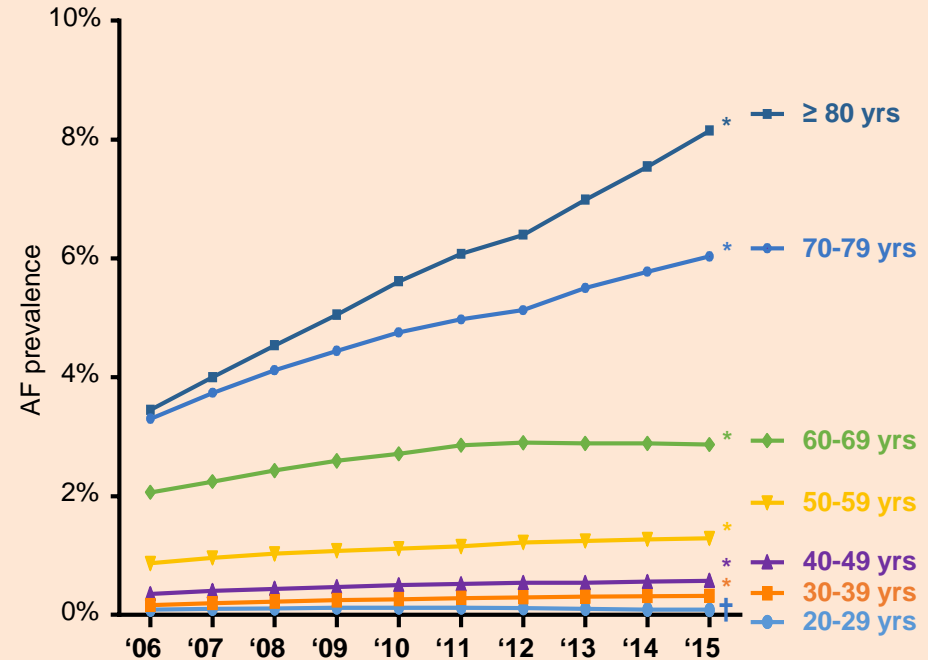
Prevalence of AF in Korea : NHIS cohort

국내 심방세동 유병률은 10년간 2배 가까이 증가했으며, 특히 연령 증가에 따른 유병률 증가세가 두드러짐

▷ 성별 심방세동 유병률('06-'15)



▷ 연령별 심방세동 유병률('06-'15)



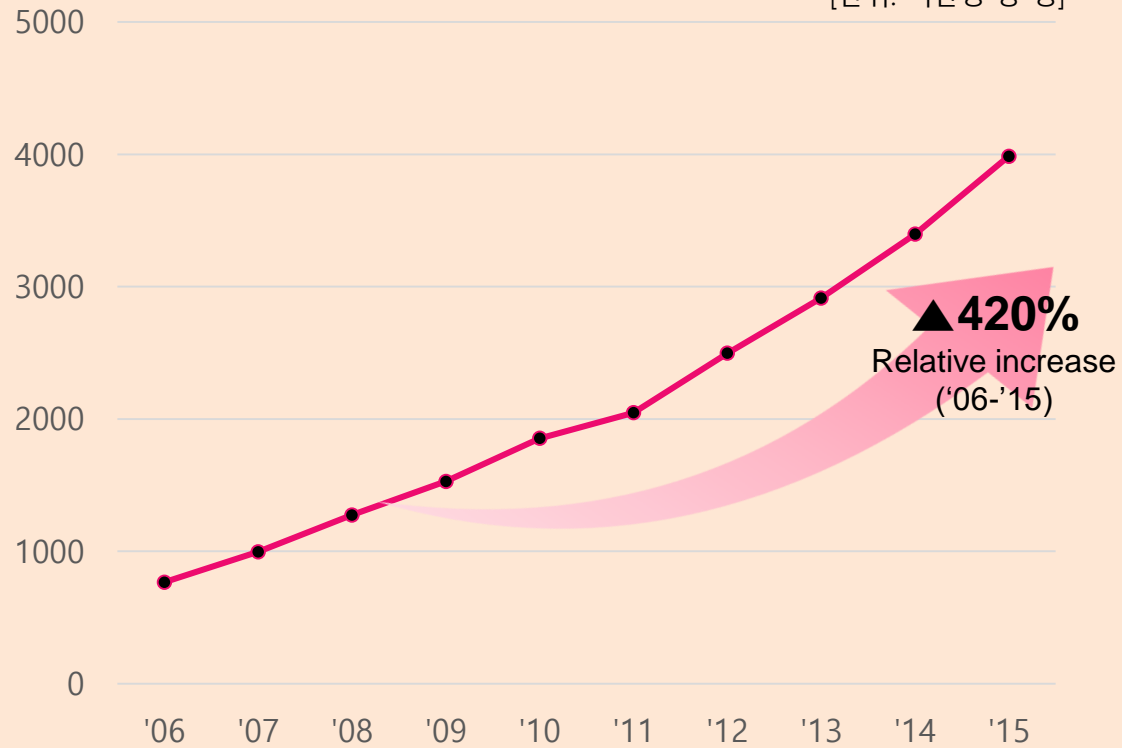
[Study design] A nationwide cohort study to investigate the 10-year trends of the prevalence and incidence of non-valvular AF and provide prevalence projections till 2060 in Korea. Using the Korean National Health Insurance Service database involving the entire Korean population, a total of 679,416 adults with newly diagnosed AF were identified from 2006 to 2015.

Increasing healthcare burden

심방세동으로 인한 입원 환자 급격히 증가하며
입원 비용도 '06-'15년 사이 약 5.7배 증가

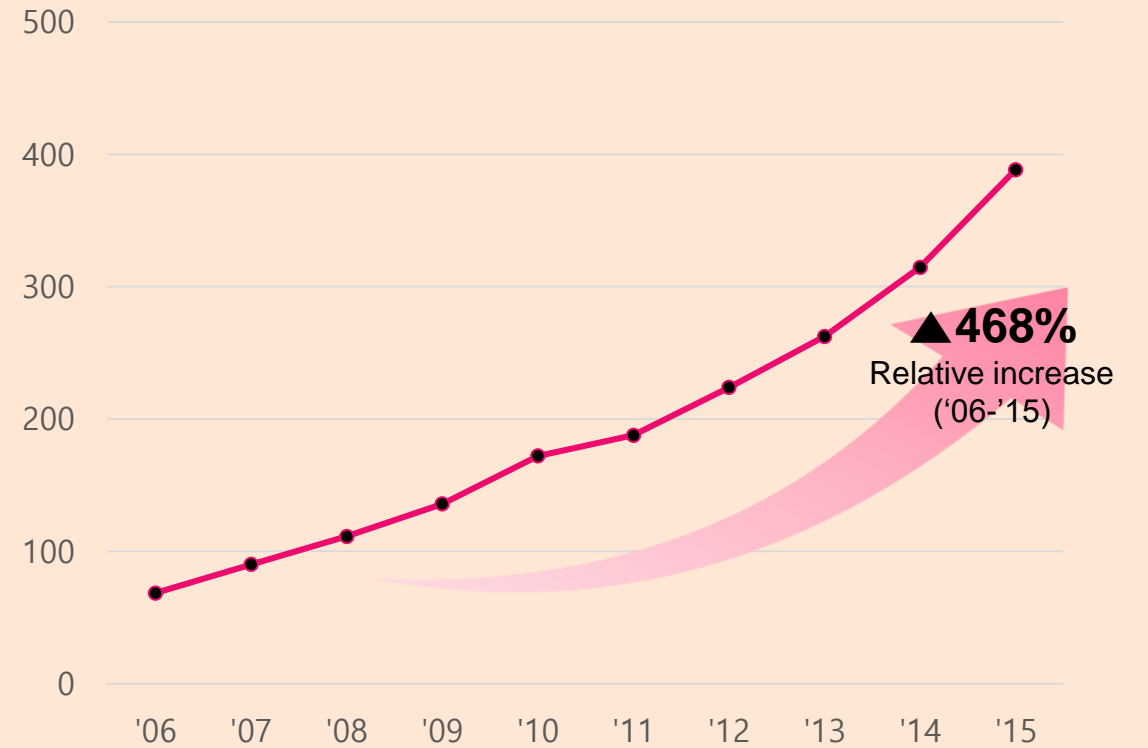
AF hospitalization

[단위: 백만명 당 명]



AF hospitalization cost

[단위: million EUR]

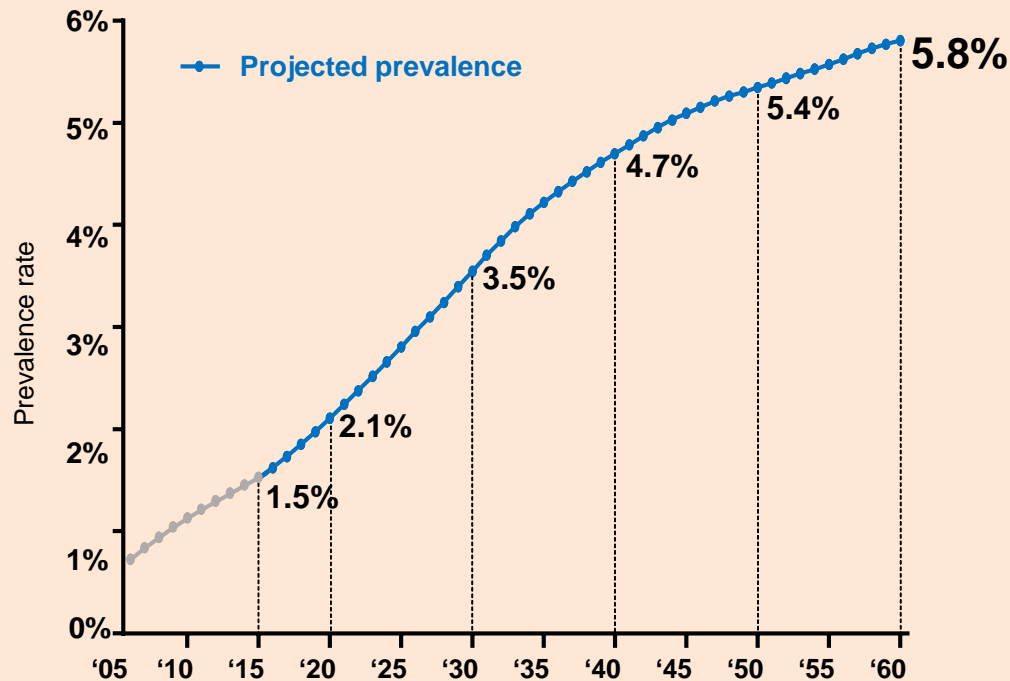


[Study design] Using the National Health Insurance Service (NHIS) database involving the entire adult Korean population (n=41 701 269 in 2015), analysed a nationwide AF cohort representing 931 138 patients with AF.

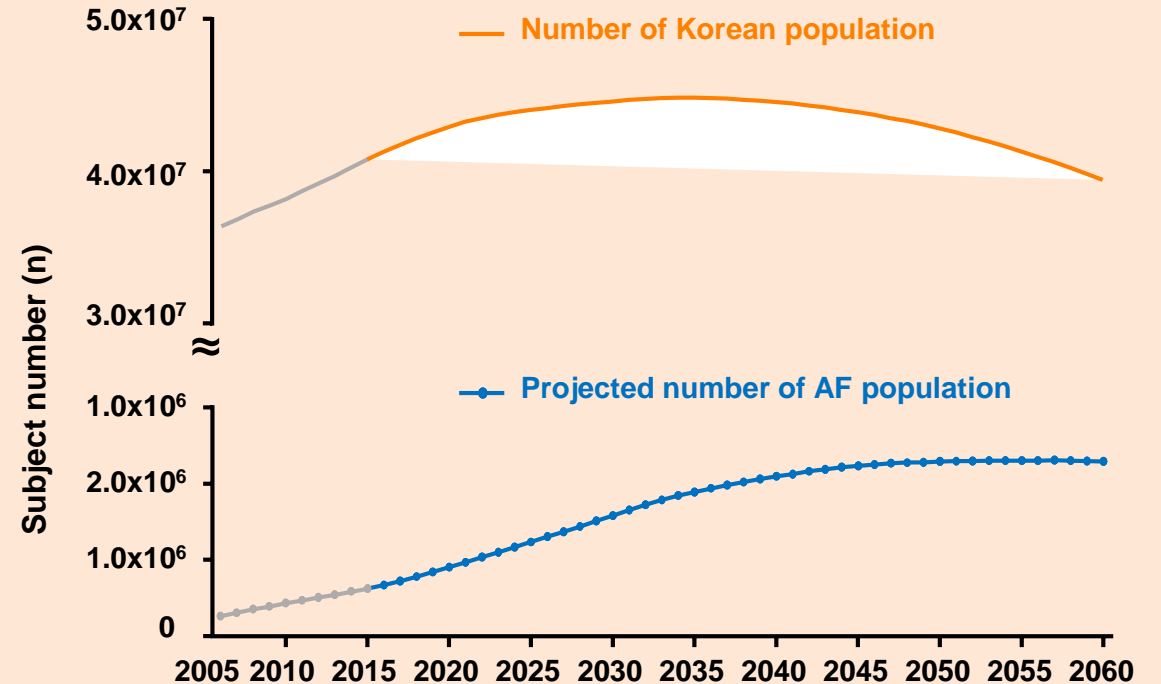
AF Prevalence Projection (~2060)

고령화와 관련 질환 증가로 인해 심방세동 환자의 지속적인 증가가 예상되며, 2060년 심방세동 예측 유병률은 6%.

▷ 심방세동 예측 유병률(~2060)



▷ 예상 환자 수(~2060)

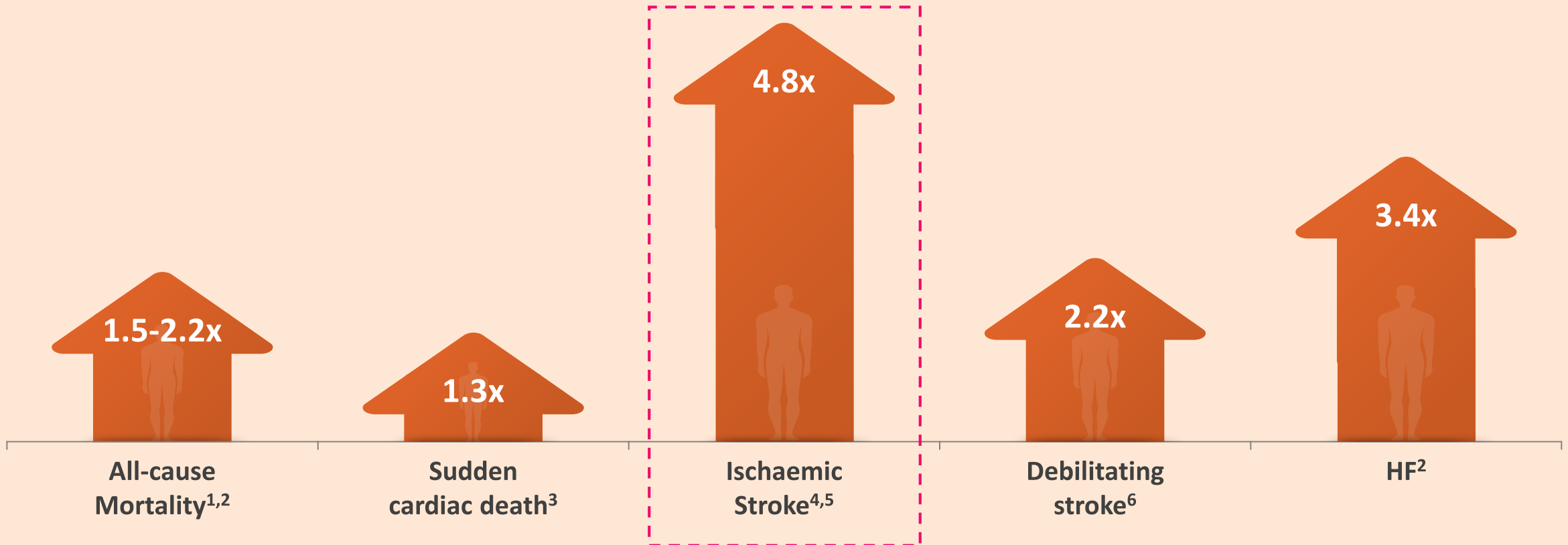


[Study design] A nationwide cohort study to investigate the 10-year trends of the prevalence and incidence of non-valvular AF and provide prevalence projections till 2060 in Korea. Using the Korean National Health Insurance Service database involving the entire Korean population, a total of 679,416 adults with newly diagnosed AF were identified from 2006 to 2015.

Progression of AF

심방세동은 사망, 심혈관 사망, 심부전 위험을 높이며, 특히 허혈성 뇌졸중 위험을 약 5배 높임

Fold risk increase with AF



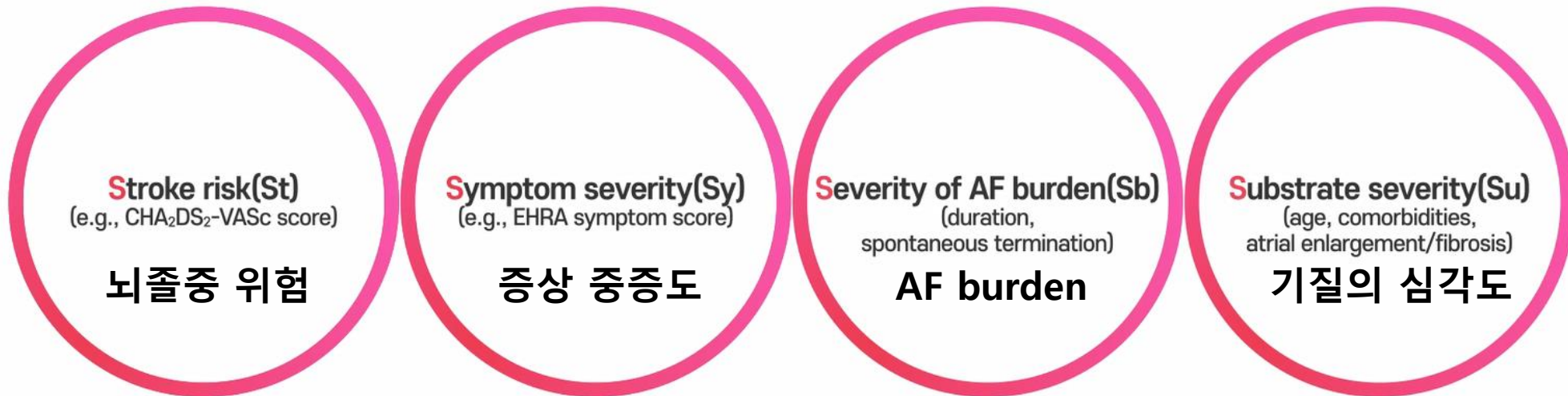
CV, cardiovascular. HF, heart failure; RR, risk ratio .

Ref) 3. Camm AJ, et al. Eur Heart J. 2010 Oct;31(19):2369-429. 4. Stewart S, et al. Am J Med. 2002 Oct 1;113(5):359-64. 5. Pdersen OD, et al. Eur Heart J. 2006 Feb;27(3):290-5. 6. Wolf PA, et al. Stroke. 1991 Aug;22(8):983-8. 7. Page RL, et al. Circulation. 2003 Mar 4;107(8):1141-5. 8. Dulli DA, et al. Neuroepidemiology. Mar-Apr 2003;22(2):118-23.

CC To ABC

Confirm AF : A 12-lead ECG or a rhythm strip showing AF pattern for ≥ 30 s

Characterise AF (the 4S-AF scheme)



CC To ABC

2020 ESC Guideline

심방세동의 통합적 치료를 위해 ABC pathway를 권장 & 특히 뇌졸중/전신색전증 예방을 위한 항응고 치료는 필수

CC To ABC

Treat AF: The ABC pathway

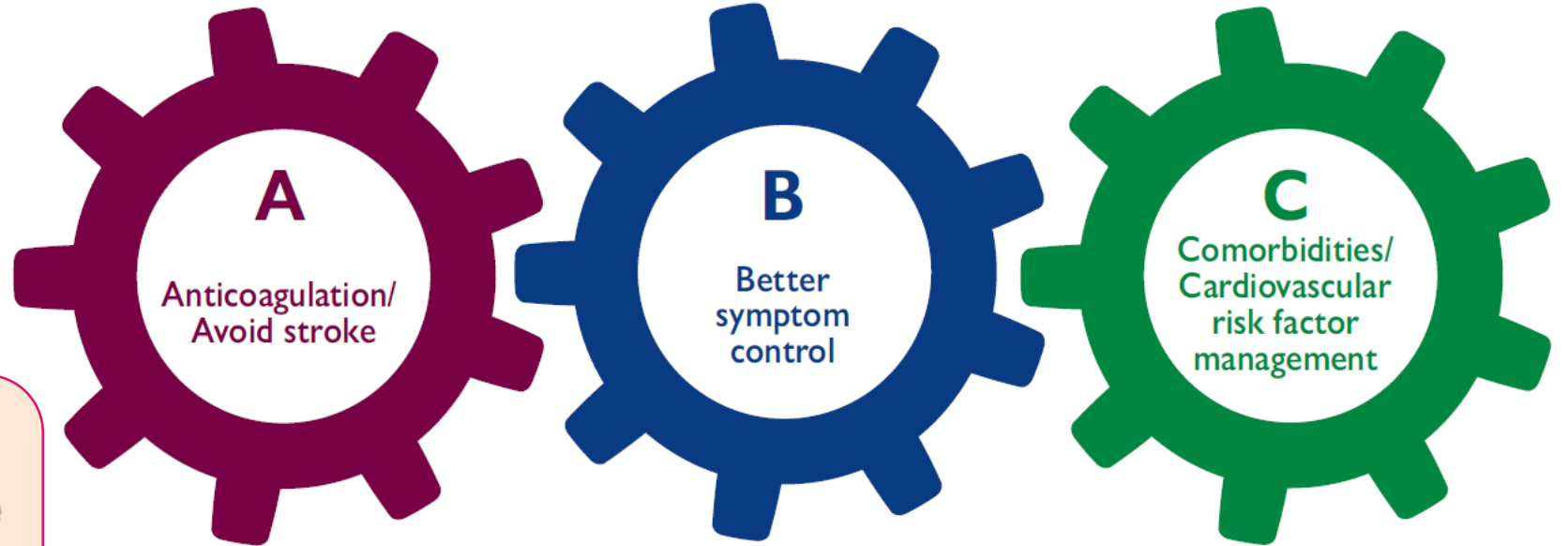
A

- ✓ Stroke risk assessment by

CHA₂DS₂-VASc score

- ✓ Bleeding risk assessment by

HAS-BLED score



항응고요법/
뇌졸중 예방

증상 조절 개선

동반질환/ 심혈관질환
위험요인 관리

CHA₂DS₂-VASc score Stroke risk assessment

심방세동 환자에서 CHA₂DS₂-VASc score를 이용해
뇌졸중 발생 위험도 판정 & 저위험군 감별

Risk factors & definitions		Score
C	Congestive heart failure Clinical HF / objective evidence of moderate-severe LV dysfunction / HCM	1
H	Hypertension	1
A	Age ≥ 75 years	2
D	Diabetes mellitus	1
S	Stroke / Transient ischaemic attack / Thromboembolism	2
V	Vascular disease Angiographically significant CAD, previous MI, PAD, or aortic plaque	1
A	Age 65 - 74 years	1
Sc	Sex category (female)	1
Maximum score		9

CHA ₂ DS ₂ -VASc Score	Ajduced rate for Thromboembolism
0	0.0
1	1.3
2	2.2
3	3.2
4	4.0
5	6.7
6	9.8
7	9.6
8	6.7
9	15.2

