Case-Based Tutorial (Practical Issues in NOAC)

Think Twice Before Prescribing or Skipping NOAC

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김 남 호

왜, 두 번 고민해야 하는가?

Case-Based Approach

80세, 여자

- 심방세동, 고혈압
- 키 : 145 ㎝, 42 ㎏ (BMI = 20 kg/m^2)
- 120/70 mmHg, 85 bpm
- 심방세동 치료 전략
  - Rate control
  - Prevention of thromboembolism
- 2013.1.15: 와파린

CHA_2DS_2 VASc – 4 (4.0%/yr)
HAS BLED – 1 (1.02%/yr)

진료일자	BP(S)	BP(D)	맥박	FBS	PP		PT INR	warfarin (mg)
					시간	값		
2013-06-11	130	69	84				2.23	2.5
2013-04-16	112	62	98				2.34	2.5
2013-03-05	134	92	95				2.18	2.5
2013-02-05	150	67	66				2.55	2.5
2013-01-22	140	62	62				1.53	2

80세, 여자

- 2013.1.15 와파린 시작

  → NOAC의 출시 및 건강보험 급여 확대(2015.7.1)

- 2015.7.22 (TTR 62.4%)

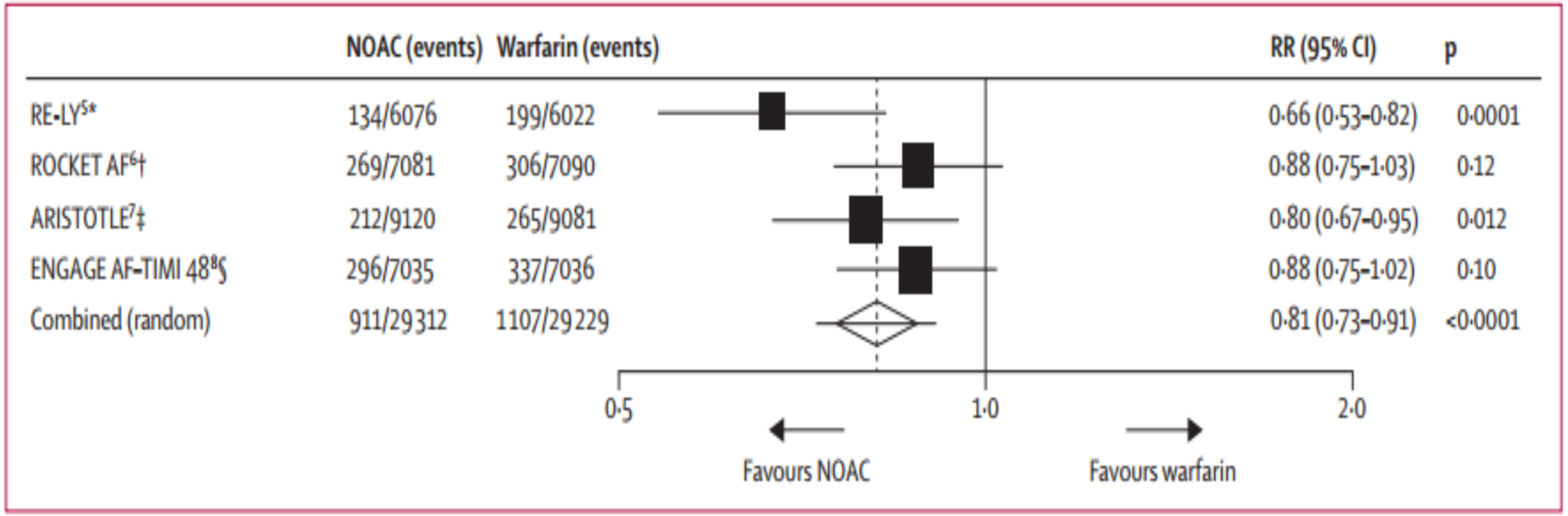
진료일자	BP(S)	BP(D)	맥박	FBS	PP		PT INR	warfarin (mg)	비고
					시간	값			
2015-07-22	120	70	85				1.65	2	
2015-05-13	125	83	96				1.05	2	백내장 수술 – 임의 중지
2015-02-03	131	82	82				3.34	2.5	결막 출혈
2014-12-09	124	64	96				2.69	2.5	
2014-10-14	123	70	78				2.17	2.5	

첫번째 질문. 항응고제 치료는 어떻게 유지할 것인가?

1. 와파린 2 mg 그대로 유지
2. 와파린 2.5 mg 증량
3. NOAC으로 변경

NOAC

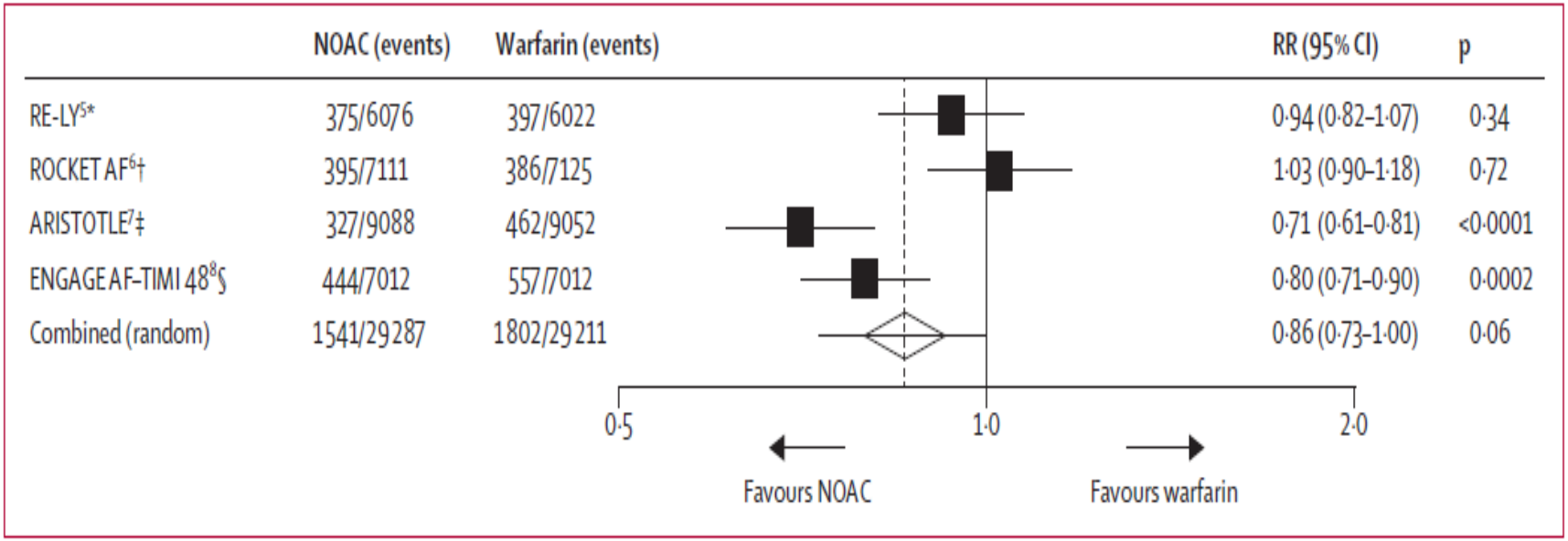
Stroke or Systemic Embolic Events



Ruff CT, et al. Lancet 2014;383:955-62.

