Personalized Treatment Strategies for Stroke Prevention in AF
- Question and Answers -

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Patients with AF in the real world have a high proportion of comorbidities

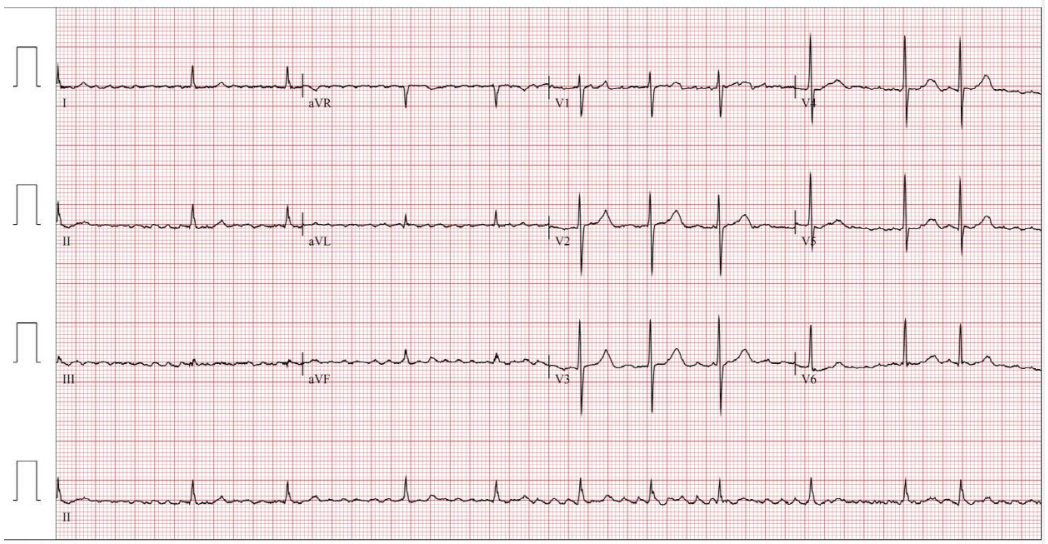
	Euro Heart Survey[1*]	AFNET[2*]	REALISE-AF[3]	EORP[4]	PREFER-AF[5]
Patients (n)	978	1035	10523	3049	7243
Mean age (years)	65.0	67.0	66.6	68.8	71.5
CKD or renal failure (%)	4.2***	9.2***	3.9***	13.2**	12.9**
Heart failure (%)	26.1	31.6	45.8	47.5	21.3
Hypertension (%)	63.4	68.9	72.2	70.9	72.0
CAD (%)	31.6	26.8	32.3	36.4	23.4
Prior stroke / TIA (%)	4.2 / 2.9	3.7 / 2.1	6.1 / 2.8	6.4 / 4.1	8.4 / NR
Period of data collestion	2003-2004	2004-2006	2009-2010	2012-2013	2012-2013

* First detected AF cohort; ** CKD; *** Renal failure **NR,** not reported

Nieuwtaat R *et al. Eur Heart J* 2005;26:2422-2434; Nabauer M *et al. Europace* 2009;11:423-434;
Steg *P et al. Heart* 2012;98:195-201; Lip G *et al. Europace* 2014; 16:308-319; Kirchhof P *et al. Europace* 2014;16:6-14.

증례 1. 76세 남자

- 주소 : 두근거림 및 호흡곤란 (NYHA 2-3)
- 병력 : 고혈압
- 몸무게 : 62 Kg
- 혈압 : 140/80 mmHg
- 복용 약물
  - Valsartan 80 mg
  - Dichlozid 12.5 mg
  - Clopidogrel 75 mg



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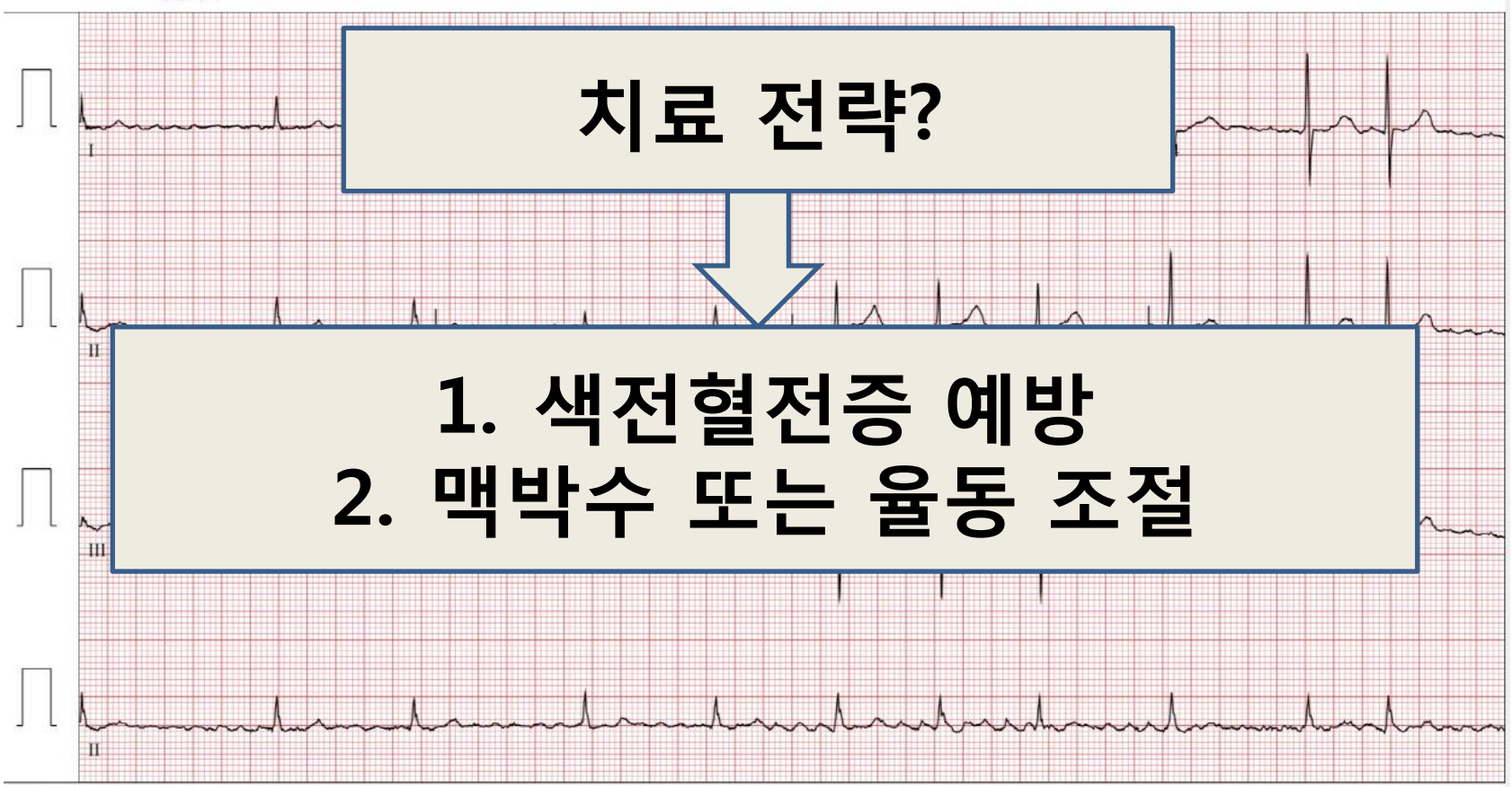
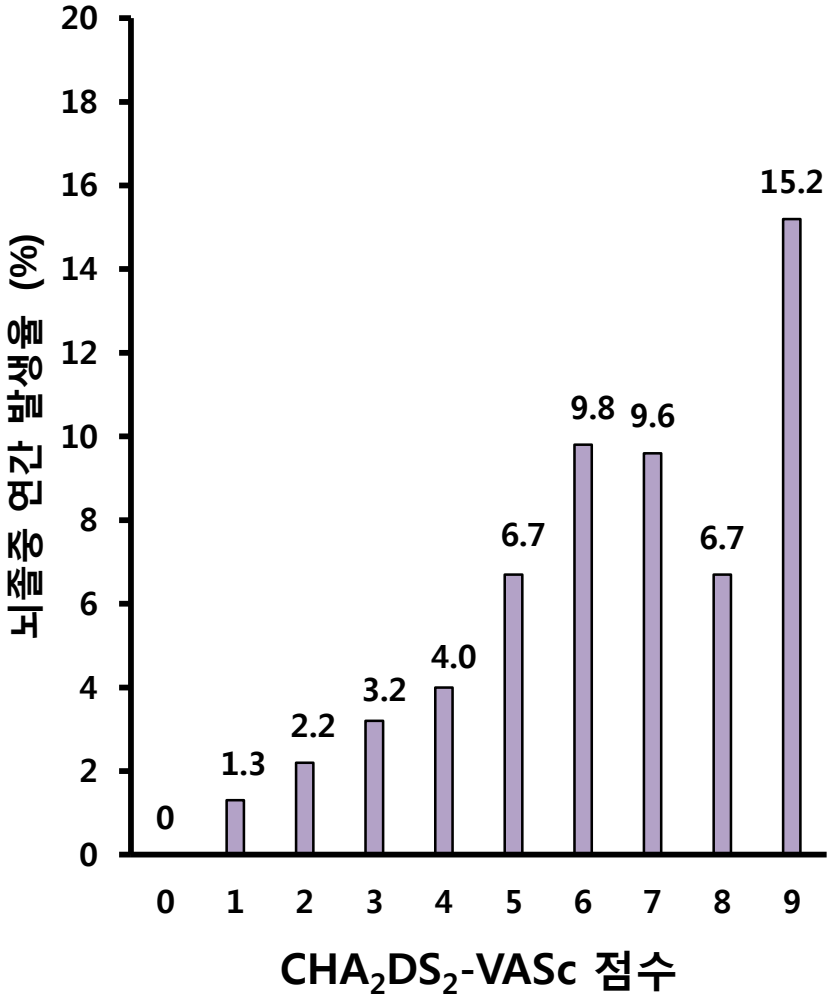
증례 1. 76세 남자