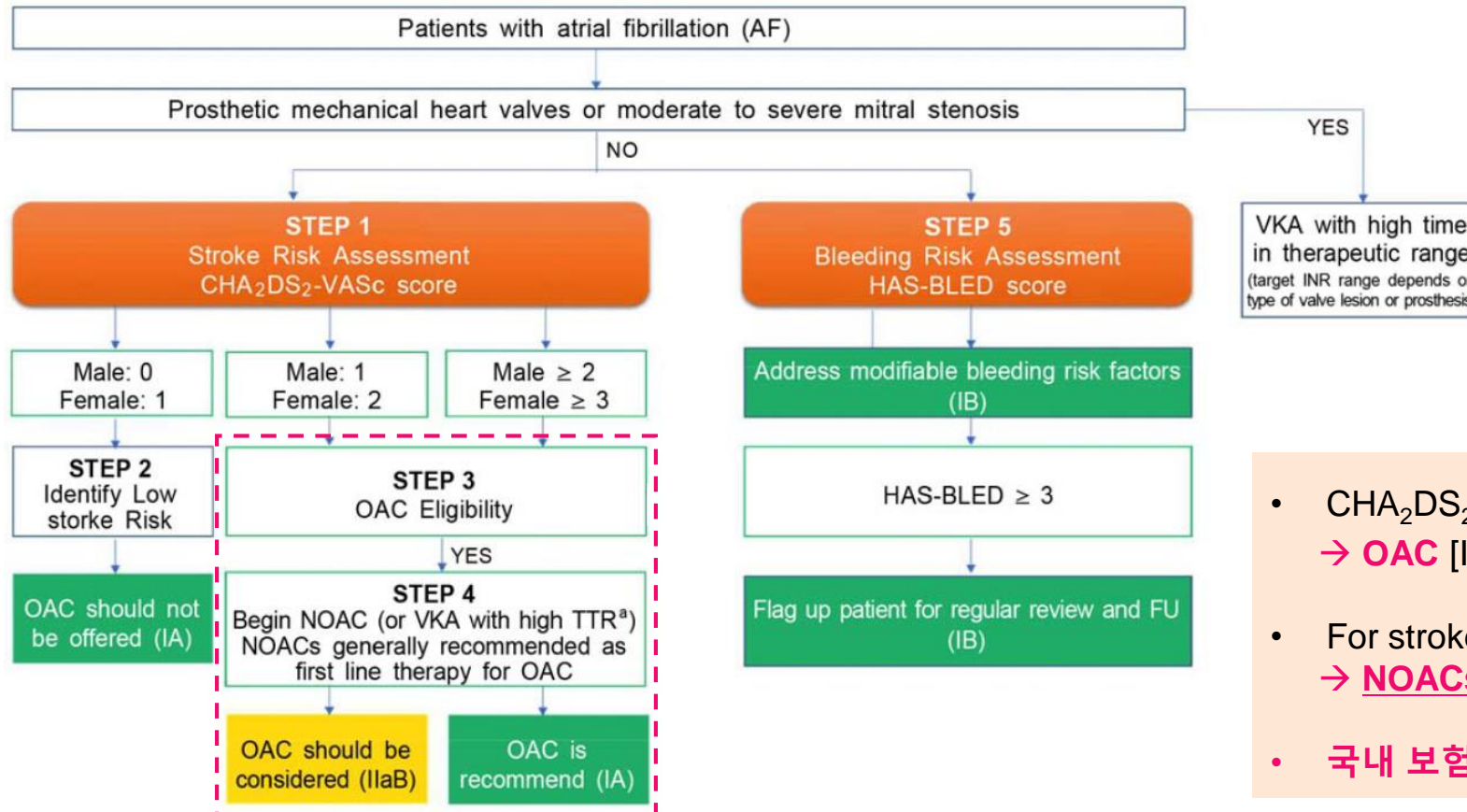
OAC recommended

CAD, coronary artery disease; HCM, hypertrophic cardiomyopathy; HF, heart failure; MI, myocardial infarction; PAD, peripheral artery disease

Adjusted for Warfarin use, Rate during 1 year

2021 KHRS Guideline for AF

CHA₂DS₂-VASc score ≥2(남), ≥3(여) 심방세동 환자는 뇌졸중 예방을 위해 NOAC 치료 강력히 권장



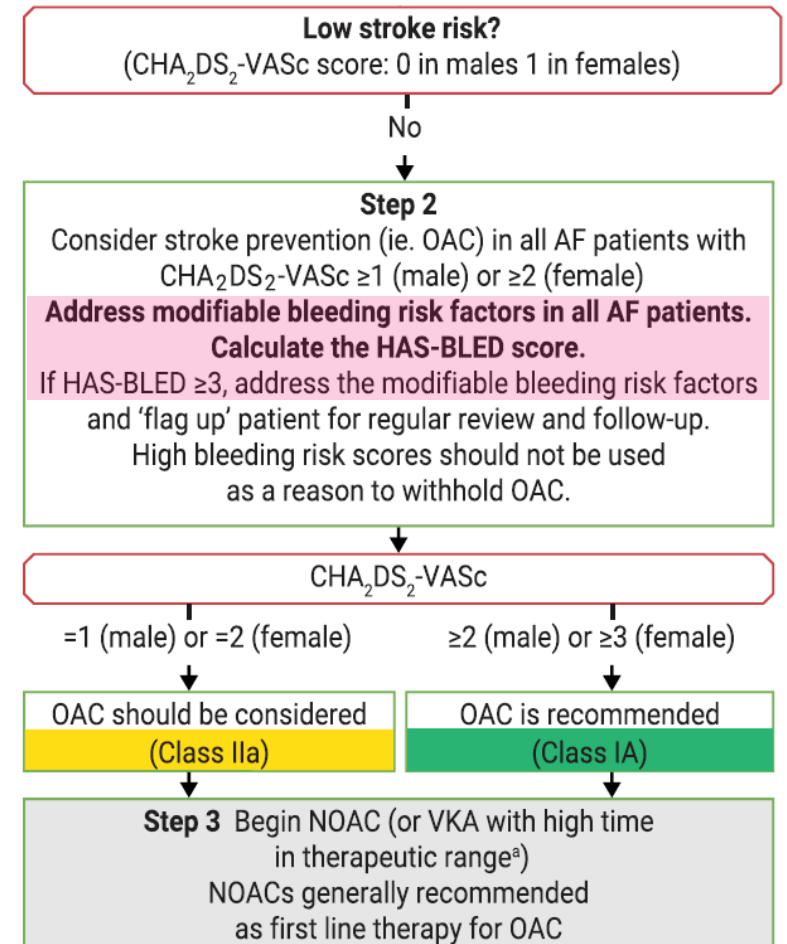
- CHA₂DS₂-VASc ≥ 2(male) or ≥3(female)
→ **OAC** [I / A]
- For stroke prevention in AF patients who are eligible for OAC
→ **NOACs are recommended in preference to VKAs** [I / A]
- 국내 보험기준 : CHA₂DS₂-VASc ≥ 2 : NOAC 급여

HAS-BLED score

Bleeding risk assessment

경구 항응고제 사용 결정 시, HAS-BLED score로
출혈위험도 평가 & 교정 가능한 출혈 위험인자 파악

Risk factors & definitions		Score
H	Uncontrolled Hypertension (SBP > 160mmHg)	1
A	Abnormal renal and/or hepatic function Dialysis, transplant, serum creatinine >200 mmol/L, cirrhosis, bilirubin > x 2 upper limit of normal, AST/ALT/ALP >3 x ULN	1 for each
S	Stroke	1
B	Bleeding history or predisposition	1
L	Labile INR (TTR <60% in patients receiving VKA)	1
E	Elderly (>65 years)	1
D	Drugs* or excessive alcohol drinking *Concomitant use of antiplatelet or NSAIDs	1 for each
Maximum score		9



Optimal Anticoagulation therapies

02

Benefits of NOACs over VKAs

NOAC의 VKA 대비 높은 임상적 유용성

	Warfarin	NOACs
Onset & Offset	Slow	Rapid
Therapeutic index	Narrow	Wide
Food effect	Yes	No
Drug interaction	Many	Few
Dosing	Variable	Fixed
Monitoring	Yes	No

Less labour-intensive

Reduced administrative costs

Lower impact on patients' daily life

Improved QoL

Improved compliance

Improved Benefit-Risk profile

Bleeding risk with VKA in Asian

VKA로 인한 출혈 위험은 아시아인에서 더 높게 나타남

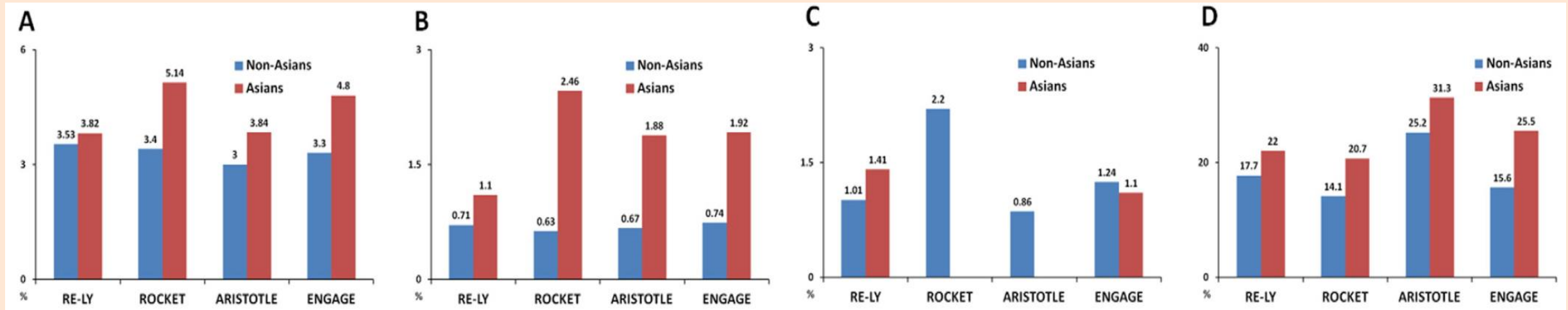
[Bleeding events on warfarin in Asians vs. non-Asians, from randomized trials]

A. Major bleeding

B. Intra-cranial haemorrhage

C. Gastrointestinal bleeding

D. All(major+minor) bleeding

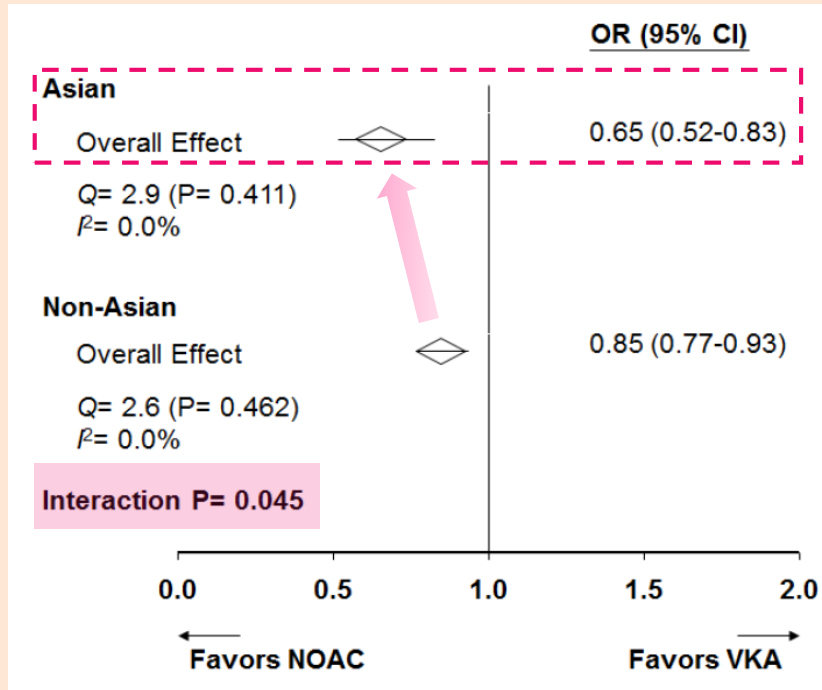


[Study Design] A review to provide an overview and reappraisal of stroke prevention in Asian patients with AF.

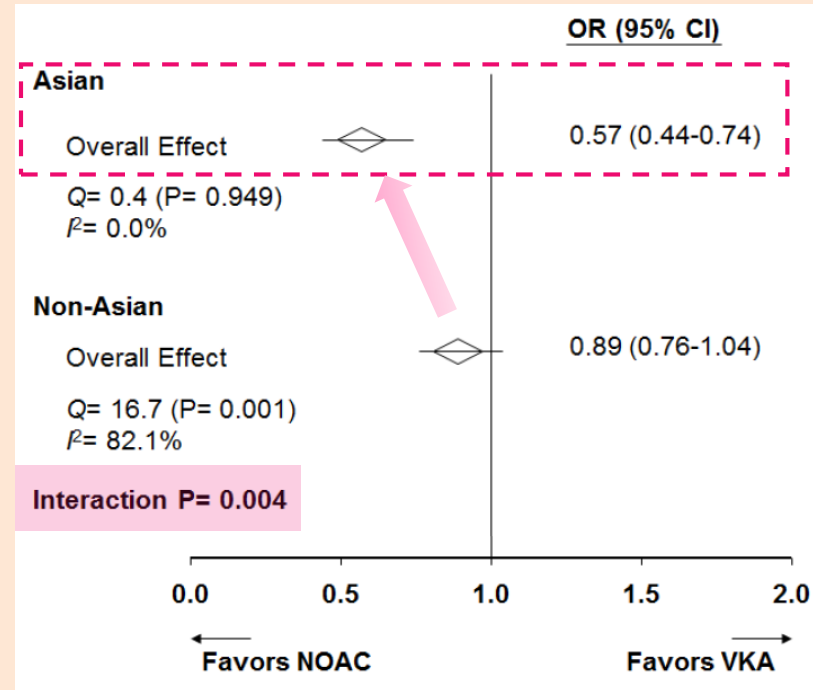
NOACs in Asian : Meta-Analysis

VKA 대비 높은 NOAC의 효과와 안전성은
아시아인에서 더 뚜렷하게 나타남

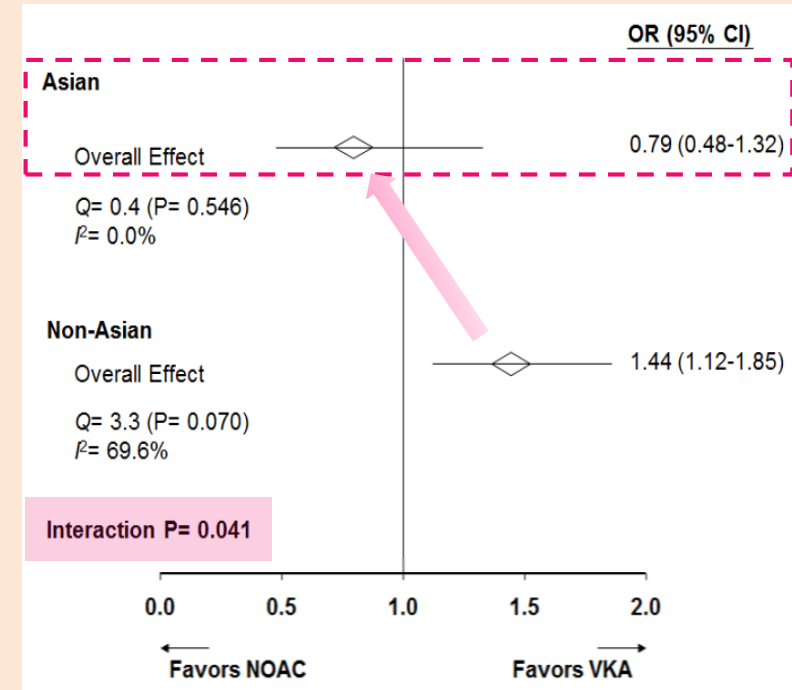
▷ Stroke or Systemic embolism



▷ Major bleeding



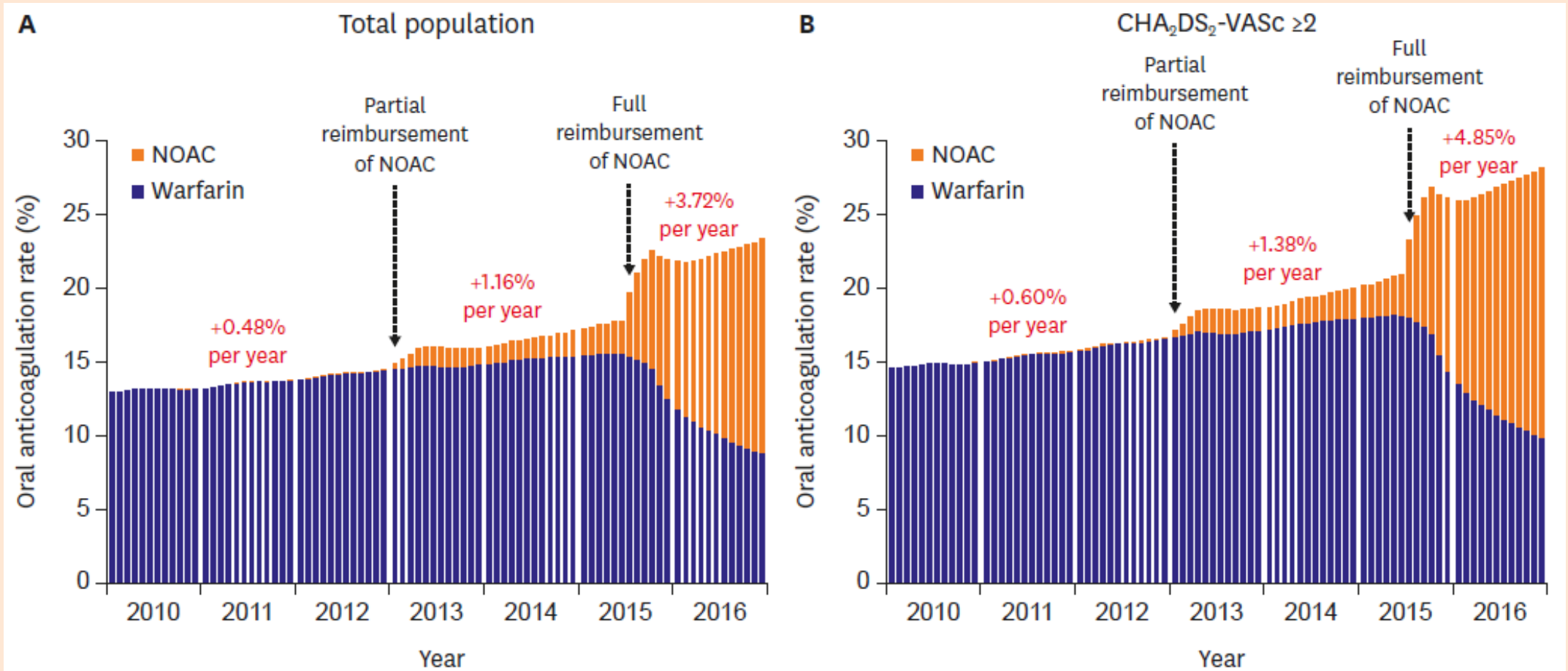
▷ Gastrointestinal bleeding



[Study Design] A meta-analysis of large phase III clinical trials to compared efficacy and safety of NOACs between patients enrolled in Asian and non-Asian countries. The 5 studies were included (RE-LY with dabigatran, ROCKET AF & J-ROCKET AF with rivaroxaban, ARSTOTLE with apixaban, ENGAGE AF-TIMI 48 with edoxaban) with 8,928 Asian patients and 64,033 non-Asian patients.

Trends in OAC therapy : NHIS cohort

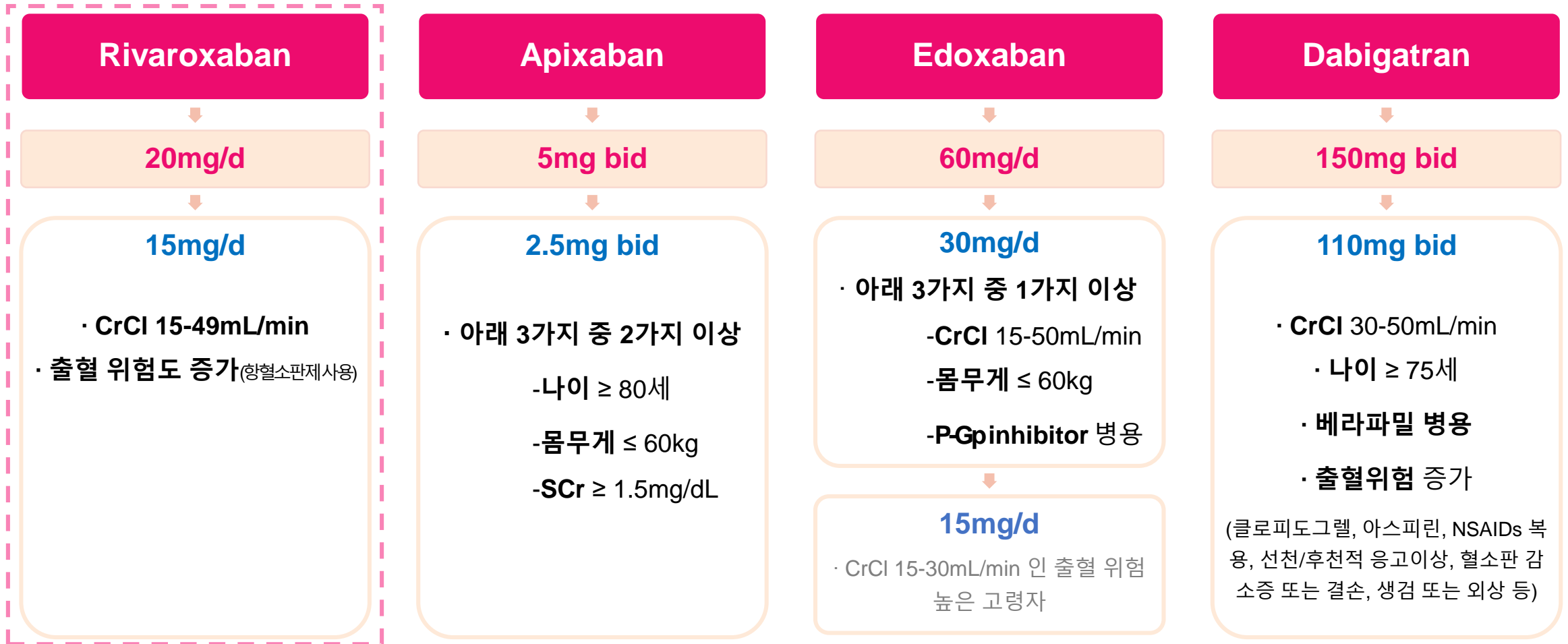
NOAC 도입과 함께 항응고제 시장도 함께 증가하였으며, 1차 약제로 급여기준 완화 이후 NOAC 사용이 크게 증가



[Study Design] Between January 2002 and December 2016, we identified 888,540 patients with AF in the Korea National Health Insurance system database. The change of OAC rate in different medical systems after the introduction of NOAC were evaluated.

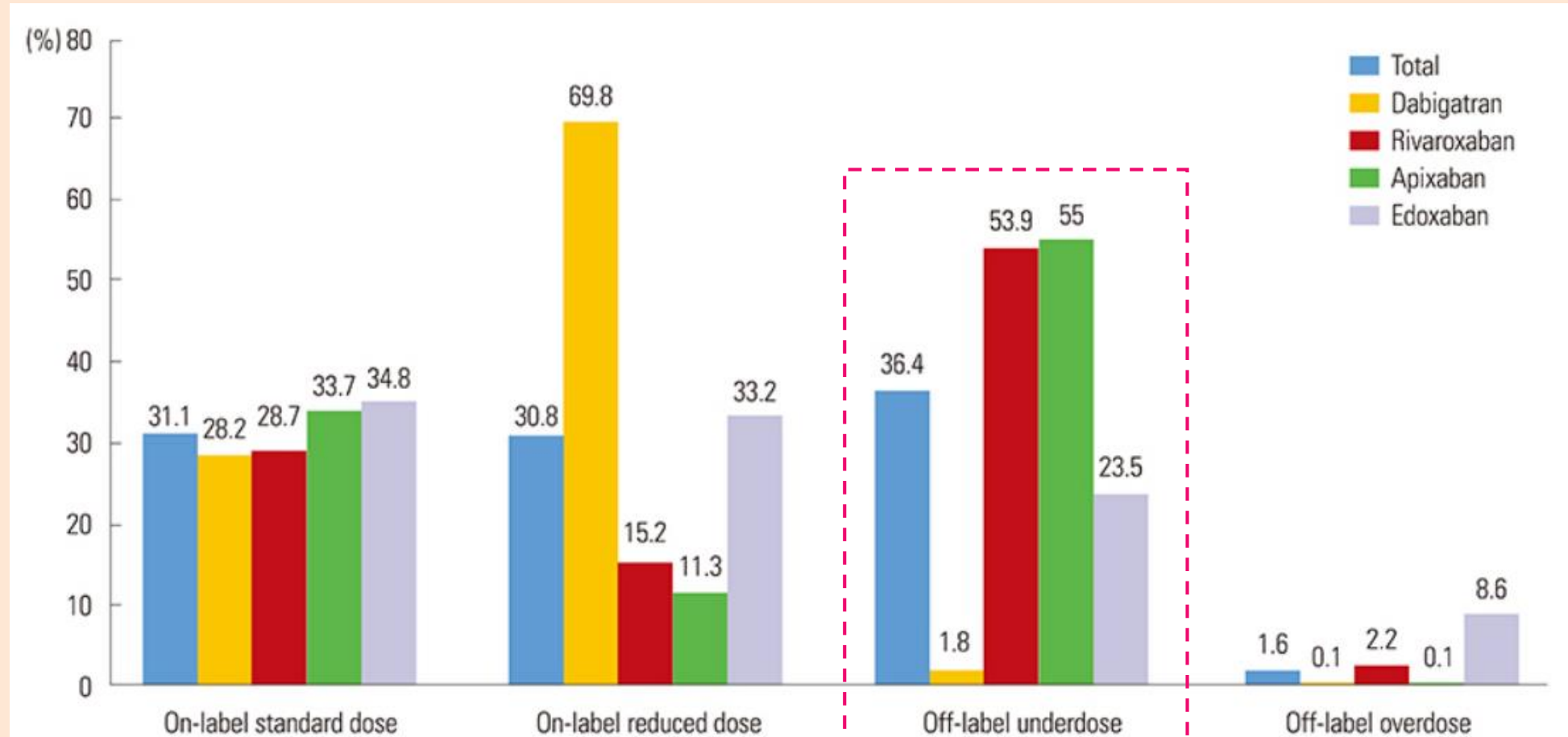
2022 KHRS AF_NOAC 용량 조절 기준

RIV 용량 조절 시 신기능과 항혈소판제 사용 여부만 고려,
그 외 NOAC 제제는 나이, 체중, 병용 약제 등 추가 고려 필요



Label adherence : CODE-AF registry

NOAC 투여 중인 국내 AF환자의 1/3은 허가 외 용량으로
치료 중 (Off-label underdose 36.4%)

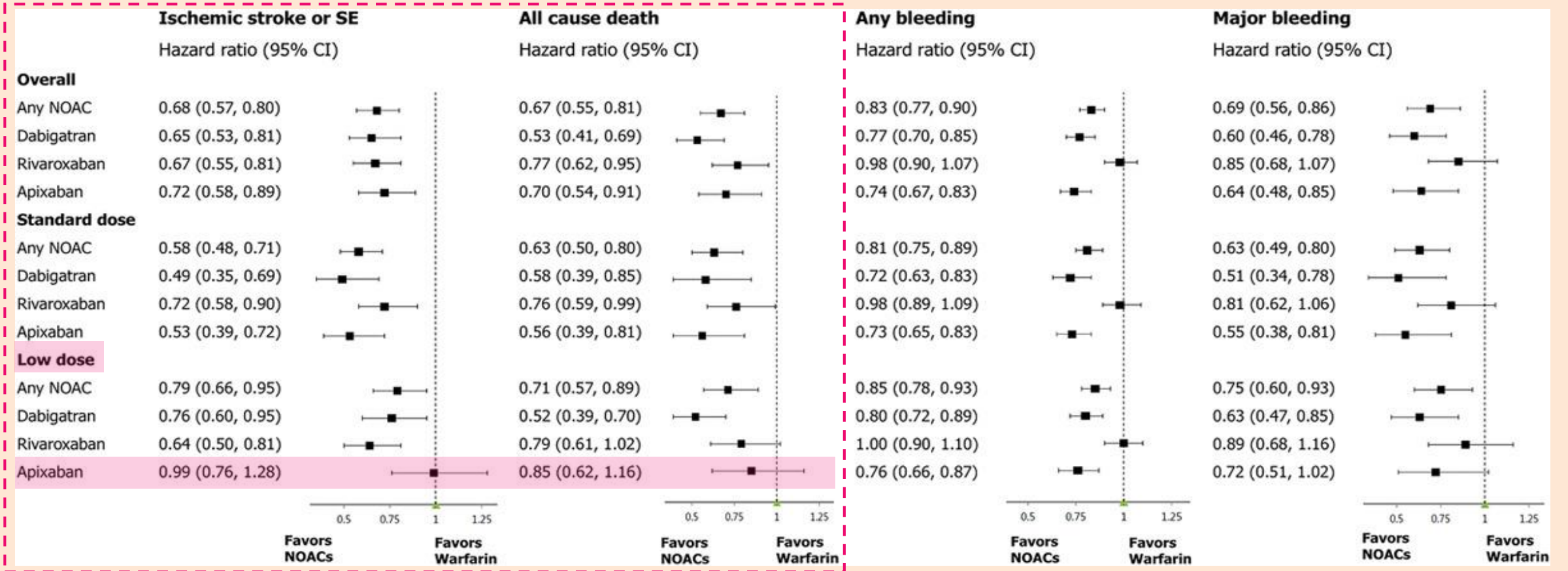


[Study Design] 3,080 AF patients who were prescribed NOACs(dabigatran 27.2%, rivaroxaban 23.9%, apixaban 36.9%, and edoxaban 12.0%) between June 2016 and May 2017 were included. Four NOAC doses were categorized as on- or off-label use according to Korea Food and Drug Regulations.