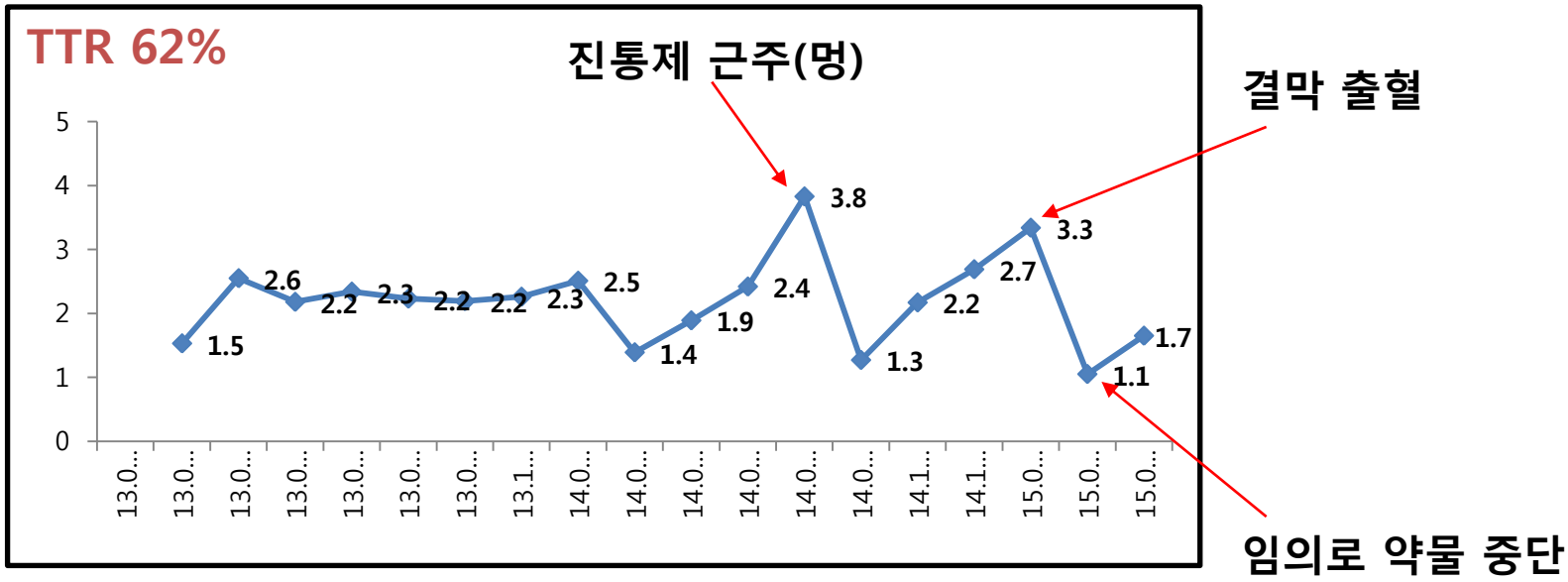
NOAC

Major Bleeding



Ruff CT, et al. Lancet 2014;383:955-62.

2015 EHRA Practical Guide



A practical algorithm for implementing SAMe-TT_2R_2 in decision-making on NOACs vs. VKA has been proposed, which could be used to prevent exposing patients to a 'trial of VKA' (when the score is > 2), whereas patients with a score of 0–2 could be treated with VKA and only switched over if poor adherence and/or TTR < 65%.

Heidbuchel H, et al. Europace 2015.