색전혈전증 위험도 평가

CHA_2DS_2-VASc	Score
Congestive heart failure/ LV dysfunction	1
Hypertension	1
Age ≥75 yrs	**2**
Diabetes mellitus	1
Stroke/TIA/TE	**2**
Vascular disease (prior myocardial infarction, peripheral artery disease or aortic plaque)	1
Age 65–74 yrs	1
Sex category (i.e. female gender)	1
Maximum score	9



2012 ESC Guideline.
2014 AHA/ACC/HRS Guideline.

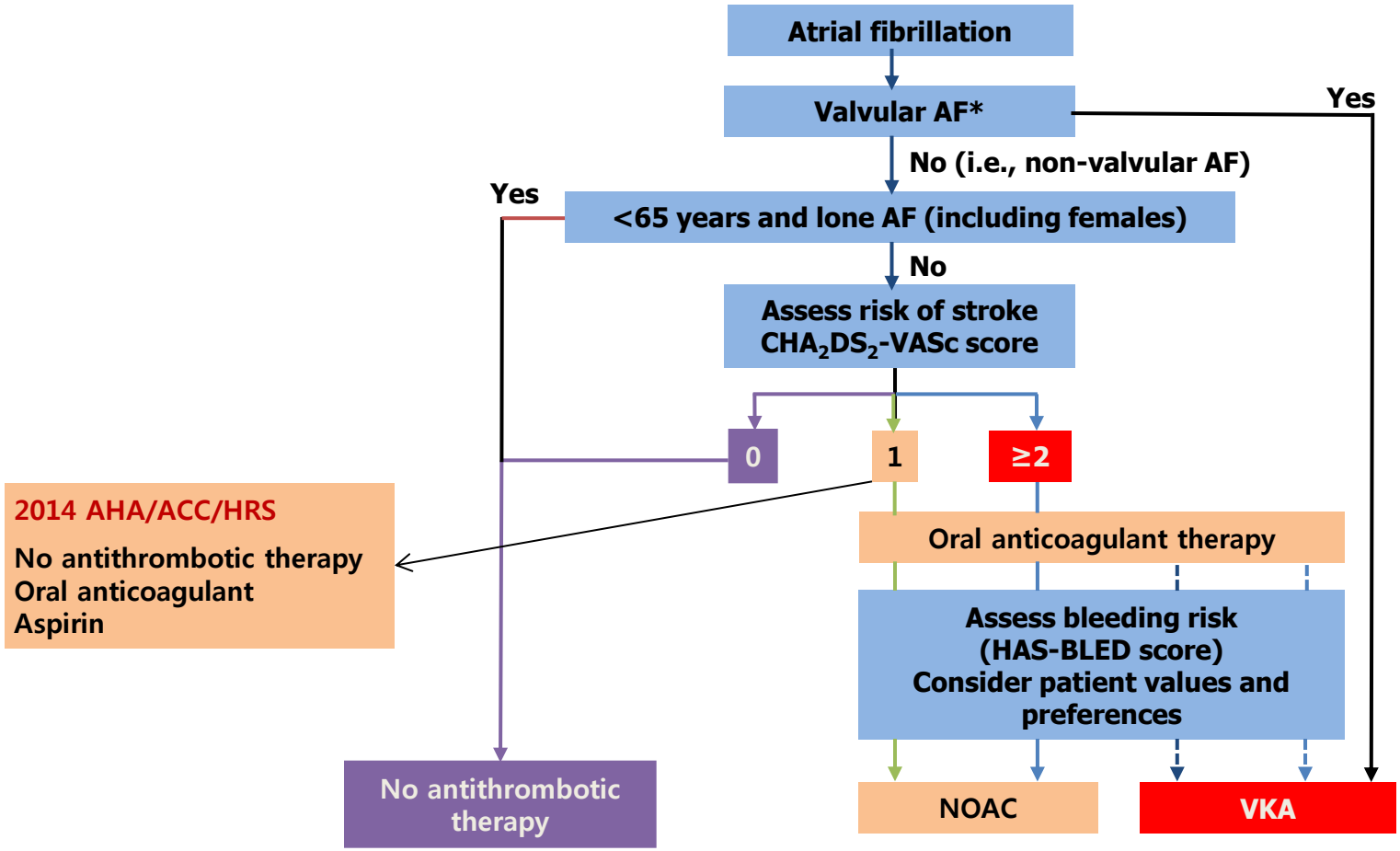
출혈 위험도 평가

HAS BLED	Score
Hypertension (SBP > 160 mmHg)	1
Abnormal renal and liver function (1 point each)	1 or 2
Stroke	1
Bleeding	1
Labile INR	1
Eldery (age > 65 years)	1
Drugs or alcohol (1 point each)	1 or 2
Maximum score	9

Abnormal kidney function is defined as the presence of chronic dialysis or renal transplantation or serum creatinine ≥200 umol/L.
Abnormal liver function is defined as chronic hepatic disease (e.g. cirrhosis) or biochemical evidence of significant hepatic derangement (e.g. bilirubin > 2 x upper limit of normal, in association with AST/ALT/ALP > 3 x upper limit normal, etc.).
Bleeding refers to previous bleeding history and/or predisposition to bleeding, e.g. bleeding diathesis, anaemia, etc.
Labile INRs refers to unstable/high INRs or poor time in therapeutic range (e.g. < 60%).
Drugs/alcohol use refers to concomitant use of drugs, such as antiplatelet agents, non-steroidal anti-inflammatory drugs, or alcohol abuse, etc.

