NOAC is More Effective in Asian AF Patients? : Con

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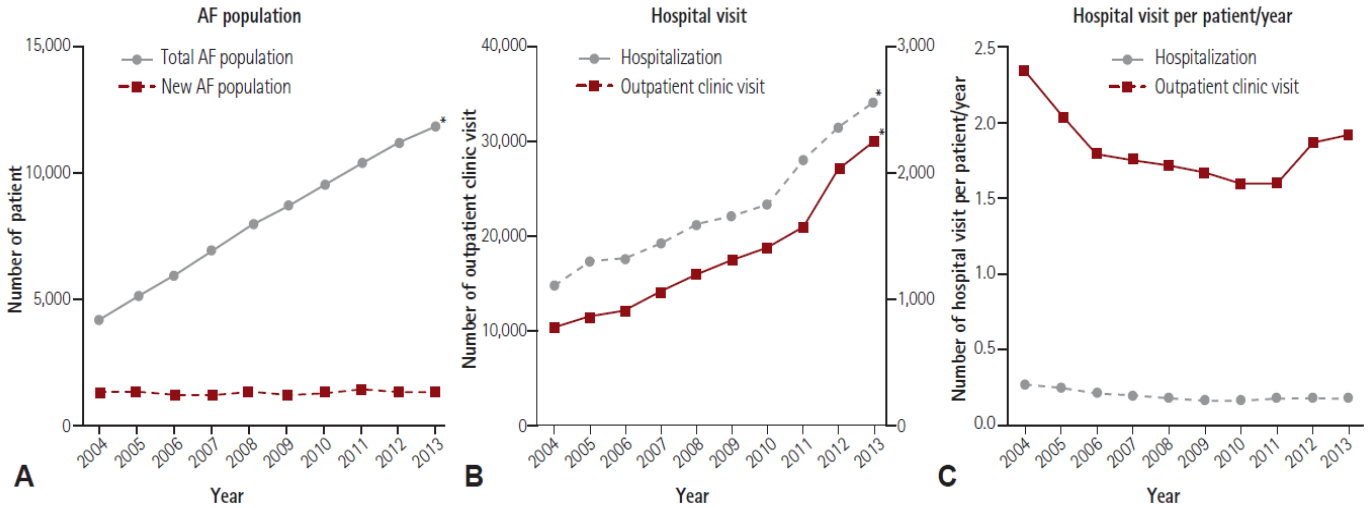
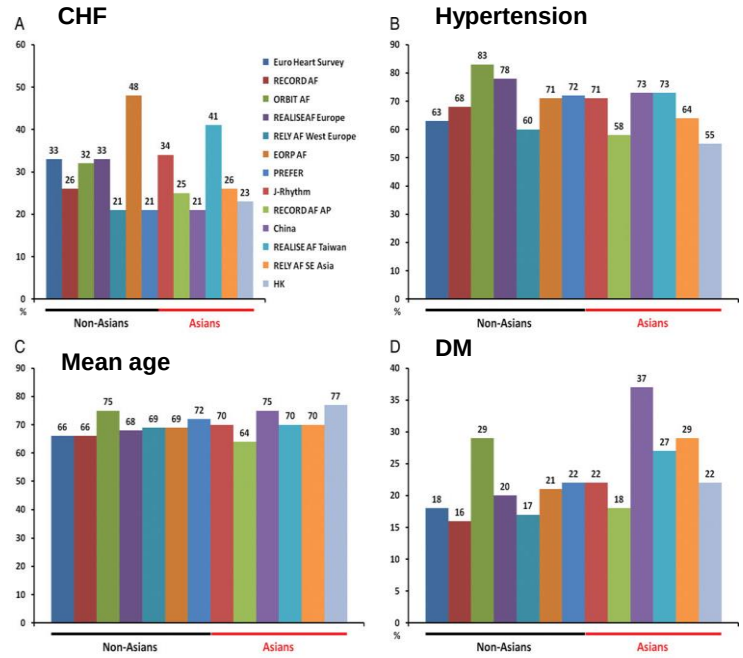
The Trends of Atrial Fibrillation-Related Hospital Visit and Cost, Treatment Pattern and Mortality in Korea : 10-Year Nationwide Sample Cohort Data