Effectiveness & Safety of low dose : NHIS cohort (2015-2016)

국내 환자는 저용량 NOAC 처방이 표준용량 대비 다빈도 & 저용량 Apixaban은 비교적 낮은 임상적 유용성 나타냄

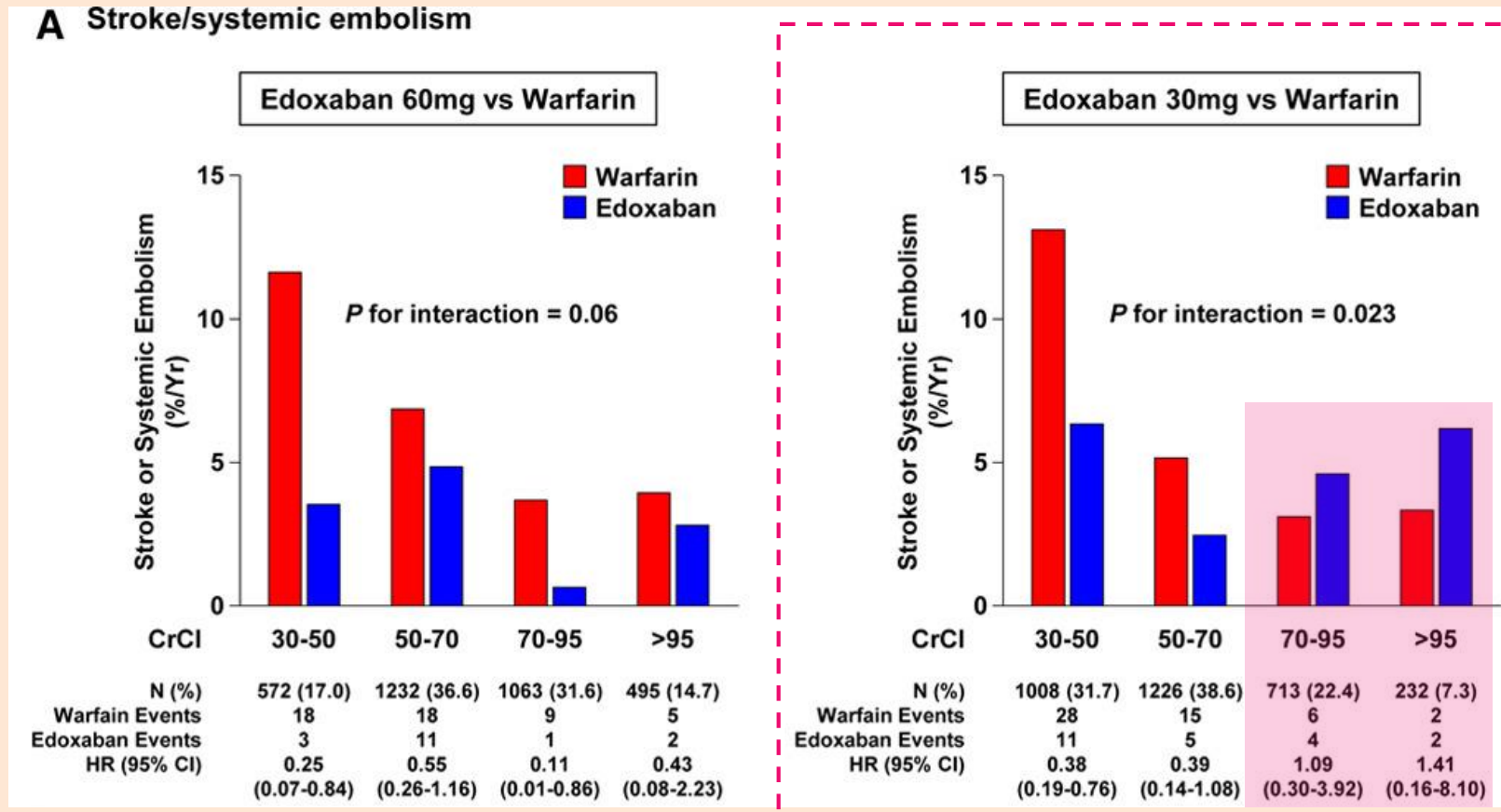
▶ Patients with AF <75 years without chronic kidney disease



[Study Design] Using nationwide administrative claims-based datasets from the Korean National Health Insurance Service Database (July 1, 2015, to December 31, 2016), this study comprised 56 504 anticoagulation-naive nonvalvular atrial fibrillation patients with high thromboembolic risk (CHA₂DS₂-VASc score, ≥2) treated with oral anticoagulants.

Effectiveness of low dose : NHIS 2016

정상 이상의 신기능 환자에서 low-dose edoxaban은 Warfarin 대비 낮은 뇌졸중/전신색전증 예방 효과 나타냄

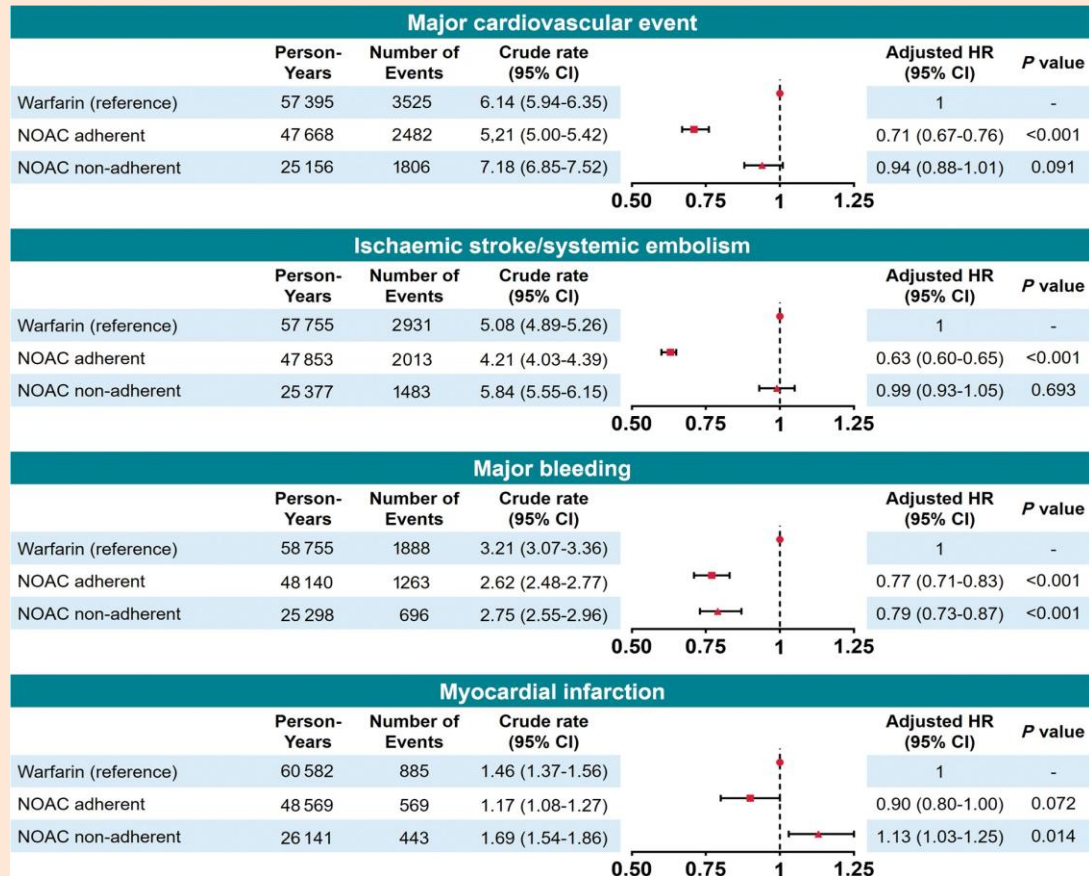


[Study Design] In the Korean National Health Insurance Service data during the period from January to December 2016, the study identified 9537 edoxaban-treated patients. Effectiveness and safety outcomes were compared between low-dose edoxaban regimen (LDER, 30 mg daily, n=3016) and matched warfarin group (n=3016).

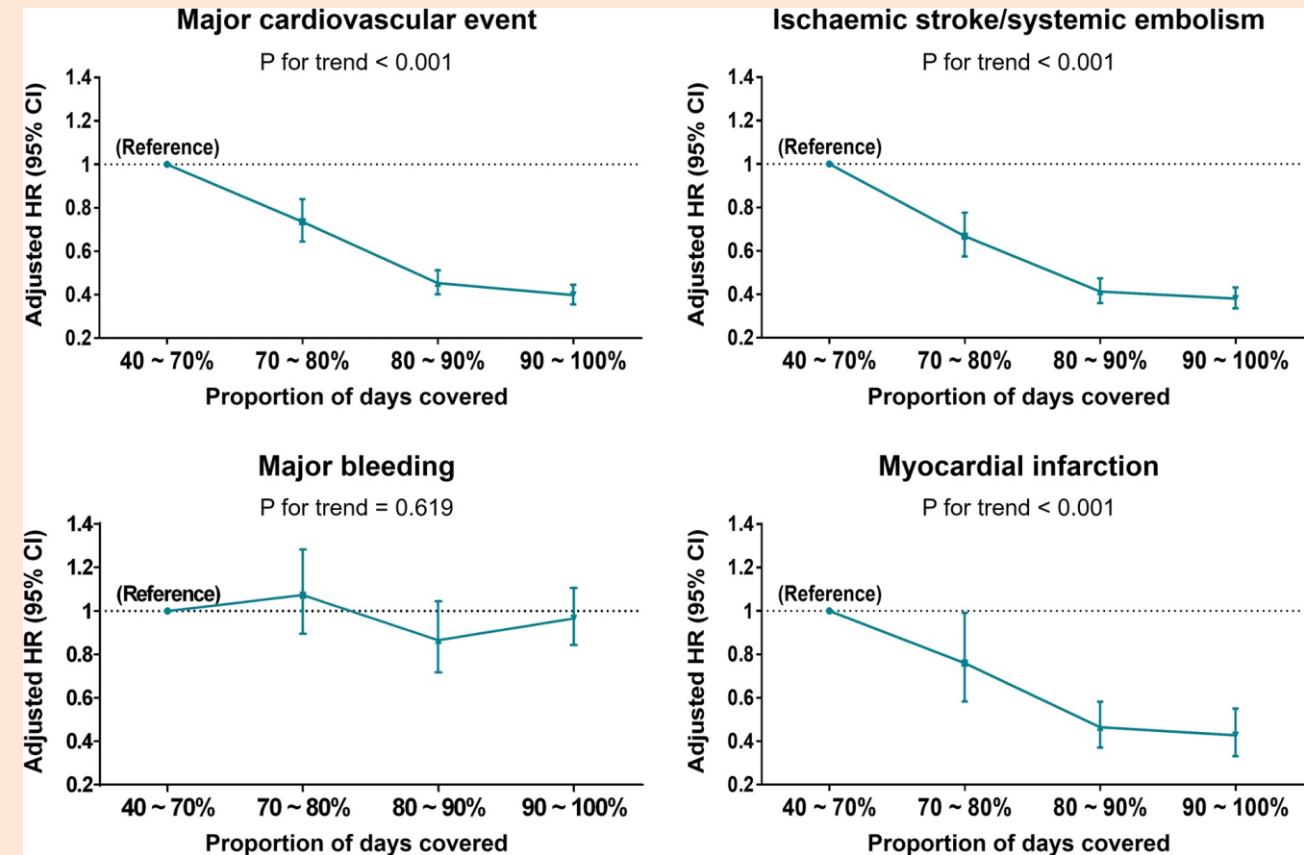
Importance of drug adherence : Real-world cohort

NOAC에 대한 높은 순응도는 출혈 위험을 증가시키지 않으면서, 더 나은 임상적 효과를 나타냄

▶ Adherent(PDC≥80%) vs. non-adherent(PDC<80%)



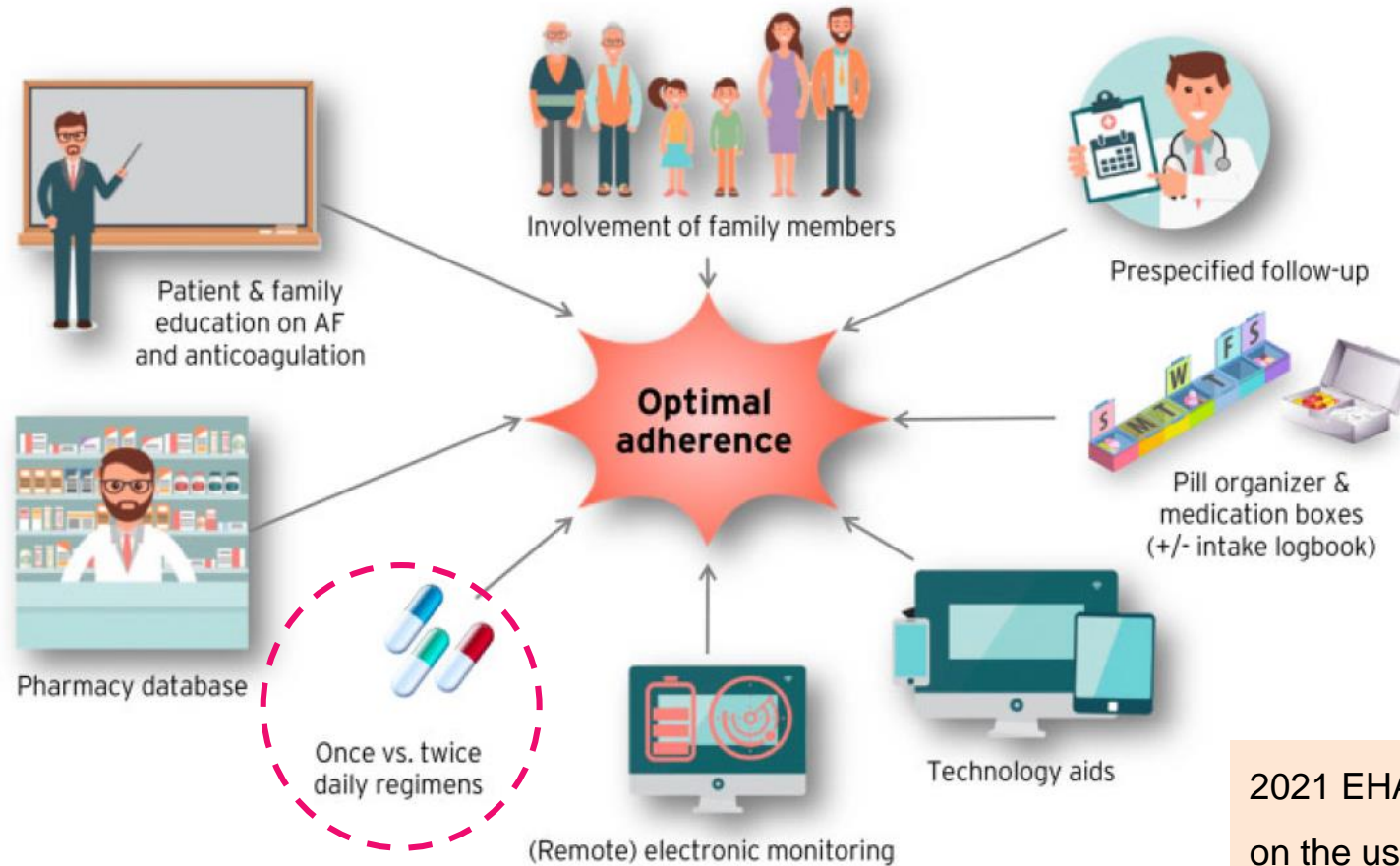
▶ Clinical outcomes according to gradual increase of adherence



[Study Design] Using the Korean National Health Insurance Service database, we identified 96,197 patients with non-valvular AF who initiated NOAC or warfarin in 2013–16. The study compared clinical outcomes between adherent [proportion of days covered (PDC) ≥80%] vs. non-adherent (PDC <80%) NOAC users, and further with warfarin users.

Practical considerations regarding adherence

심방세동 환자에서 뇌졸중 예방을 위해 적절한 용량의 NOAC 처방과 환자의 순응도 향상은 필수적

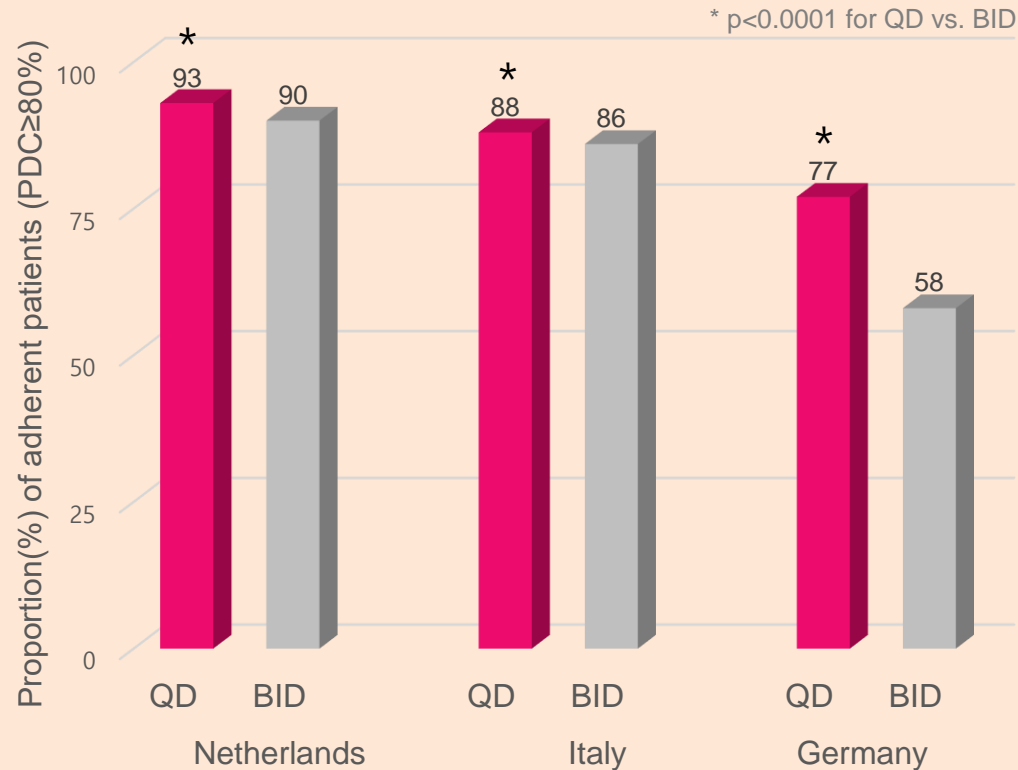


2021 EHAR Practical Guide
on the use of NOAC in patients with AF

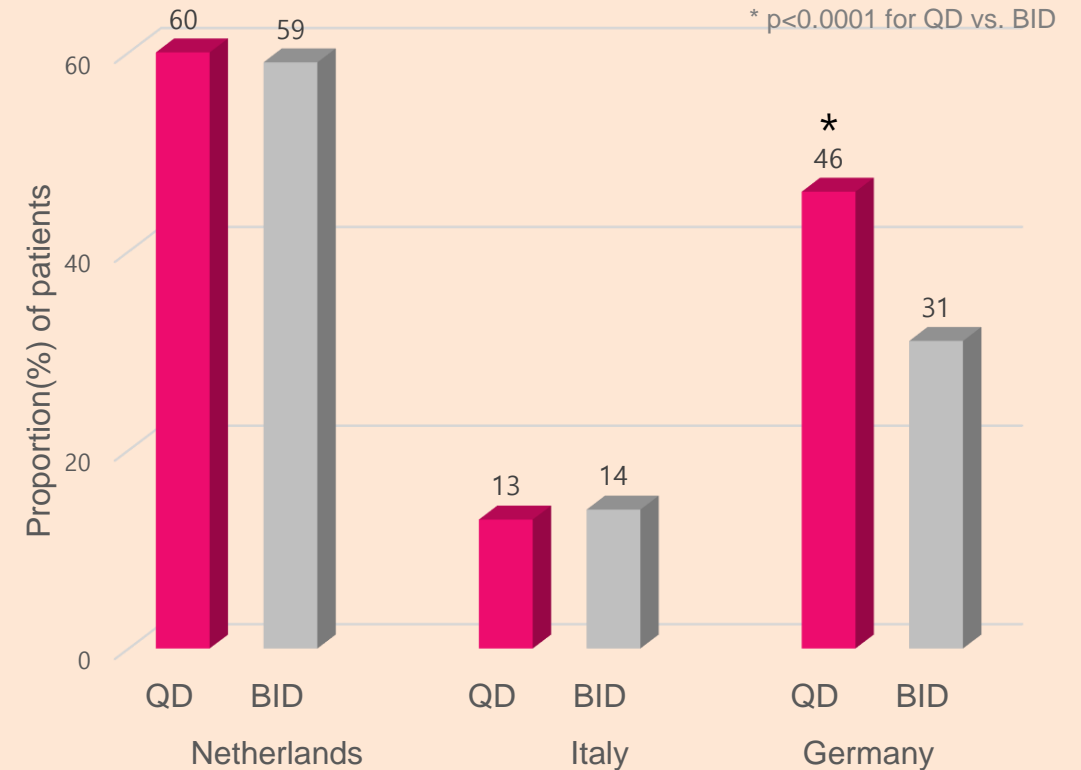
Adherence with Once-daily dosing : Real-world cohort

유럽의 최신 리얼월드 코호트 연구 결과,
NOAC의 QD 복용은 BID에 비해 높은 순응도를 보임

Adherence (during exposure period)



Persistence (at 12 months)



[Study Design] A cohort study was conducted in three databases in the Netherlands, Italy and Germany. Patients with AF starting direct oral anticoagulants after drug approval date were included. The index date was the date of first dispensing. Study patients were restricted to those aged ≥ 18 years, ≥ 1 year database history and ≥ 1 year follow-up.

Ref) 22. Smits E, et al. *Drugs Real World Outcomes*. 2022 Jun;9(2):199-209.