2010 ESC Guideline

색전혈전증 예방



Non-valvular AF
: absence of rheumatic MS, mechanical or bioprosthetic heart valve, or mitral valve repair

Antiplatelet therapy with ASA plus clopidogrel or – less effectively – ASA only, should be considered in patients who refuse any OAC or cannot tolerate anticoagulation for reasons unrelated to bleeding. If there are contraindications to OAC or antiplatelet therapy, left

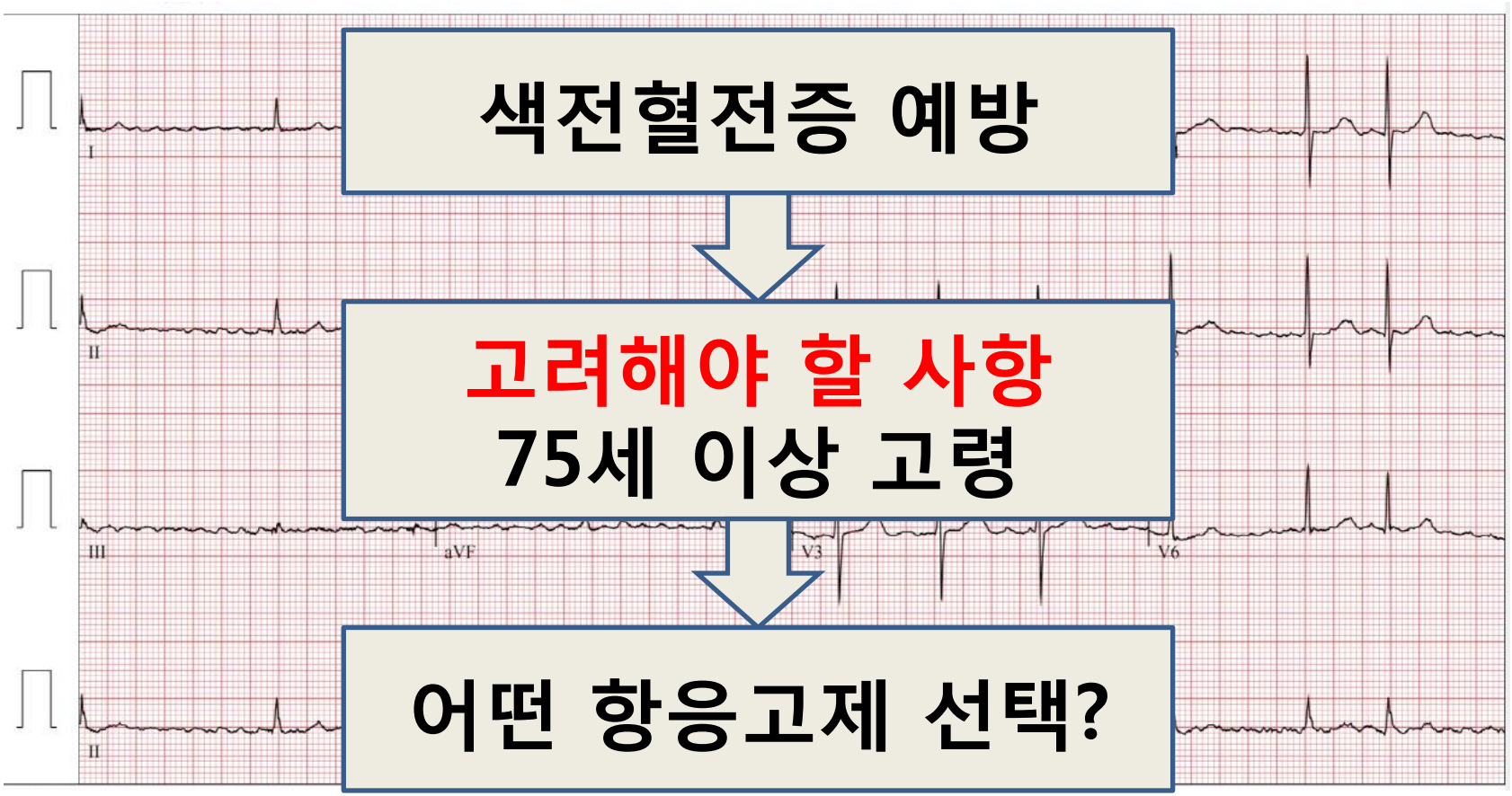
NOACs are considered to be preferentially indicated in Asians.

Heart 2012;33:2719-47

경구용 항응고제 선택시 고려사항

- 연령
- 체중
- 동반된 질환
  - 간, 신장질환
  - 출혈성 질환
- 복용 중 약물
  - 항혈소판제
  - Drug-drug interaction

증례 1. 76세 남자



Age-related Organ Changes Affecting Drug Pharmacokinetics

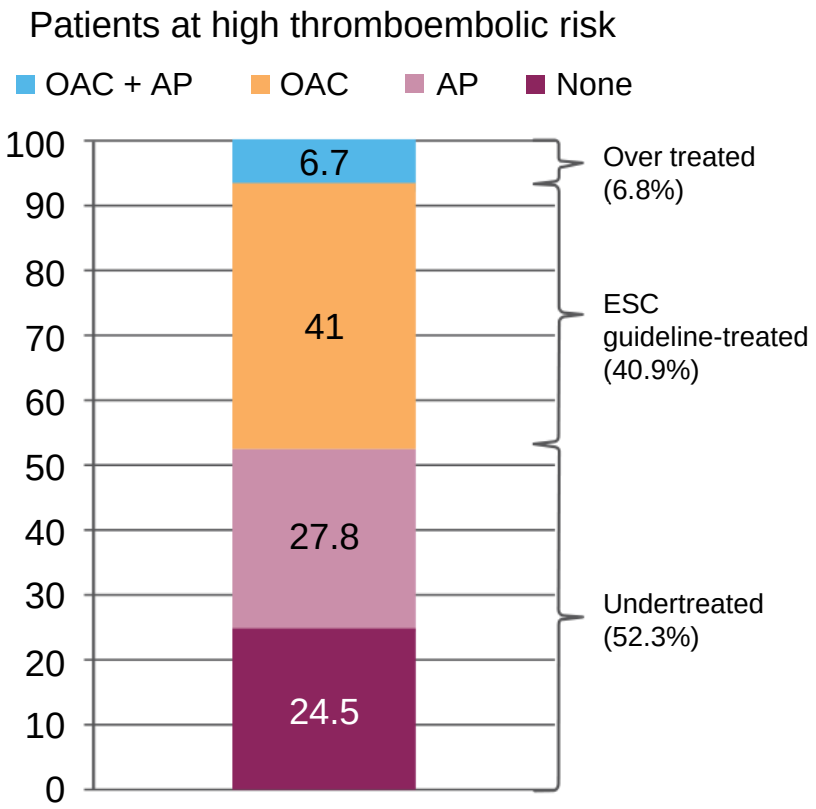
PHYSIOLOGICAL CHANGE	PHARMACOLOGICAL CONSEQUENCE
GASTROINTESTESTINAL TRACT	
Stight increase in gastnc pH	Stightly decreased absorption (rarely clinically significant)
Delaysd gastnc emptying	Different bioavailability/solubility of pH-sensitive drugs
Reduced spianchnic blood flow	
Decreased absorption surface	
Decreased mobility	
BODY COMPOSITION AND DRUG DISTRIBUTION	
Increased body fat and/or decreased lean (muscie) body mass	Increased V_d and increased half-life of lipophilic drugs
10-15% decrease in total water	Decreased V_d and increased plasma concentration of hydrophilic drugs
-10% decrease in serum albumin	Increased free fraction in plasma of highly protein-bound acidic drugs
Stable or increased α1–acid glycoprotein	Variable free fraction of basic drugs
LIVER	
30-50% decrease in blood flow	First-pass metabolism less effective
20-40% decreased hepatocyte functional mass	Some phase I enzymatic families impaired
Modified architecture	Phase II enzymes usually unaffected
KIDNEY	
Decreased renal blood flow	Impaired elimination
Decreased glomerular filtration rate	
Changes in tissue histology	

Andreottii F, et al. Eur Heart Journal 2015; 36:3238-3249

Oral Anticoagulation for the Elderly

REPOSI: Prospective observational study in Italian elderly patients (> 65 years) (2012-2014)

- Internal medical and geriatric wards
- Mean age: 82 (76-86)
- CKD: −29%
- −99 % of patients had a CHA_2DS_2-VASc score >2 (high risk)
- Internal medical and geriatric wards
- Under-treatment associated with:
  - all-cause deaths
    (OR 2.30, 95% CI 1.32, 4.02, *p=0.003)*
  - CV deaths
    (OR 2.88, 95% CI 1.13, 7.39, *p=0.027)*



AF, atrial fibrillation; AP, antiplatelet; OAC, oral anticoagulant; SE, systemic embolism

Yiin GSC, *et al. Circulation.* 2014; 130:1236-44, Proietti M. et al. *Clin Res Cardiol* 2016 May 31

Oral Anticoagulation for the Elderly

AGE IN NOAC-RCTs

	RELY n=18 113	ROCKET n=14 264	ENGAGE n=21 105	ARISTOTLE n=18 201
Median age (years)	72*	73	72	70
<65 years	16%	56%	26%	30%
65 – 74 years	44%		34%	39%
≥75 years	40%	44%	40%	31%
of which ≥80 years	NR	NR	NR	13%

