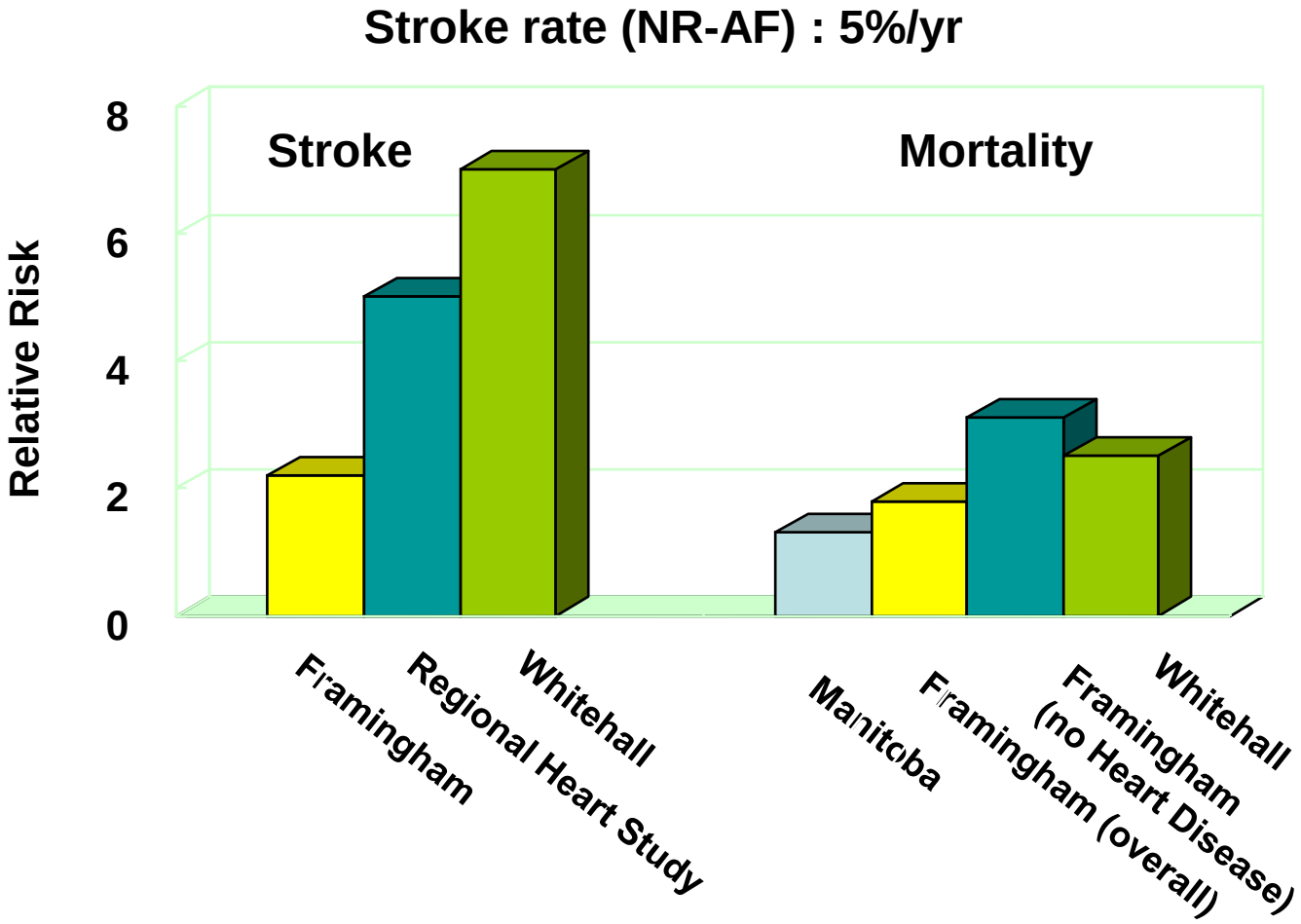
What's New for Anticoagulation in Non-Valvular AF in 2016

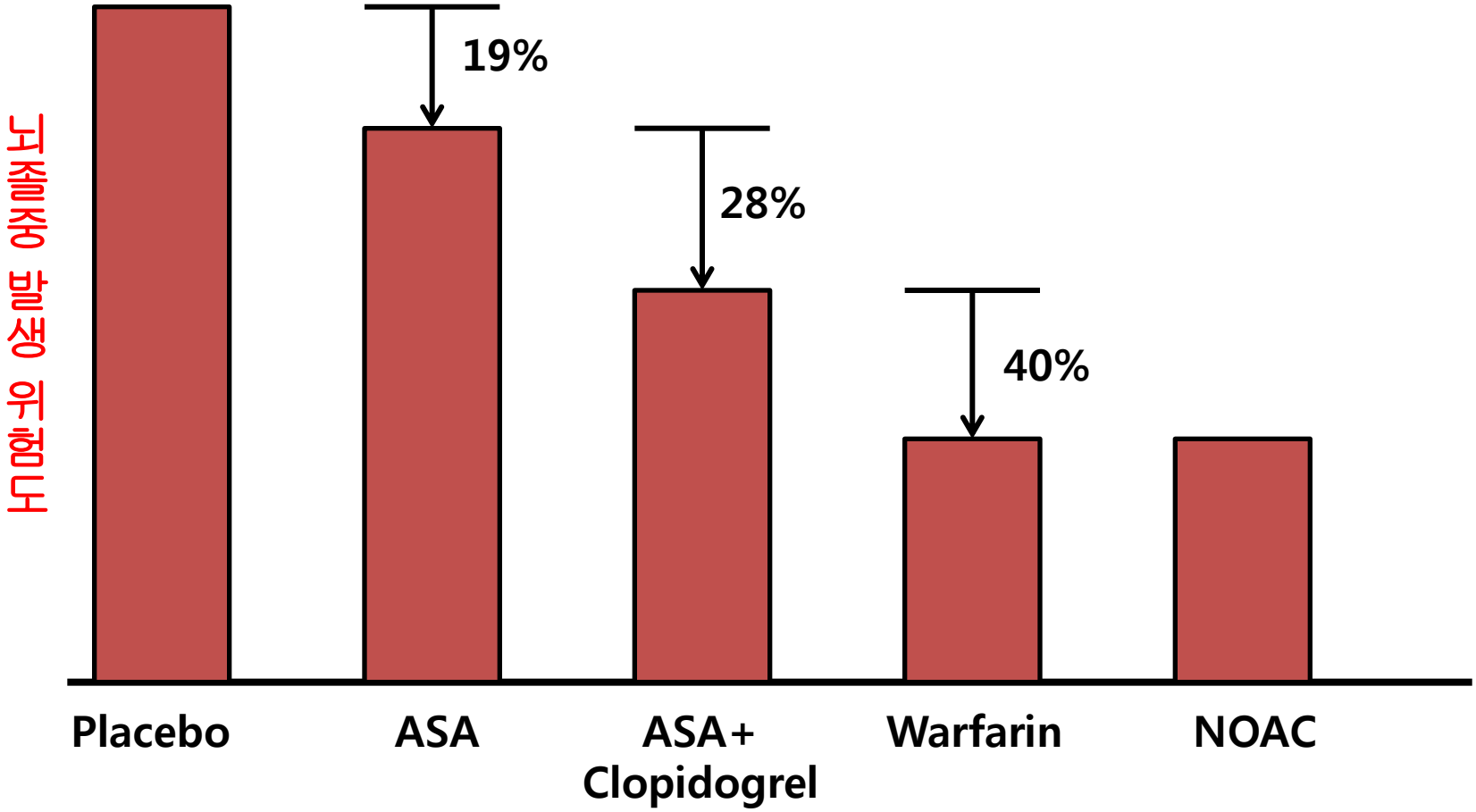
원광대학교 내과학교실

김 남 호

뇌졸중과 사망률 위험도


Stroke rate (NR-AF) : 5%/yr
Relative Risk
8
6
4
2
0
Stroke
Mortality
Framingham
Regional Heart Study
Whitehall
Manitoba
Framingham (overall)
Framingham (no Heart Disease)
Whitehall