Clinical Evidence of Rivaroxaban in AF

03

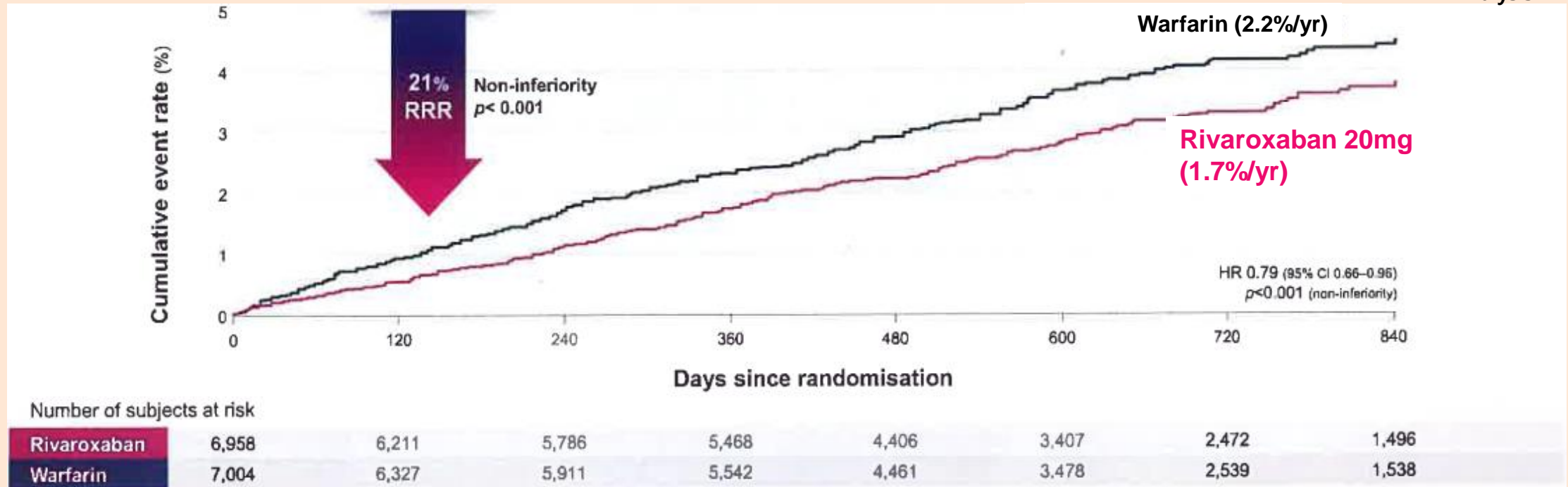
ROCKET-AF

Global Phase III trial

비판막성 심방세동 환자의 뇌졸중/전신색전증 예방에 Warfarin 대비 비열등성 입증

Primary Efficacy Endpoint : Stroke / SE

PPP Analysis



[Study Design] A multicenter, randomized, double-blind, double-dummy, event-driven trial to compare once-daily oral rivaroxaban with dose-adjusted warfarin for the prevention of stroke and systemic embolism in 14,264 patients with nonvalvular atrial fibrillation who were at moderate-to-high risk for stroke.

AF, Atrial Fibrillation; CI, confidence interval; HR, Hazard Ratio; NVAF, Non-Valvular Atrial Fibrillation; SE, Systemic Embolism; PPP, per-protocol population; RRR, Relative Risk Reduction

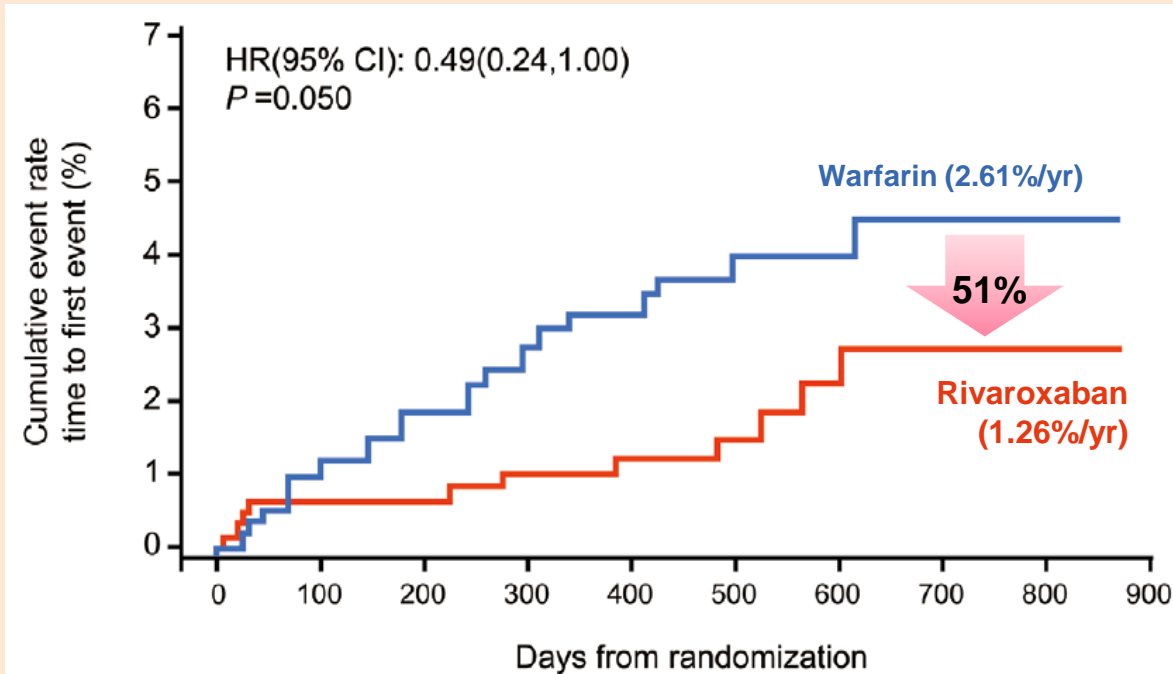
J-ROCKET AF

Phase III trial in Japan

Rivaroxaban은 일본인 대상 3상 임상 시험을 통해
15mg/day 으로 유효성 및 안전성 입증

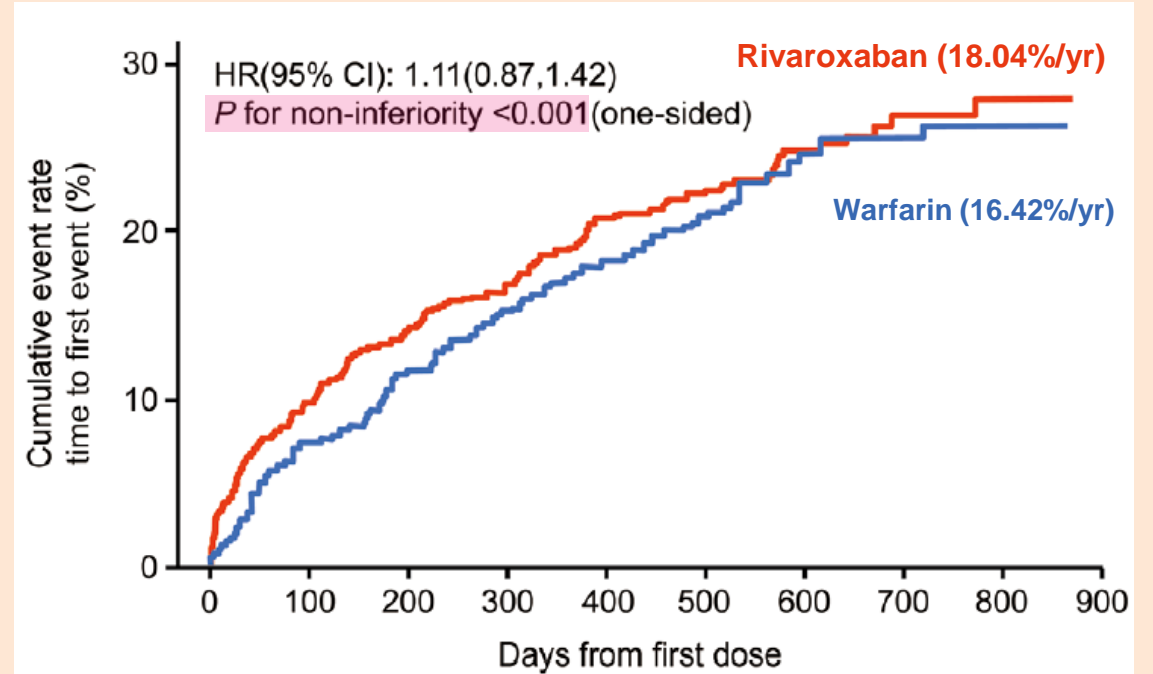
Efficacy outcome

(Stroke & non-CNS systemic embolism)



Safety outcome

(Major or Non-major clinically relevant bleeding)



[Study Design] A prospective, randomized, double-blind, phase III trial to determine non-inferiority of rivaroxaban against warfarin for the principal safety outcome of major and non-major clinically relevant bleeding. Patients (n=1,280) with non-valvular AF at increased risk for stroke were randomized to receive 15mg once-daily rivaroxaban or warfarin dose-adjusted according to Japanese guidelines.

XANAP : Design

Real-world study in Asia

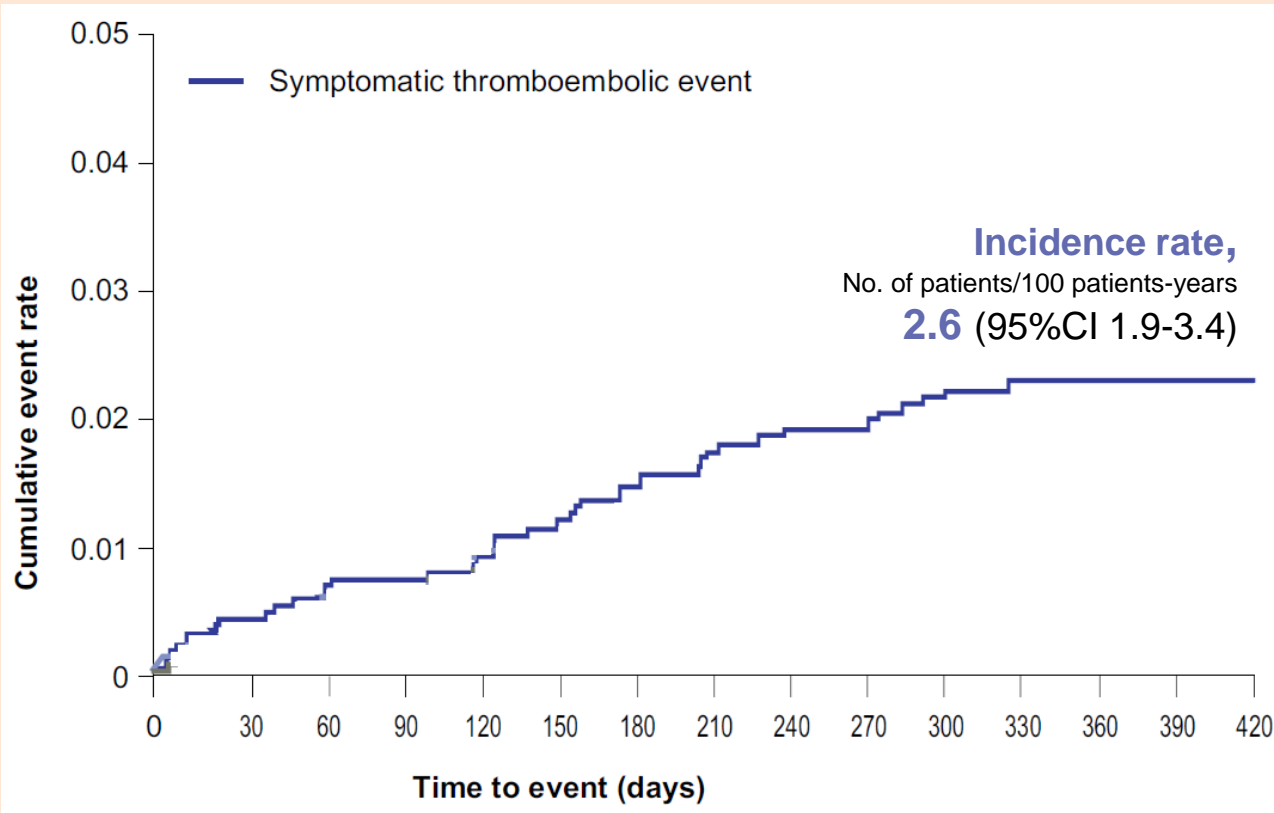
아시아태평양 비판막성 심방세동 환자를 대상으로 Rivaroxaban의 리얼 월드 데이터 확인

- **2,273 patients, 10 countries** : Hong Kong, Indonesia, Malaysia, Pakistan, Philippines, Singapore, **South Korea(844 [37.1%])**, Taiwan, Thailand, Vietnam
- **Primary outcome (Safety)** : Adverse events(AE), serious SAEs, all-cause mortality, Major bleeding
- **Secondary outcome** : Symptomatic thromboembolic events, non major bleeding, treatment satisfaction, etc.

	ROCKET AF global ^{a,b} 5,24 (N = 7131) ^c	XANTUS ^{a,g} 9 (N = 6784)	XANAP ^{a,g} (N = 2273)
Age, y, mean	73 ^h	71.5	70.5
Weight, kg, mean	–	83	66
CrCl <50 mL/min, %	20.7 ⁱ	9.4	16.3
Congestive heart failure, %	63	19	20
Hypertension, %	90	75	74
Diabetes, %	40	20	27
Prior stroke/SE/TIA, %	55	19	33
Mean CHADS ₂ score	3.5	2.0	2.3
Mean CHA ₂ DS ₂ -VASc score	–	3.4	3.7

XANAP : Efficacy Real-world study in Asia

아시아태평양 환자(한국인 37.1%) 대상 리얼월드에서 뇌졸중 및 전신색전증 예방 효과 입증



	Incidence proportion, % of patients (95%CI)	Incidence rate, No. of patients/100 patients-yrs (95%CI)
Thromboembolic events	2.1 (1.5-2.7)	2.6 (1.9-3.4)
Stroke/ non-CNS SE	1.5 (1.0-2.1)	1.9 (1.3-2.6)
Stroke	1.4 (1.0-2.0)	1.7 (1.2-2.5)
Non-CNS SE	0.1 (0.0-0.3)	0.1 (0.0-0.4)
TIA	0.2 (0.0-0.4)	0.2 (0.1-0.6)
MI	0.4 (0.2-0.8)	0.5 (0.2-0.9)

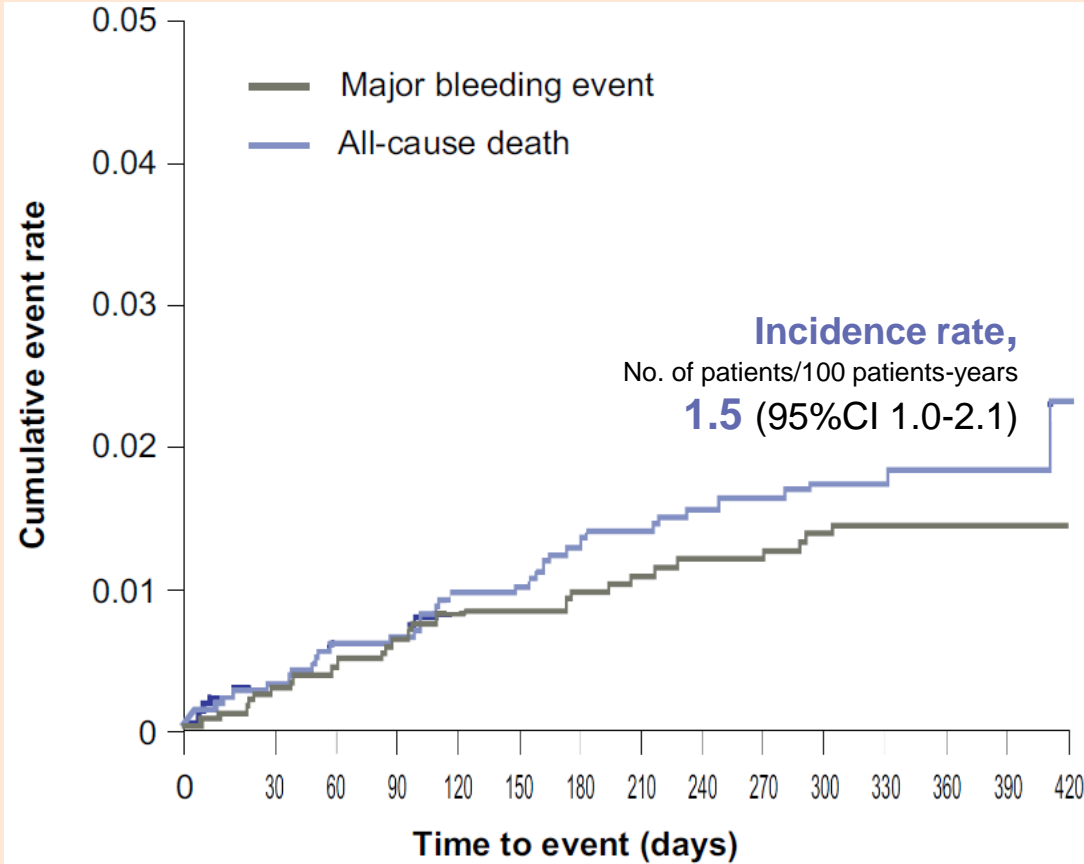
CNS, central nervous system; GI, gastrointestinal; MI, myocardial infarction; SE, systemic embolism; TIA, transient ischemic attack.

[Study Design] A real-world, prospective, observational study in 2,273 patients with NVAf newly starting rivaroxaban for stroke prevention in 10 countries across the Asia. The largest patients population were from South Korea(844 [37.1%]). Mean age was 70.5 years, mean treatment duration was 296 days, and 72.8% of patients had received prior anticoagulation therapy.

XANAP : Safety

Real-world study in Asia

아시아 비판막성 심방세동 환자(한국인 37.1%)에서 출혈에 대한 안전성 프로파일 확립



	Incidence proportion, % of patients (95%CI)	Incidence rate, No. of patients/100 patients-yrs (95%CI)
Major bleeding	1.2 (0.8-1.7)	1.5 (1.0-2.1)
Fatal	0.2 (0.0-0.4)	0.2 (0.1-0.6)
Bleeding at a critical site	0.6 (0.3-1.0)	0.8 (0.4-1.3)
Intracranial hemorrhage	0.6	0.7 (0.4-1.2)
GI	0.4 (0.2-0.8)	0.5 (0.2-0.9)
Non-major bleeding events	8.8 (7.6-10.0)	11.2 (9.7-12.9)
All-cause death	1.6 (1.1-2.2)	2.0 (1.4-2.7)

[Study Design] A real-world, prospective, observational study in 2,273 patients with NVAf newly starting rivaroxaban for stroke prevention in Asia. (R20mg-49.8%, R15mg-43.8%, R10-5.9%) Mean age was 70.5 years, mean treatment duration was 296 days, and 72.8% of patients had received prior anticoagulation therapy. The largest patients population were from South Korea(844 [37.1%]).

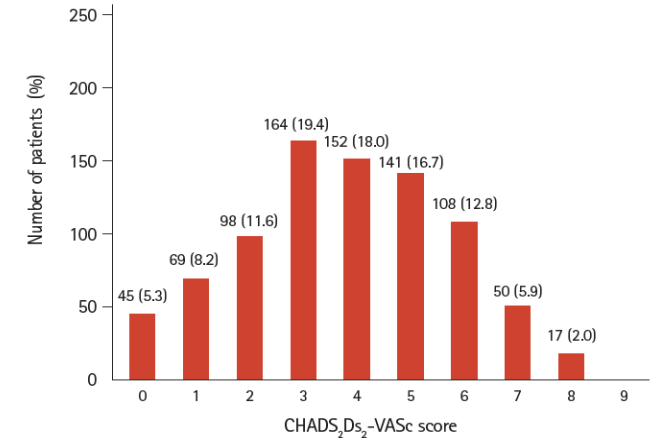
XANAP Korea

Sub-analysis of XANAP

한국인 환자는 비교적 높은 뇌졸중 위험 나타냈으나, Rivaroxaban의 임상적 효과는 유사, MB 발생은 1%에 불과

Characteristic	XANTUS [8,10] (n = 6,784)	XANAP [10] (n = 2,273)	XANAP Korea (n = 844)
Baseline characteristics			
CrCl < 50 mL/min, %	9.4	16.3	13.1
Co-morbidities, %			
Congestive heart failure	19	20	15.2
Hypertension	75	74	70.3
Diabetes mellitus	20	27	25.8
Prior stroke/non-CNS SE/TIA	19	33	47.0
CHADS ₂ score (mean)	2.0	2.3	2.5
CHA ₂ DS ₂ -VASc score (mean)	3.4	3.7	3.8
Prior VKA use, %	40.8	35.8	57.8
Major outcomes (events/100 patient-years)			
Major bleeding	2.1	1.5	1.1
Fatal	0.2	0.2	0.3
Bleeding at a critical site ^a	0.7	0.8	0.6
Thromboembolic events (stroke, non-CNS SE, TIA, and MI)			
Stroke	0.7	1.7	1.6
MI	0.4	0.5	0.3
Death	1.9	2.0	1.6

No.(%) of patients by CHA₂DS₂-VASc score



No.(%) of Hospitalization due to drug-related serious adverse event

Variable	XANAP Korea (n = 844)	
	Patients	Hospitalizations
Thromboembolic events	8 (0.9)	8
Bleeding	7 (0.8)	7
Stroke	2 (0.2)	2
Other	2 (0.2)	2

Efficacy profile of Rivaroxaban

Rivaroxaban은 글로벌 임상3상에서부터 국내 리얼월드 데이터까지 일관성 있는 임상적 효과를 나타냄

Symptomatic Thromboembolic events

(stroke, non-CNS SE, TIA, or MI)
Events/100patient-years

Randomized Clinical trial
ROCKET AF^{1*}
(n=7,111)

2.1%

Observational study (West)
XANTUS Pooled²
(n=11,121)

1.8%

Observational Study (Asia-Pacific)
XANAP³
(n=2,273)

2.6%

Observational study
XANAP Korea⁴
(n=844)

2.0%

Mean CHADS₂ score

3.5

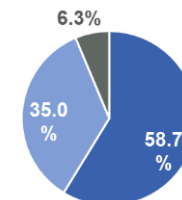
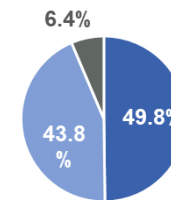
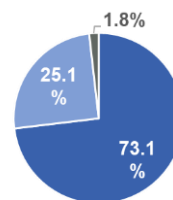
2.0

2.3

2.5

Dose

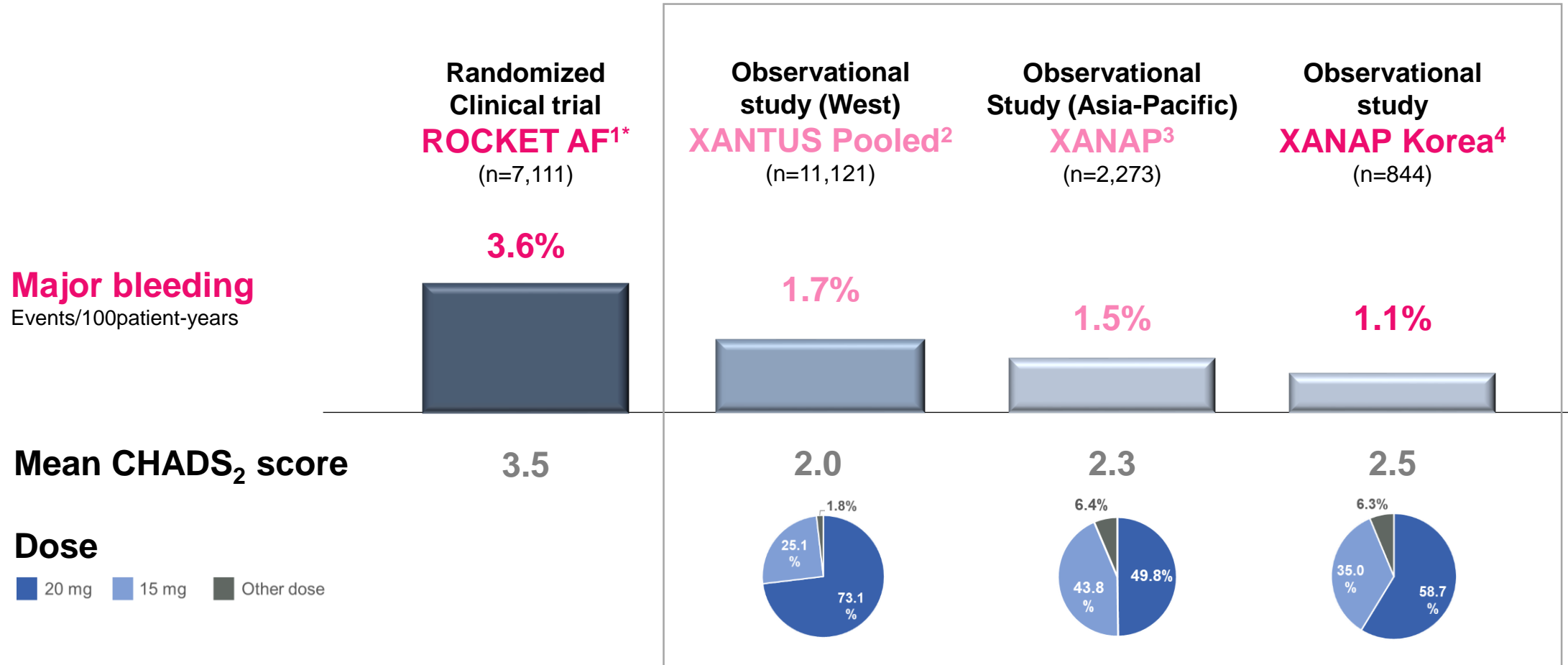
■ 20 mg ■ 15 mg ■ Other dose



※ Please note this information is from separate, Independent studies and the studies are not directly comparable owing to different study design. Therefore it should be carefully interpreted.