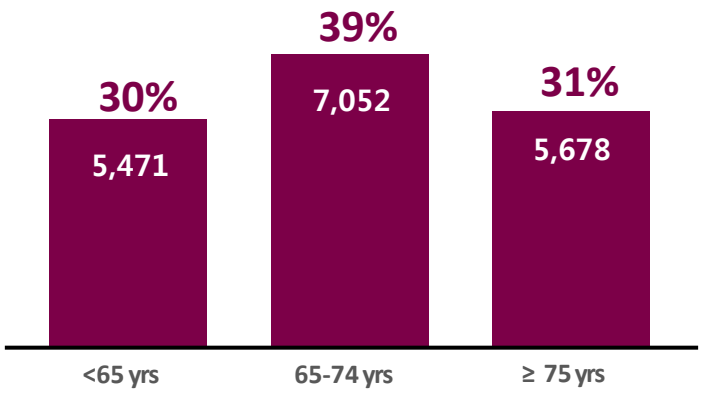
***Mean age, RCT : randomised controlled trial**

Eikelboom *et al. Circulation*. 2011; 123:2363-2372; Halperin *et al. Ciculation* 2014; 130(2): 138-46; Patel *et al. N Engl J Med* 2011;365:863-91; Kato *et al. abstract, Circulation* 2014; 130: A16612; Giugliano *et al. N Engl J Med* 2013;369:2093-104; Halvorsen *et al. Eur Heart J* 2014;35(28): 1864-72. Granger *et al. N Engl J Med* 2011;365:981-92.

Efficacy and Safety of NOACs vs Warfarin by Age

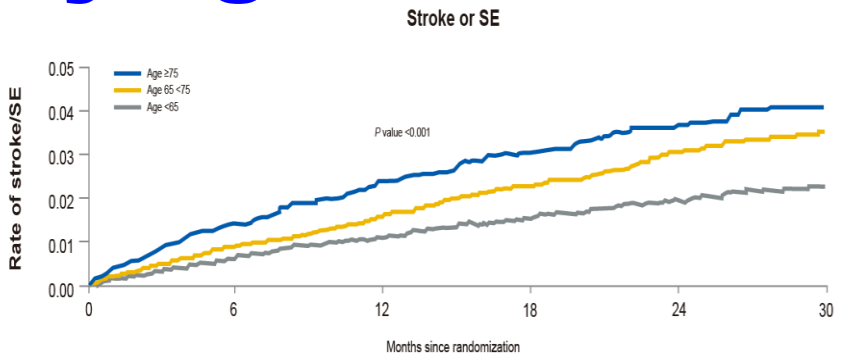
- The risk of stroke in atrial fibrillation increases with age
- Warfarin is particularly underused in elderly patients

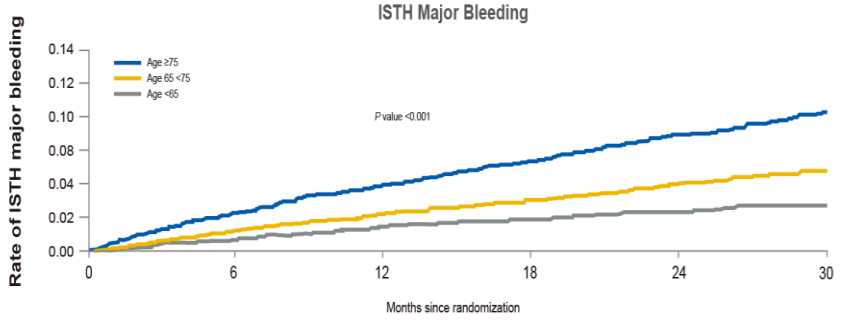
Age distribution in ARISTOTLE[17]

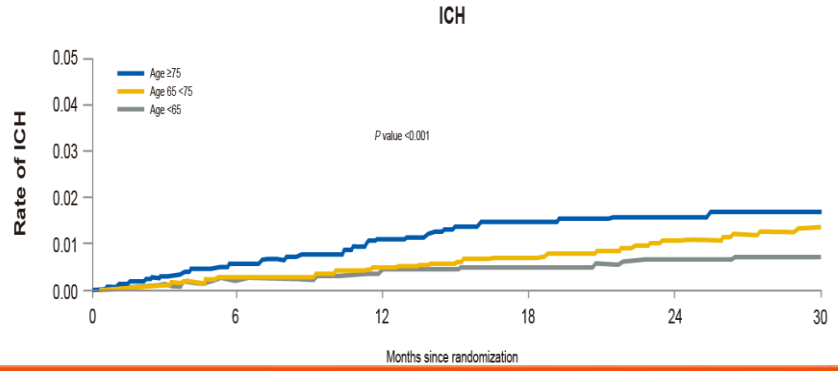


n = 18,201
Range 19-100 yrs

- **2,436 patients (13%) were ≥80 yrs**





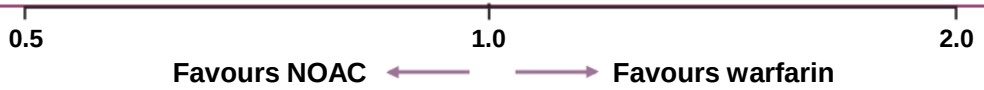


Halvorsen S et al. *Eur Heart J* 2014.35(28):1864-72
Hyleket EM al. *Circulation* 2007;115:2689–96
Waldo AL et al. *J Am Coll Cardiol* 2005;46:1729–36

Efficacy and Safety of NOACs vs Warfarin by Age

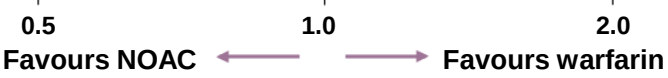
Stroke/SE

Age (yrs)	Pooled NOAC events	Pooled warfarin events	Relative risk (95% CI)	*p* interaction
<75	496/18073	578/18004	**0.85** (0.73 – 0.99)	**0.38**
≥75	415/11188	532/11095	**0.78** (0.68 – 0.88)	



Major bleeding

Age (yrs)	Pooled NOAC events	Pooled warfarin events	Relative risk (95% CI)	*p* interaction
<75	1317/18460	1543/18396	**0.79** (0.67 – 0.94)	**0.28**
≥75	1328/10771	1346/10686	**0.93** (0.74 – 1.17)	