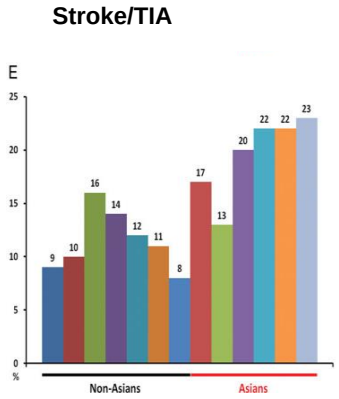


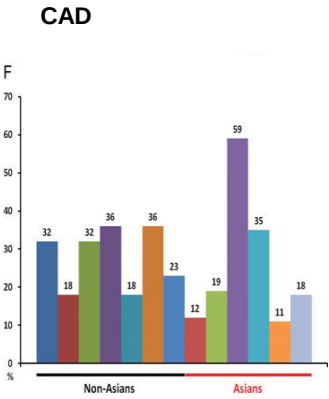
Lee H, Kim T, et al. Korean Circ J 2017;47:56-64

Racial Difference?

Prevalence of co-morbidities of AF in non-Asians and Asians

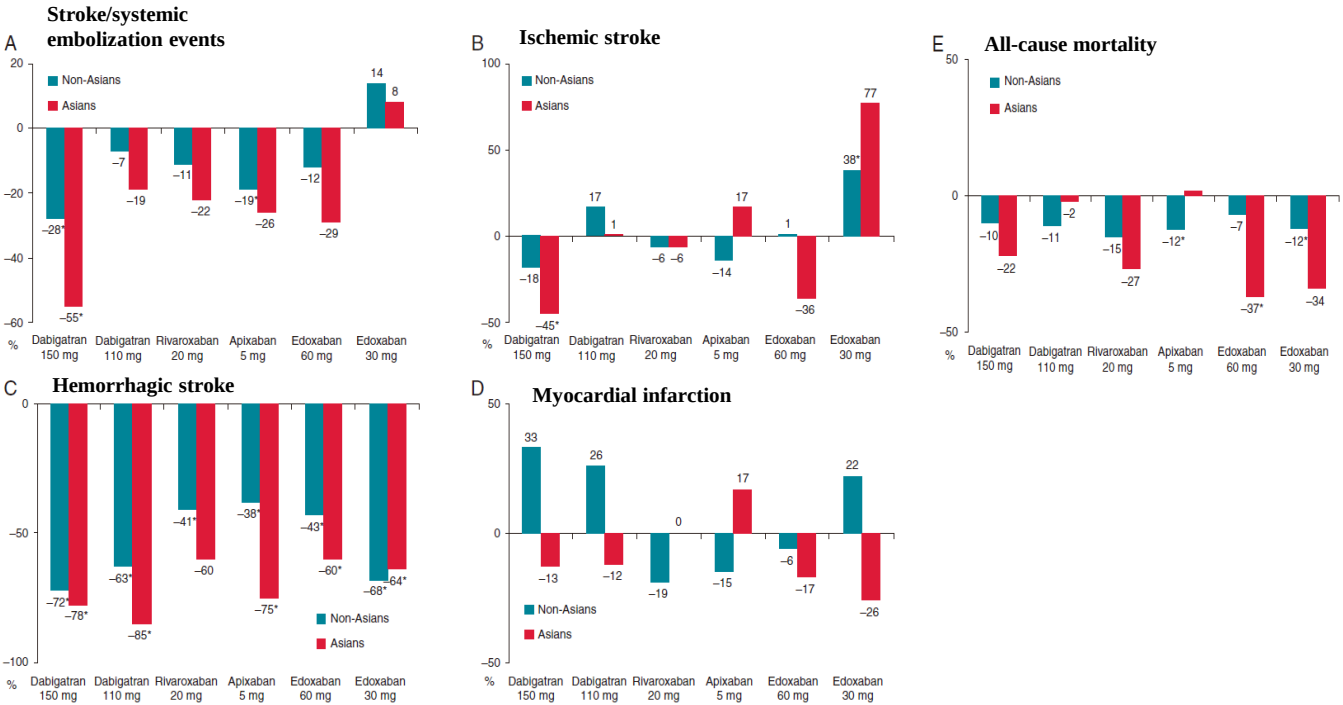






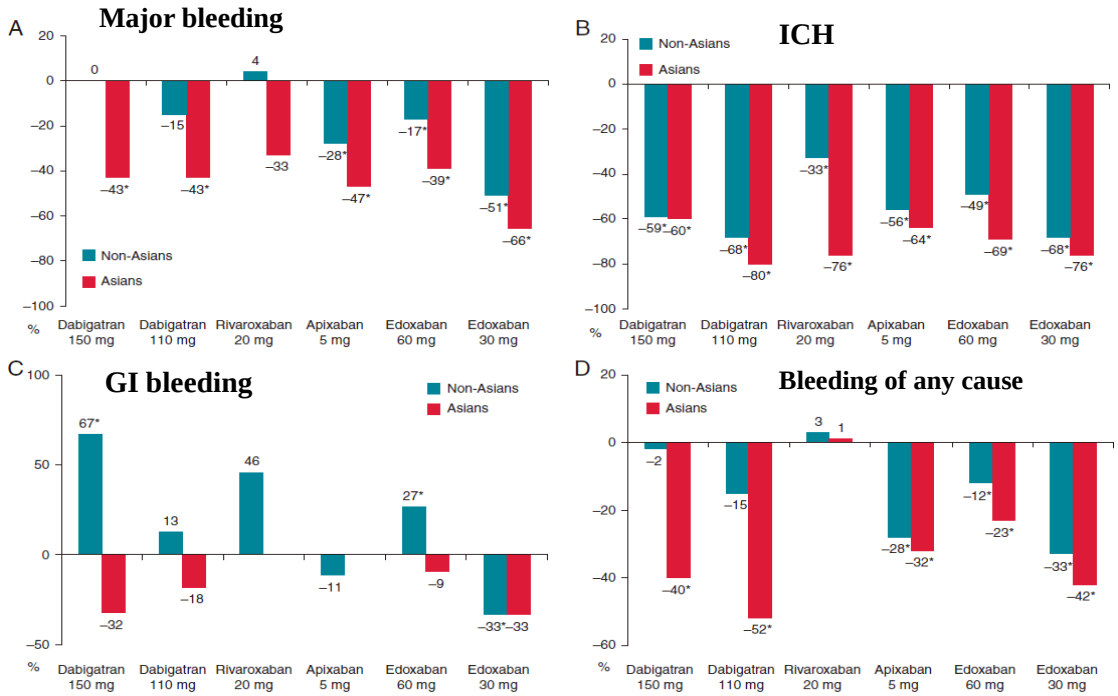
Chiang C et al. Europace2015;17:ii31

Relative risk reduction in five major efficacy endpoints in Asians and non-Asians



Chiang C et al. Europace2015;17:ii31

Relative risk reduction in four major safety endpoints in Asians and non-Asians



Chiang C et al. Europace2015;17:ii31

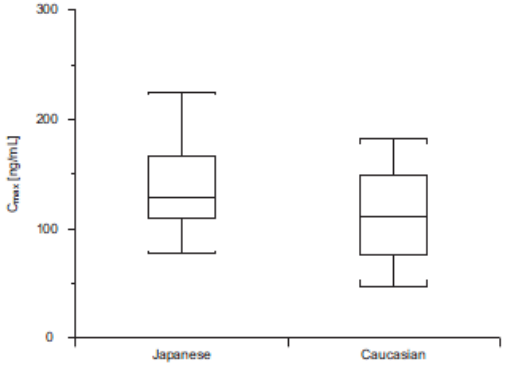
Asian strategy for stroke prevention in AF