Safety profile of Rivaroxaban

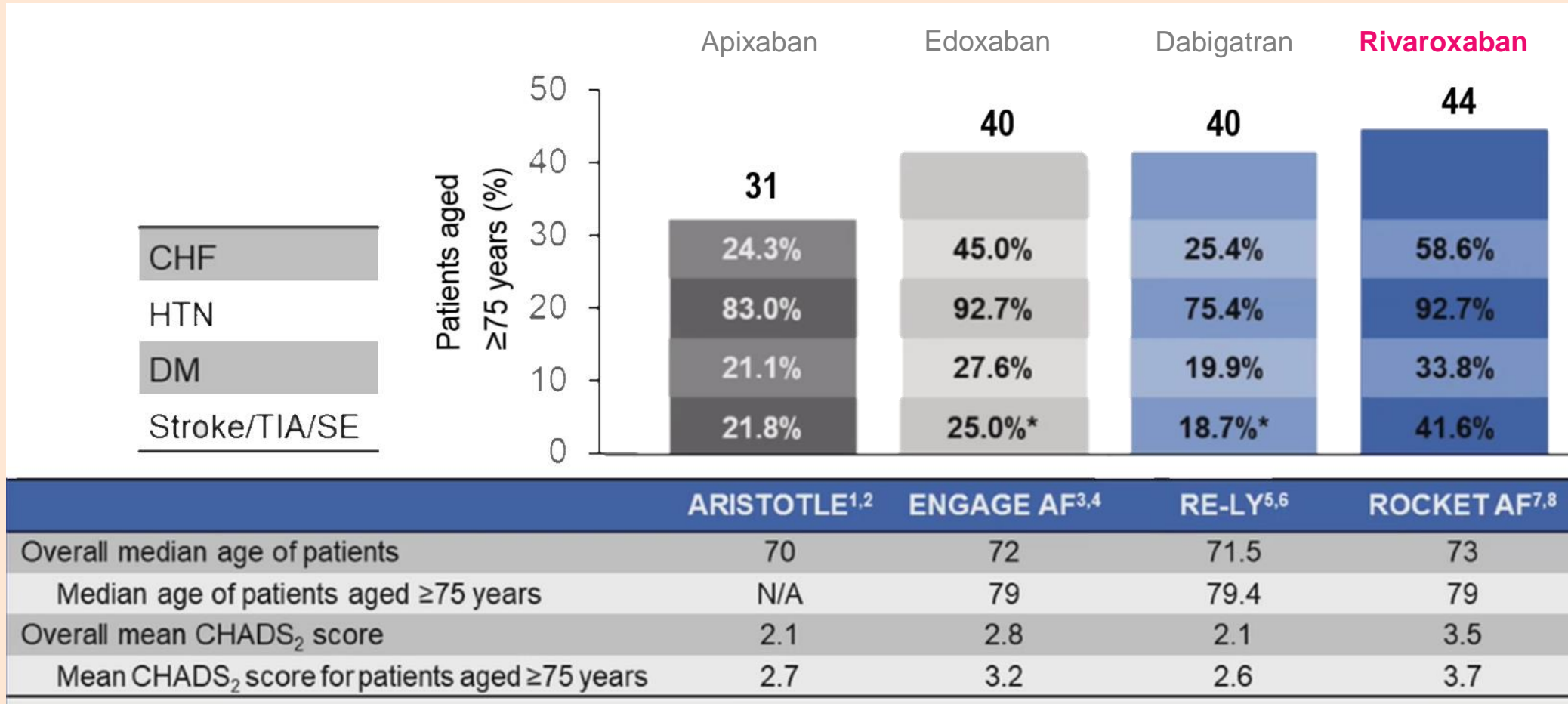
Rivaroxaban의 출혈 위험은 아시아인과 한국인에서 더 낮은 경향을 보임



※ Please note this information is from separate, Independent studies and the studies are not directly comparable owing to different study design. Therefore it should be carefully interpreted.

Elderly Patients in Phase III of NOACs

NOAC 의 3상 임상연구 대상자 중 Rivaroxaban 연구의 초고령 인구 비율이 가장 높았음

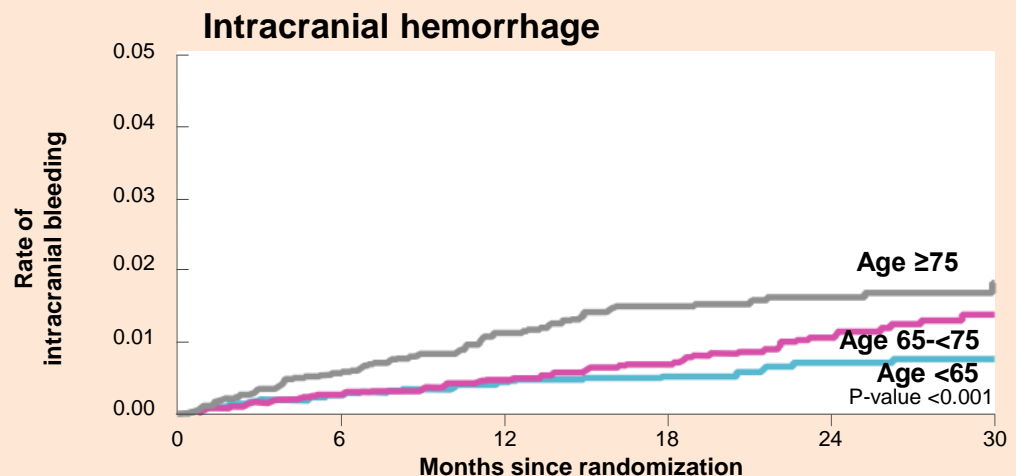
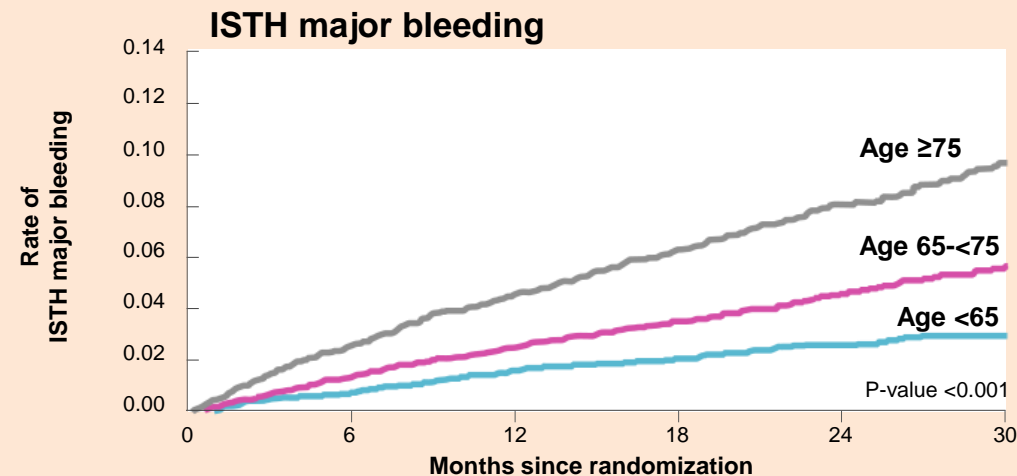
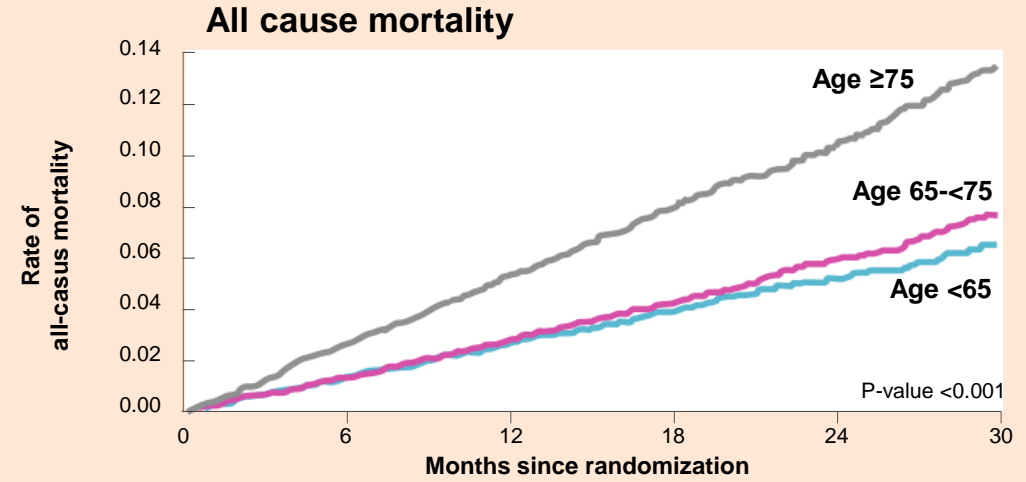
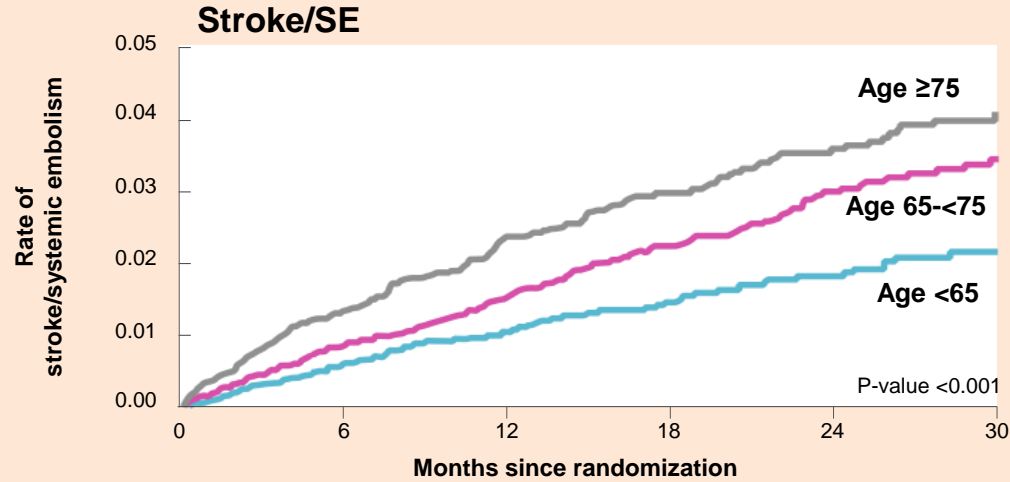


Ref) 33. Granger CB, et al. N Engl J Med. 2011 Sep 15;365(11):981-92. 31. Halvorsen S, et al. Eur Heart J. 2014 Jul 21;35(28):1864-72. 34. Giugliano RP, et al. N Engl J Med. 2013 Nov 28;369(22):2093-104. 35. Kato ET, et al. J Am Heart Assoc. 2016 May 20;5(5):e003432. 36. Connolly SJ, et al. N Engl J Med. 2009 Sep 17;361(12):1139-51. 37. Lauw MN, et al. Heart. 2017 Jul;103(13):1015-1023. 25. Patel MR, et al. N Engl J Med. 2011 Sep 8;365(10):883-91. 38. Halperin JL, et al. Circulation. 2014 Jul 8;130(2):138-46.

Elderly AF Patients

Observation from ARISTOTLE

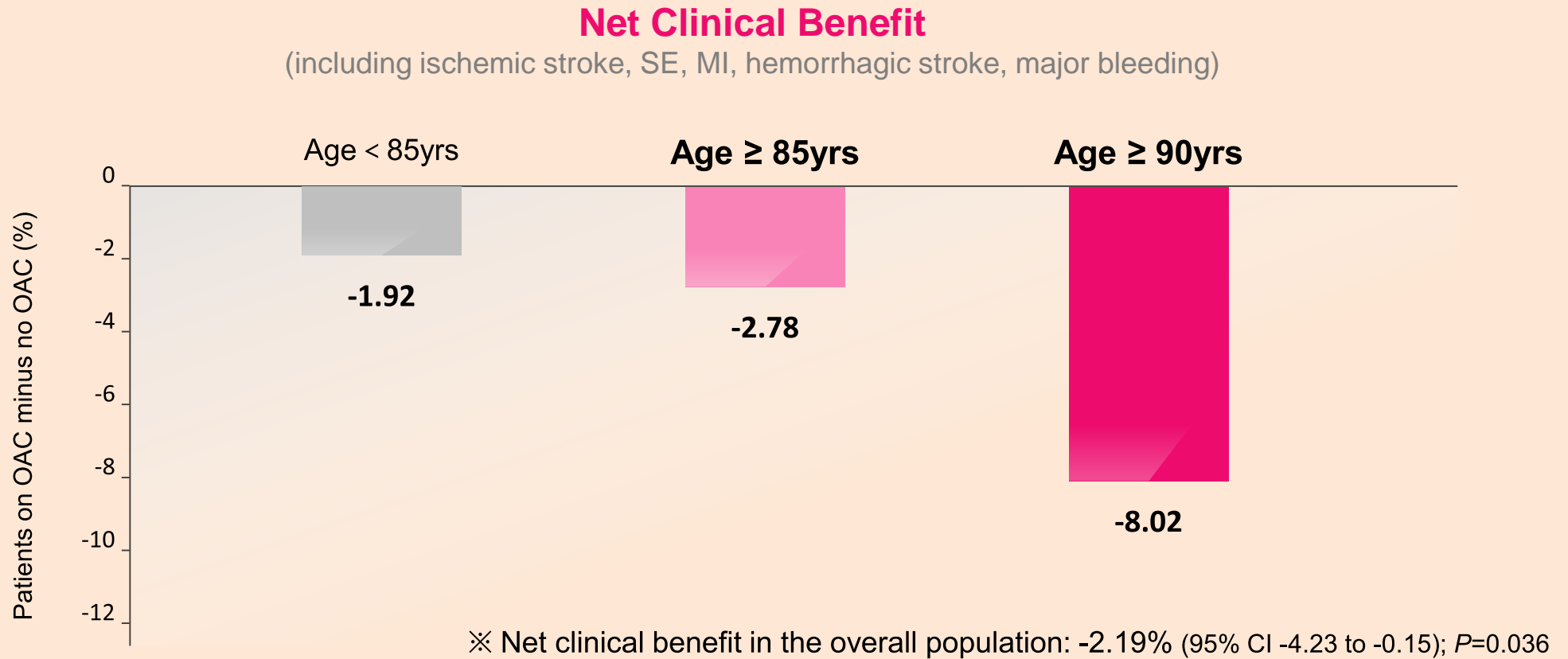
고령의 심방세동 환자일수록
뇌졸중, 사망, 및 출혈 위험이 모두 증가



PREFER in AF

absolute benefit in Elderly

연령 증가에 따른 뇌졸중 위험의 증가가 출혈 위험 증가를 상회하므로, NOAC 치료의 순이익은 연령과 함께 증가

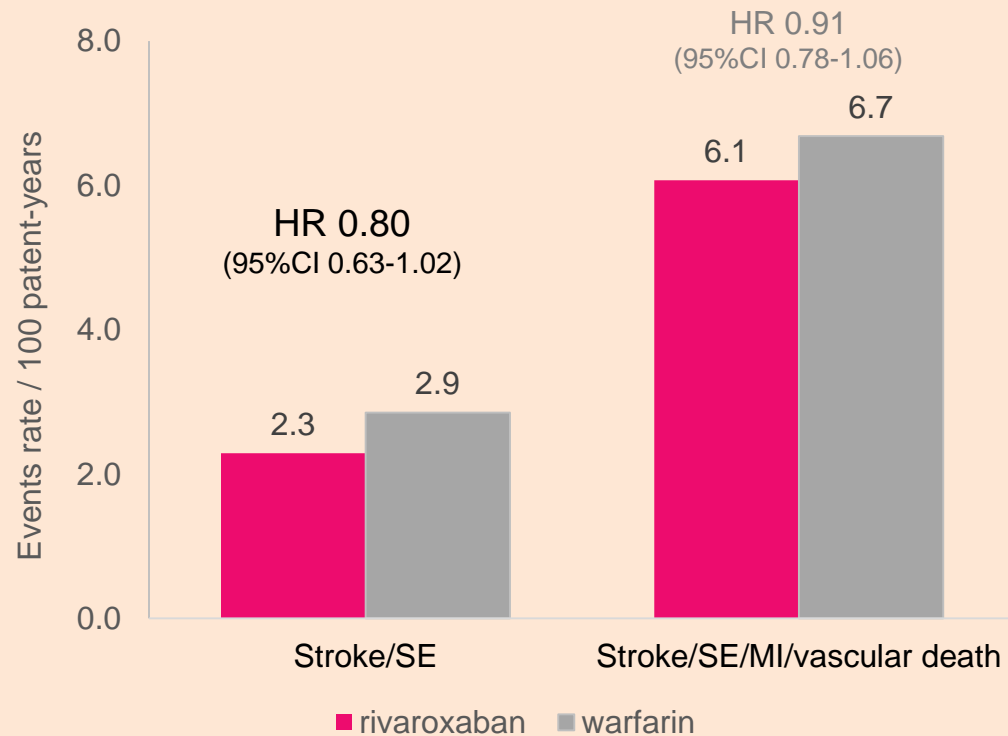


[Study Design] The PREFER in AF registry enrolled consecutive patients with AF from January 2012 to January 2013 in 461 centres in seven European countries. A sub-analysis of the PREFER in AF, compared outcomes with/without OAC, and estimated weighed net clinical benefit in different age groups. A total of 6412 patients, 505 of aged ≥85years were analyzed.

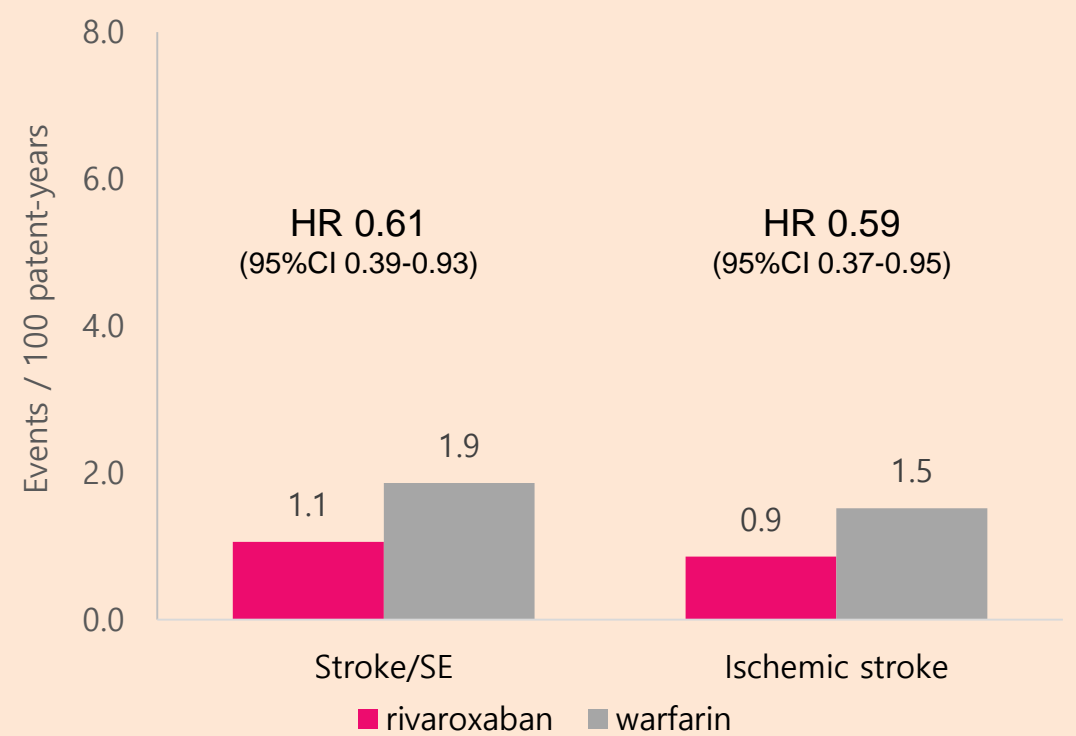
Efficacy of RIV in Elderly patients

Rivaroxaban은 글로벌 3상 및 리얼월드 데이터를 통해
고령환자에서의 임상적 효과 확인 (warfarin 대비 우월)

▷ ROCKET AF : patients ≥ 75 years old ¹⁾



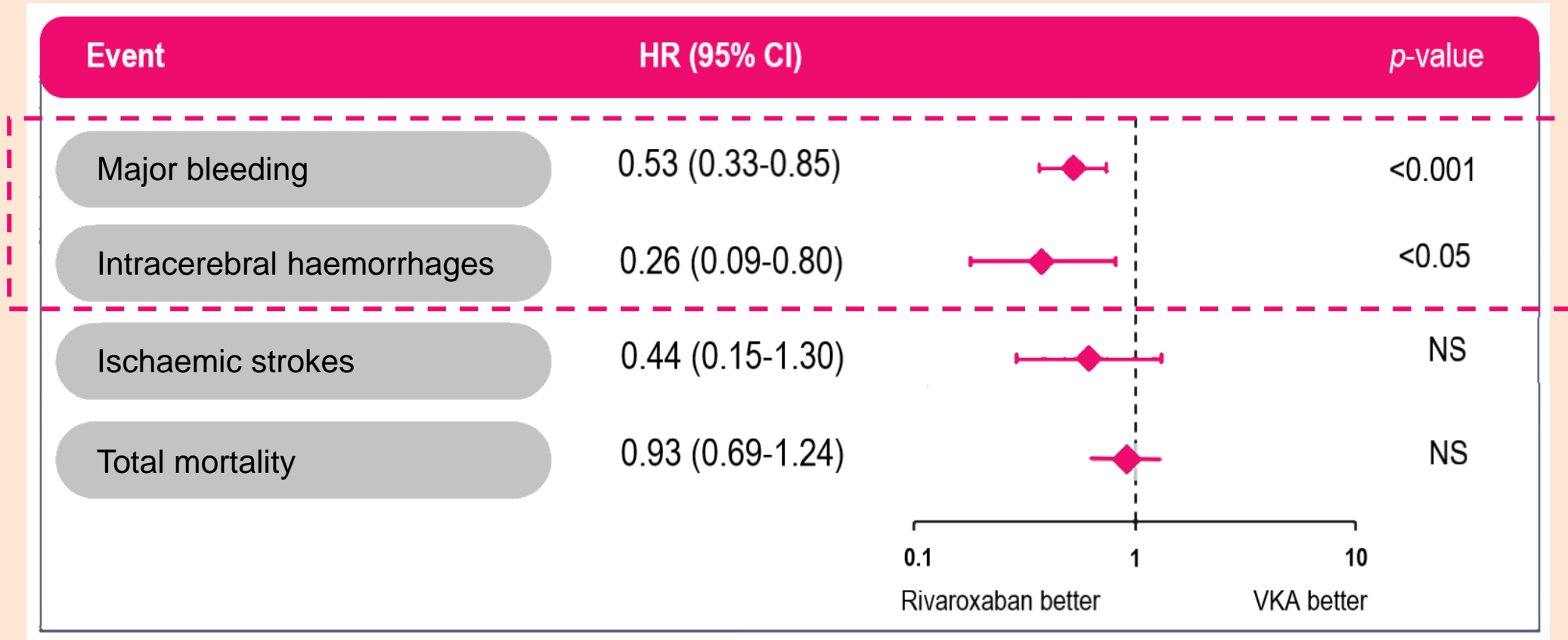
• Real-World Evidence : patients ≥ 80 years old ²⁾