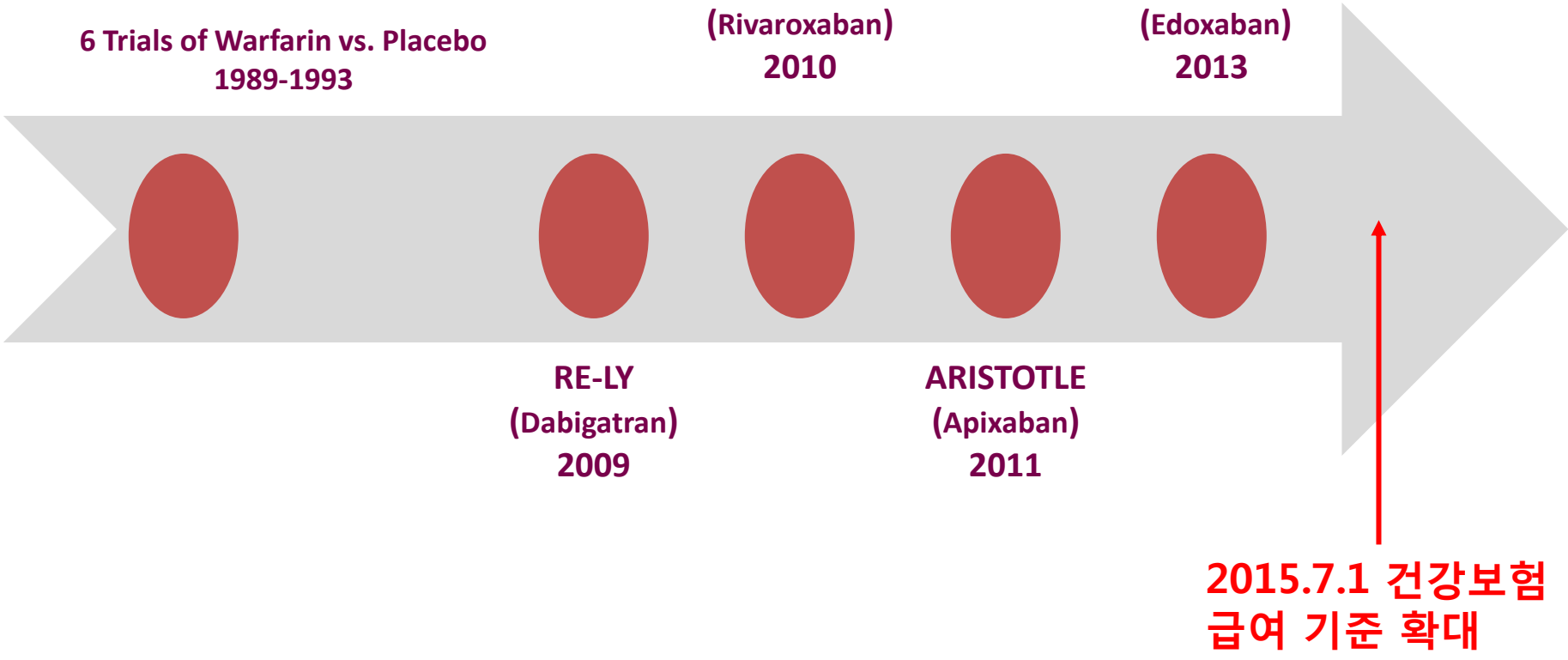
색전혈전증 예방


뇌졸중 발생 위험도
19%
28%
40%
Placebo
ASA
ASA+
Clopidogrel
Warfarin
NOAC

NOAC의 시대

Warfarin vs. Placebo
2,900 Patients

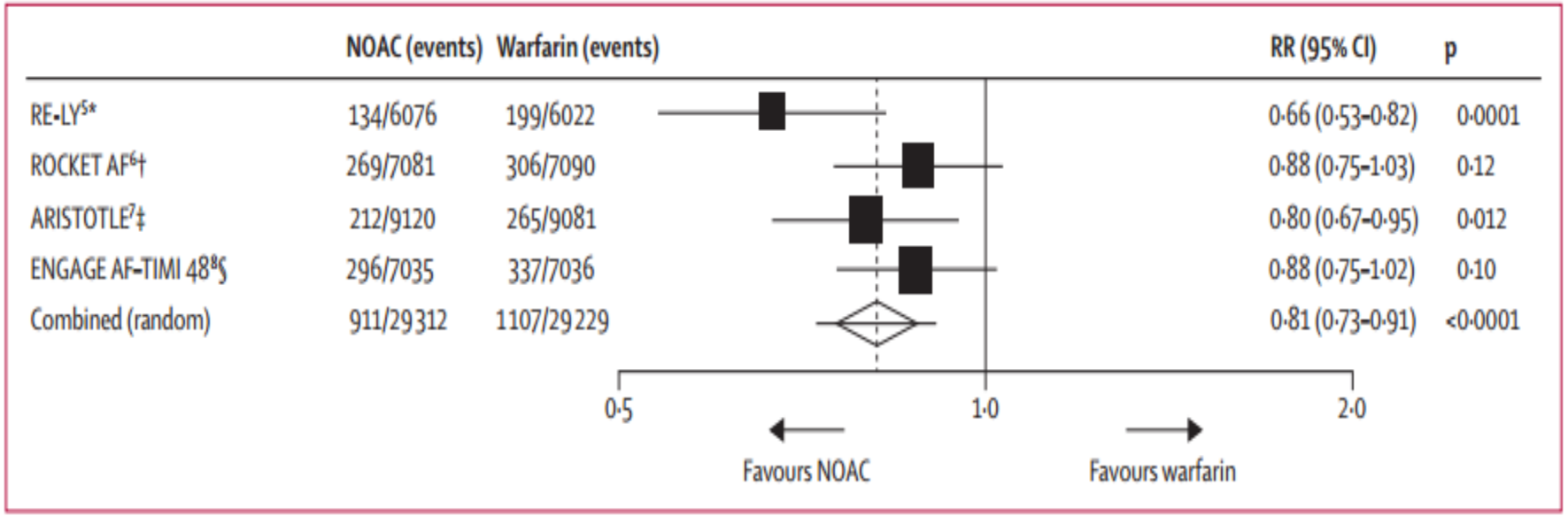
NOACs vs. Warfarin
71,683 Patients



NOAC

(RELY, ROCKET AF, ARISTOTLE, ENGAGE AF-TIMI 48)

Stroke or Systemic Embolic Events



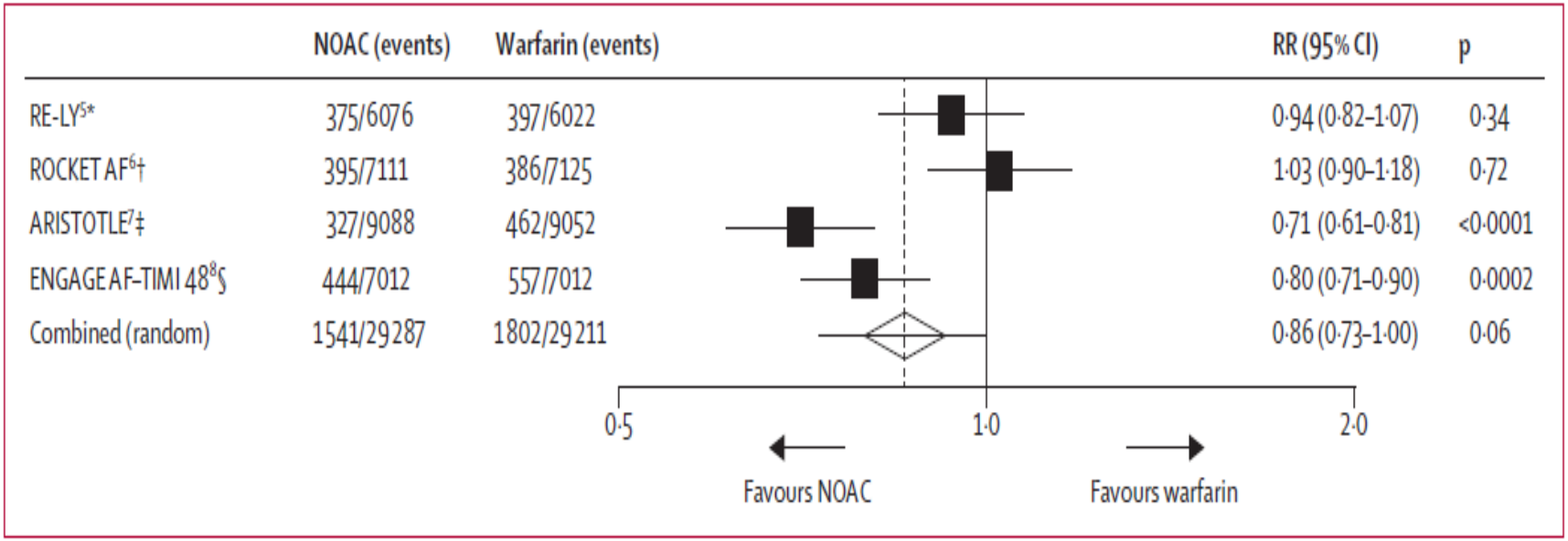
Superior : Dabigatran 150 mg, Apixaban

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

NOAC

(RELY, ROCKET AF, ARISTOTLE, ENGAGE AF-TIMI 48)

Major Bleeding



Superior : Dabigatran 110 mg, Apixaban, Edoxaban

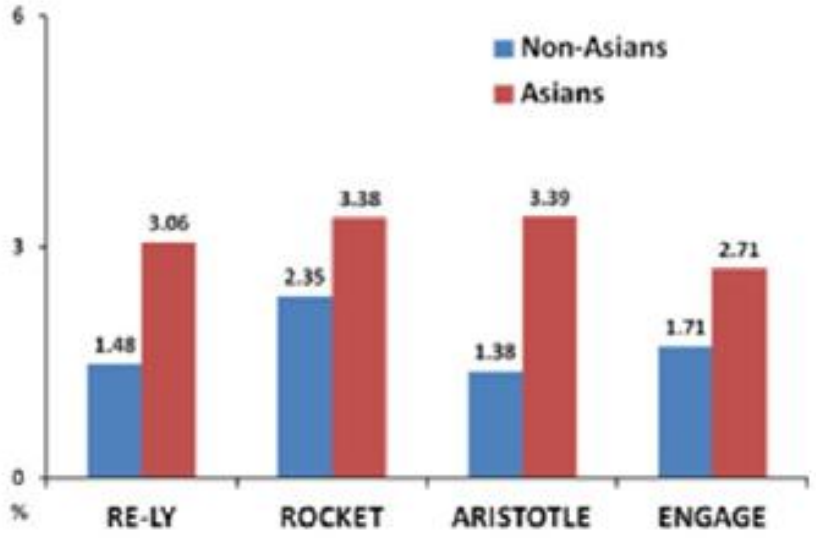
Ruff CT, et al. Lancet 2014;383:955-62.

NOAC의 시대

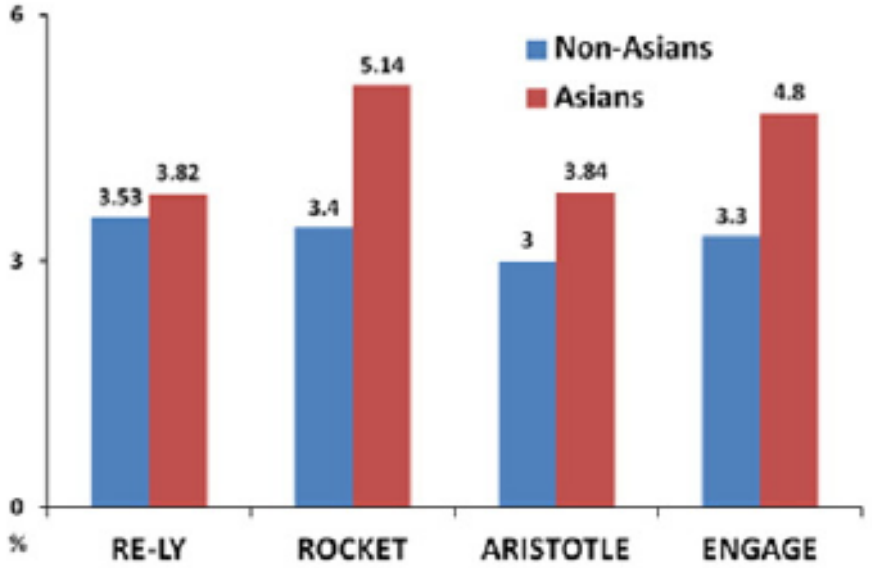
- **What's New in 2016?**
  - Race : Asian
  - Elderly
  - GI Bleeding
  - Renal dysfunction
  - Real world data
    - Efficacy and safety
    - Persistence

NOAC in Asian?