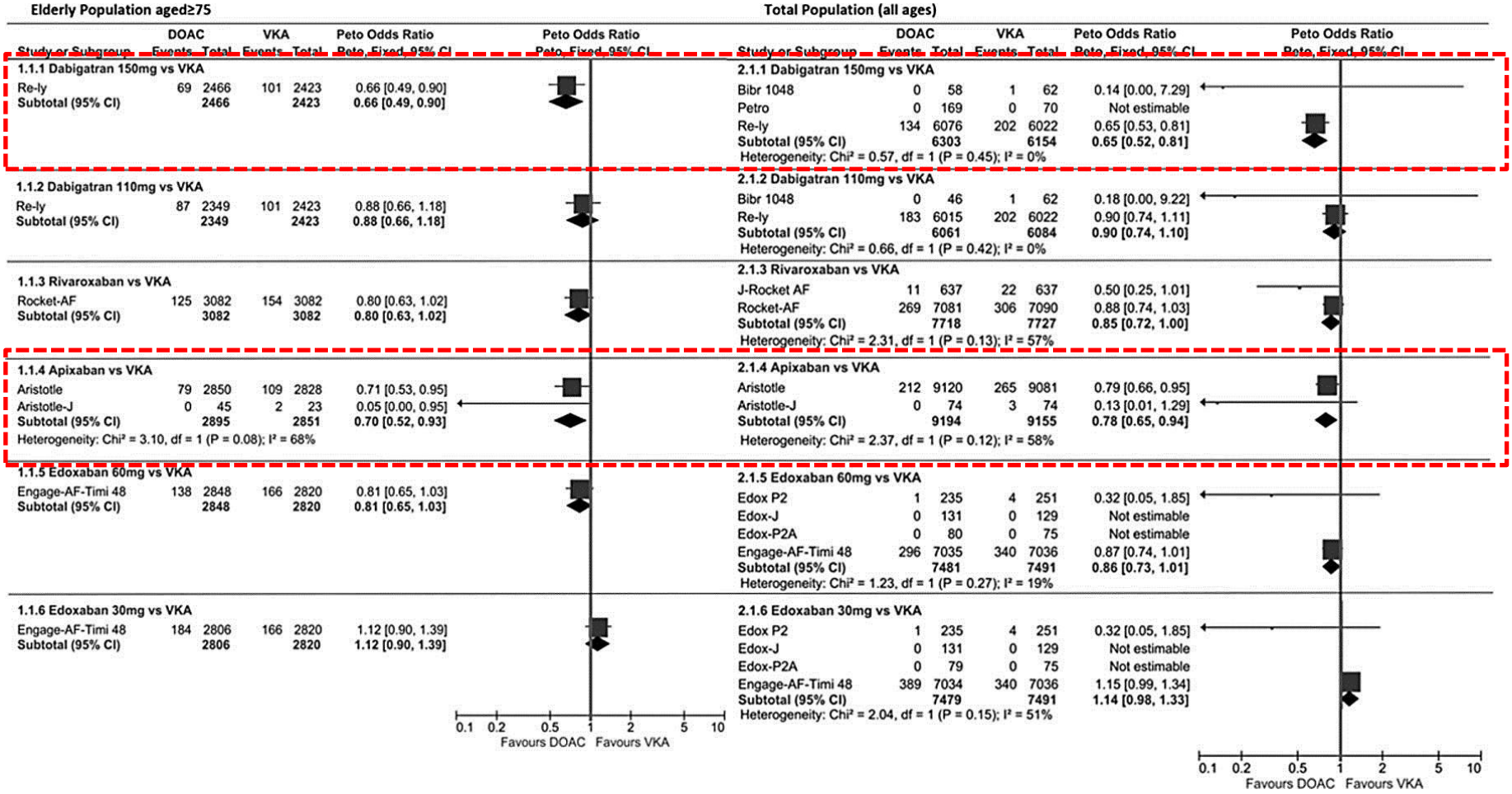


Efficacy analyses performed in ITT population; safety analyses in safety population
Dabigatran 150 mg BD only; Rivaroxaban 20 mg OD; reduced to 15 mg OD in selected patients;
Apixaban 5 mg BD; reduced to 2.5 mg BD in selected patients; Edoxaban 60 mg OD; reduced to 30 mg OD in selected patients
CI, confidence interval; ITT, intent-to-treat; NOAC, non-vitamin K antagonist oral anticoagulant.

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

Elderly Patients > 75 yrs

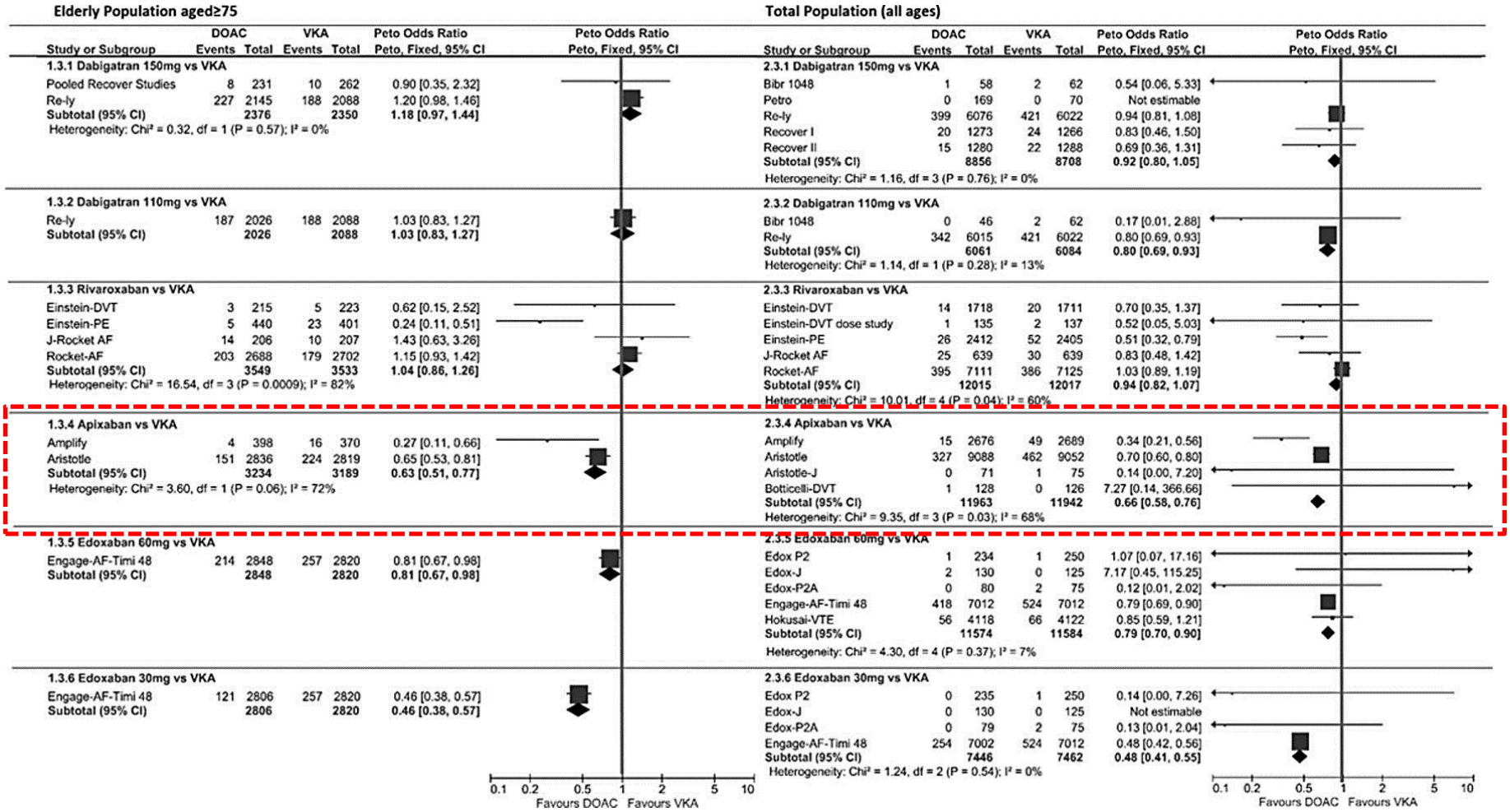
Risk of stroke or systemic embolism in atrial fibrillation studies



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

Elderly Patients > 75 yrs

Risk of major bleeding



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

ARISTOTLE ≥ 80 years

- 2,436 patients (13%) were ≥80 years of age in ARISTOTLE

	Apixaban	Warfarin	HR (95%CI)	$P_{interaction}$
Major Bleeding				0.11
Age<80	260 (1.93)	366 (2.78)	0.70 (0.60, 0.82)	
Age ≥80	67 (3.55)	96 (5.41)	0.66 (0.48, 0.90)	
All bleeding				0.43
Age<80	1964 (17.0)	2558 (24.4)	0.71 (0.67, 0.76)	
Age ≥80	392 (26.4)	502 (37.4)	0.73 (0.64, 0.83)	
Intracranial Bleeding				0.63
Age<80	43 (0.32)	98 (0.73)	0.43 (0.30, 0.62)	
Age ≥80	9 (0.47)	24 (1.32)	0.63 (0.17, 0.77)	
Stroke/Systemic Embolism				0.94
Age<80	179 (1.23)	225 (1.55)	0.79 (0.65, 0.96)	
Age ≥80	33 (1.53)	40 (1.90)	0.81 (0.51, 1.29)	
All-cause Mortality				0.18
Age<80	452 (3.03)	507 (3.42)	0.88 (0.78, 1.00)	
Age ≥80	151 (6.86)	162 (7.44)	0.93 (0.74, 1.16)	

HR,

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.