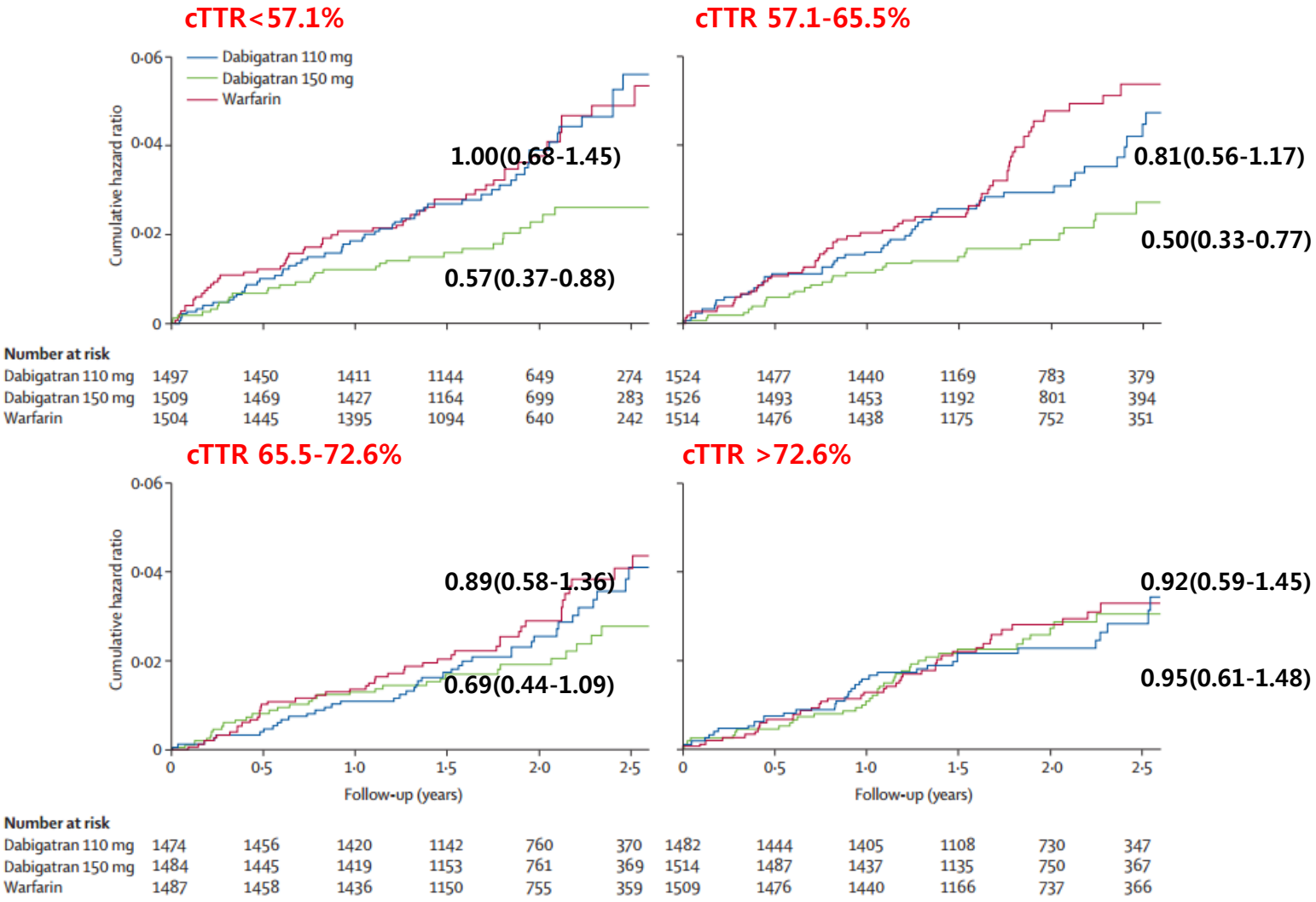
SAMe-TT_2R_2 Score

Acronym	Definitions	Points
S	Sex (female)	1
A	Age (<60 y)	1
M	Medical history[a]	1
e		
T	Treatment (interacting drugs, eg, amiodarone for rhythm control)	1
T	Tobacco use (within 2 y)	2
R	Race (nonwhite)	2
Maximum points		8

[a]Defined as more than two of the following: hypertension, diabetes, coronary artery disease/myocardial infarction, peripheral arterial disease, congestive heart failure, previous stroke, pulmonary disease, and hepatic or renal disease. SAMe-TT_2R_2 = sex female, age <60 years, medical history (more than two comorbidities), treatment (interacting drugs, eg, amiodarone for rhythm control), tobacco use (doubled), race (doubled).

Apostolakis S, et al. Chest 2013;144:1555-63.

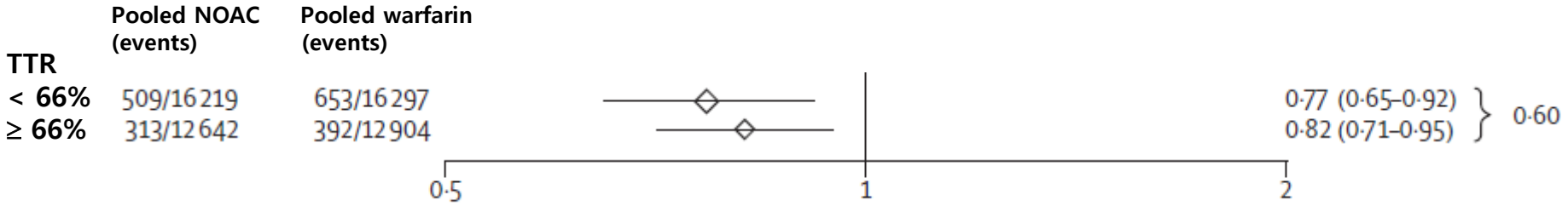
Dabigatran at Different Levels of INR



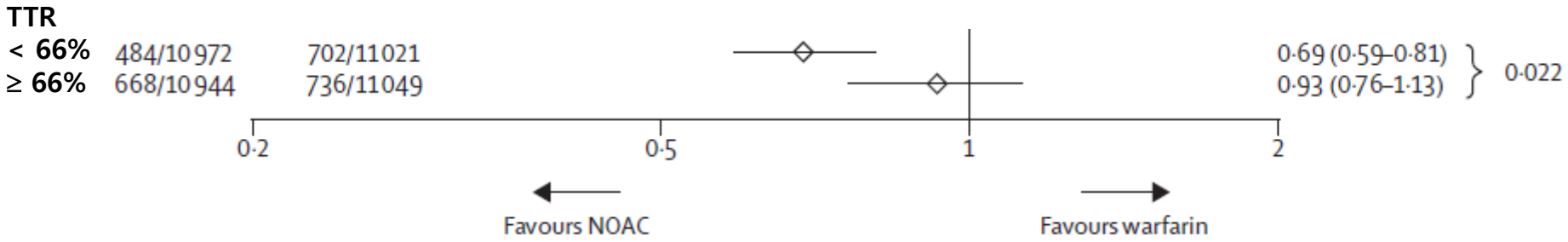
Wallentin L, et al. Lancet 2010;376:975-83.

NOAC in Optimal INR

Stroke or systemic embolism



Major Bleeding



Ruff CT, et al. Lancet 2014;383:955-62.

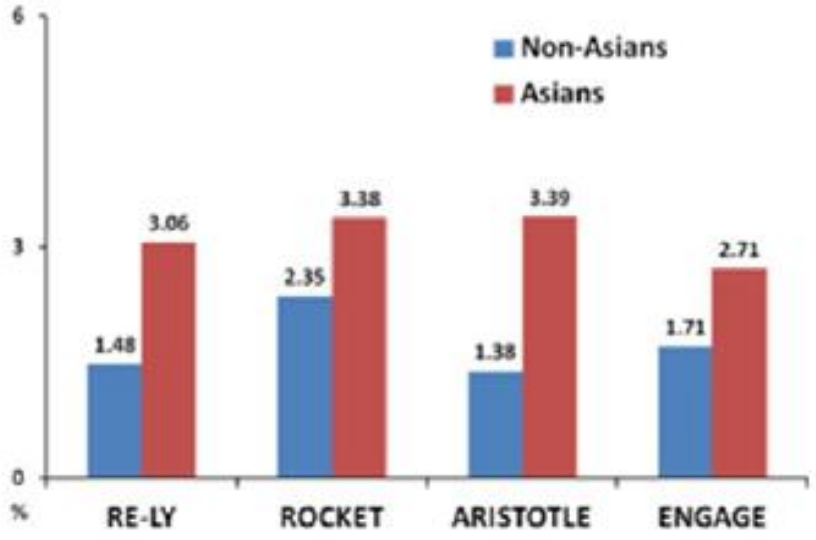
Expert Comment
TTR > 70%

- First choice
  - It is reasonable to continue with VKA treatment, with careful monitoring to ensure that TTR remains > 70%