Asians on Warfarin



Stroke and SE

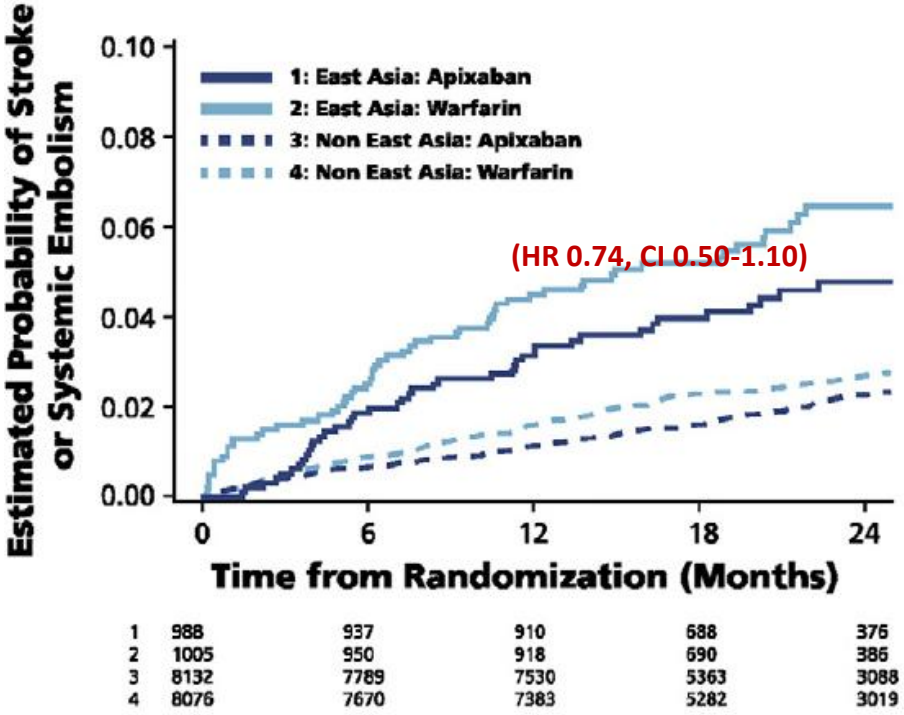


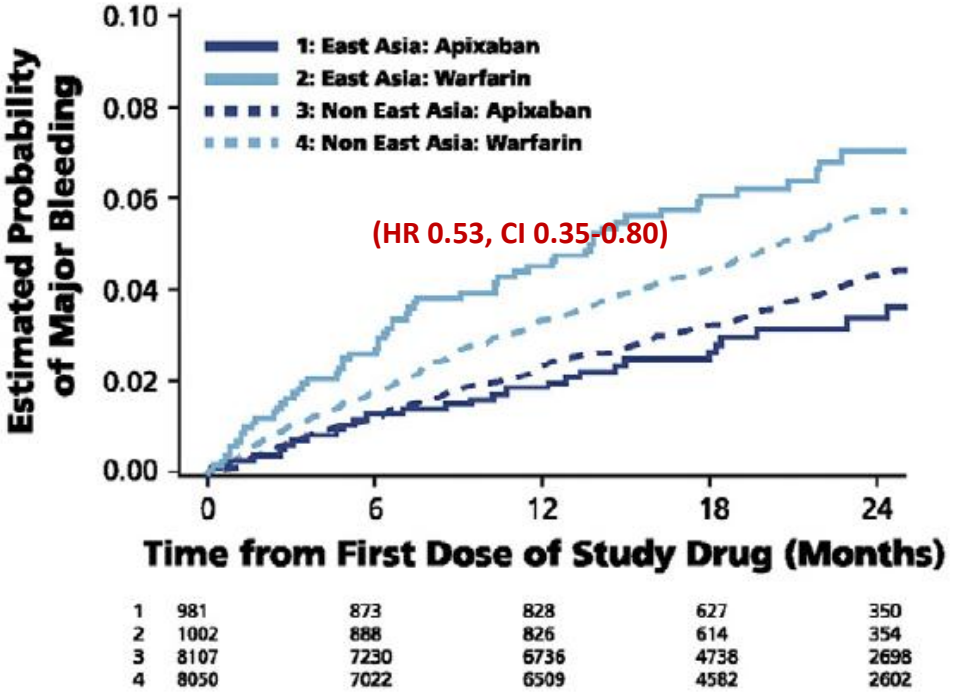
Major Bleeding

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

Apixaban (Aristotle: East Asia)

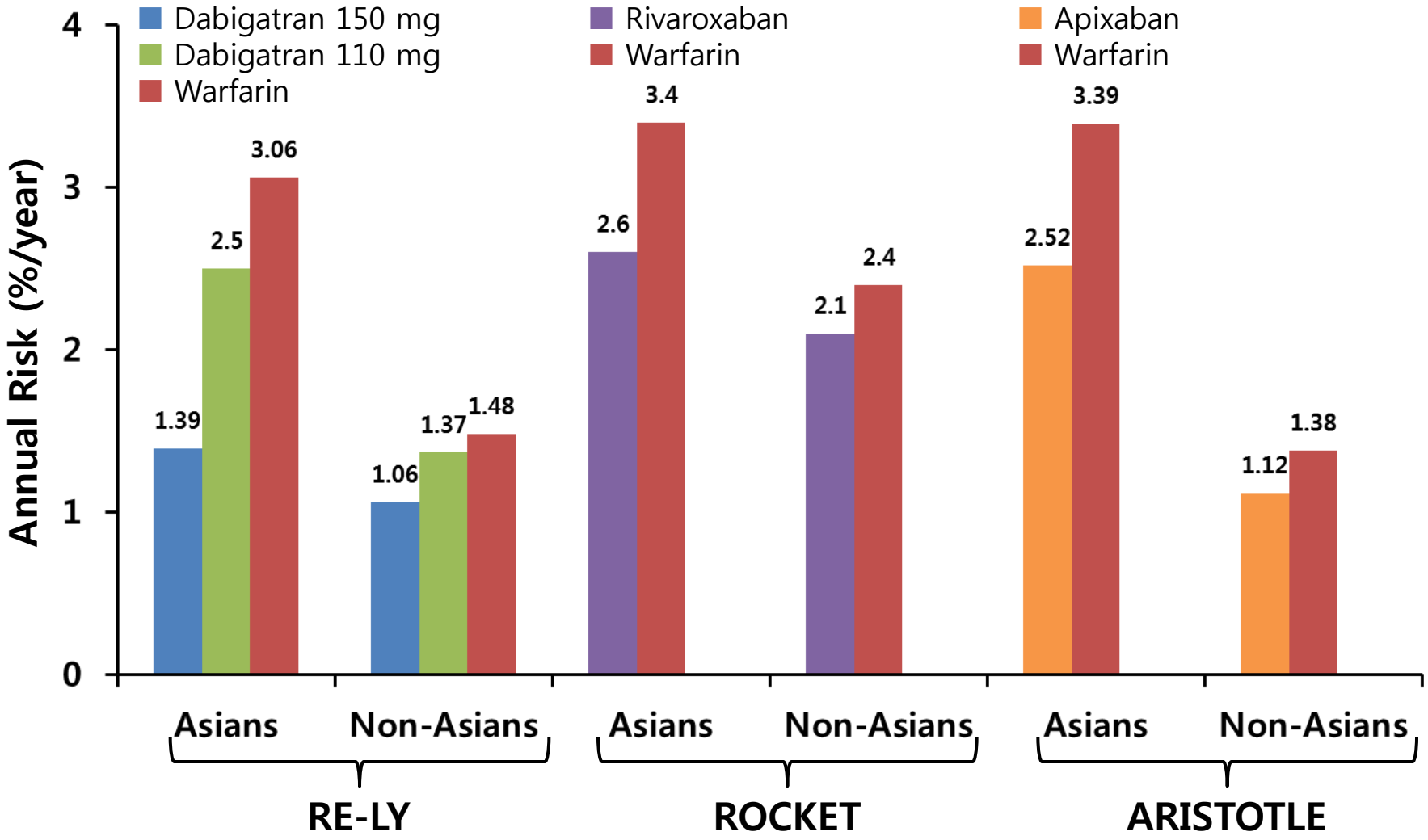
- Randomized, double blind trial
- 18,201 NVAF patients (1,993 East Asia patients)
- 1.8 years f/u





Goto S, et al. Am Heart J 2014;168:303-9

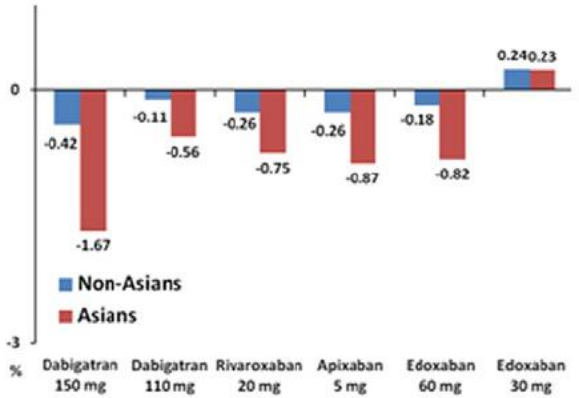
Stroke and Systemic Embolism for Asians



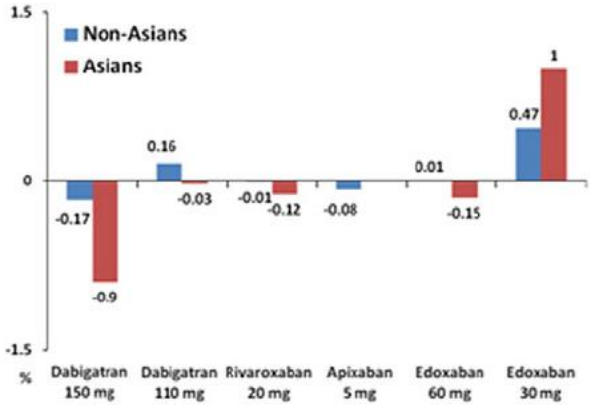
Thromb Haemost 2014;111:789-797

Asians
(Absolute Risk Reduction in Efficacy)

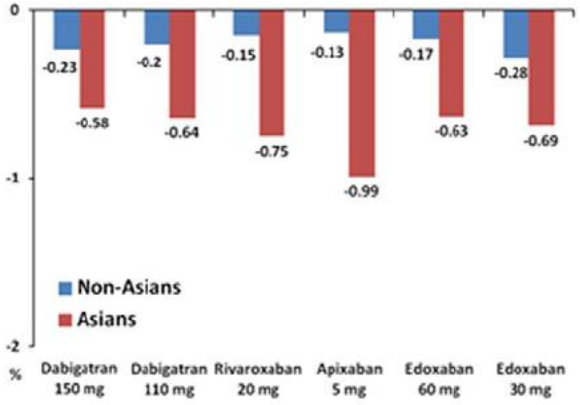
Stroke and Systemic Embolism



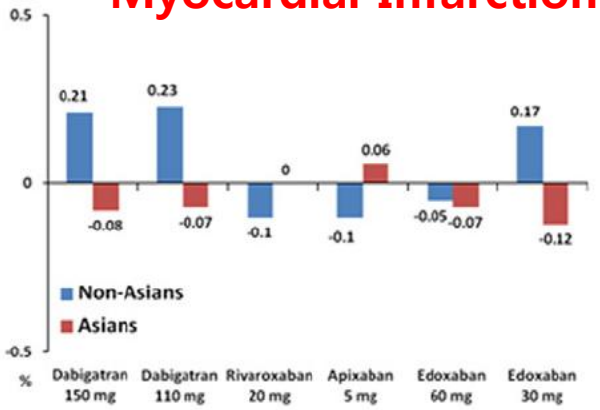
Ischemic Stroke



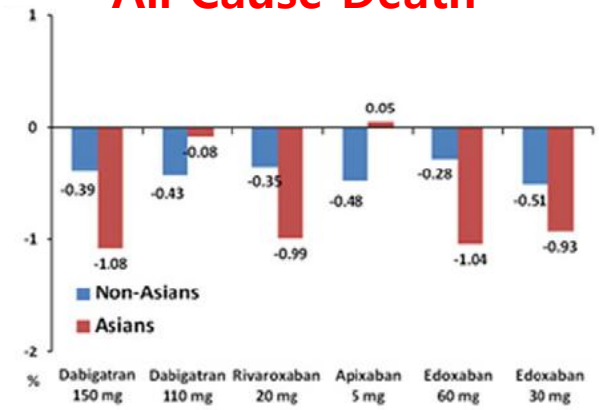
Hemorrhagic Stroke



Myocardial Infarction



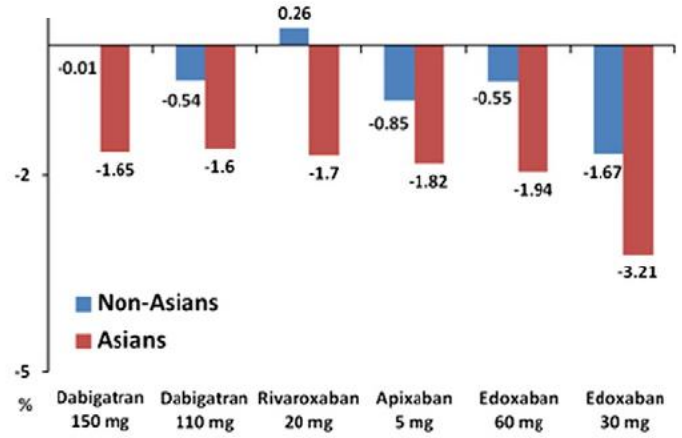
All Cause Death



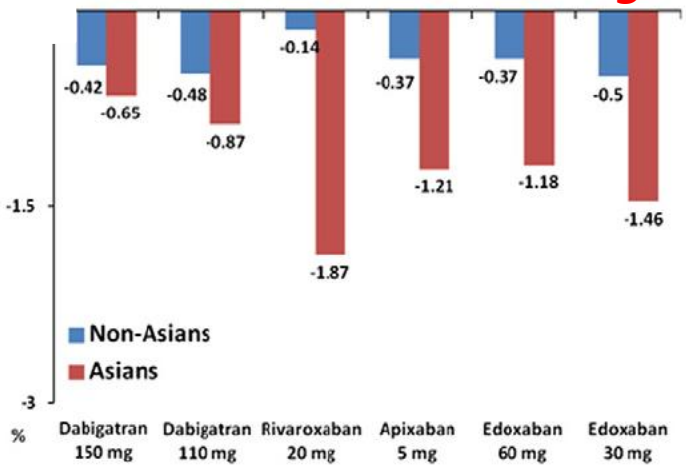
Lip GY, et al. Int J Cardiol 2015;180:246-54.