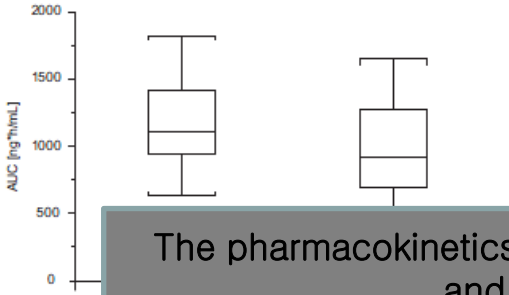
- **Asian AF patients have similar cardiovascular co-morbidities as westerns, and the recently developed CHA2DS2-VASc score remains valid in predicting stroke risk in Asians, outperforming other scoring systems.**
- **There is little evidence supporting a role of aspirin in preventing AF-associated stroke in Asians.**
- **Warfarin is effective for the prevention of stroke in Asians, but is very difficult to use.**
- **Warfarin-induced bleeding events are more common in Asians. Warfarin produced higher risk of major bleeding and intra-cranial haemorrhage in Asians compared with those in non-Asians, even though anticoagulation intensity was lower in Asians.**
- **All these trials consistently demonstrated that NOACs were superior or non-inferior to warfarin. The benefits of NOACs were especially robust in Asians.**
- **There was no evidence of increased risk of gastro-intestinal bleeding associated with NOACs in Asians.**
- **Unless in a few conditions when NOACs are contraindicated, NOACs are preferred medications in the stroke prevention for AF in Asians.**

Chiang C et al. Europace2015;17:ii31

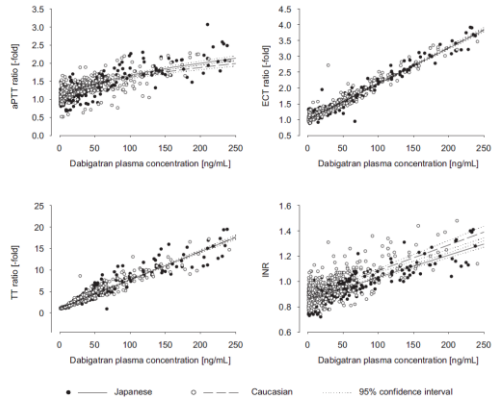
Pharmacokinetic Effect of Dabigatran in Japanese and Caucasian

A. Cmax and total AUC after oral administration of dabigatran etexilate 150 mg





B. Anti-coagulation parameters vs plasma concentration of dabigatran



C. Correlation between trough plasma concentration and dabigatran dose

The pharmacokinetics of dabigatran are similar in Japanese and Caucasian subjects.

J Thromb Haemost 2012;107:260-269

Higher Stroke Rate in Asian AF patients?

Stroke Rates among Studies Reporting CHA2DS2-VASc Stratified Results by Increasing Rate

	Women's Health Initiative (17)	Stockholm Area Database (20)	Taiwan NHI Database (15)	ATRIA (18)	Iwate Cohort (30)	J-Rhythm, Shinken, Fushimi (32)	Euro Heart Survey on AF (8)	Swedish AF Study (22)	General Practice Research Database (28)	Clalit Health Services AF (34)	PLA General Hospital AF (25)	J-Rhythm (44)	AVERROES ACTIVE-A, and ACTIVE-W * (45)	Alberta AF Cohort † (46)	Taiwan NHIRD - 1996-2011 (14)	Danish National Patient Registry (6)	Queen Mary Hospita (35)
CHA_2DS_2-VASc Score																	
0	--	0.3	0.35	0.04	0	0.53	0	0.2	0.38	0.42	0	0.7	--	--	1.15	0.78	2.41
1	0.2	0.5	0.5	0.55	0.6	0.55	0.6	0.6	0.78	0.82	0.9	0.9	1.1	1.3	2.11	2.01	6.64
2	0.48		0.91	0.83	0.95	1.11	1.6	2.2	1.92	1.81	1.7	1.9	2.3	6.5‡	3.39	3.71	7.84
3	0.82		1.35	1.66	1.96	1.38	3.9	3.2	2.84	2.57	2.7	1.2	3.3‡		3.89	5.92	9.56
4	1.3		2.12	2.8	5.45	1.52	1.9	4.8	3.7	3.71	1.8	2.3			4.61	9.27	11.58
5	1.71		2.59	4.31	9.06	4.43	3.2	7.2	5.08	4.52	8.8	4.5			5.12	15.26	12.69
6	2.02		4.42‡‡	4.77	13.7‡	4.07	3.6	9.7	7.09	5.1	9	2			5.18	19.74	13.18
7				4.82		1.56	8	11.2	8.98	5.6		1.8			6.22	21.5	
8				7.82		6.95	11.1	10.8	9.01			0			7.98	22.38	
9				16.62		211	100	12.23	15.49			0			10.5	23.64	