SAFIR-AC

Safety in Elderly patients

Rivaroxaban은 80세 이상 초고령 환자에서도 출혈 위험을 감소시키며 일관성 있는 안전성 데이터 확인



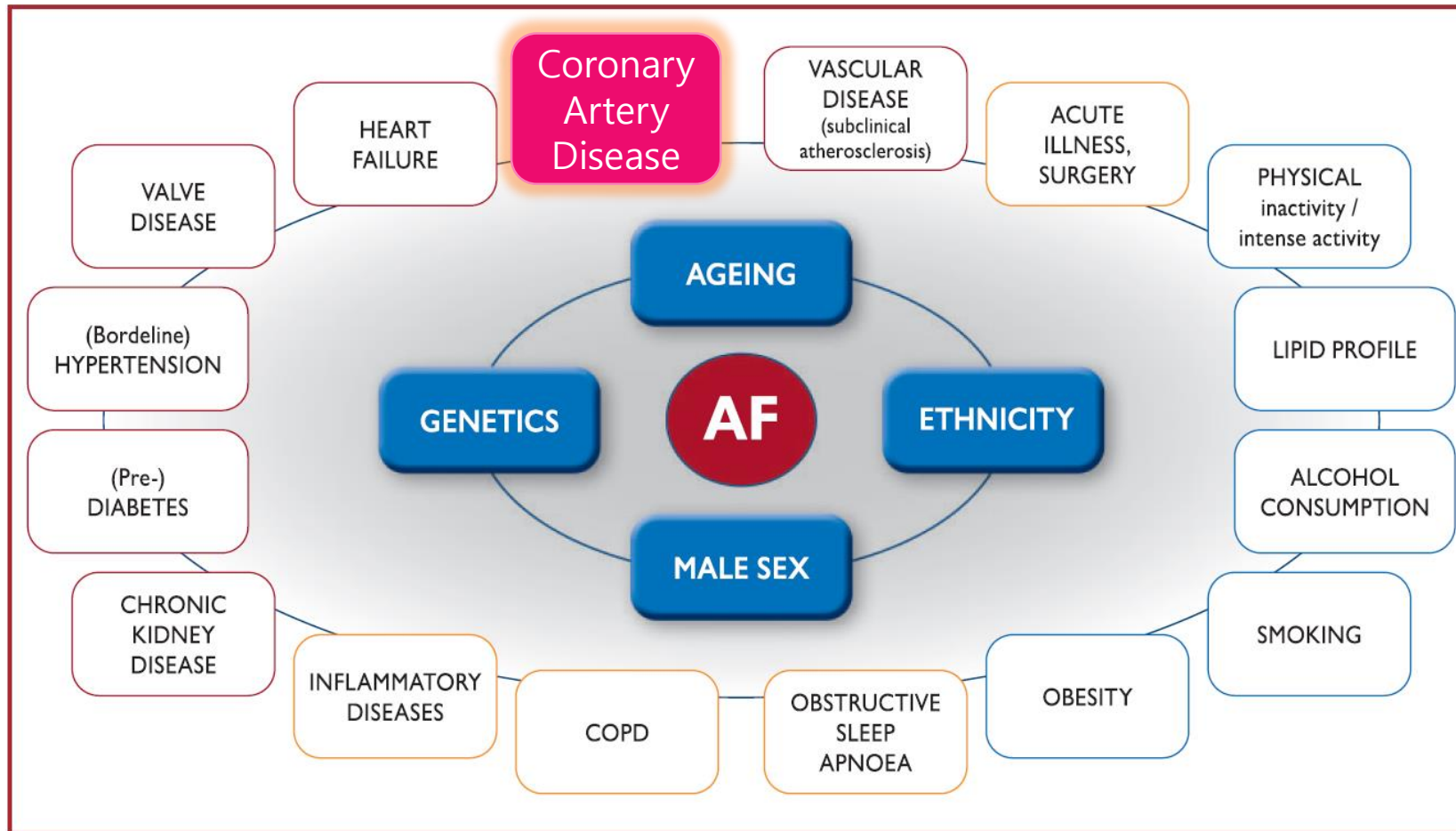
-Observational prospective cohort study using data from 33 geriatric centres. 1,045 patients, newly initiated on VKAs or Rivaroxaban. Follow up 12 months. Mean age=86 years
 -Major bleeding : 7.4/100 patient-years (RIV) vs. 14.6/100 patient-years (VKA)

Rivaroxaban in patients with **Coronary Artery Disease**

04

Risk factors for incident AF

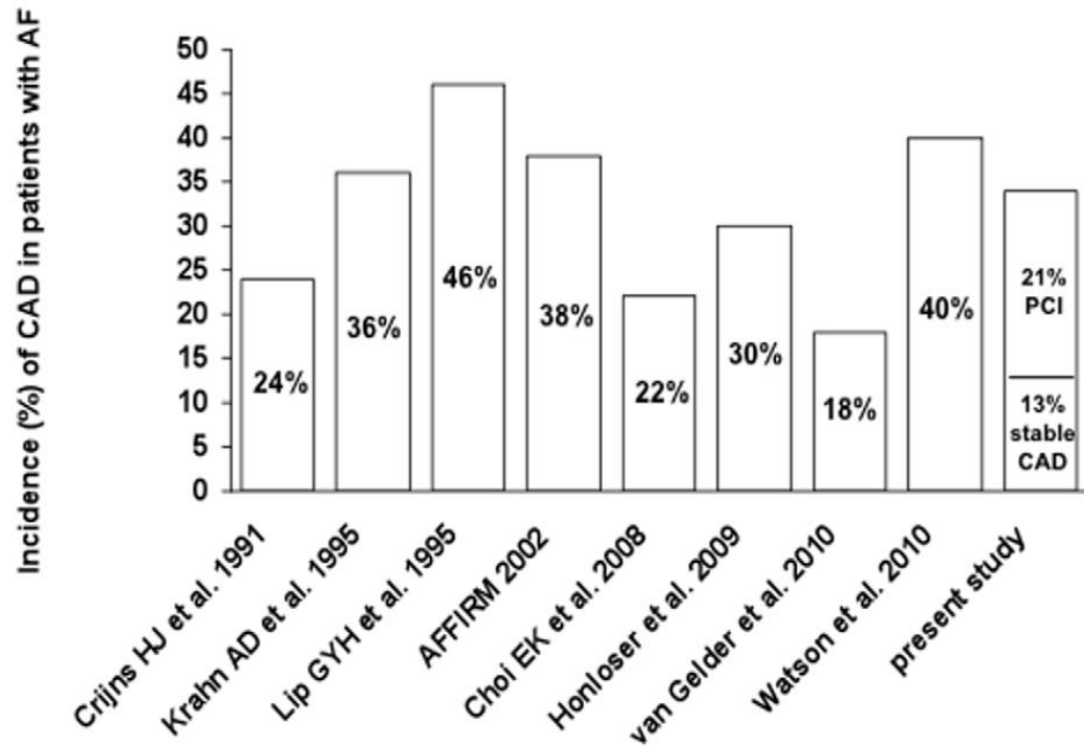
관상동맥질환과 심방세동은 여러 위험인자를 공유하며, 상호 발생 위험을 높임



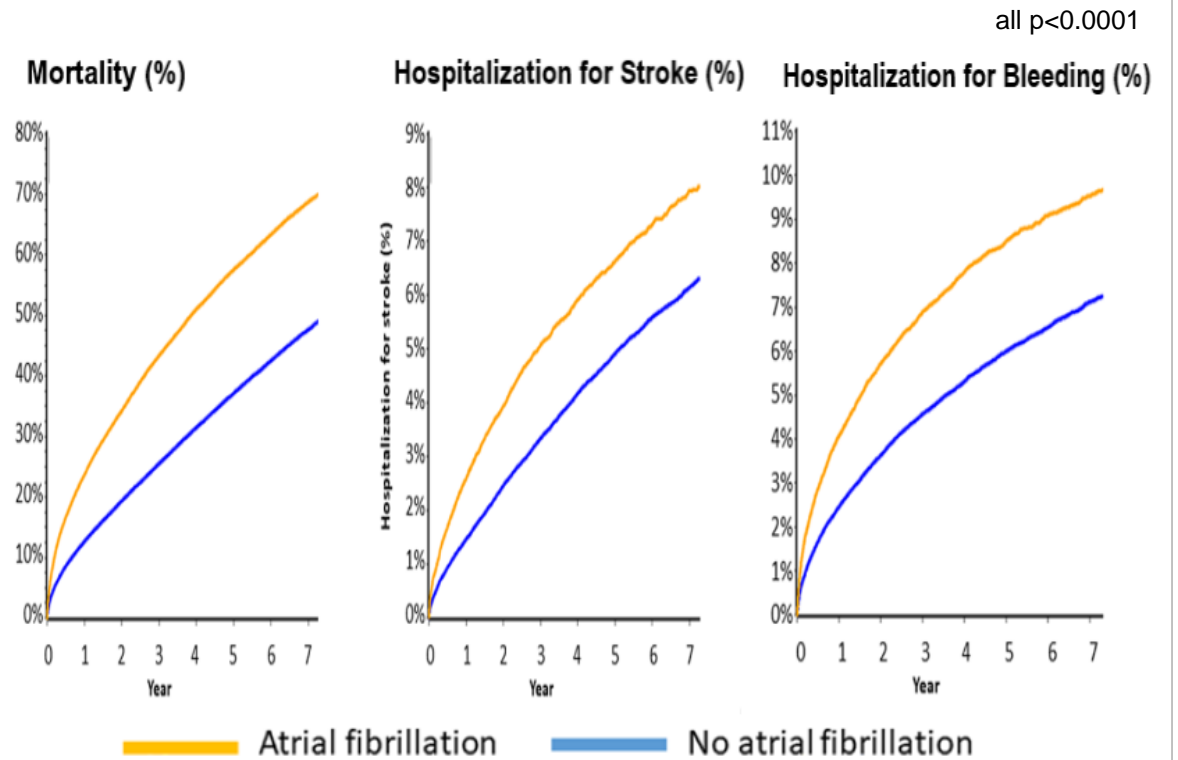
Status of AF with CAD

심방세동 환자에서 CAD 발생률은 24-46% 에 달하며, 심방세동이 없는 CAD 환자들보다 사망, 뇌졸중 등 예후 악화

• AF 환자에서의 CAD 발생률¹⁾



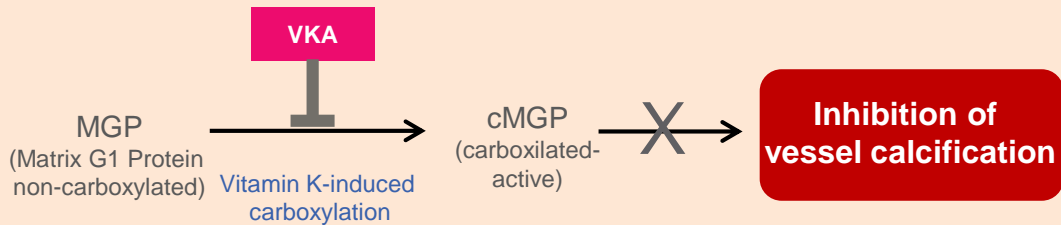
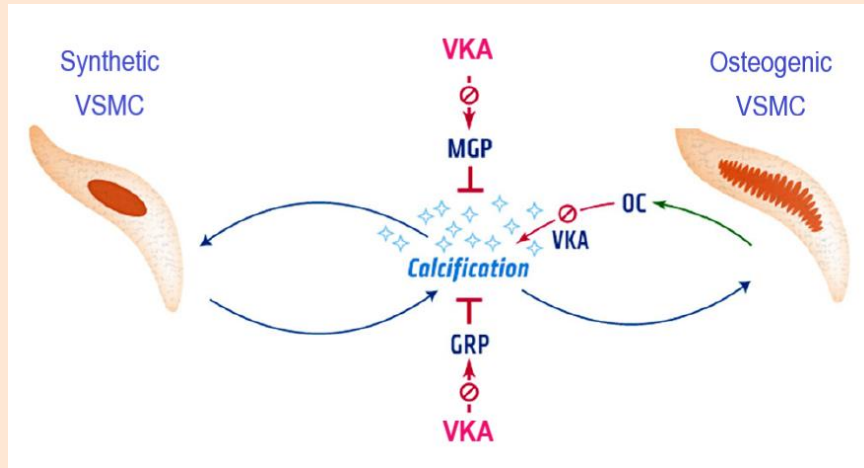
• Long-term outcome after MI, with/without AF²⁾



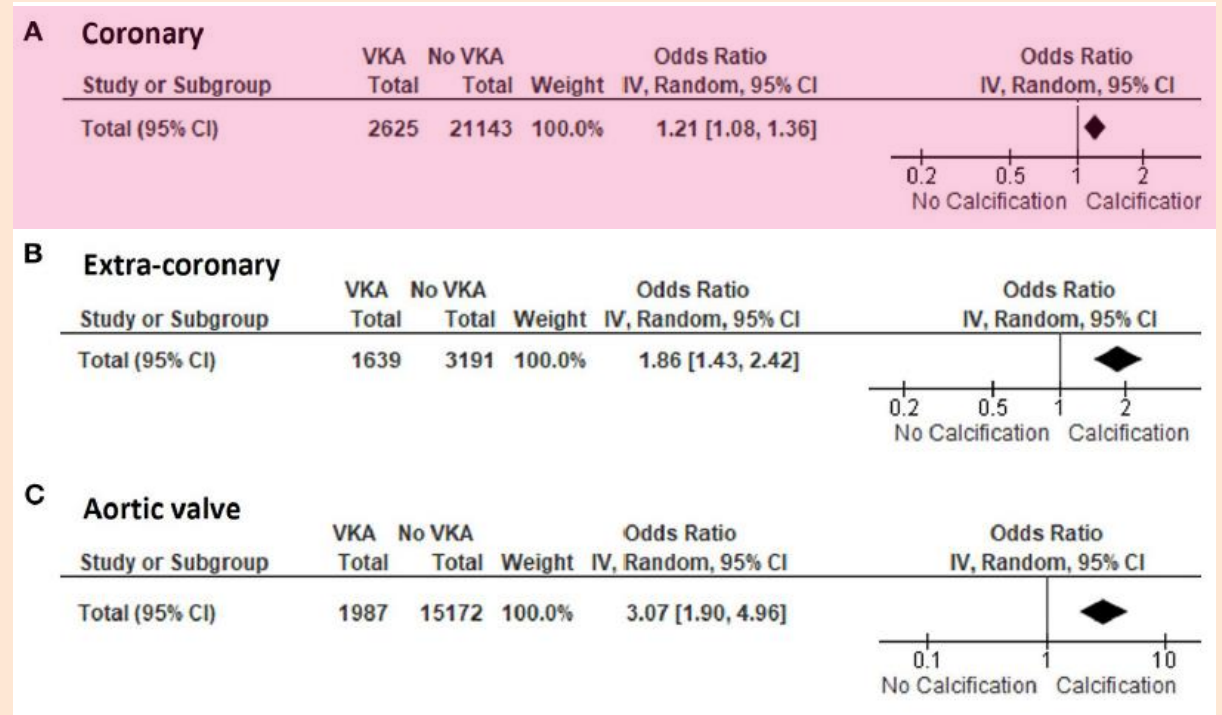
VKA promotes CV Calcification

VKA는 기전적으로 혈관과 판막의 석회화를 유도 & 메타분석을 통해 관상동맥석회화의 유의한 증가를 확인

▷ VKA는 MGP를 저해하여 혈관석회화 유도¹⁾



▷ VKA 치료로 인한 석회화 위험 증가²⁾

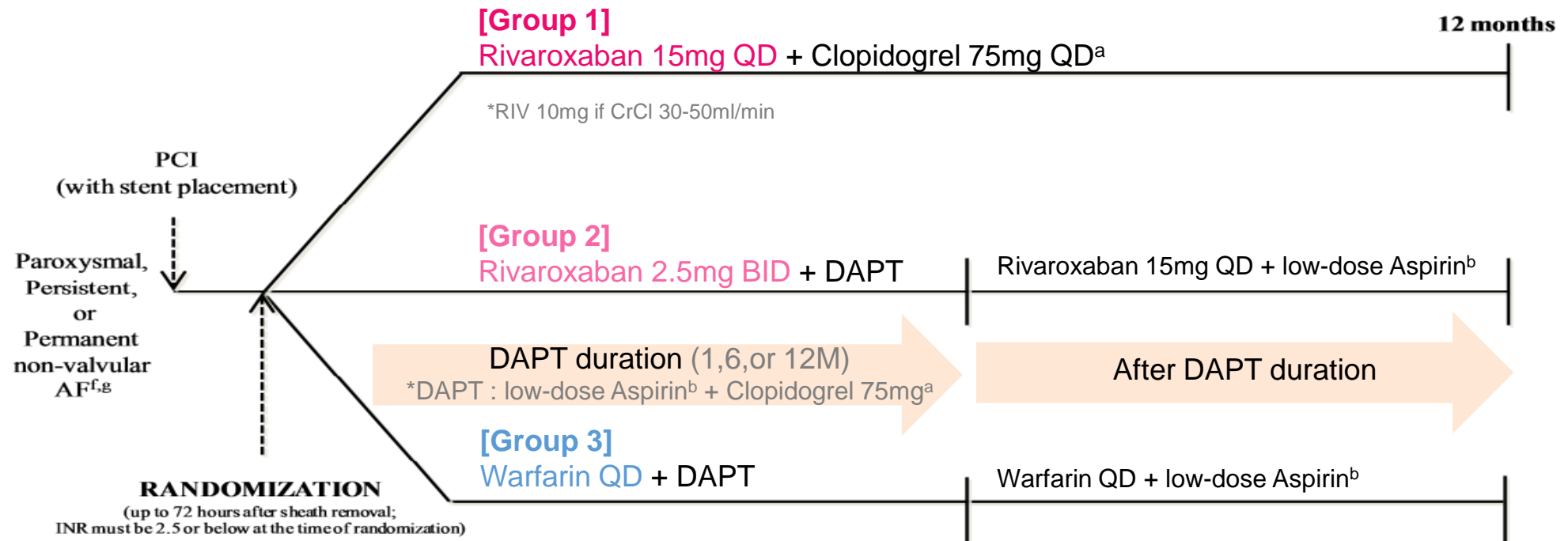


[Study Design] A meta-analysis of 35 studies (45,757 patients, 6,215 VKA users, median f/u 2.3yrs) to evaluate the associations between VKA use and vascular and valvular calcification.

PIONEER AF-PCI NVAF undergoing PCI

PCI 시행 후 항혈소판제 치료를 받는 NVAF 환자에서
VKA 와 Rivaroxaban을 비교한 첫 대규모 전향적 RCT

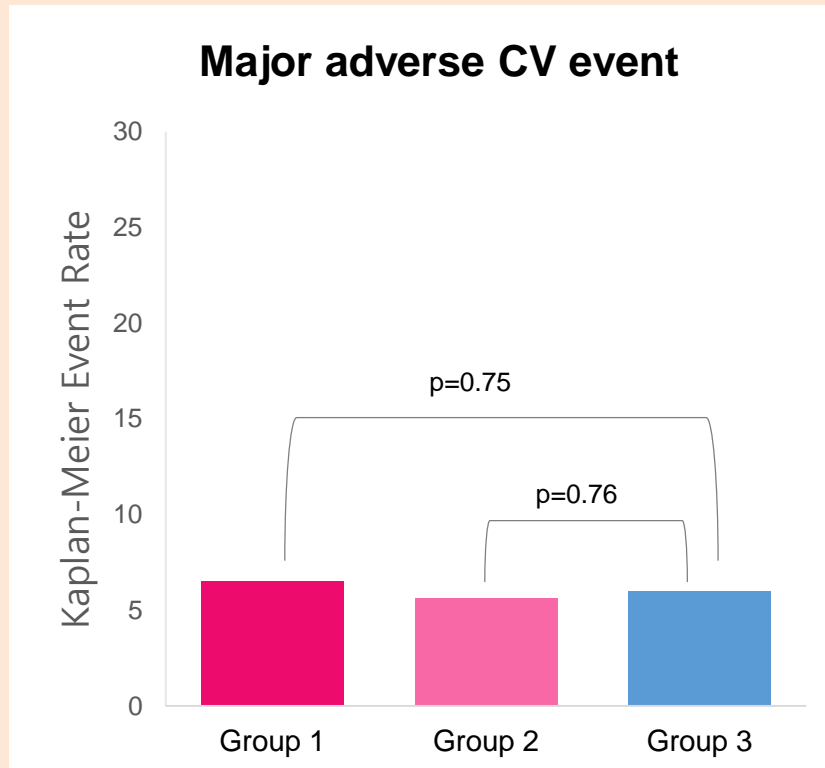
- **Design** : an international, multicenter, randomized, open-label trial
- **2,124 patients**(≥18 yrs) with paroxysmal, persistent, or permanent **NVAF, undergone PCI** with stenting(~72 hrs after sheath removal).
- **Primary safety endpoint** : **Clinically significant bleeding** (Major or minor bleeding according to TIMI criteria or bleeding requiring medical attention)
- **Secondary endpoint (efficacy)** : **MACE** (death from cardiovascular cause, MI, or stroke) and each component



PIONEER AF-PCI

Efficacy & Safety

Rivaroxaban+ 항혈소판요법은 VKA+DAPT 와 비교 시 유사한 효과를 나타내며, 출혈 위험은 유의하게 감소

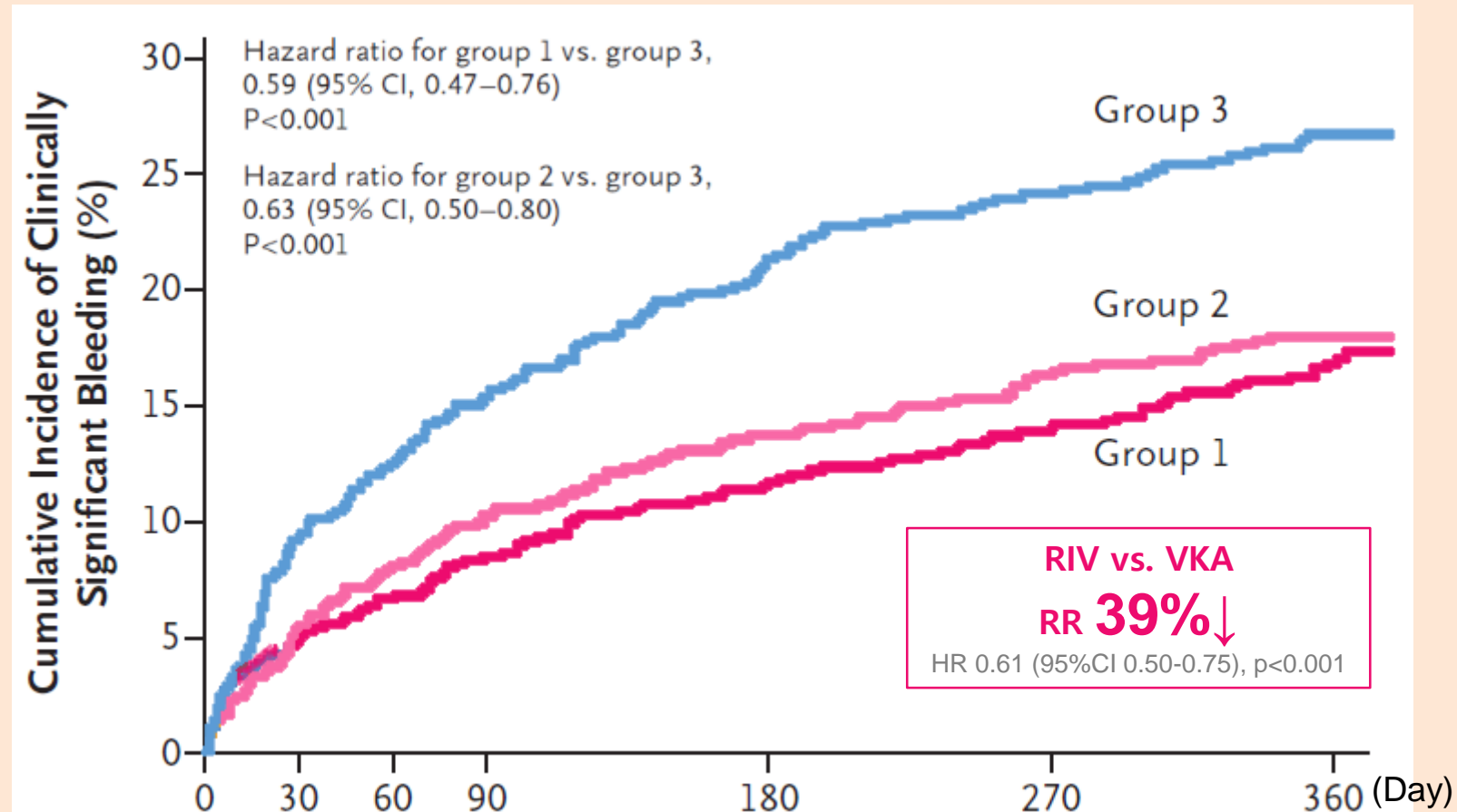


G1: RIV 15mg + P2Y12i (12M)

G2: RIV 2.5mg + DAPT (1,6,12M)

G3: VKA + DAPT (1,6,12M)

Ref) 45. Gibson CM et al. *N Engl J Med* 2016 Dec 22;375(25):2423-2434.