Asians
(Absolute Risk Reduction in Safety)

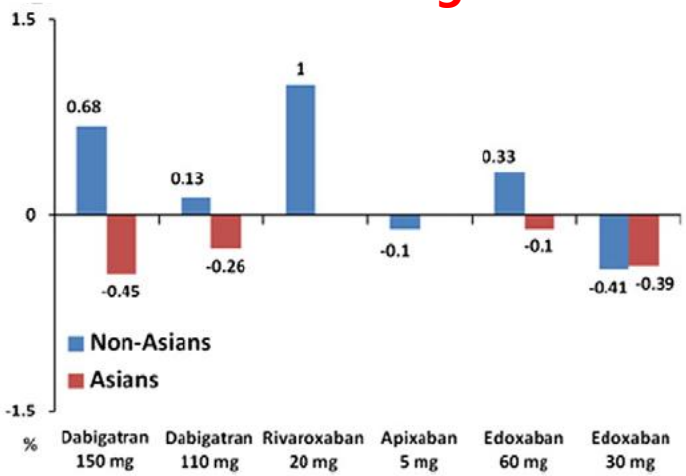
Major Bleeding



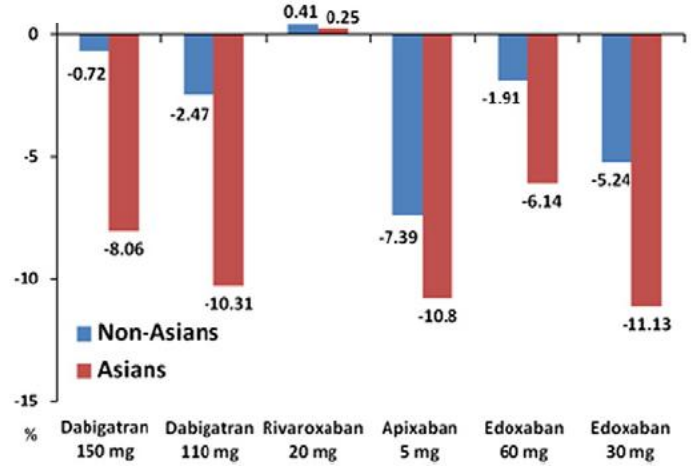
Intracranial Hemorrhage



GI Bleeding



All Bleeding



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

Asian

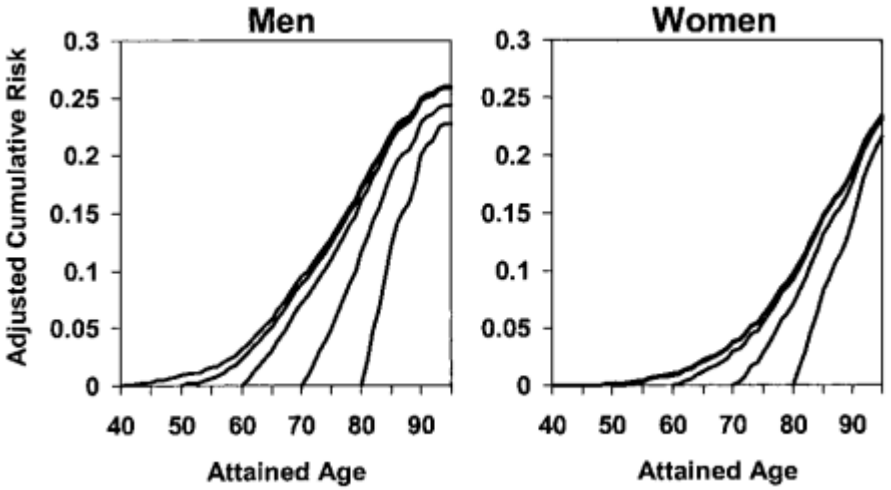
- 2015 EHRA Clinical Practice Guide
  - NOACs are considered to be preferentially indicated in Asians.

Heidbuchel H, et al. Europace 2015;17:1467-507.

NOAC in Elderly Patients?

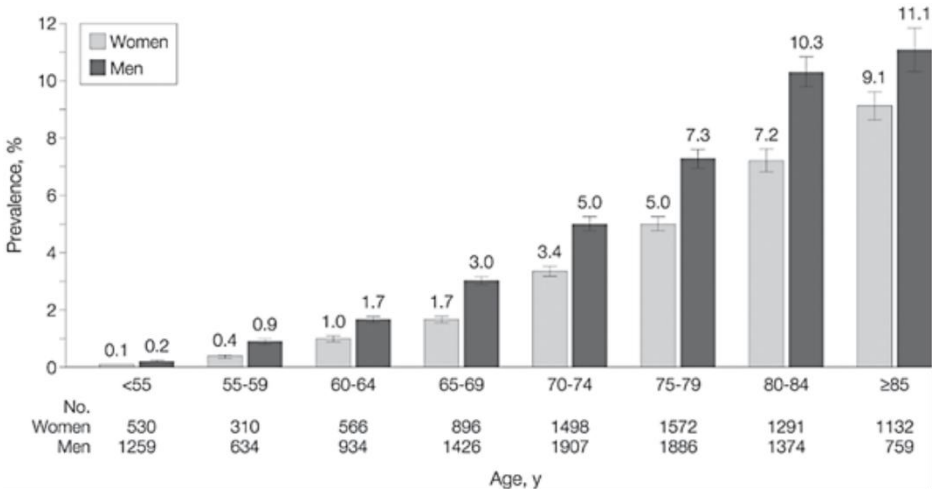
Age

Framingham Heart Study



Cumulative risk of AF at selected index age

ATRIA



Prevalence of diagnosed AF

Lloyd-Jones DM, et al. Circulation 2004;110:1042-6.

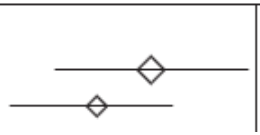
Go AS, et al. JAMA 2001;285:2370-5.

Elderly > 75 years

(RELY, ROCKET AF, ARISTOTLE, ENGAGE AF-TIMI 48)

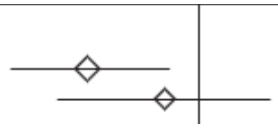
Stroke or Systemic Embolic Events

	Pooled NOAC (events)	Pooled warfarin (events)	RR (95% CI)	$p_{interaction}$
Age (years)				
<75	496/18 073	578/18 004	0·85 (0·73–0·99)	0·38
≥75	415/11 188	532/11 095	0·78 (0·68–0·88)	



Major Bleeding

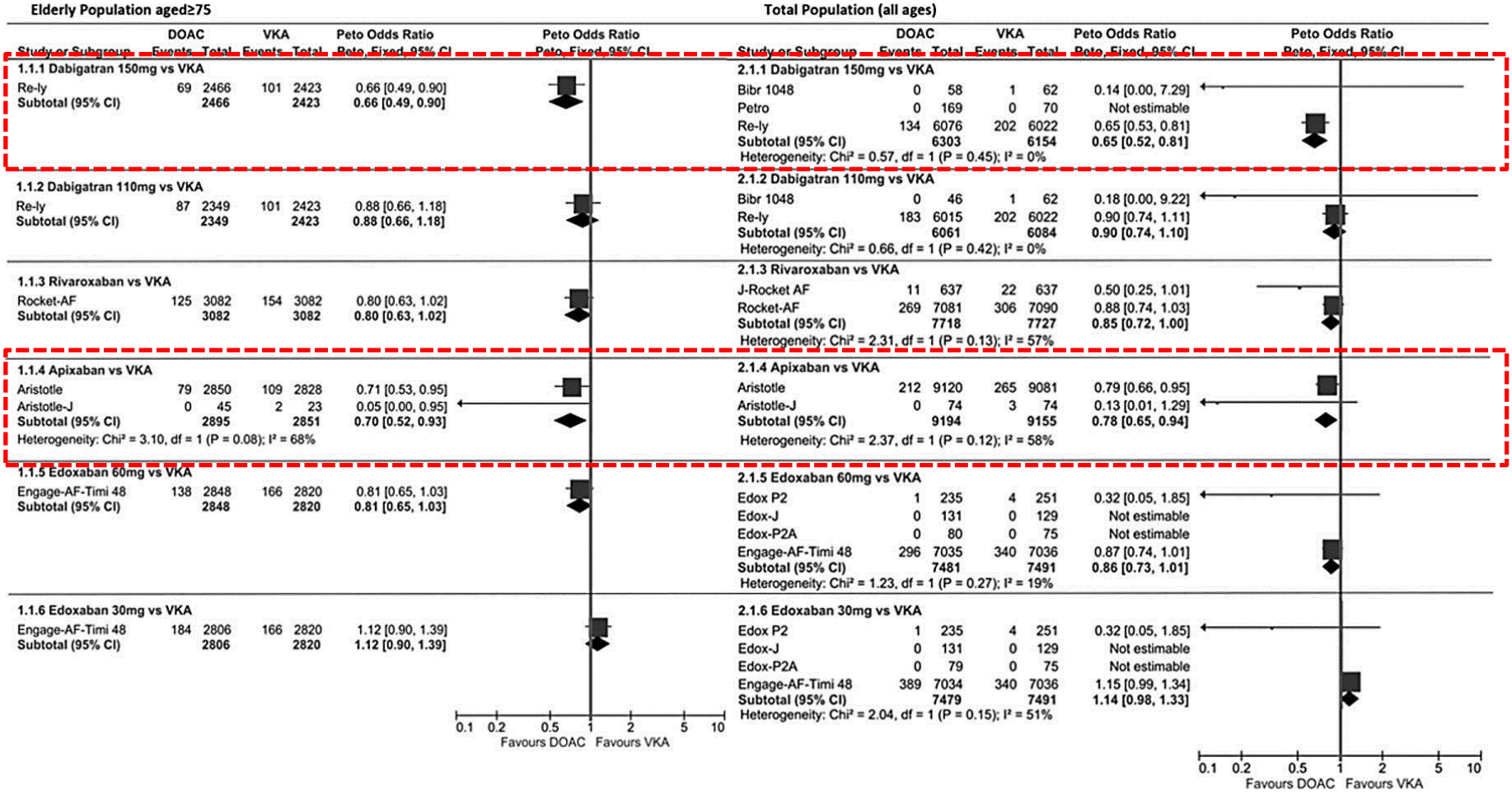
	Pooled NOAC (events)	Pooled warfarin (events)	RR (95% CI)	$p_{interaction}$
Age (years)				
<75	1317/18 460	1543/18 396	0·79 (0·67–0·94)	0·28
≥75	1328/10 771	1346/10 686	0·93 (0·74–1·17)	