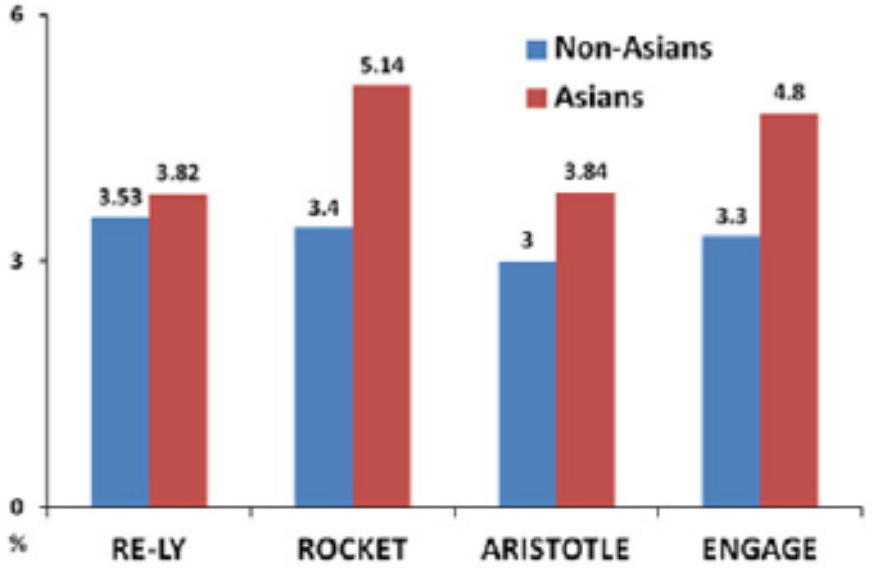
- Second choice
  - Substitution of VKA therapy with an NOAC may be considered in relation to the following
    - Previous complications (major bleeding event, ischemic stroke) on VKA therapy
    - SAMe-TT_2R_2 score (those with score > 2 are less likely to fare well on VKA therapy over the long term, and may be considered for NOAC therapy)
    - The patient's individual values and preferences

Diener HC, et al. 2016 Eur Heart J Epub ahead of print

Asians on Warfarin



Stroke and SE

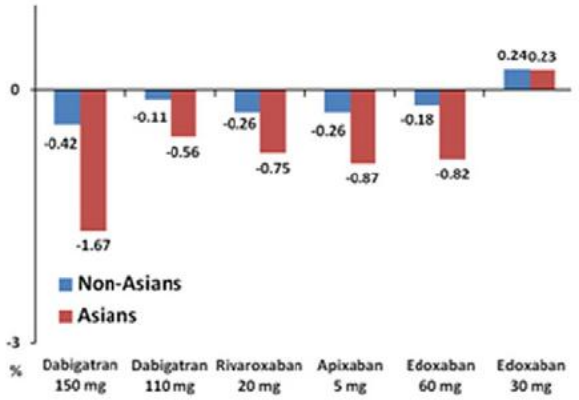


Major Bleeding

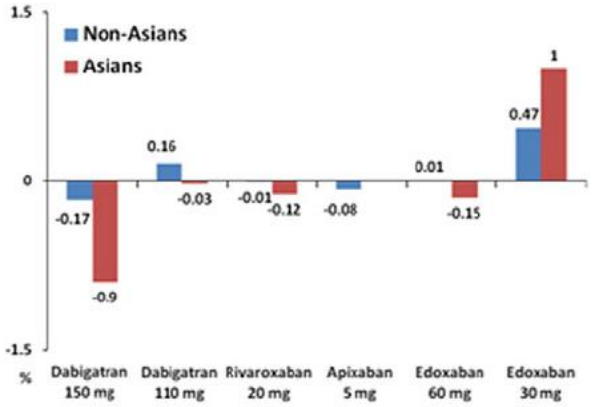
Lip GY, Int J Cardiol 2015; 180:246-254

Asians
(Absolute Risk Reduction in Efficacy)