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Expert Comment
- NOAC and Age -

European Heart Journal (2017) **38**, 860–868
doi:10.1093/eurheartj/ehw069

REVIEW

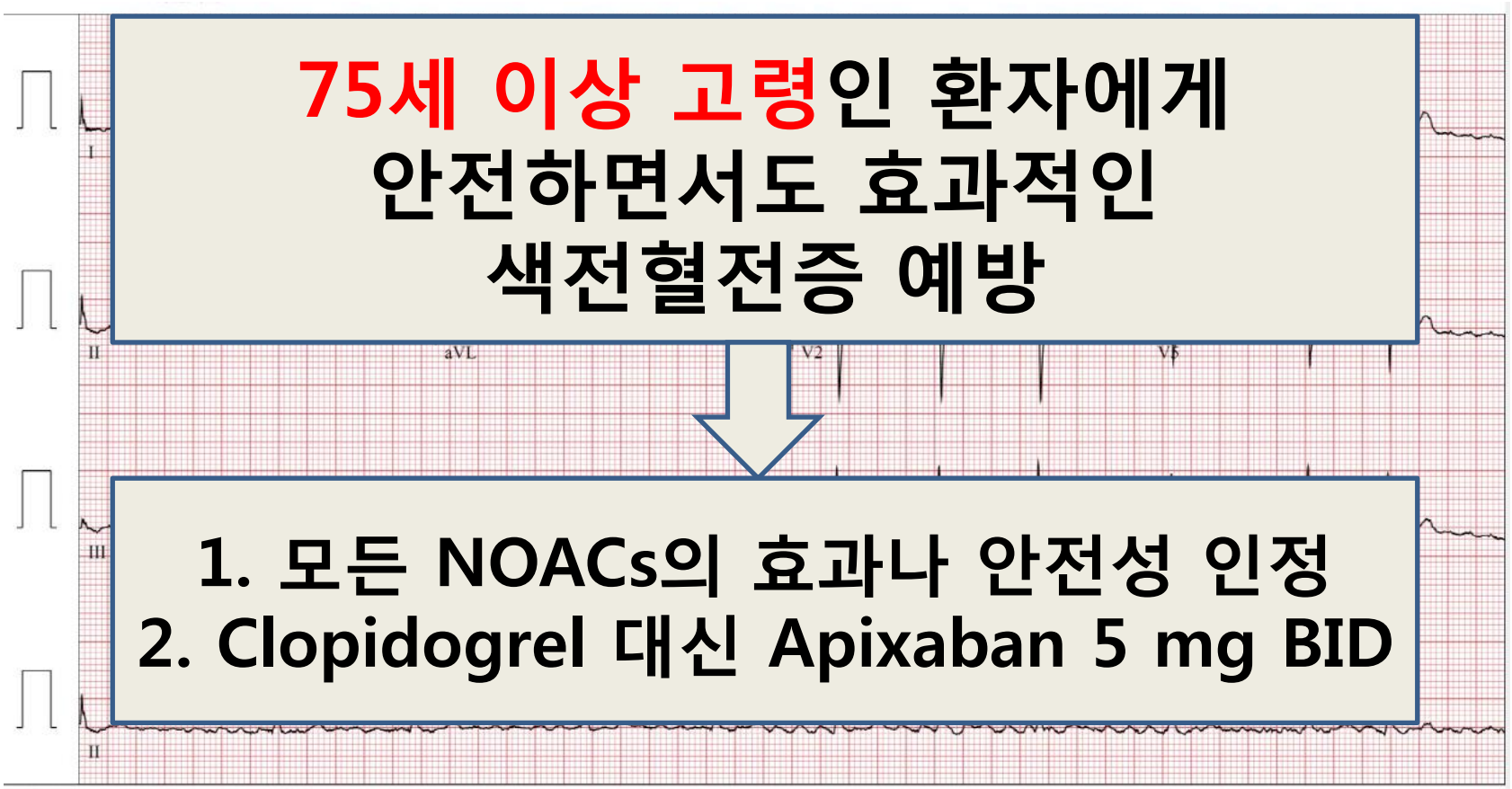
Prevention

Choosing a particular oral anticoagulant and dose for stroke prevention in individual patients with non-valvular atrial fibrillation: part 2

First choice	In patients ***older than 75 years***, we suggest ***Apixaban 5mg twice daily*** [2.5mg if ≥ 2 of the following: age ≥ 80 years, body weight ≤ 60 kg, or creatinine ≥ 1.5 mg/dl (133 umol/L)]
Second choice	Dabigatran 110 mg twice daily, rivaroxaban 20 mg once daily, or edoxaban 60 mg once daily

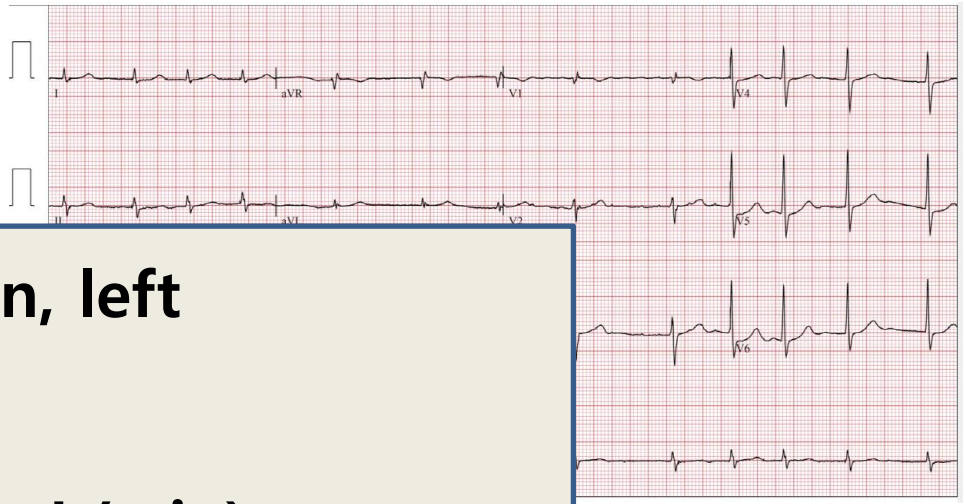
Diener HC, et al. *Eur Heart J* 2017;38:860-868

증례 1. 76세 남자


75세 이상 고령인 환자에게
안전하면서도 효과적인
색전혈전증 예방
1. 모든 NOACs의 효과나 안전성 인정
2. Clopidogrel 대신 Apixaban 5 mg BID

증례 2. 78세 남자

- 주소 : 좌측 옆구리 통증 (12시간)
- 병력 : 고혈압, 심방세동
- 키 : 176 cm, 몸무게 : 67 Kg, S-Cr 1.27 mg/dL
- 혈압 : 120/80 mmHg
- 복용 약물
  - Aspirin 100 mg
  - Dig
  - Losa



1. Renal Infarction, left
2. Persistent AF
3. Hypertension
4. CKD (CrCL 45 mL/min)

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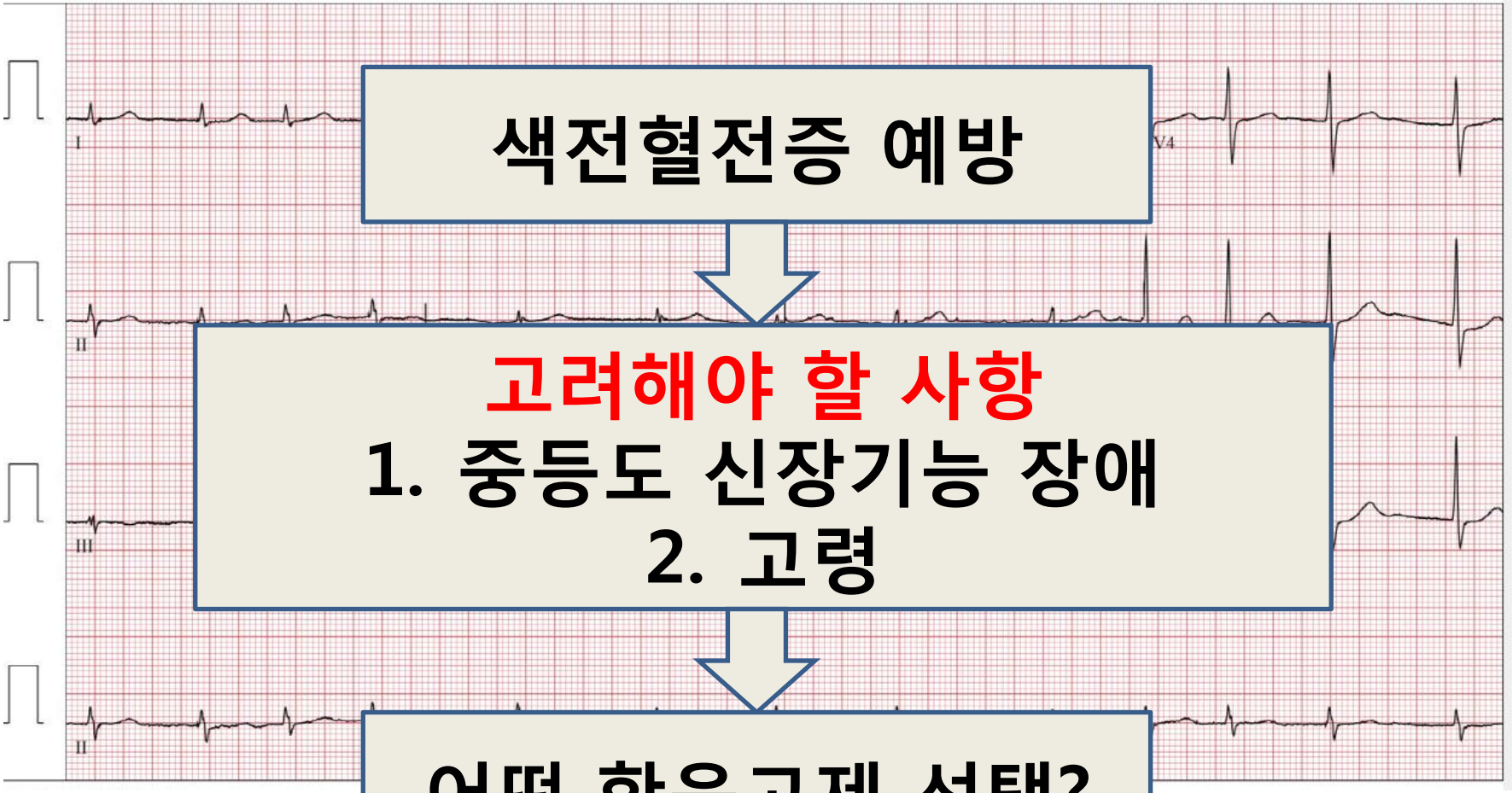
증례 2. 78세 남자