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

Elderly Patients > 75 yrs

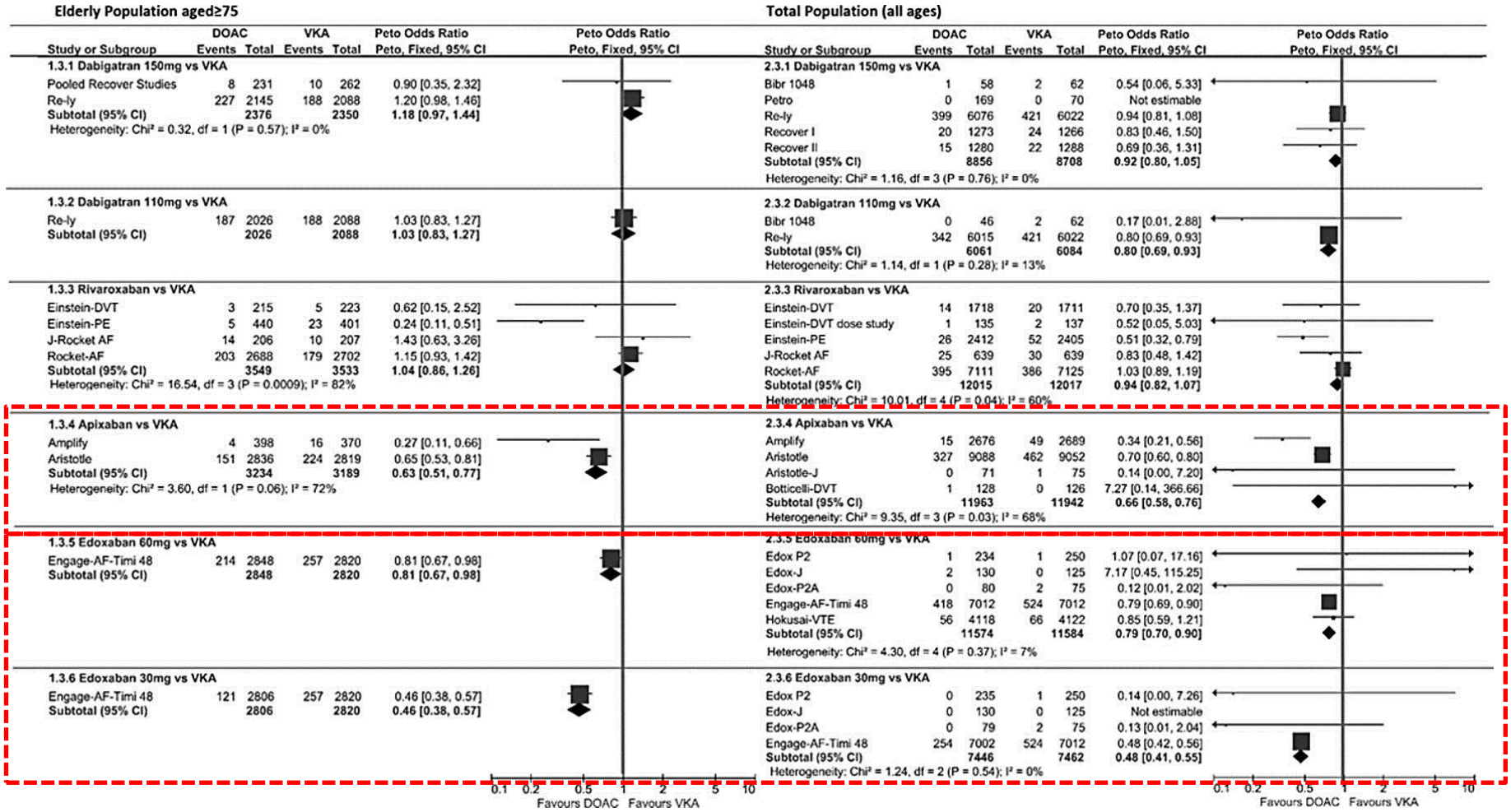
Risk of stroke or systemic embolism in atrial fibrillation studies



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

Expert Comment in Elderly Patients > 75 years

- **First choice**
  - Apixaban 5 mg twice daily or
  - 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

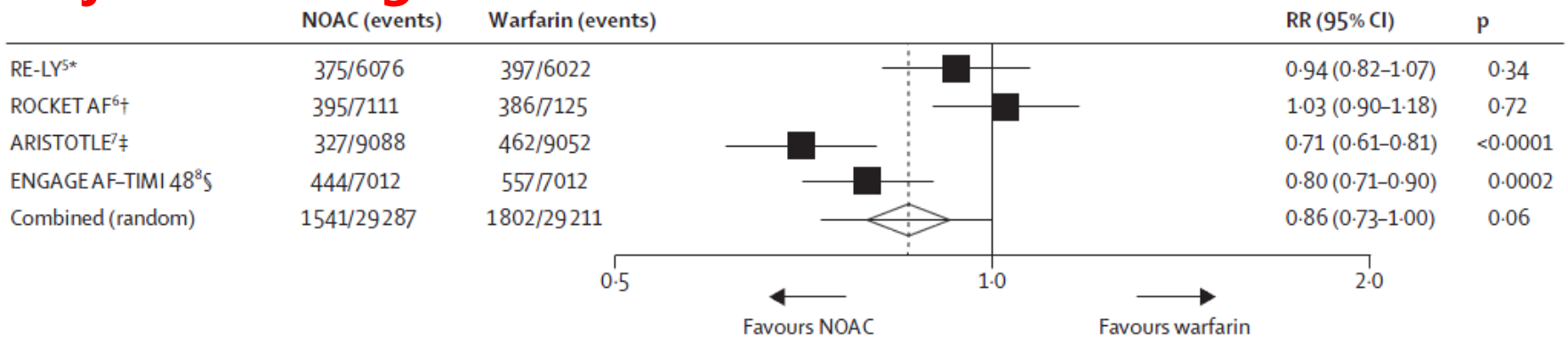
Diener HC, et al. 2016 Eur Heart J Epub ahead of print

GI Bleeding?

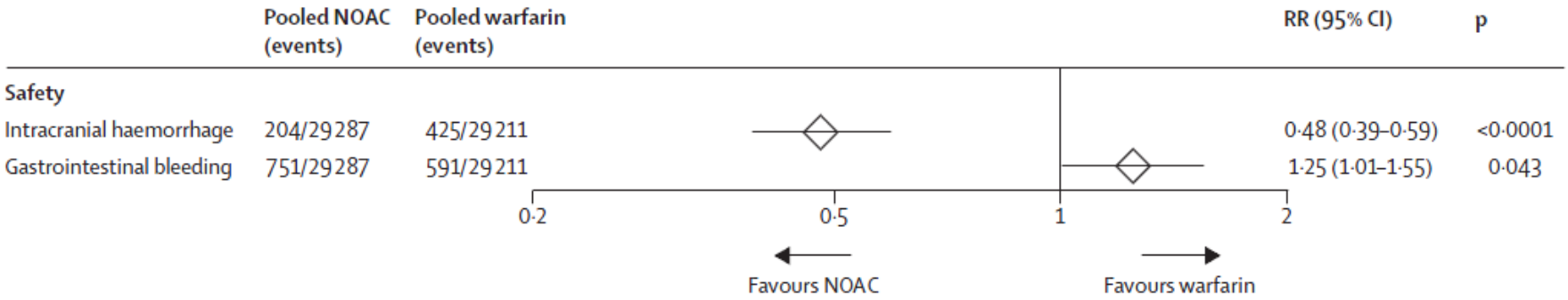
GI Bleeding

(RELY, ROCKET AF, ARISTOTLE, ENGAGE AF-TIMI 48)

Major Bleeding



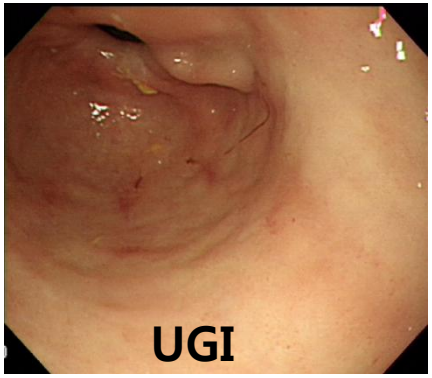
GI Bleeding

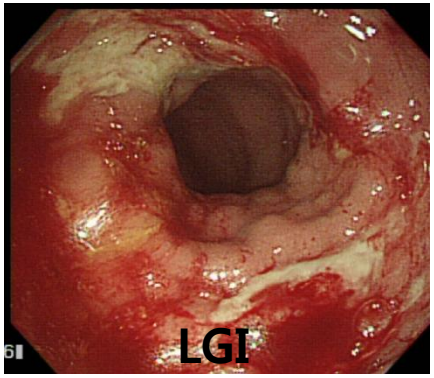


Ruff CT, et al. Lancet 2014;383:955-62.

85세 여자

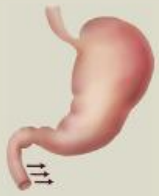
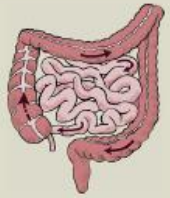
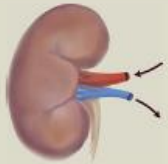
- NOAC 복용 중 혈변 (Hb 12>8.4 g/dL)
- Endoscopy : Stercoral ulcers





GI Bleeding

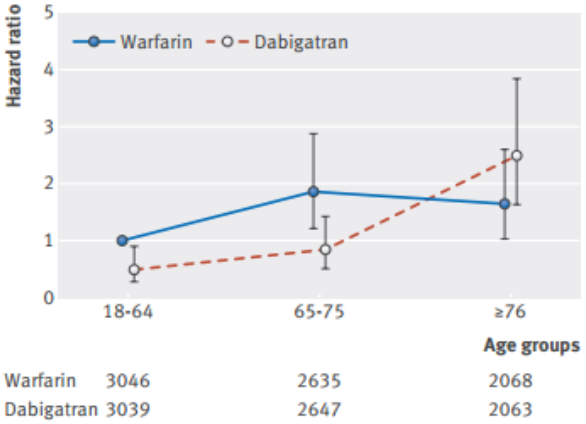
	Dabigatran 150 mg twice daily	Rivaroxaban 20 mg daily	Apixaban 5 mg twice daily
Total patients (n)	6076	7131	9088
Major GI bleeding (n)	223	224	105
Major GI bleeding (%/year)	1.85	2.00	0.76
Hazard ratio for major GI bleeding (vs. warfarin)	1.49 [CI 1.21–1.84]	1.61 [CI 1.30–1.99]	0.89 [CI 0.70–1.15]

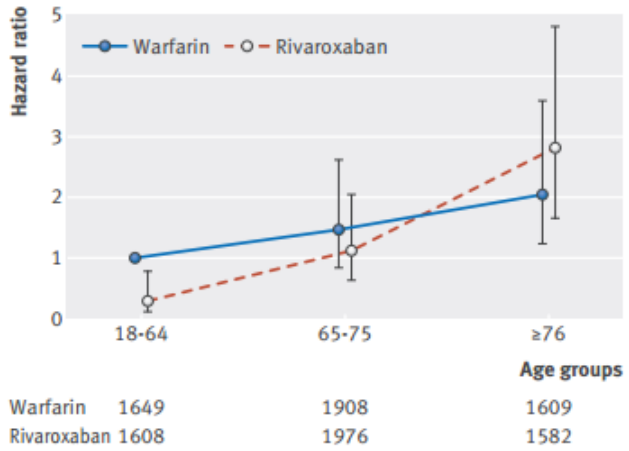
	Bioavailability	Active anticoagulant present in GI tract	Renal excretion	Hepatic metabolism
				
Warfarin	100%	None	None	High
Dabigatran	7%	High	High	Low
Rivaroxaban	66%	Moderate	Moderate	Moderate
Apixaban	50%	Moderate	Moderate	Moderate

Desai J, et al. Gastroint Endoscopy 2013;78:227-239

High Risk of GI Bleeding

- Old age ≥ 75 years
  - Dabigatran 150 mg bid, Rivaroxaban





Abraham NS, et al. BMJ 2015

- Concurrent use of antiplatelet agents
  - Aspirin

Expert Comment in Patients with High Risk of GI Bleeding

- **First choice**
  - Apixaban 5 mg twice daily
  - Dabigatran 110 mg twice daily
- **Second choice**
  - Dabigatran 150 mg twice daily
  - Rivaroxaban 20 mg once daily

GI bleeding, even in the setting of anticoagulation, dose usually not cause death or permanent major disability. Thus the choice of OAC should be driven mainly by stroke prevention considerations.