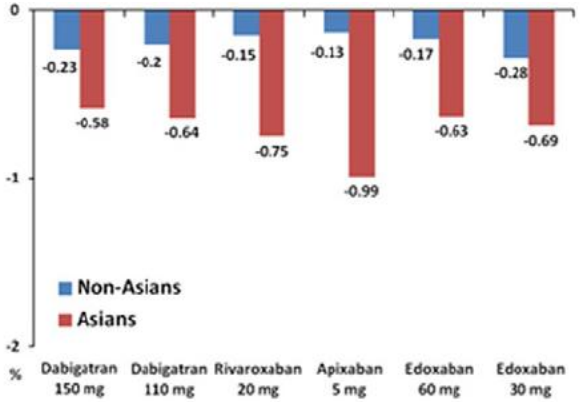
Stroke and Systemic Embolism



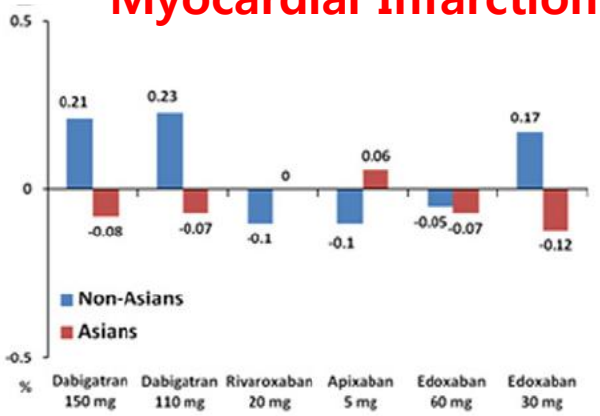
Ischemic Stroke



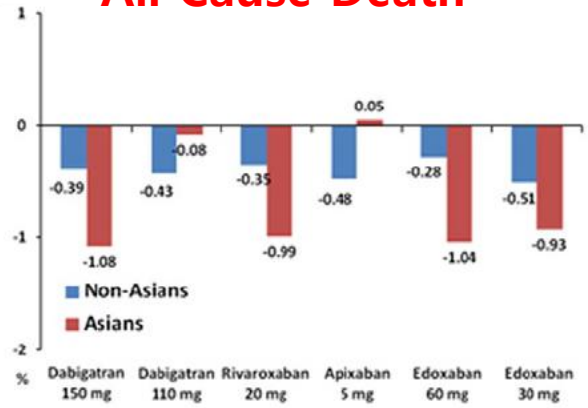
Hemorrhagic Stroke



Myocardial Infarction



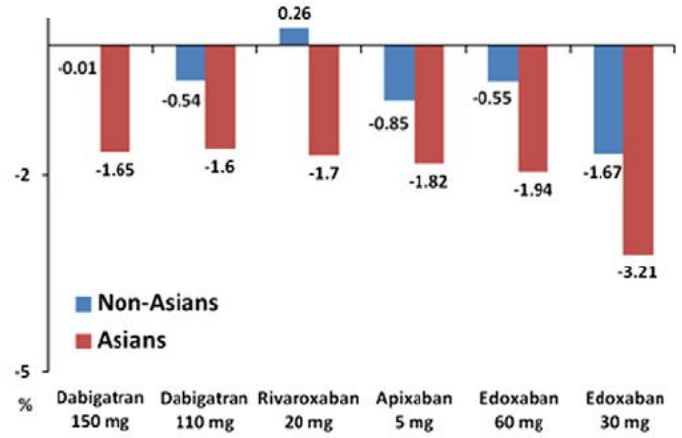
All Cause Death



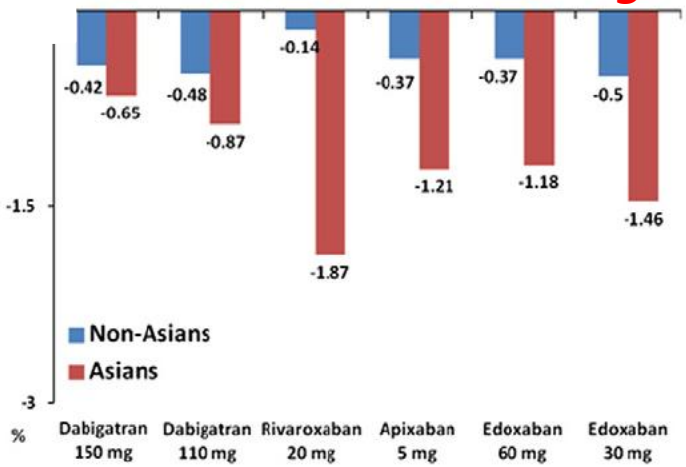
Lip GY, et al. Int J Cardiol 2015;180:246-254

Asians
(Absolute Risk Reduction in Safety)

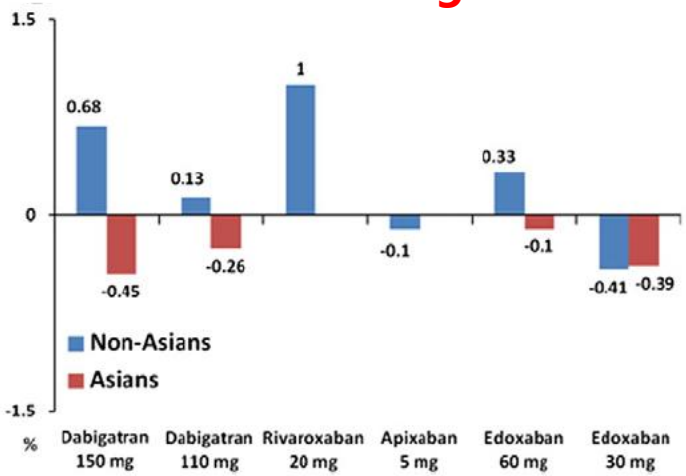
Major Bleeding



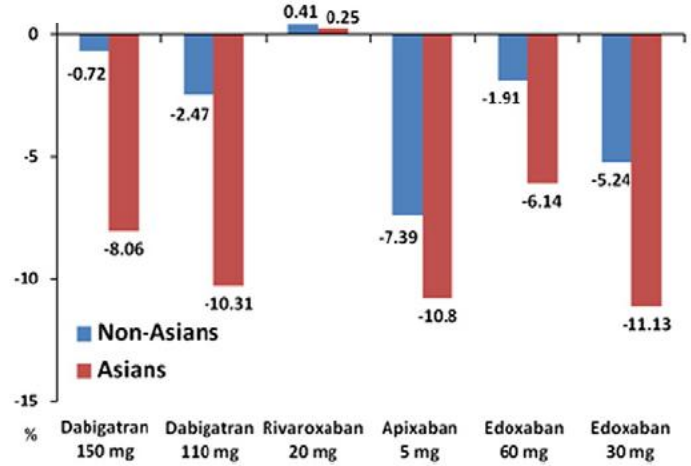
Intracranial Hemorrhage



GI Bleeding



All Bleeding



Lip GY, et al. Int J Cardiol 2015;180:246-254

NOAC 적응증

Recommendation	Class	Level
When adjusted-dose VKA (INR 2–3) cannot be used in a patient with AF where an OAC is recommended, due to difficulties in keeping within therapeutic anticoagulation, experiencing side effects of VKAs, or inability to attend/undertake INR monitoring, one of the NOACs, either: •a direct thrombin inhibitor (**dabigatran**); or •an oral Factor Xa inhibitor (e.g. rivaroxaban, apixaban*) … **is recommended**	I	B
Where an OAC is recommended, one of the NOACs – either • a direct thrombin inhibitor (dabigatran) or • an oral Factor Xa inhibitor (e.g. rivaroxaban, apixaban) **--- should be considered** rather than adjusted-dose VKA (INR 2–3) for most patients with non-valvular AF, based on their net clinical benefit.	IIa	A

NOACs are considered to be preferentially indicated in Asians.

2012 ESC Guideline
2015 updated EHRA Clinical Practice Guide

80 > 82세, 여자

- 2015.7.22 항응고제 선택은?

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1. 와파린 2 mg 그대로 유지
2. 와파린 2.5 mg 증량
3. NOAC으로 변경

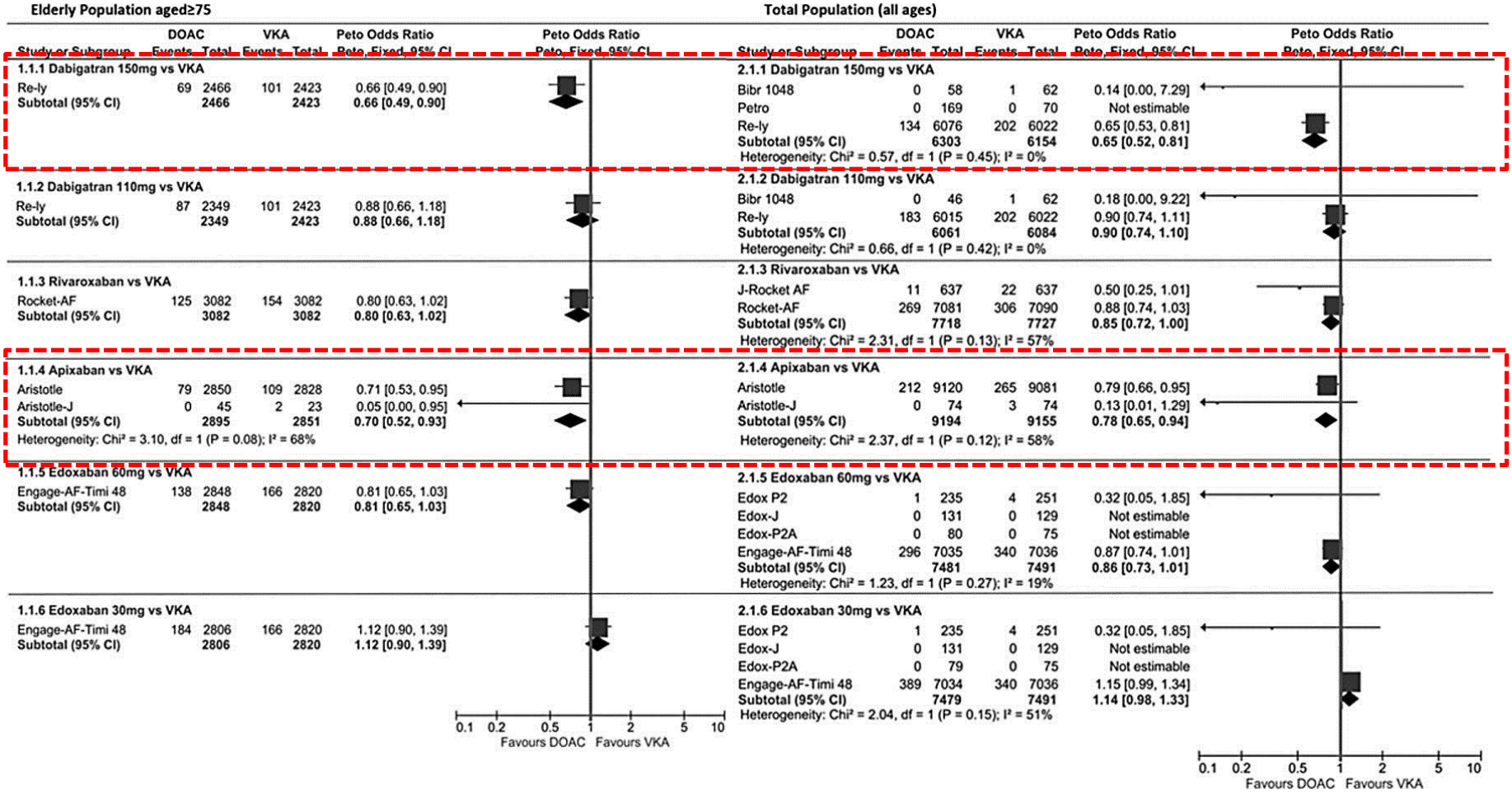
두번째 질문. NOAC 중 어떤 것을 선택할 것인가?