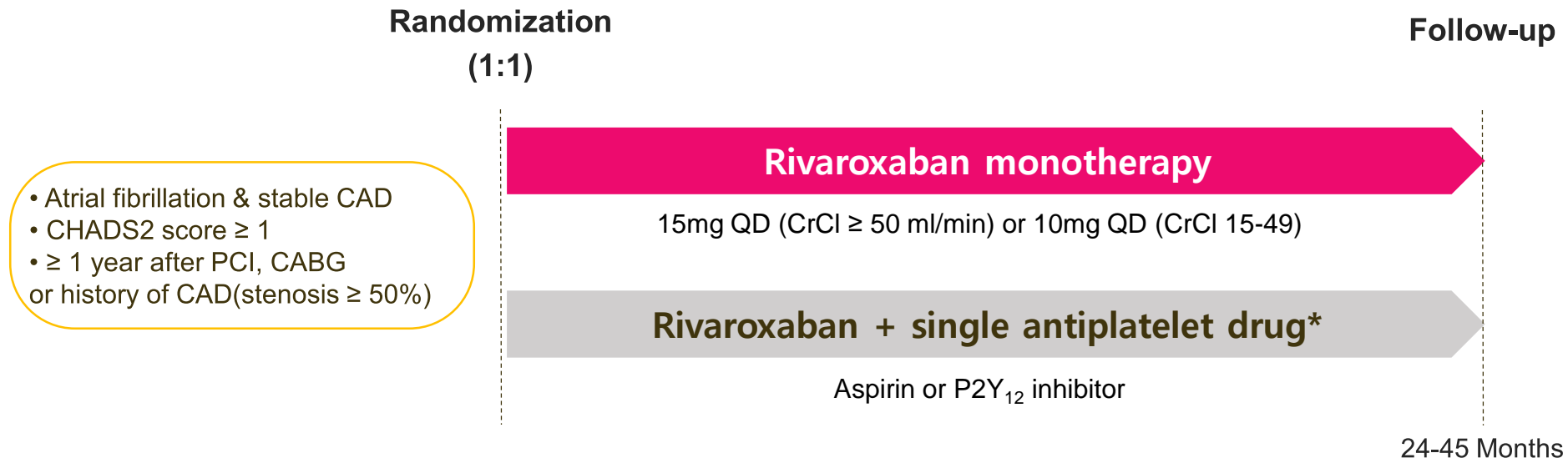


AFIRE

AF with stable CAD

AFIRE 연구 결과를 통해 안정형 CAD 환자에서의 Rivaroxaban 단독 요법에 대한 근거 마련

- **Design** : a multicenter, randomized, open-label, parallel-group trial in Japan.
- **2,236 patients**(≥20 yrs) with **AF and stable coronary artery disease (>1year after PCI or CABG)**
- **Primary Efficacy endpoint** : Composite of **stroke, systemic embolism, myocardial infarction, unstable angina, or all-cause death**
- **Primary Safety endpoint** : **Major bleeding** according to ISTH



CABG, coronary-artery bypass grafting ; CAD, coronary artery disease

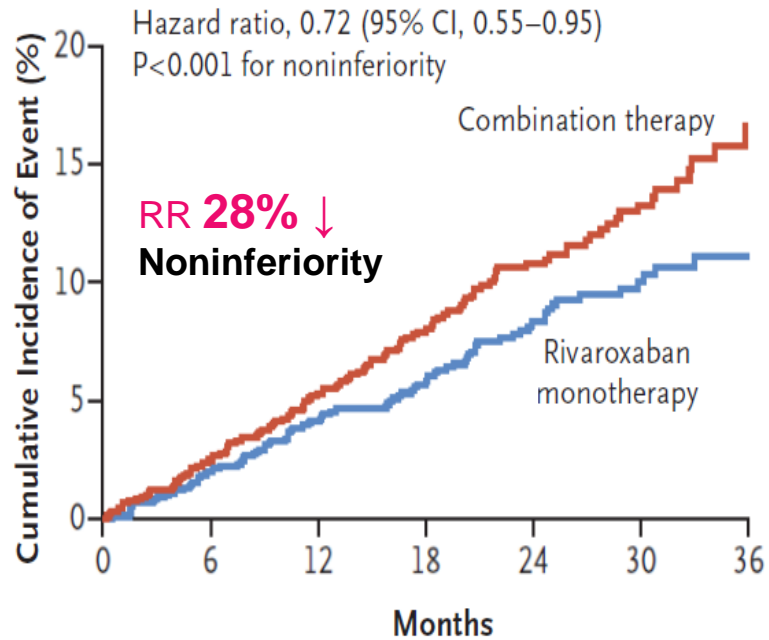
Ref) 46. Yasuda S, et al. *N Engl J Med.* 2019 Sep 19;381(12):1103-1113.

AFIRE

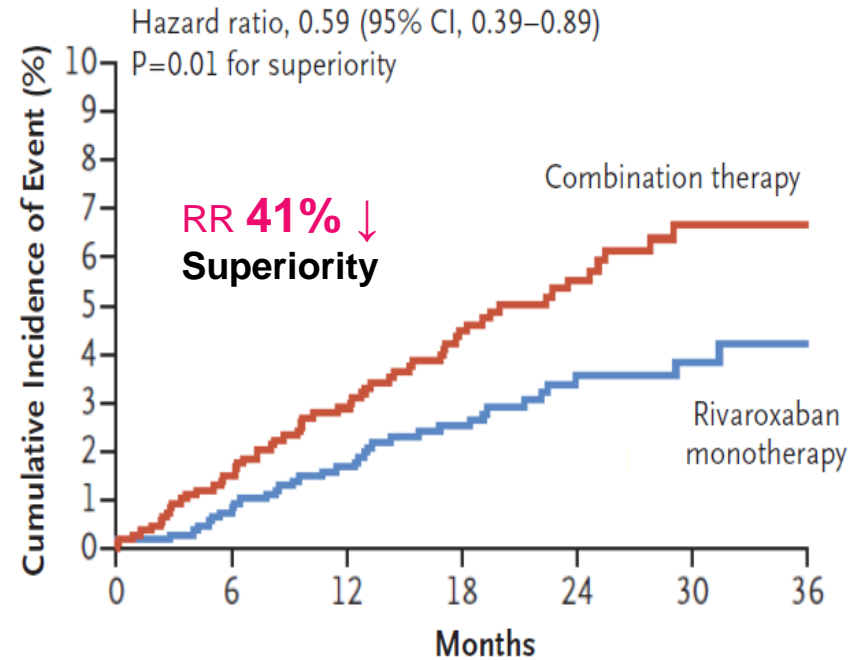
Efficacy & Safety

안정형 CAD 환자에서 RIV 단독 요법의 효과 및 안전성 입증
(Noninferiority for Efficacy & Superiority for Safety) & 사망률 감소

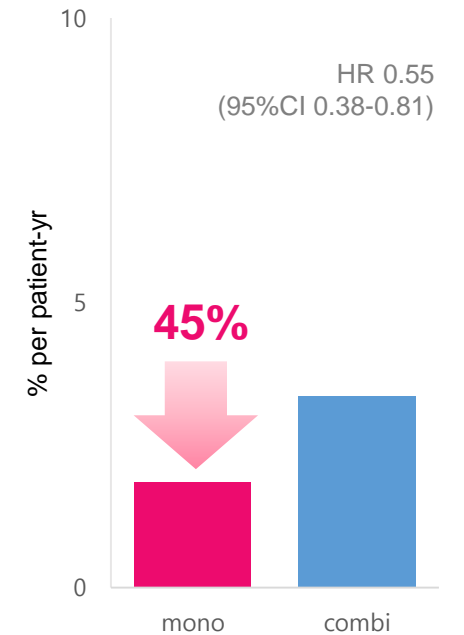
Primary Efficacy End Point



Primary Safety End Point

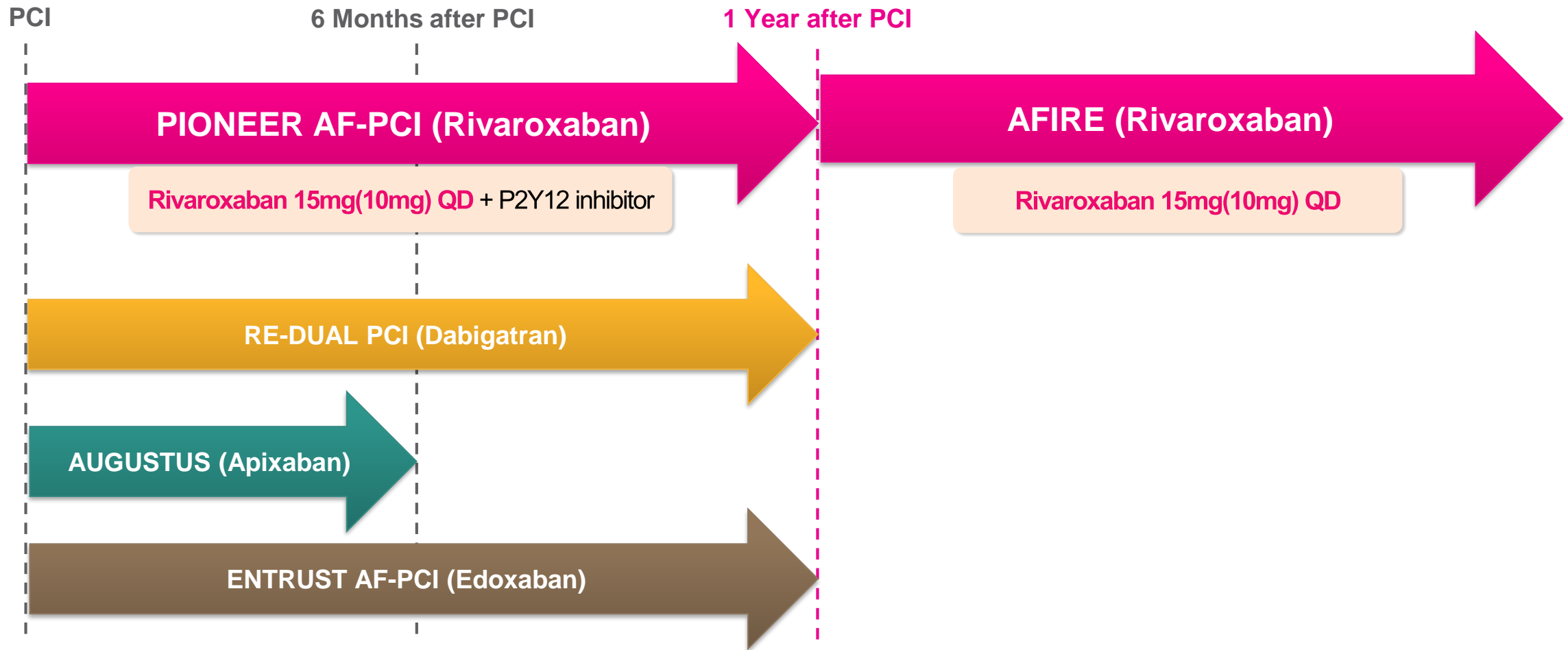


Death (CV / non-CV)



PIONEER AF-PCI & AFIRE

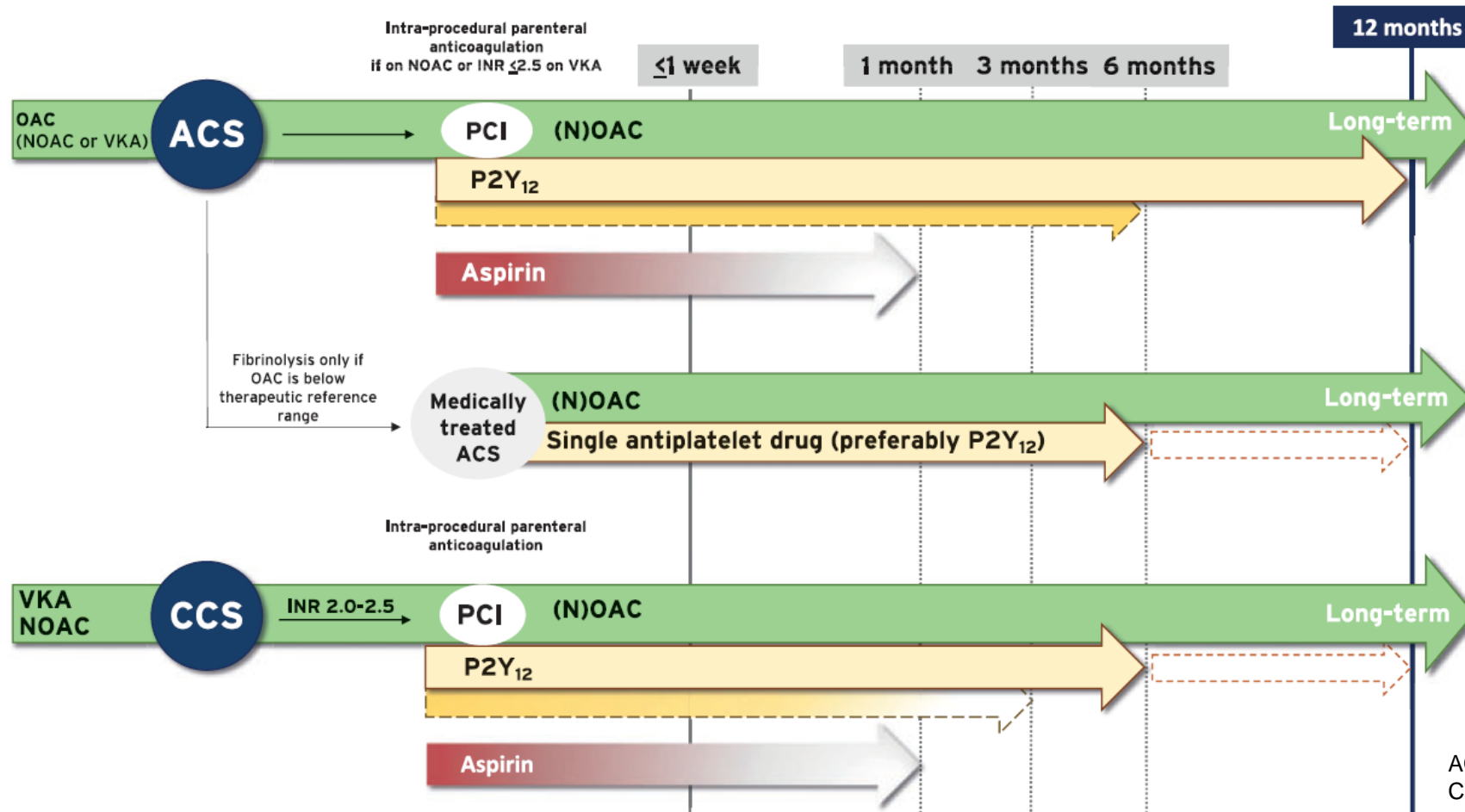
Rivaroxaban은 PCI 시행한 환자에서 장기적인 임상적 근거 마련



2020 ESC

AF patients undergoing PCI

항혈소판제 병용요법 시 VKA보다 NOAC 우선 권고 & ACS, CCS 환자 모두 장기간 NOAC 사용이 권장됨



ACS, acute coronary syndrome
CCS, chronic coronary syndrome

Preserving Kidney Function with Rivaroxaban

05

Association of AF with Renal function

심방세동, CKD, CAD는 위험인자를 공유하며 동반률 높음.
심방세동 동반 시 신기능 저하 위험이 더욱 증가

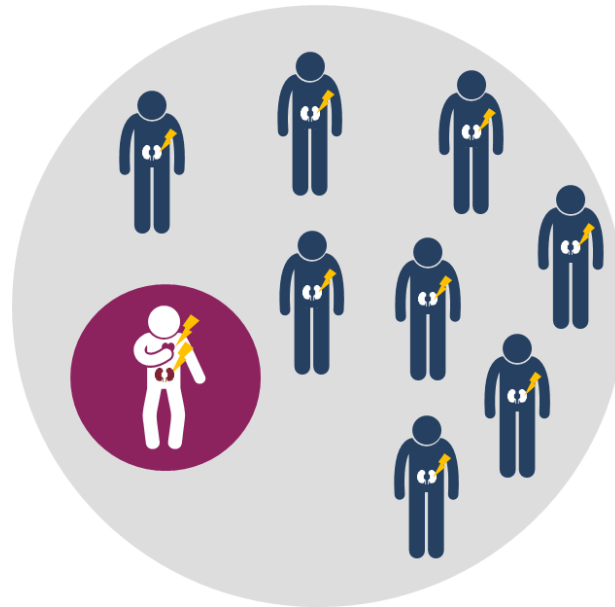
40-50 %

심방세동 환자에서 CKD 동반률¹⁾



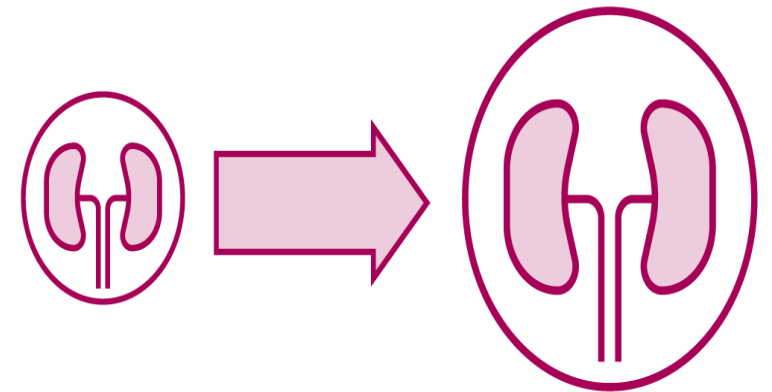
5-10 %

CKD 환자에서 AF & CAD 동반률²⁾



~ 80 %

CKD 환자의 AF 동반 시 신기능 악화 위험³⁾

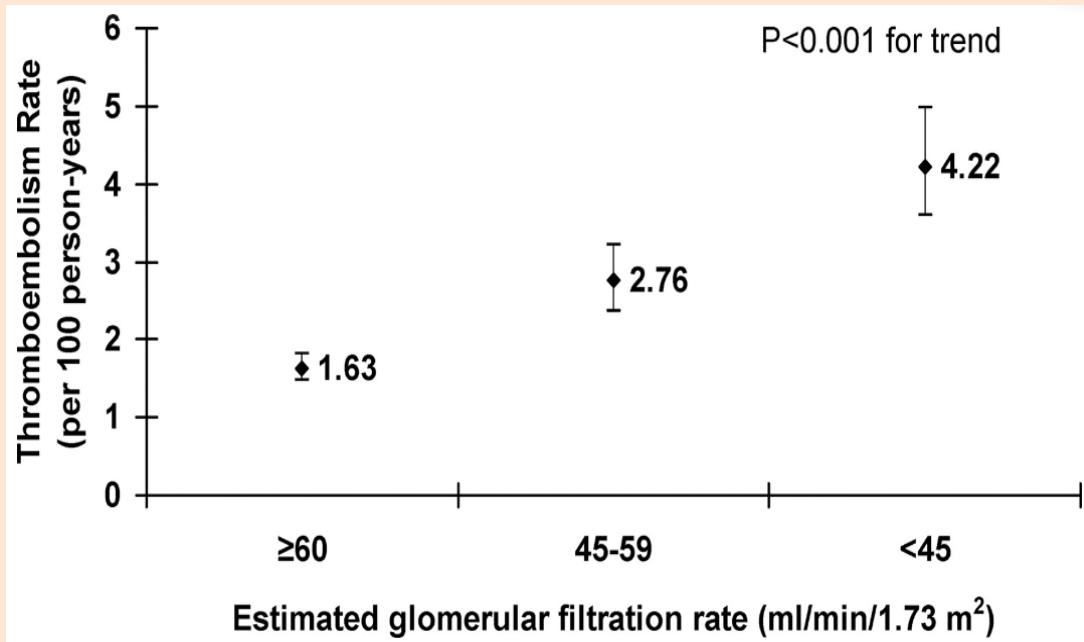


Thromboembolism & Bleeding risk in CKD

심방세동 환자에서 신기능 저하는
혈전 사건 및 출혈 위험을 증가시키는 중요한 위험인자

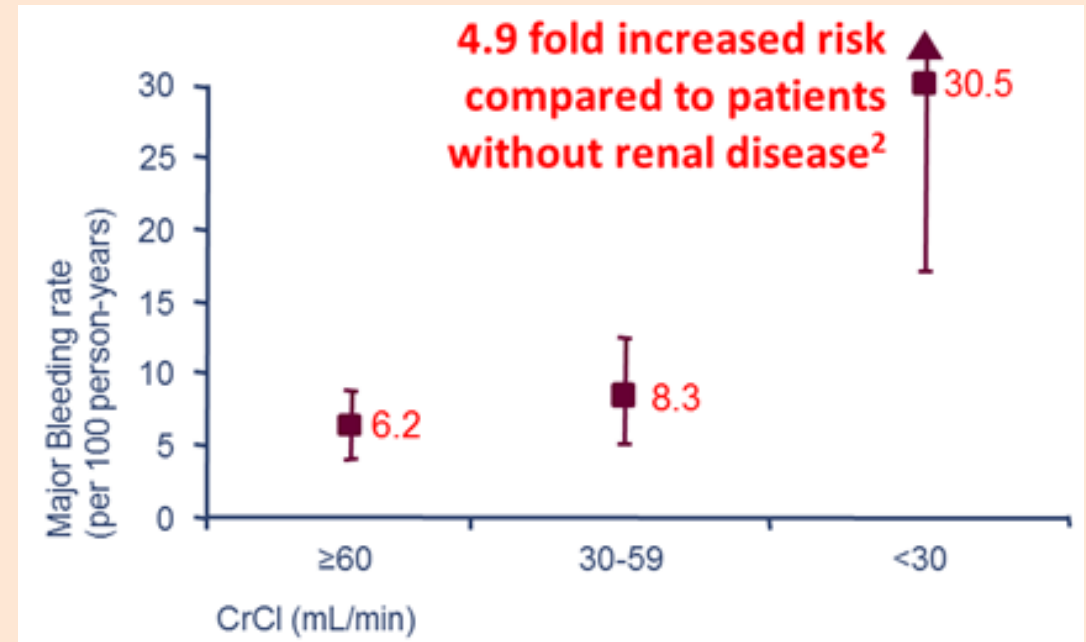
▷ **ARIA cohort¹⁾** (n=10,908, NVAf patients off warfarin)

< Thromboembolism (% person-years) >



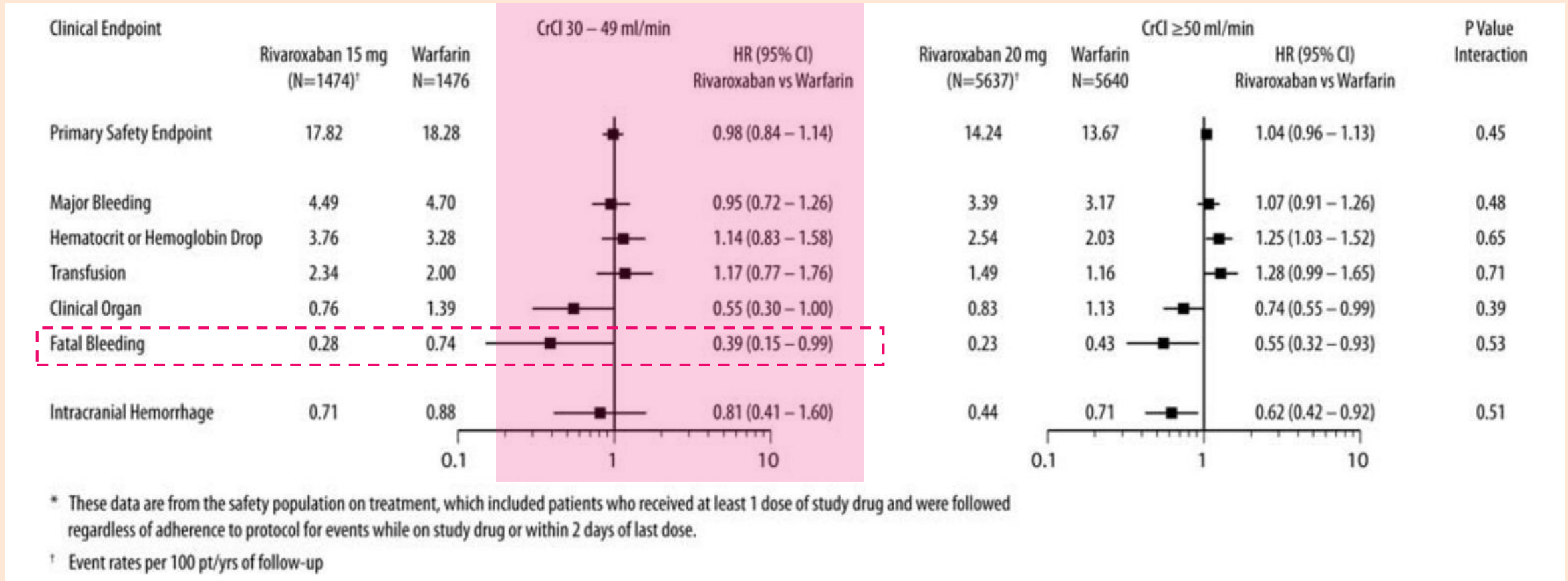
▷ **Systemic review²⁾** (patients on warfarin)

< Major Bleeding (% person-years) >



ROCKET-AF in Moderate CKD patients

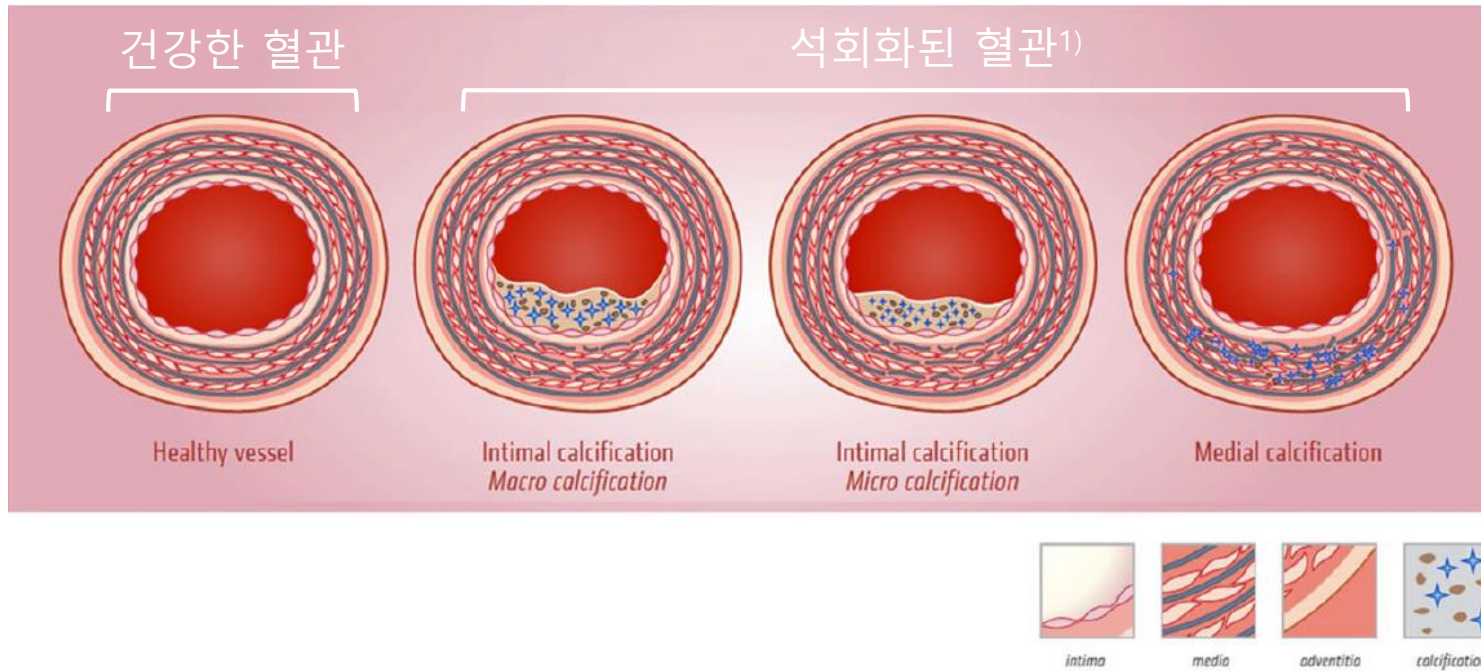
중등도 신장애 환자에서 Rivaroxaban 치료 시
Warfarin 대비 치명적 출혈 위험 61% 유의하게 감소



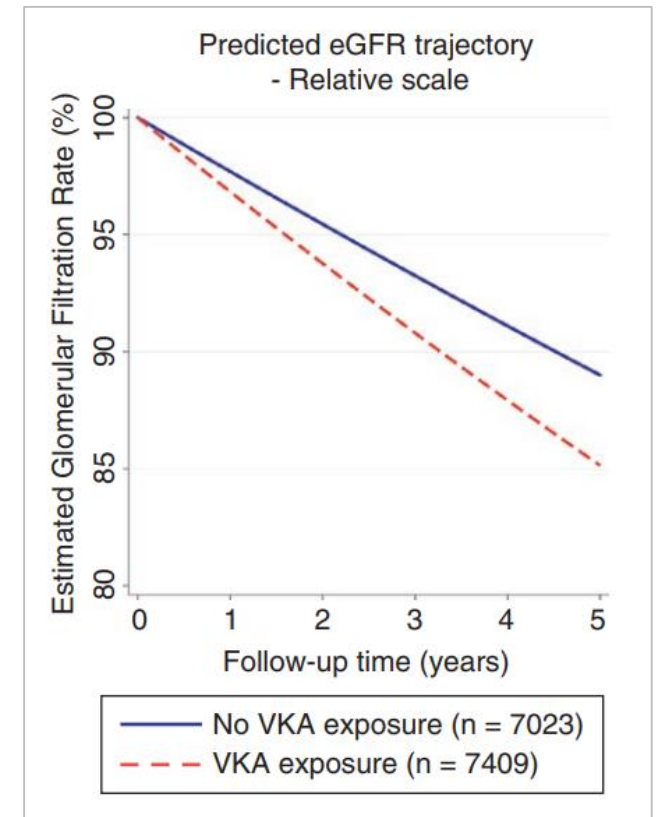
[Study Design] A pre-specified secondary analysis of ROCKET-AF trial to assess the risks and benefits of lower dose of rivaroxaban compared with warfarin in the patients with moderate renal insufficiency.