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

Renal Function?

Elimination of NOACs

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Mechanism of action	Selective direct FIIa inhibitor	Selective direct FXa inhibitor	Selective direct FXa inhibitor	Selective direct FXa inhibitor
Bioavailability	Oral prodrug with poor oral bioavailability (6.5%)	Good oral bioavailability	Good oral bioavailability	Good oral bioavailability
$T_{½}$	12 - 17 hours	6 - 9 hours	12 hours	9 - 11 hours
Dosing	Twice daily	Once or twice daily	Twice daily	Once or twice daily
Time action	1 - 4 hrs post-dose for max. inhibition	1 - 4 hrs post-dose for max. inhibition	1 - 4 hrs post-dose for max. inhibition	1 - 4 hrs post-dose for max. inhibition
Platelet aggregation	No direct effect	No direct effect	No direct effect	No direct effect
Elimination	80% renal	35% renal	25% renal	50% renal

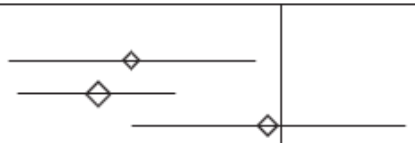
Edoxaban approval status and label may vary from country to country
For individual products please refer to the local label information in your country

Eriksson BI, et al. Clin Pharmacokinet. 2009;48:1-22.

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)	



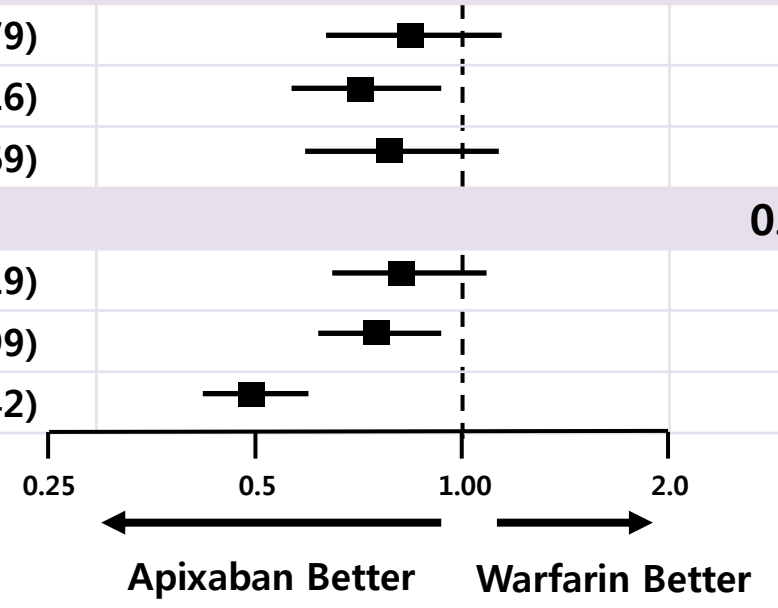
Major Bleeding

	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.

Outcomes of ARISTOTLE According to Renal Function

	Apixaban	Warfarin	Hazard Ratio (95% CI)	p value for Interaction
	%/yr (No. of Events)			
Stroke / systemic embolism				0.705
eGFR >80 mL/min*	0.99 (70)	1.12 (79)		
eGFR >50-80 mL/min†	1.24 (87)	1.69 (116)		
eGFR ≤50 mL/min‡	2.11 (54)	2.67 (69)		
Major bleeding				0.030
eGFR >80 mL/min*	1.46 (96)	1.84 (119)		
eGFR >50-80 mL/min†	2.45 (157)	3.21 (199)		
eGFR ≤50 mL/min‡	3.21 (73)	6.44 (142)		



*n=7,518 (42%); †n=7,587 (42%); ‡n=3,017 (17%)

Cockcroft-Gault method displayed here; Results were consistent regardless of methods for GFR estimation

ELIQUIS® (apixaban) was more effective and was associated with less major bleeding events than warfarin across all ranges of eGFRs

Apixaban is not recommended in patients with CrCl of < 15 mL/min or patients undergoing dialysis

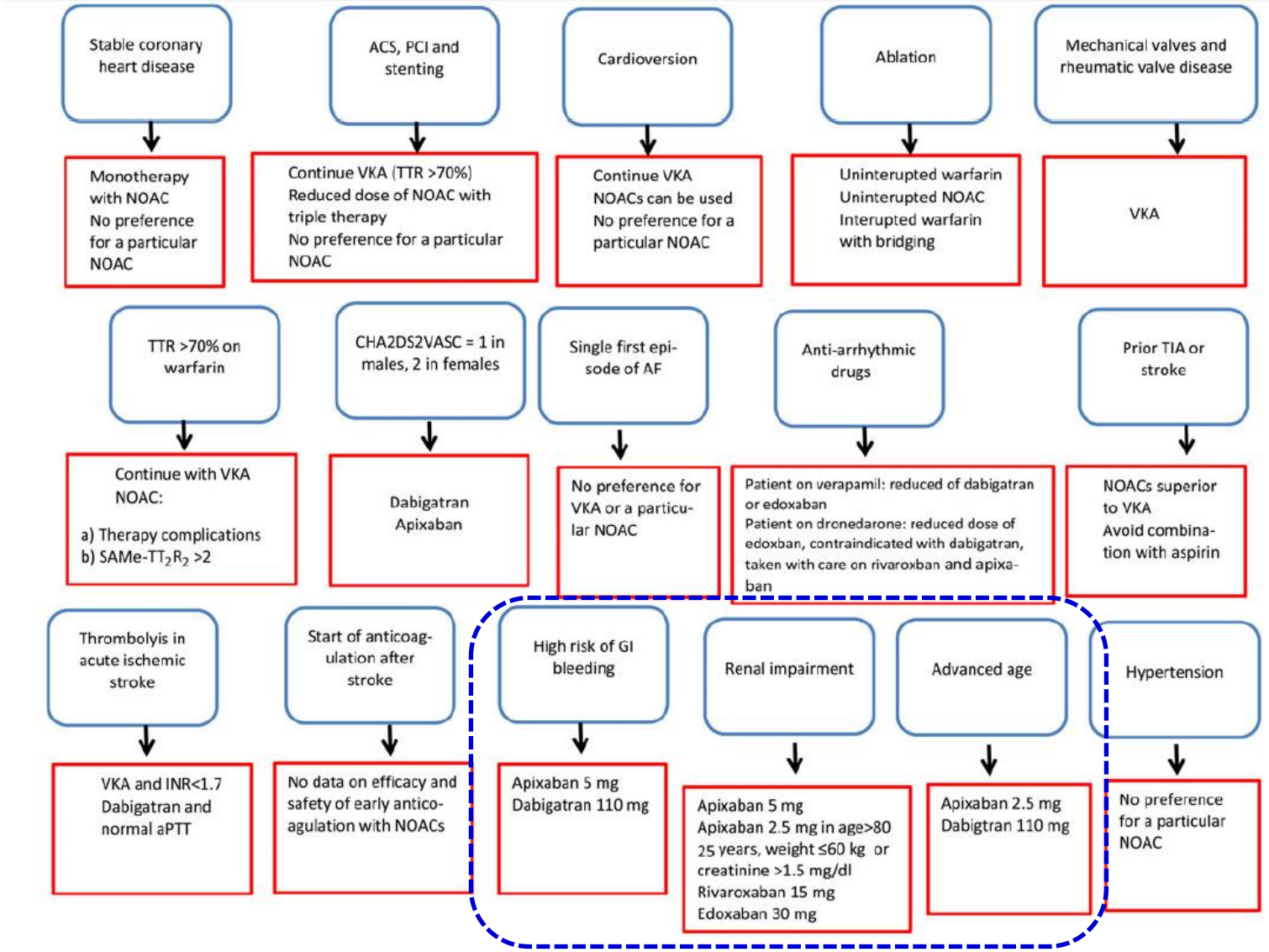
1. Hohnloser et al. Eur Heart J 2012;22:2821–2830.
2. Apixaban SmPC. Available at http://www.ema.europa.eu.

Expert Comment in Patients with Renal Impairment (CrCl 30-49 mL/min)

- **First choice**
  - Apixaban 5 or 2.5 mg twice daily
  - Rivaroxan 15 mg once daily
  - Edoxaban 30 mg once daily
- **Second choice**
  - Dabigatran 110 mg twice daily
- **Not recommended**
  - Dabigatran 150 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

Expert Comment

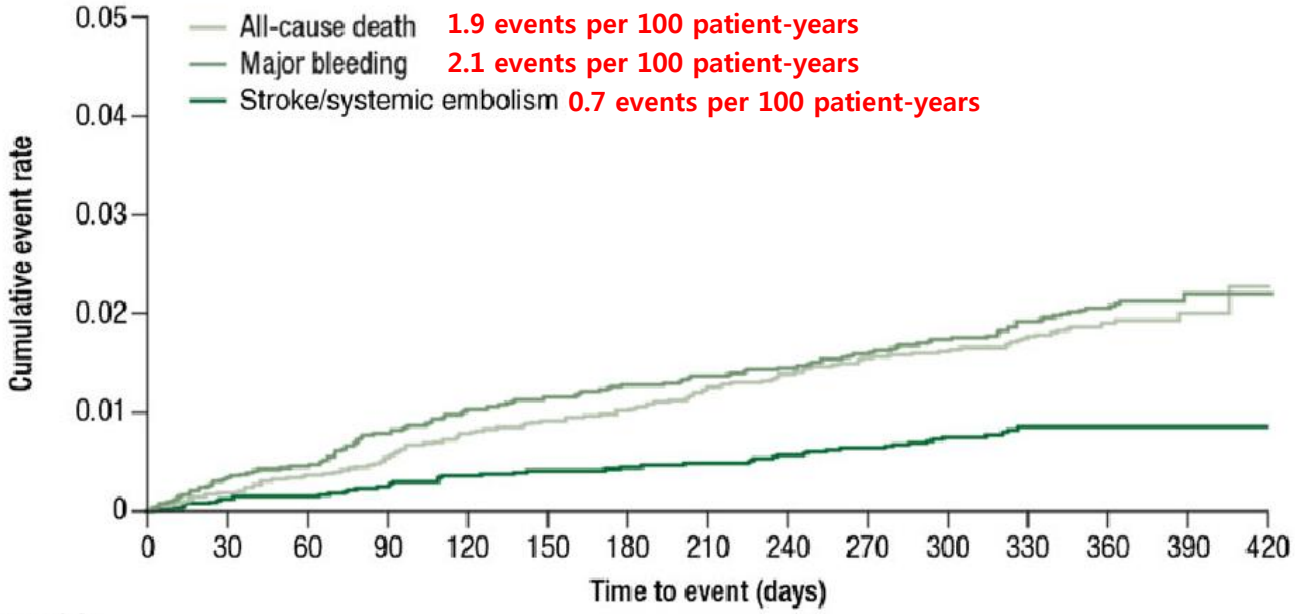


Diener HC, et al. 2016 Eur Heart J Epub ahead of print

Real-world Data?