색전혈전증 예방

고려해야 할 사항

1. 중등도 신장기능 장애
2. 고령

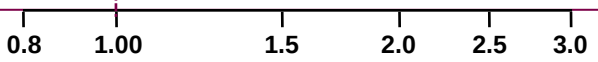
어떤 항응고제 선택?

00819698

CKD Increases the Risk of Stroke, Bleeding and All-cause Death in AF Patients

Danish registry (1997-2008)

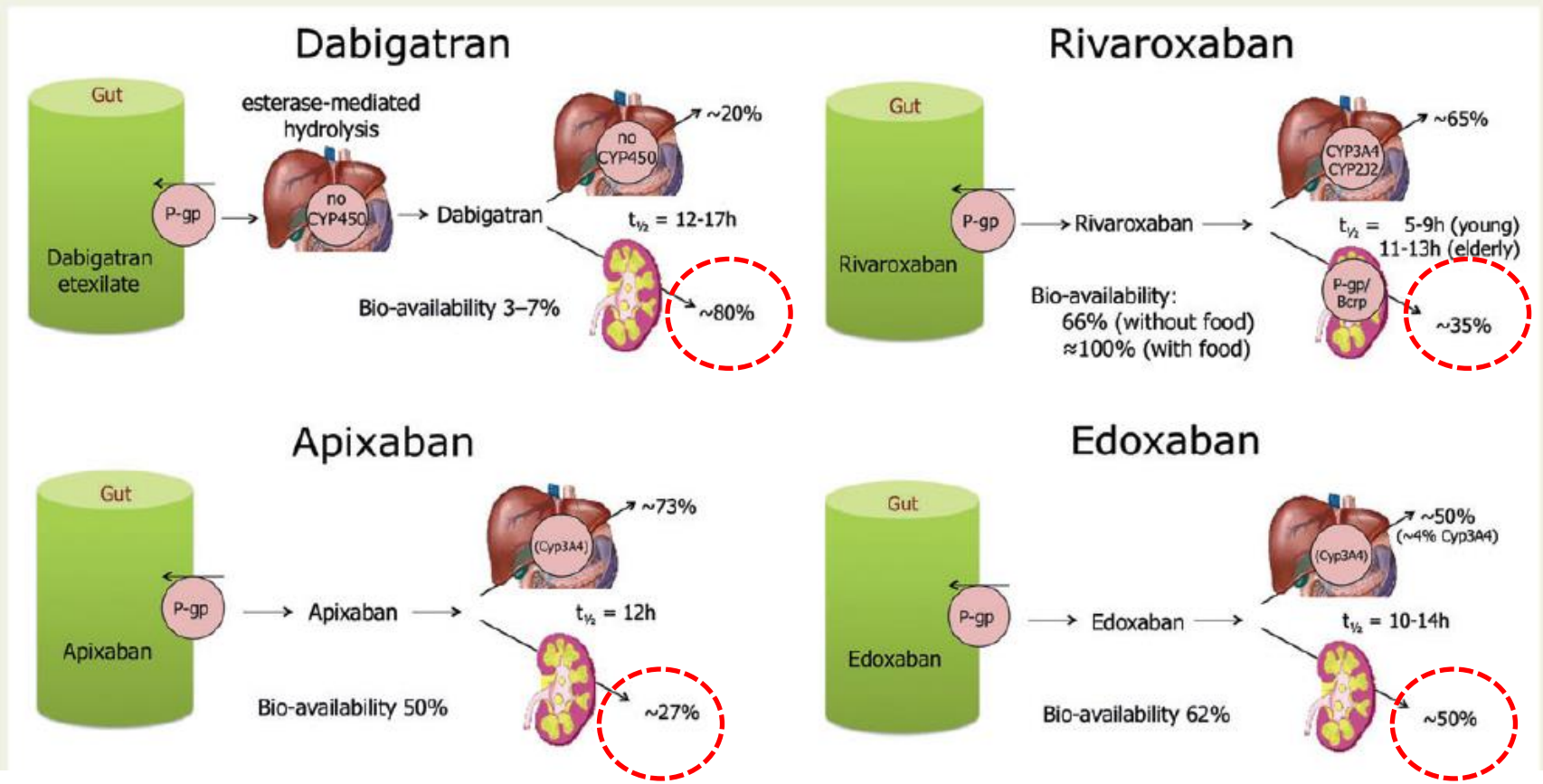
REFERENCE: NVAF PATIENTS WITH NO RENAL DESEASE (n=127 884)	HR (95% CI)*
STROKE /SE	
Non-end-stage CKD	1.49 (1.38; 1.59)
CKD requining renal replacement therapy	1.83 (1.57; 2.14)
MAJOR BLEEDING	
Non-end-stage CKD	2.24 (2.10; 2.38)
CKD requining renal replacement therapy	2.70 (2.38; 3.07)
DEATH FROM ANY CAUSE	
Non-end-stage CKD	2.37 (2.30; 2.44)
CKD requining renal replacement therapy	3.35 (3.13; 3.58)



*** Adjusted for baseline characteristics**
127864 NVAF patients with no renal disease; 3587 patients with non-end stage CKD; 901 patients with CKD requiring renal replacement therapy

Olesen *et al. N Engl J Med* 2012;367:625-35

Absorption and Metabolism



Heidbuchel H, et al. Eurpace 2015 EHRA Practical Guide

Estimated Drug Half-lives in Different Stages of CKD

	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
CrCl >80 mL/min	12–17 h[61]	12 h	10–14 h[51,65]	5–9 h (young) 11–13 h (elderly)
CrCl 50–80 mL/min CKD Stages I and II	~17 h[122] (+50%)	~14.6 h[123] (+16%)	~8.6 h[124] (+32%)[SmPC]	~8.7 h[125] (+44%)[126]
CrCl 30–50 mL/min CKD Stage III	~19 h[122] (+320%)	~17.6 h (+29%)	~9.4 h[124] (+74%)[SmPC]	~9.0 h (+52%)[126]
CrCl 15–30 mL/min CKD Stage IV	~28 h[122] (+530%)	~17.3 h (+44%)	~16.9 h[124] (72%)[SmPC]	~9.5 h (+64%)[126]
CrCl ≤ 15 mL/min CKD Stage V; off-dialysis	No data	– (+36%)	– (+93%)[SmPC]	– (+70%)[127]

CKD, chronic kidney disease; CrCl, creatinine clearance.