Calcification risk in CKD patients

혈관 석회화 위험이 높은 CKD 환자에서
VKA 치료 시 석회화 위험은 더욱 증가하여 신기능 악화

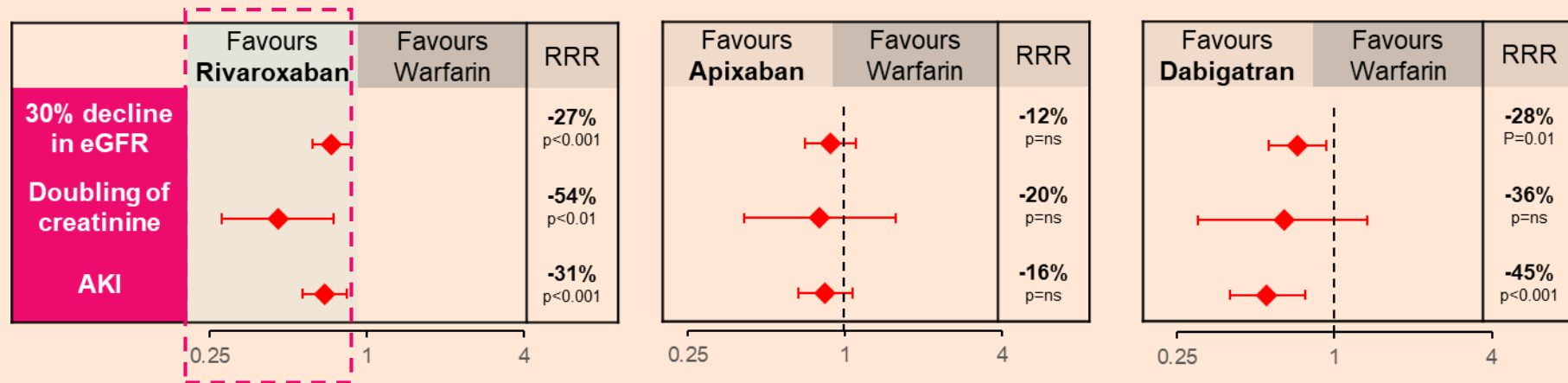
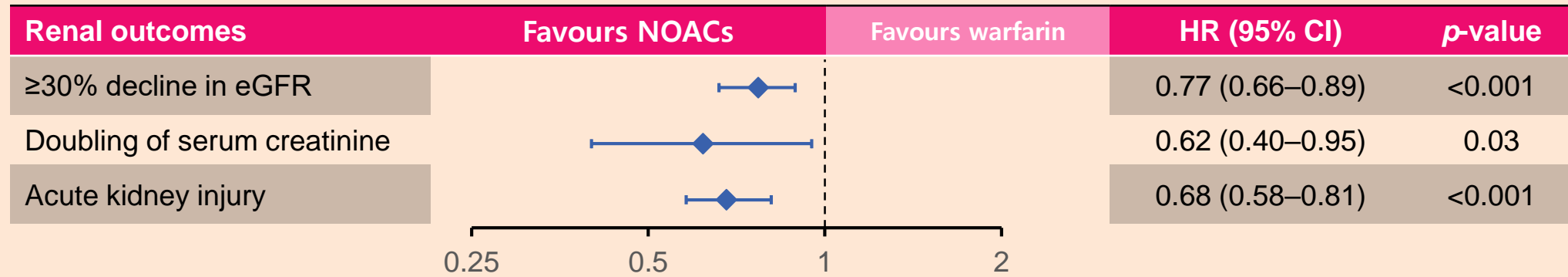


<VKA 치료에 따른 신기능 저하²⁾>



Real World data NOAC vs. VKA

AF환자에서 Warfarin 대비 NOAC이 신기능 보호에 효과적,
특히 Rivaroxaban에서 유의한 혜택 확인

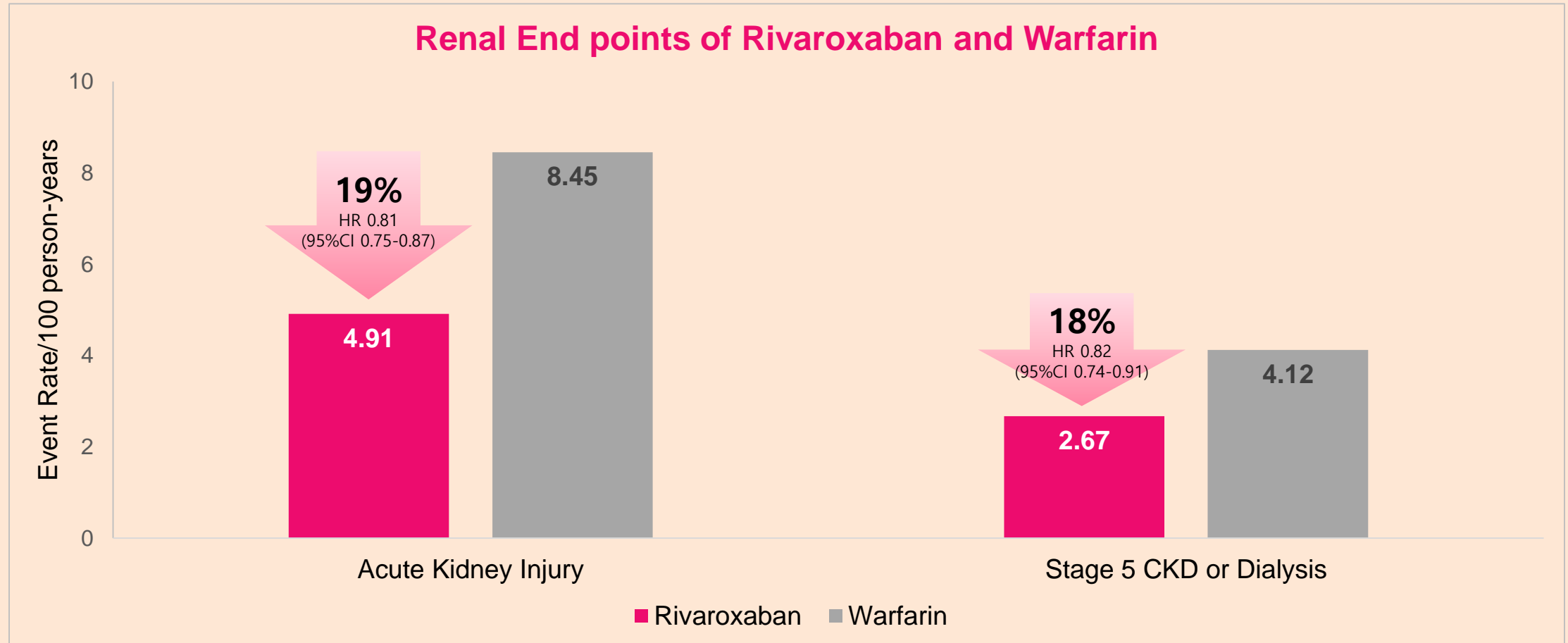


* Results are not intended for direct comparison between NOACs.

[Study Design] Using a large U.S. administrative database linked to laboratory results, the authors identified 9,769 patients with nonvalvular AF who started taking an oral anticoagulant agent (apixaban, dabigatran, rivaroxaban, warfarin) between 2010-2016 to compare their effects on 4 renal outcomes.

US Claims data in Stage 3-4 CKD patients

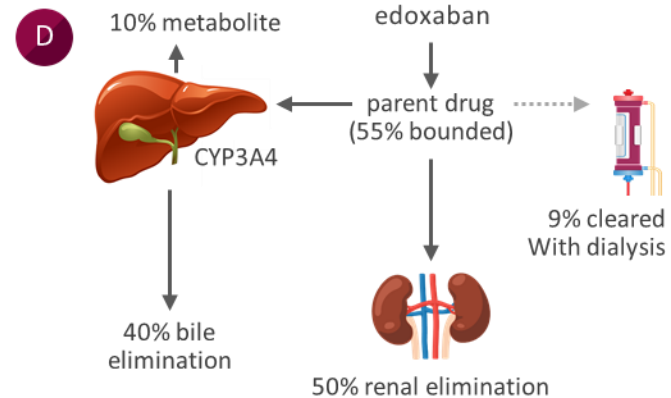
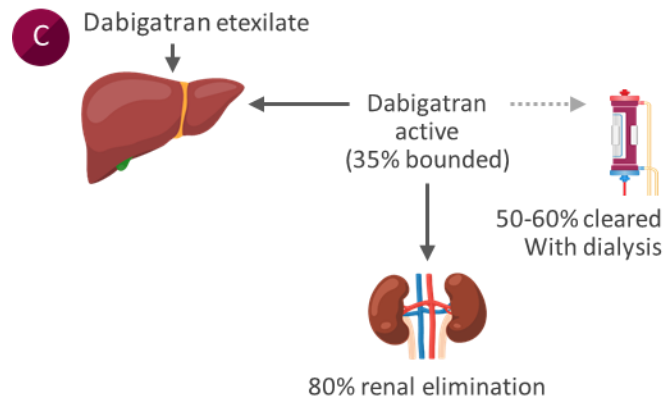
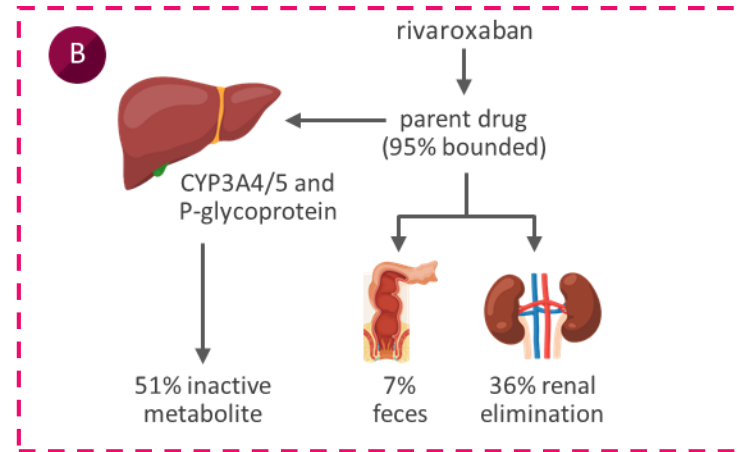
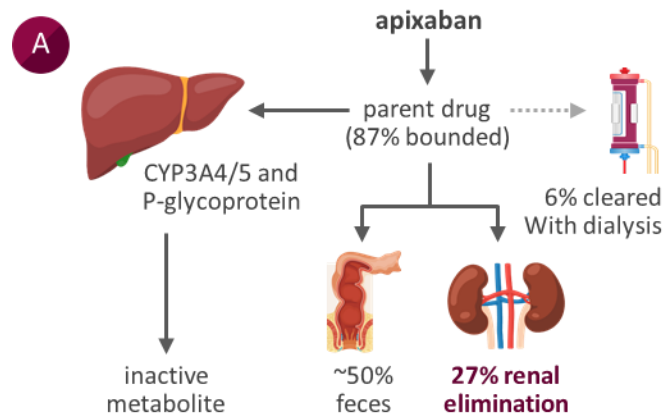
Stage 3-4 CKD 환자까지 포함한 리얼월드 데이터를 통해 Rivaroxaban의 신기능 보호에 대한 임상적 이득을 확인



[Study Design] A retrospective claims analysis using US Truven MarketScan data from January 2012 through December 2017. This analysis included NVAF patients who were oral anticoagulant naive during the 12 months before the initiation of rivaroxaban or warfarin. Stages 3 and 4 CKD were present in 5% and 1% of patients at baseline, and proteinuria was present in 2%.

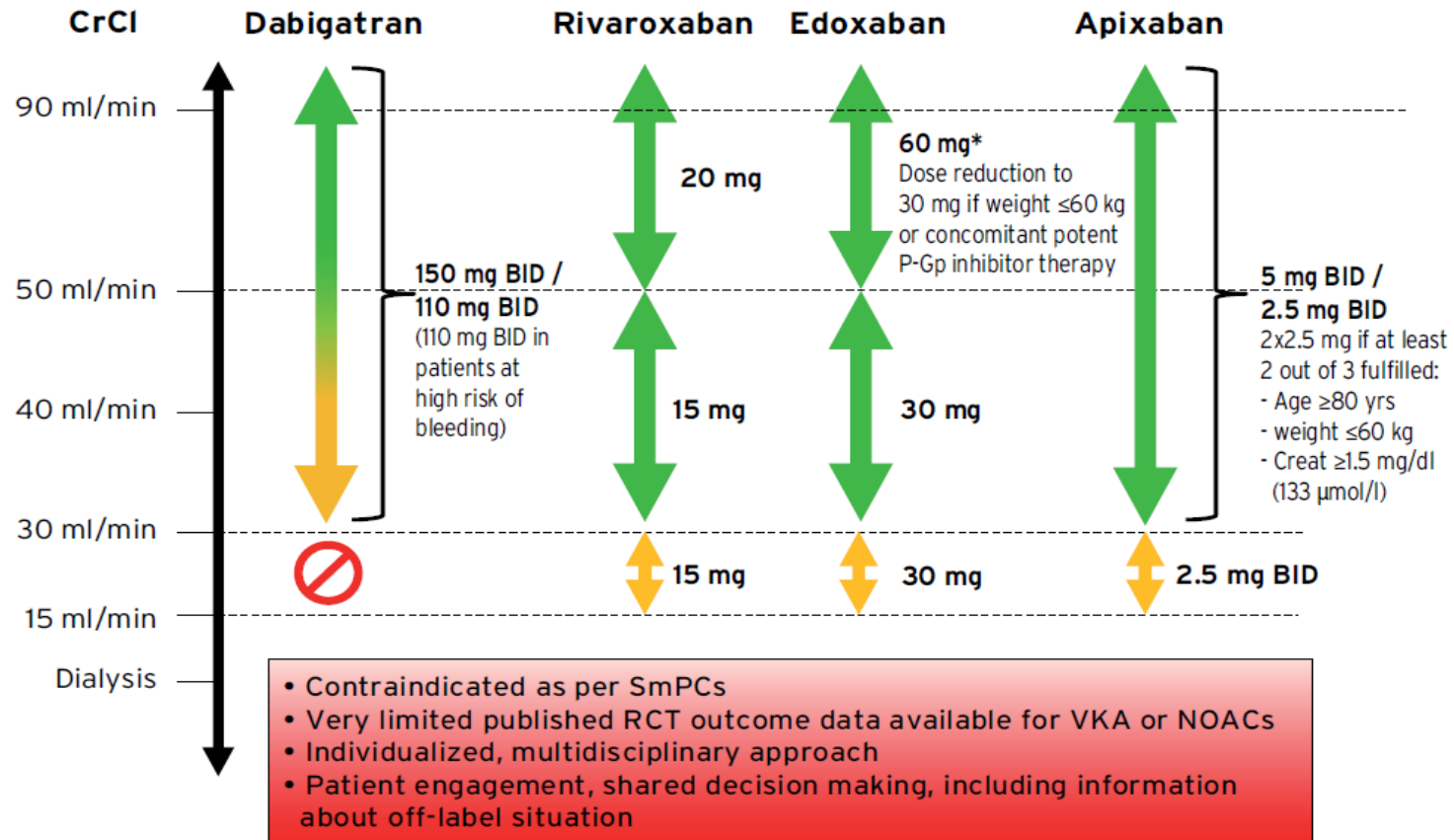
Renal elimination of NOACs

신장에서 제거되는 NOAC 의 비율



2021 EHRA Practical guide on NOACs

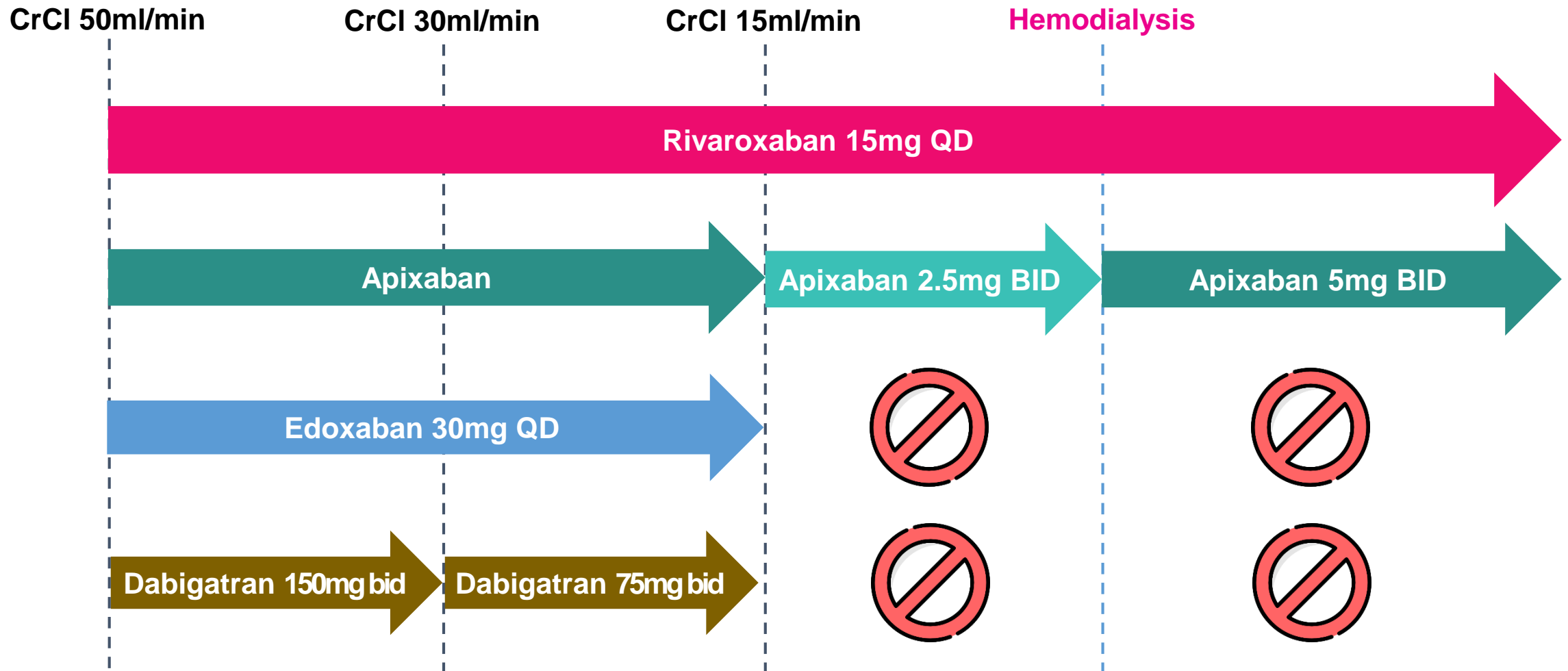
신기능에 따른 NOAC 용량 조절



*According to EMA SmPC edoxaban should be used in "high CrCl only after a careful evaluation of the individual thromboembolic and bleeding risk".

FDA Label Use in Renal Impairment

신기능 저하 환자에서 NOAC 사용 (FDA 허가 기준)



리록스반 정

Drug Information

05

보험인정기준 (15mg, 20mg)

허가사항 범위 내에서 아래와 같은 기준으로 투여 시 요양급여를 인정하며, 동 인정기준 이외 에는 약값 전액을 환자가 부담토록 함.

- 아 래 -

☞ CHA₂DS₂-VASc 점수 2점 이상의 뇌졸중 고위험군 환자에게 투여 시 보험급여 인정

- 고위험군 기준

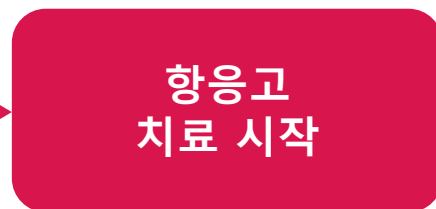
① 뇌졸중, 일과성 허혈발작, 혈전 색전증의 과거력이 있거나 75세 이상인 환자

② 다음의 6가지 위험인자 중 2가지 이상의 조건을 가지고 있는 환자

- 심부전
- 고혈압
- 당뇨
- 혈관성질환(심근경색, 말초동맥질환, 대동맥 죽상반의 과거력[4mm이상의 두께 또는 꺾양성 또는 유동성 죽상반])
- 여성
- 65~74세



CHA₂DS₂-VASc 점수



CHA₂DS₂-VASc 점수
2점 이상의 남자
3점 이상의 여자



CHA₂DS₂-VASc 점수
2점 이상의 뇌졸중
고위험군 환자

특장점

리록스반은 비판막성 심방세동 환자에서 QD 복용 가능하며, 타 NOAC 중 가장 다양한 적응증을 보유하고 있습니다.





허가사항(NOAC)	리록스반 (QD)		Apixaban (BID)	Dabigatran (BID)	Edoxaban (QD)
비판막성 심방환자의 뇌졸중 및 전신색전증 위험 감소	20mg 15mg	○	○	○	○
심재성 정맥혈전증 및 폐색전증의 치료		○	○	○	○
심재성 정맥혈전증 및 폐색전증의 재발 위험 감소	10mg	○	○	○	○
슬관절 또는 고관절 치환술을 받은 성인 환자의 정맥혈전색전증 예방		○	○	○	
심장표지자(cardiac biomarker) 상승을 동반한 급성관상동맥증후군을 경험한 환자에서 아스피린과의 병용 혹은 아스피린 및 클로피도그렐과 병용투여 시 죽상동맥혈전성 사건(심혈관계 이상으로 인한 사망, 심근경색) 발생률 감소	2.5mg	○	X	X	X
허혈성 사건의 발생 위험성이 높은 관상동맥질환 또는 증상이있는 말초동맥질환 성인환자에서 아스피린과 병용하여 죽상동맥혈전성사건(뇌졸중, 심근경색 및 심혈관계 이상으로 인한 사망)의 위험 감소		○			

Ref) 식품의약품 안전처, 리록스반정 허가사항

특장점

리록스반은 타 NOAC 대비 경제적 약가를 보유하여 환자들의 부담을 줄여줍니다.

NOAC 성상

리록스반	Apixaban
	
Dabigatran	Edoxaban
	

리록스반의 경제적 약가

Rivaroxaban (QD)		Apixaban (BID)		Dabigatran (BID)		Edoxaban (QD)	
리록스반	대조약						
20mg	1,300원	5mg	2,206원	150mg	2,438원	60mg	2,151원
15mg	1,312원	2.5mg		110mg	2,332원		
10mg	1,250원					30mg	
2.5mg	700원					15mg	859원
경제적 이익 (NVAF 환자 권장용량기준)		1%	41%	47%	40%		

경청해 주셔서 감사합니다.



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g.heartrhythm