XANTUS

Real-world, Prospective, Observational Study



Patients at risk:

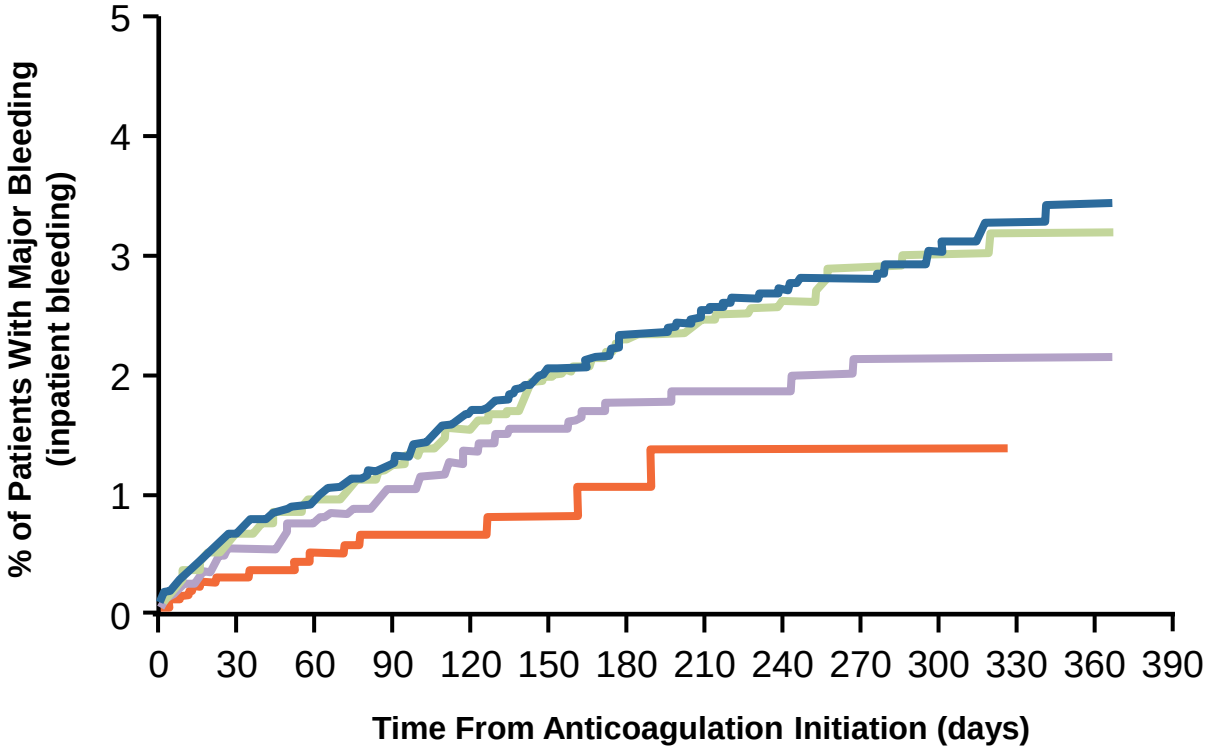
All-cause death	6784	6530	6349	6211	6054	5938	5853	5754	5679	5597	5512	5295	4307	1153	514
Major bleeding	6784	6522	6340	6197	6033	5909	5824	5726	5649	5559	5471	5256	4273	1144	513
Stroke/systemic embolism	6784	6532	6353	6216	6053	5933	5848	5752	5674	5587	5499	5282	4296	1149	513

Rates of stroke and major bleeding were low in patients receiving rivaroxaban in routine clinical practice.

Camm AJ, et al. Eur Heart J 2016;37:1145-53.

Real-world Bleeding Data

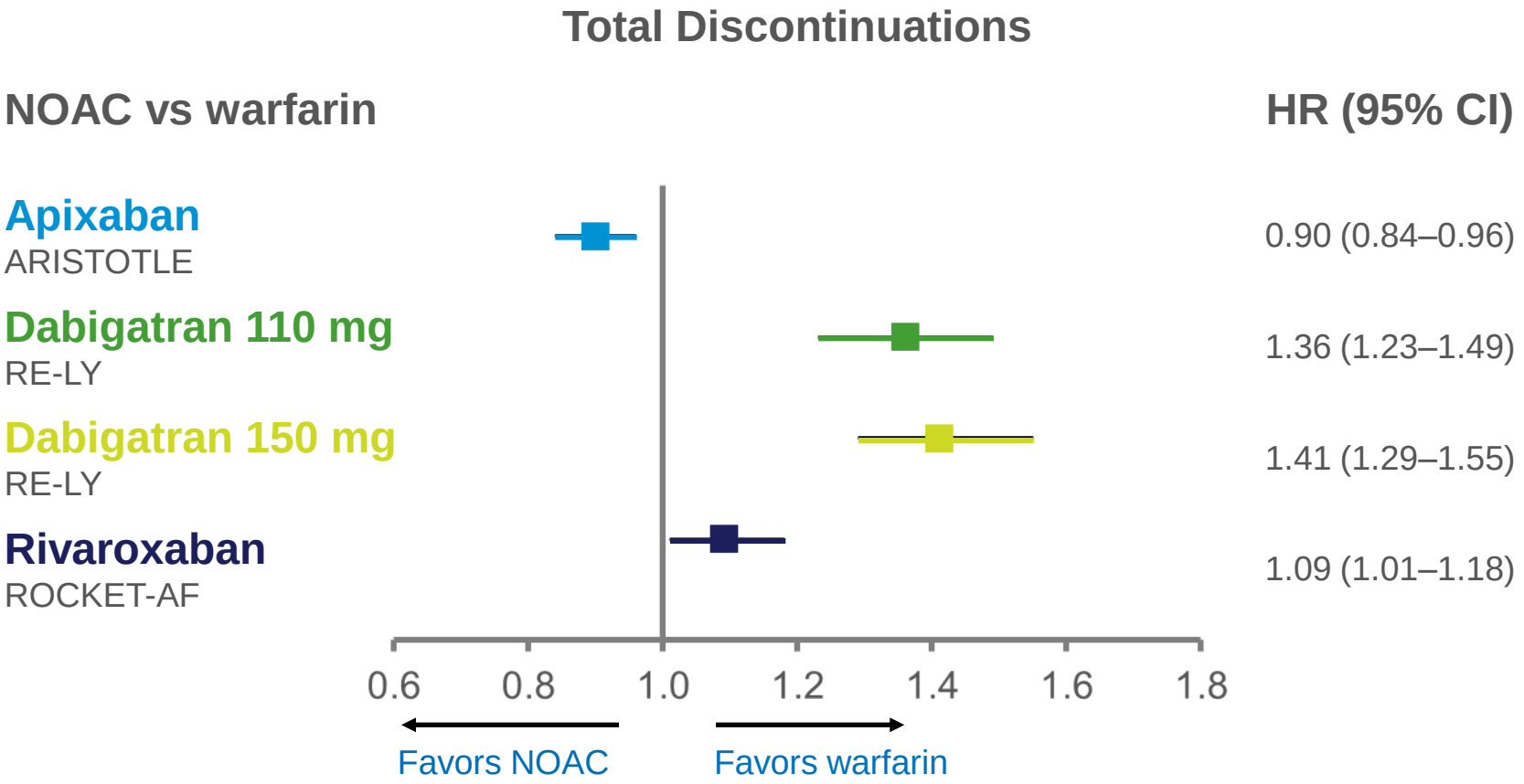
Warfarin vs apixaban:	Adjusted HR: 1.93 (95% CI: 1.12–3.33) *P*=0.018
Rivaroxaban vs apixaban:	Adjusted HR: 2.19 (95%CI: 1.26 –3.79) *P*=0.0052
Dabigatran vs apixaban:	Adjusted HR: 1.71 (95% CI: 0.94–3.10) *P*=0.079



Apixaban (N=2402)	
5 mg	Dose NR
N=2057	N=345
Dabigatran (N=4173)	
150 mg	Dose NR
N=3768	N=405
Rivaroxaban (N=10,050)	
20 mg	Dose NR
N=8066	N=1984
Warfarin (N=12,713)	

Lip GYH et al. Presented at: European Society of Cardiology Congress; August 29-September 2, 2015; London, UK.

RCT
NOAC Discontinuation

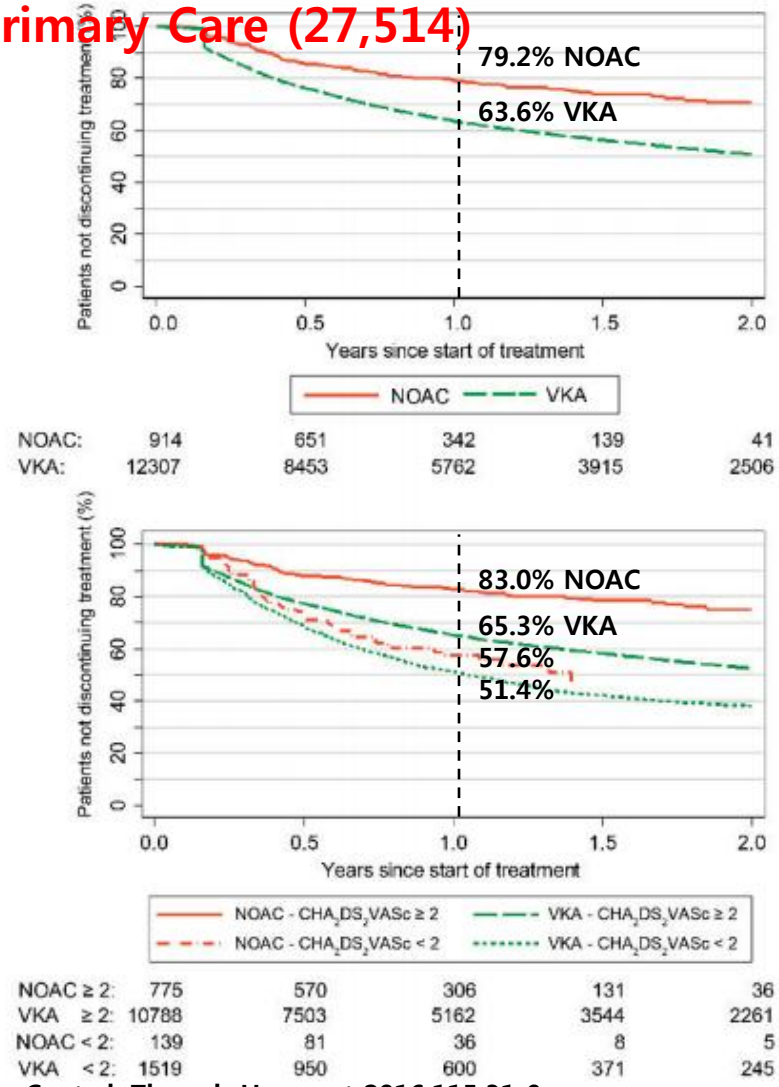


These are not head-to-head comparisons between NOACs

Mitchell SA et al. *Clin Appl Thromb Hemost.* 2013;19:619-631.