Quinn et al. Circulation 2017

The CHA_2DS_2-VASc score for ischemic stroke and thromboembolic event rates in Asian patients with non-valvular AF : A nationwide sample cohort study using the Korean NHIS Data

	Korea NHIS Cohort Database				The Euro Heart Survey	Denmark Nationwide Cohort
	Low Risk (CHA_2DS_2-VASc 0 or 1 [Female])	Intermediate Risk (CHA_2DS_2-VASc 1 [Male])	High Risk (CHA_2DS_2-VASc ≥2)	Total (n=5855)	Total (n=1084)	Total (n=73 538)
Age, y	44±12	53±11	69±12	64±15	66±14	N/A
<65	0 (0)	0 (0)	1561 (35.1)	2594 (44.3)	N/A	15 130 (20.5)
65–74	0 (0)	76 (13.8)	1624 (36.5)	1700 (29.0)	N/A	14 544 (19.8)
>75	860 (100)	474 (86.2)	1260 (28.3)	1561 (26.7)	309 (28.5)	43 864 (59.7)
Women	446 (51.9)	0 (0)	2389 (53.7)	235 (48.4)	442 (40.8)	37 651 (51.2)
CHA_2DS_2-VASc score	0.52±0.50	1.00	4.09±1.69	3.28±2.08	N/A	N/A
History of TIA/ischemic stroke	0 (0)	0 (0)	1433 (32.2)	1433 (24.5)	97 (9.1)	13 368 (18.2)
Atherosclerotic disease						
Myocardial infarction	0 (0)	8 (1.5)	756 (17.0)	764 (13.0)	N/A	N/A
Peripheral arterial disease	0 (0)	7 (1.3)	604 (13.6)	611 (10.4)	62 (5.8)	N/A
Vascular disease	0 (0)	15 (2.7)	1191 (26.8)	1206 (20.6)	N/A	12 873 (17.5)
Heart failure	0 (0)	17 (3.1)	1852 (41.7)	1869 (31.9)	253 (23.5)	13 126 (17.9)
Hypertension	0 (0)	405 (73.6)	4017 (90.4)	4422 (75.5)	729 (67.3)	25 060 (34.1)
Diabetes mellitus	0 (0)	37 (6.7)	1131 (25.4)	1168 (19.9)	187 (17.3)	6496 (8.8)
ESRD	2 (0.2)	5 (0.9)	82 (1.8)	89 (1.5)	N/A	N/A
COPD	38 (4.4)	26 (4.7)	609 (13.7)	673 (11.5)	N/A	N/A
Aspirin use	86 (10.0)	225 (40.9)	2325 (52.3)	2636 (45.0)	802 (74.0)	25 503 (34.7)

Kim TH, Yang PS, Joung B, Lip G et al. Stroke 2017 (In press)

Ischemic stroke or the composite thromboembolism endpoint /100 person-years at risk in relation to CHA_2DS_2-VASc scores in 5,855 patients without anticoagulation throughout follow-up