환자의 특성

- 아시아
- 80세 > 82세의 극노인
- 저체중 : 42 kg
- 2년의 치료 중 동반 질환 및 증상
  - 심부전 : mild aortic stenosis
  - CBD stone : ERCP
  - 퇴행성 관절염 : 진통제 복용 및 주사 > 멍
  - 결막 출혈
  - 백내장 수술

Elderly Patients > 75 yrs

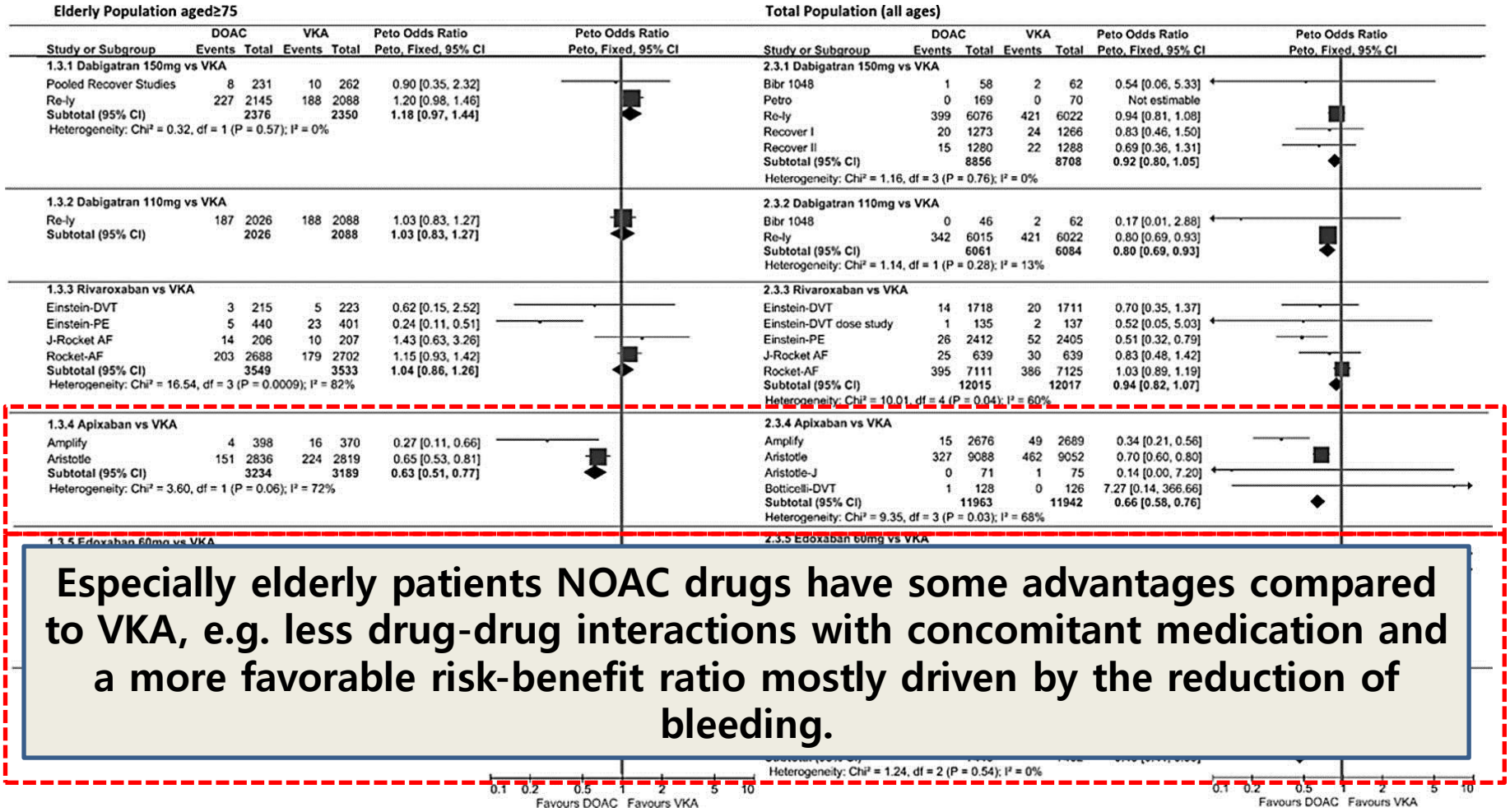
Risk of stroke or systemic embolism in atrial fibrillation studies



Manuj Sharma et al. Circulation. 2015;132:194-204

Elderly Patients > 75 yrs

Risk of major bleeding



Especially elderly patients NOAC drugs have some advantages compared to VKA, e.g. less drug-drug interactions with concomitant medication and a more favorable risk-benefit ratio mostly driven by the reduction of bleeding.