CrCL = (140-age) X weight (Kg) X [0.85 if female] X serum creatinine (mg/dL)

Incidence of Renal Impairment in NOAC Trials

	RE-LY (Dabigatran)[1,5]	ARISTOTLE (Apixaban)[2,6]	ROCKET-AF (Rivaroxaban)[3,7]	ENGAGE-AF (Edoxaban)[4,8]
Renal clearance	85%	~27%	~33%	
CrCl (mL/min)	**NUMBER OF PATIENTS IN TRIAL**			
>80	n = 5844 (33%)	n = 7518 (41%)	n = 11 277 (79%) ; CrCl ≥50 mL/min	11 331 (80.5%) (>50 mL/min)
>50-80	n = 8553 (48%)	n = 7587 (42%)		
≤50	n = 3554 (20%)	n = 3017 (17%)	n = 2950 (17%)	2740(19.5%)
Exclusion criteria	<30 mL/min	<25 mL/min	<30 mL/min	<30 mL/min

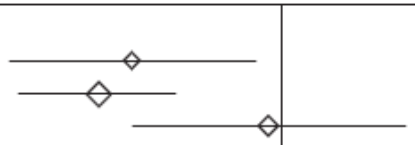
***Direct renal excretion as unchanged active substance;**
† Figures based on patients randomized to the approved higher-dose edoxaban regimen vs warfarin
CrCl, creatinine clearance; NOAC, novel oral anticoagulant

1. Dabigatran SmPC; 2. Apixaban SmPC; 3. Rivaroxaban SmPC; 4. Edoxaban SmPC; all SmPCs available at http://www.ema.Europa.eu;
5. Hijazi *et al. Circulation* 2014; 129:961-970; 6. Hohnloser *et al. Eur Heart J* 2012;33:2821-30; 7. Foxx *et al. Eur Heart J* 2011;32:2387-94;
8. Bohula *et al. Circulation* 2016; 134:24-36;

Renal Function : Meta-analysis
(RELY, ROCKET AF, ARISTOTLE, ENGAGE AF-TIMI 48)

Stroke or Systemic Embolic Events

	Pooled NOAC (events)	Pooled warfarin (events)	RR (95% CI)	$p_{interaction}$
Creatinine clearance (mL/min)				
<50	249/5539	311/5503	0·79 (0·65–0·96)	0·12
50–80	405/13055	546/13155	0·75 (0·66–0·85)	
>80	256/10626	255/10533	0·98 (0·79–1·22)	



Major Bleeding

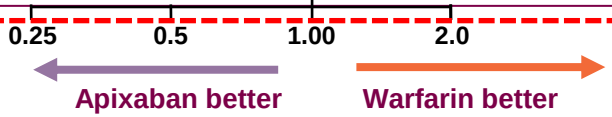
	Pooled NOAC (events)	Pooled warfarin (events)	RR (95% CI)	$p_{interaction}$
Creatinine clearance (mL/min)				
<50	514/4376	620/4346	0·74 (0·52–1·05)	0·57
50–80	1104/10139	1174/10228	0·91 (0·76–1·08)	
>80	625/8681	672/8595	0·85 (0·66–1·10)	

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

Apixaban – ARISTOTLE

- Outcomes According to Renal Function -

eGFR	APIXABAN 5 mg BID*	WARFARIN	HAZARD RATIO (95% CI)	P VALUE FOR INTERACTION
	% / yr (no. of events)			
STROKE /SE				0.71
>80 mL/min[a]	**0.99% (70)**	1.12% (79)		
>50-80 mL/min[b]	**1.24% (87)**	1.69% (116)		
≤50 mL/min[c]	**2.11% (54)**	2.67% (69)		
MAJOR BLEEDING				0.03
>80 mL/min[a]	**1.46% (96)**	1.84% (119)		
>50-80 mL/min[b]	**2.45% (157)**	3.21% (199)		
≤50 mL/min[c]	**3.21% (73)**	6.44% (142)		



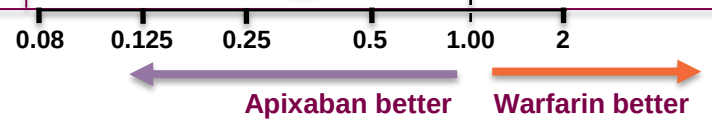
***n=7518 (41%); [b]n=7587 (42%); [c]n=3017 (17%).**
Results were consistent regardless of methods for GFR estimation.
Patients with severe renal insufficiency [serum creatinine >2.5 mg/dL (221 µmol/L) or calculated creatinine clearance <25 mL/min] were excluded from the trial.
CI, confidence interval
***Refer to SmPC for specific dose reduction criteria**

Hohnloser *et al. Eur Heart J* 2012;33:2821-30

Apixaban – ARISTOTLE

- Outcomes in Elderly Patients(≥ 75 years) by Renal Function -

COCKROFT-GAULT(eGFR)	N≥75	APIXABAN 5 mg BID*	WARFARIN	HAZARD RATIO (95% CI)	P VALUE FOR INTERACTION
		% / yr (no. of events)			
STROKE /SE					0.50
>80 mL/min	597	**1.41 (8)**	2.16 (11)		
>50-80 mL/min	2922	**1.45 (39)**	1.70 (45)		
>30-50 mL/min	1906	**1.74 (28)**	2.69 (44)		
≤30 mL/min	222	**1.70 (3)**	5.57 (9)		
MAJOR BLEEDING					0.16
>80 mL/min	596	**2.10 (11)**	3.39 (15)		
>50-80 mL/min	2912	**3.53(85)**	4.45 (104)		
>30-50 mL/min	1898	**3.32 (47)**	6.27 (87)		
≤30 mL/min	221	**4.64 (7)**	13.4 (17)		



***Refer to SmPC for specific dose reduction cirteria;**
Patients with severe renal insufficiency [serum creatinine >2.5 mg/dL (221 μmol/L) or calculated creatinine clearance <25 mL/min] were excluded from the trial.

Halvorsen S, *et al. European Heart J* 2014;35:1864-1872.

Recommended NOAC Dose in Different Stages of CKD

Creatinine clearance (CrCL)	Apixaban	Rivaroxaban	Dabigatran	Edoxaban
Normal renal function CrCL ≥ 80mL/min	5mg BID 2.5 mg BID (2 of three criteria; age ≥ 80 years, weight ≤ 60 kg, creatinine ≥ 1.5 mg/dL)	20mg QD	150mg/110mg BID	60mg QD With caution
Mild renal impairment 50mL/min ≤ CrCL < 80mL/min				60mg QD
Moderate renal impairment 30mL/min ≤ CrCL < 50mL/min		15mg QD	110mg BID	30mg QD
Severe renal impairment 15mL/min ≤ CrCL < 30mL/min	2.5mg BID 연령 체중 상관없이	15mg QD With caution	75mg BID(US only)	

Expert Comment

- NOACs and Renal Impairment -

European Heart Journal (2017) **38**, 860–868
doi:10.1093/eurheartj/ehw069

REVIEW

Prevention

Choosing a particular oral anticoagulant and dose for stroke prevention in individual patients with non-valvular atrial fibrillation: part 2

First choice	Patients with AF and **stage III CKD (creatinine clearance 30–49 mL/min)** may be treated with **apixaban 5mg twice daily** [2.5mg if ≥ 2 of the following: age ≥ 80 years, body weight ≤ 60 kg, or creatinine ≥ 1.5 mg/dl (133 umol/L)], **rivaroxaban 15 mg daily, or edoxaban 30 mg once daily**
Second choice	Dabigatran 110 mg twice daily
Not recommended	Dabigatran 150 mg twice daily, rivaroxaban 20 mg once daily, or edoxaban 60 mg once daily

Diener HC, et al. *Eur Heart J* 2017;38:860-868

증례 2. 78세 남자

중등도의 신장기능 장애 환자에게
안전하면서도 효과적인
색전혈전증 예방

1. 대부분 NOACs의 효과나 안전성 인정
2. Aspirin 대신 Apixaban 5 mg BID
(특히 apixaban은 용량선택에 신중)

요약

- 비판막성 심방세동 환자에서 NOACs은 안전하면서도 효과적으로 사용할 수 있는 항응고제이다.
- 고령 및 중등도의 신장 기능 장애 환자에서도 NOACs의 안전성 및 효과는 일관되게 유지된다.
- 환자의 임상적 상황에 맞는 적절한 항응고제 선택이 중요하다.

감사합니다.