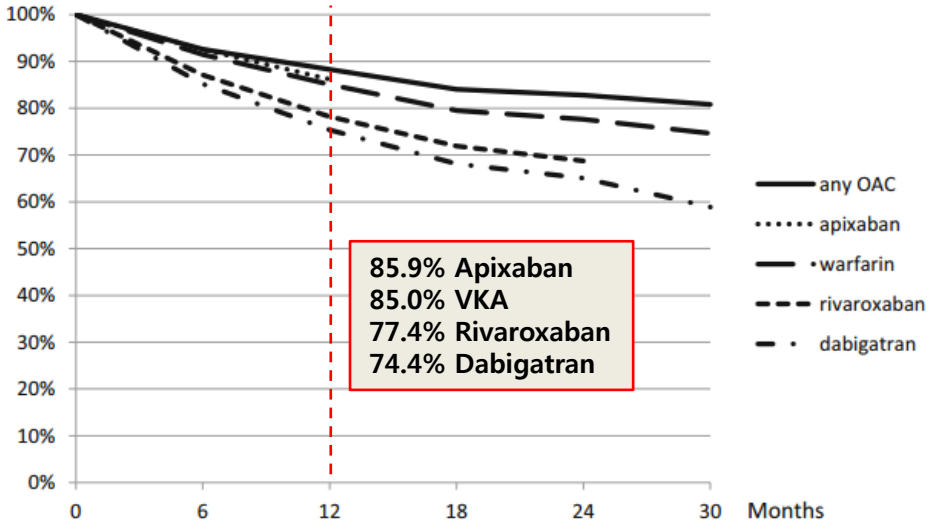
Real-world Persistence Data

UK Primary Care (27,514)

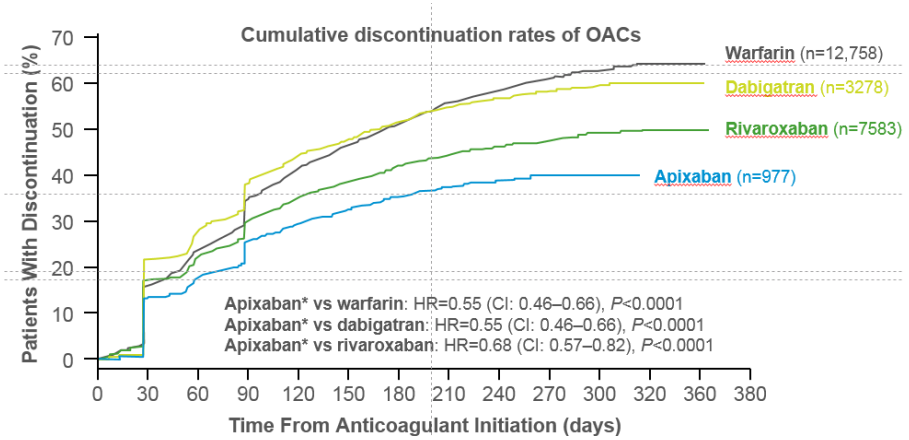


Martinez C, et al. Thromb Haemost 2016;115:31-9.

Stockholm primary Care (14,426)



Forslund T, et al. Eur J Clin Pharmacol 2016;72:329-38



Pan X et al. JACC 2014;63:S0735-1097

요약

- Non-valvular AF 환자에서 NOAC이 색전 혈전증 예방에 효과적이면서도 안전하게 사용할 수 있다.
- NOAC는 특히 아시아인, 75세 이상의 노인에게 유용하다.
- 환자 개개인의 특성 및 동반 질환을 잘 파악하여 맞춤치료가 필요하다.
- 약물의 효과를 최대화시키기 위해 복약 순응도를 올리기 위한 노력들이 필요하겠다.

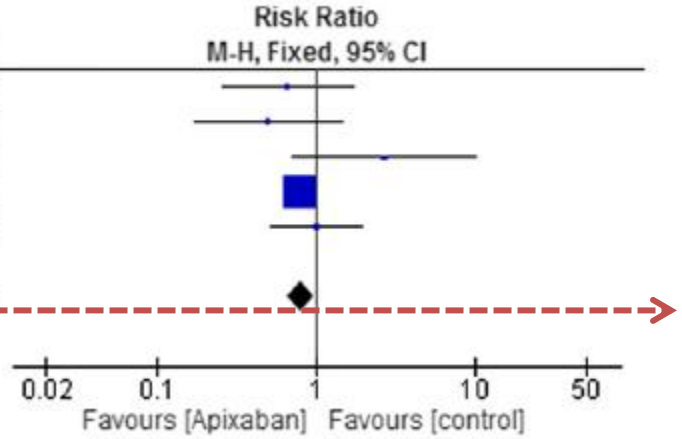
감사합니다.

Renal Impairment
(Bleeding Events on Apixaban)

Mild renal impairment (CrCl 50-80 mL/min)

Study or Subgroup	Apixaban Events	Apixaban Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
ADVANCE-2 & 3	7	1289	11	1328	4.5%	0.66 [0.25, 1.69]
AMPLIFY	5	549	10	544	4.2%	0.50 [0.17, 1.44]
AMPLIFY-EXT	7	168	3	193	1.2%	2.68 [0.70, 10.20]
ARISTOTLE	157	3817	199	3770	83.1%	0.78 [0.64, 0.96]
AVERROES	17	1188	17	1188	7.1%	1.00 [0.51, 1.95]
Total (95% CI)		7011		7023	100.0%	0.80 [0.66, 0.96]
Total events	193		240			

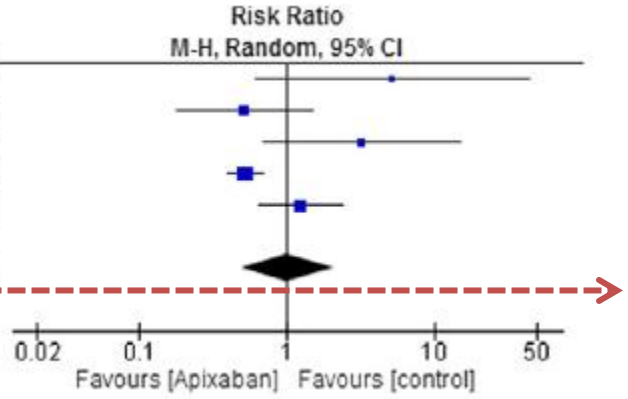
Heterogeneity: Chi² = 4.58, df = 4 (P = 0.33); I² = 13%
Test for overall effect: Z = 2.37 (P = 0.02)



Moderate to severe renal impairment (CrCl 30-50 mL/min)

Study or Subgroup	Favours [experimental] Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
ADVANCE-2 & 3	5	209	1	217	8.6%	5.19 [0.61, 44.06]
AMPLIFY	5	175	9	163	19.4%	0.52 [0.18, 1.51]
AMPLIFY-EXT	6	43	2	46	13.3%	3.21 [0.68, 15.05]
ARISTOTLE	73	1502	142	1515	32.1%	0.52 [0.39, 0.68]
AVERROES	20	568	16	561	26.5%	1.23 [0.65, 2.36]
Total (95% CI)		2497		2502	100.0%	1.01 [0.49, 2.10]
Total events	109		170			

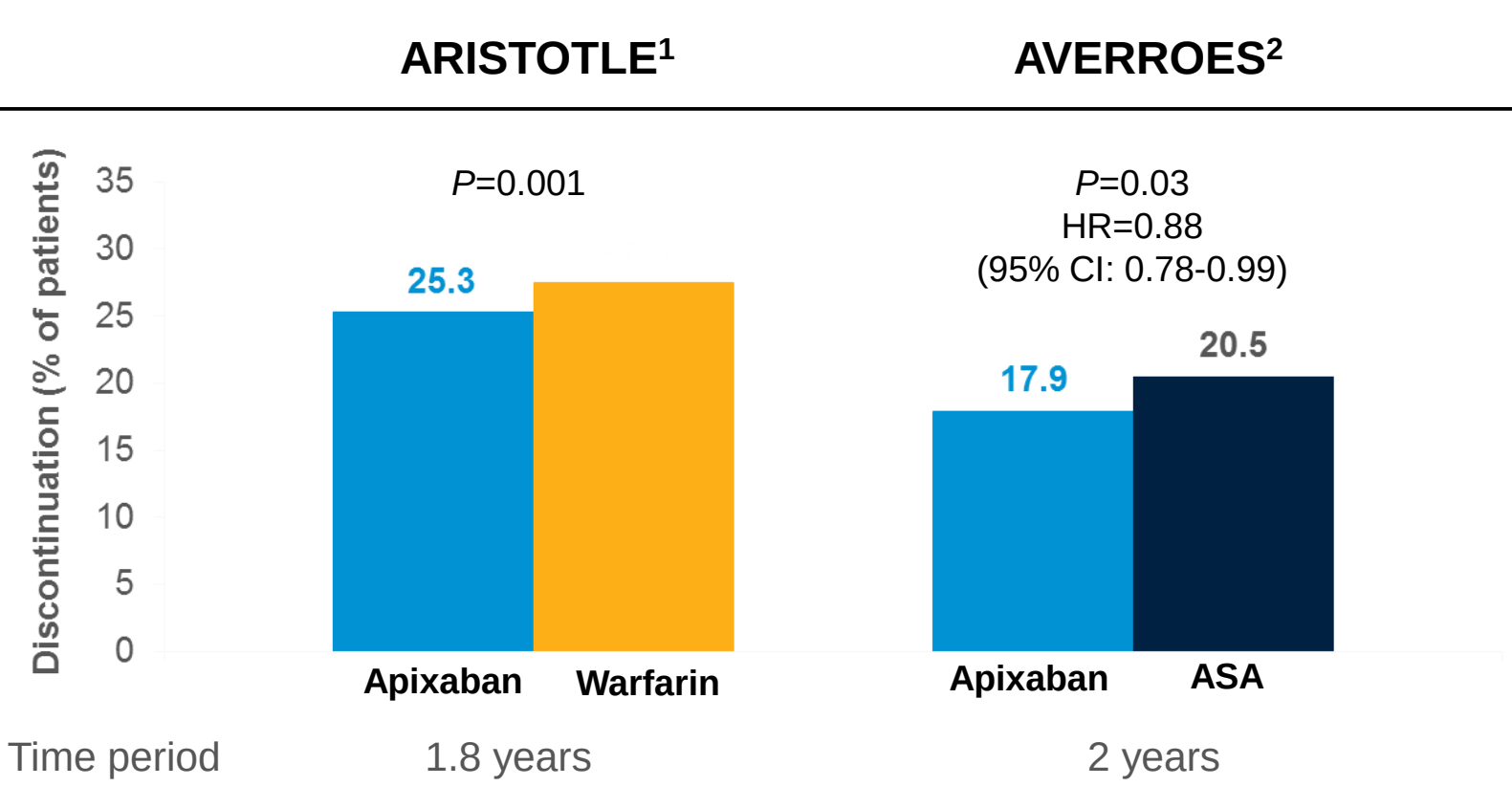
Heterogeneity: Tau² = 0.41; Chi² = 14.27, df = 4 (P = 0.006); I² = 72%
Test for overall effect: Z = 0.04 (P = 0.97)



- **6 Apixaban RCT**

Pathak R, et al. Am J Cardiol 2015;115:323-327

RCT
Apixaban Discontinuation



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1. Granger CB et al. *N Engl J Med.* 2011;365:981-992.
2. Connolly SJ et al. *N Engl J Med.* 2011;364:806-817.