Manuj Sharma et al. Circulation. 2015;132:194-204

Expert Comment
75세 이상 고령

- First choice
  - Apixaban 5 mg twice daily
  - Apixaban 2.5 mg
    - If ≥ 2 of following : age ≥ 80 years, body weight ≤ 60 kg, or creatinine ≤ 1.5 mg/dL
- Second choice
  - Dabigatran 110 mg twice daily
  - Rivaroxaban 20 mg once daily
  - Edoxaban 60 mg once daily

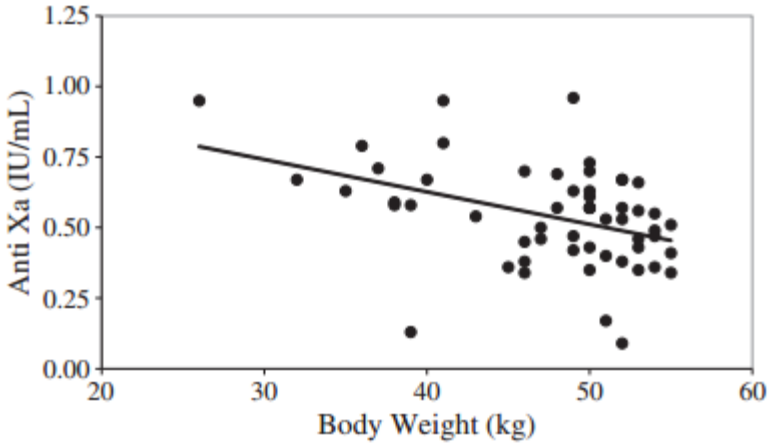
Diener HC, et al. 2016 Eur Heart J Epub ahead of print

체중과 항응고제와의 관계

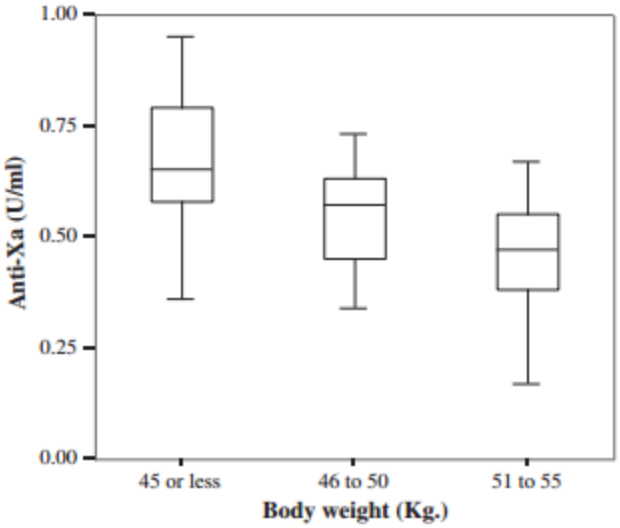
- Dabigatran
- Rivaroxaban
- Apixaban
  - 60 kg 미만, 80세 이상, Cr 1.5 mg/dL 이상 중 2개 이상

특별한 언급이 없으나 고도 비만 및 극저체중 환자에서의 NOAC 용량에 대한 연구가 필요할 것으로 생각됨

Anti-Xa Activity and Body Weight After Enoxaparin Prophylaxis



Correlation between BW and anti-Xa level.
Spearman's rho = -0.428, p<0.001.

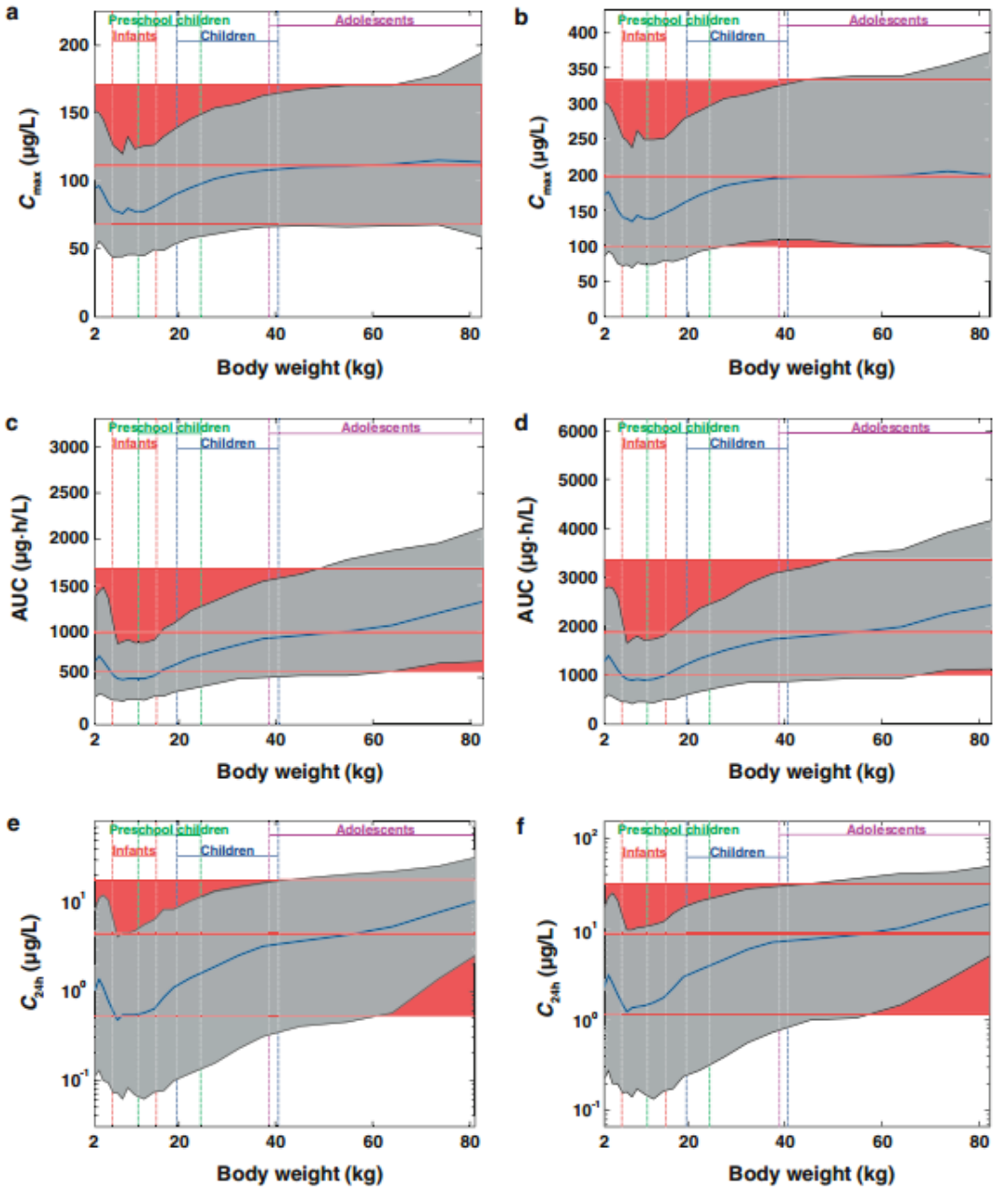


Comparison of mean anti-Xa level.

Rojas L, et al. Thromb Res 2013;132:761-4

Pharmaco-kinetics of Rivaroxaban

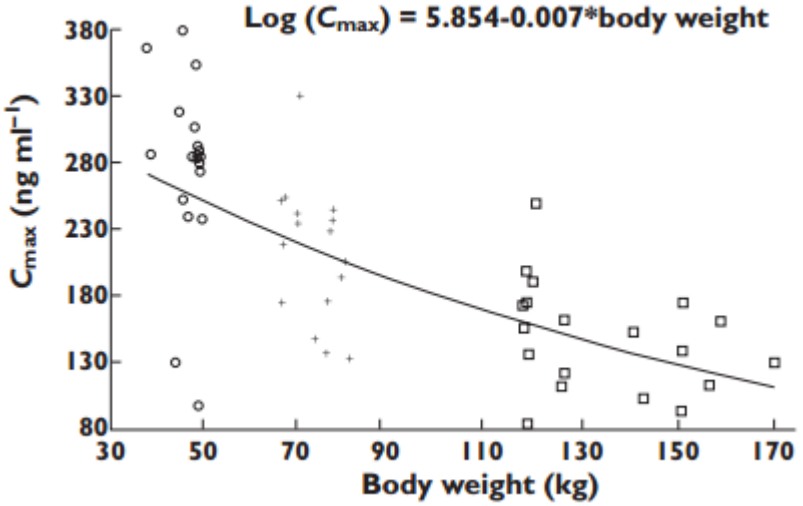
For children with body weight between 40 and 70 kg, simulated plasma pharmacokinetic parameters (C_{max}, C_{24h} and AUC) overlapped with the values obtained in the corresponding adult reference simulation, indicating that body weight-related exposure was similar between these children and adults

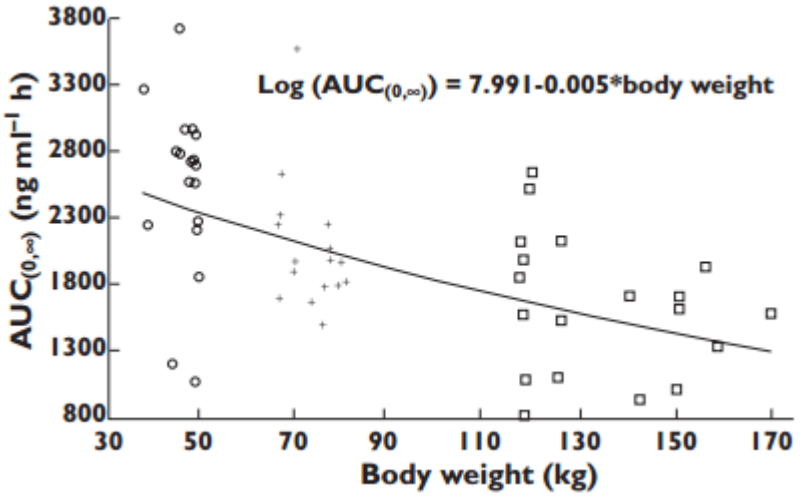


0.143 mg/kg (10 mg) 0.286 mg/kg (20 mg)

Willmann S, et al. Clin Pharmacokinet 2014;53:89-102

Effect of Body Weight on Pharmacokinetics of Apixaban in Healthy Subjects





The modest change in apixaban exposure is unlikely to require dose adjustment for apixaban based on body weight alone. However, caution is warranted in the presence of additional factors (such as severe renal impairment) that could increase apixaban exposure.

Upreti VV, et al. Br J Clin Pharmacol 2013;76:908-16.

환자의 특성

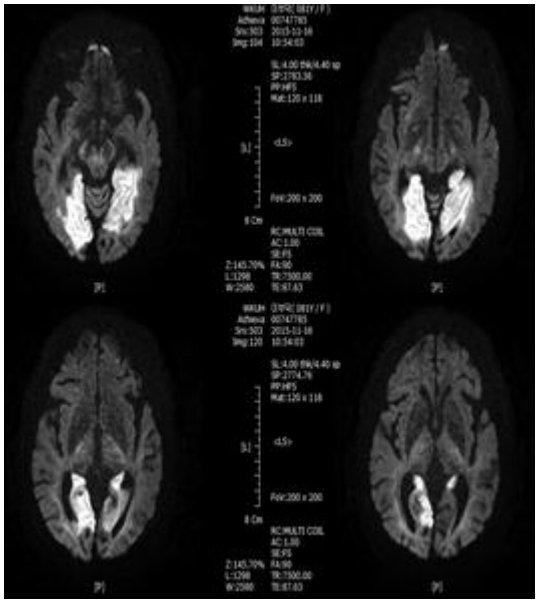
- 아시아 warfarin < NOAC
- 80세 > 82세의 극노인 warfarin < NOAC (apixaban)
- 저체중 : 42 kg warfarin ≈ NOAC
- 2년의 치료 중 동반 질환 및 증상
  - 심부전 : mild aortic stenosis
  - CBD stone : ERCP
  - 백내장 수술

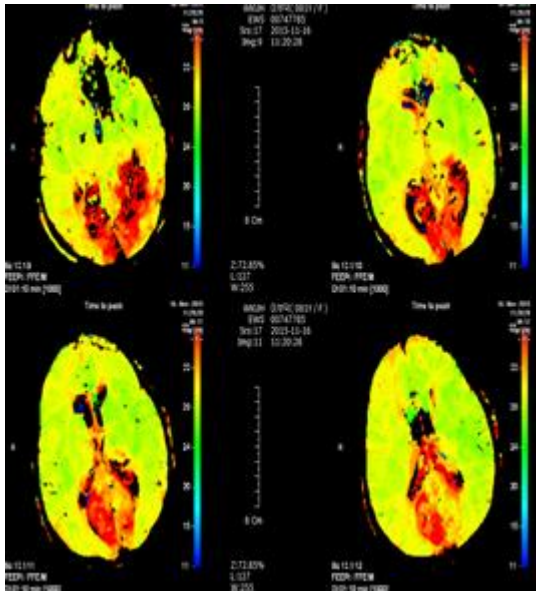
warfarin

와파린에서 NOAC (Apixaban 2.5 mg BID)로 변경

80 > 82세, 여자

- 2013.01.15 : 와파린 시작
- 2015.07.22 : 엘리퀴스 2.5 mg BID
- 2015.11.16 : 두 눈이 안보이고 어지러움





acute cerebral infarction

결론

- 와파린을 사용하고 있는 환자에서 NOAC 으로의 변경은 환자의 색전혈전증의 위험도 및 출혈의 위험성에 대한 상호 평가가

Think Twice Before Prescribing or Skipping NOAC

- 극이 <u>[illegible]</u> 환자, <u>기능 장애 환자, 극도의 비만 또는 저체중</u> 환자에서의 NOAC 사용은 신중하여야 한다.

감사합니다.