	Korea NHIS Cohort Database (n=5855)						The Euro Heart Survey (n=1084)	Denmark Nationwide Cohort (n=73 538)
		Ischemic Stroke		Ischemic Stroke/Systemic Embolism			Ischemic Stroke/Systemic Embolism	Ischemic Stroke/Systemic Embolism
CHA_2DS_2-VASc Score	No. of Patients	Unadjusted	Adjusted for Aspirin*	Unadjusted	Adjusted for Aspirin*	CHA_2DS_2-VASc Score	Adjusted for Aspirin	Unadjusted
0 (male) or 1 (female)	860	0.23	0.26	0.26	0.29	0	0	0.69
1 (male)	550	1.04	1.18	1.20	1.35	1	0.7	1.51
2	975	1.91	2.21	2.04	2.35	2	1.9	3.01
3	911	2.54	2.88	2.67	3.04	3	4.7	4.41
4	836	4.72	5.34	5.10	5.76	4	2.3	6.69
5	770	5.79	6.54	5.98	6.76	5	3.9	10.42
6	513	8.36	9.50	8.61	9.77	6	4.5	12.85
≥7	440	8.82	9.97	9.03	10.21	≥7	11.4	14.0
Total	5855	3.32	3.79	3.49	3.98	Total	2.3	5.29

Kim TH, Yang PS, Joung B, Lip G et al. Stroke 2017 (In press)

Stroke rate in OAC naïve AF patients

score	N, %	Stroke event	Mean duration until stroke event (year)	Mean follow-up duration (year)	Annual stroke rate
0 (male) or 1 (female)	131,638 (20.8)	6,990 (5.3)	2.09	6.48	0.82%
1 (male)	69,139 (10.9)	7,350 (10.6)	2.34	5.56	1.91%
2	112,002 (17.7)	13,960 (12.5)	2.25	5.55	2.25%
3	104,283 (16.5)	16,716 (16.0)	1.98	4.87	3.29%
4	87,109 (13.7)	15,814 (18.2)	1.79	4.32	4.20%
5	62,424 (9.9)	11,545 (18.5)	1.55	3.86	4.79%
6	38,124 (6.0)	7,286 (19.1)	1.17	3.52	5.44%
≥7	29,273 (4.6)	5,473 (18.7)	0.94	2.95	6.34%

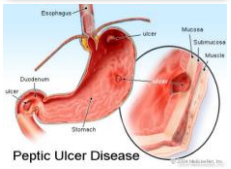
Yang PS, Ryu S, Hwang J, Joung B, Lip G et al. (Unpublished)

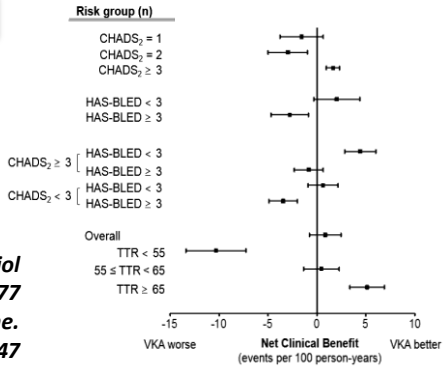
Aged Asian

Patients with High Risk of Bleeding?

High risk AF patients & OAC

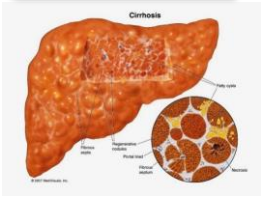
Peptic Ulcer

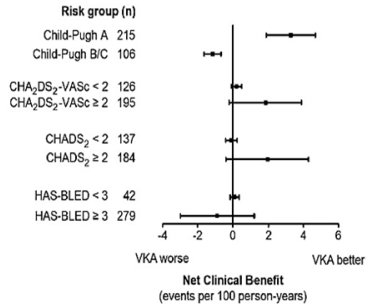




Lee SJ. Am J Cardiol 2012;110:373-377
Lee SJ, et al. Medicine. 2016;95:47

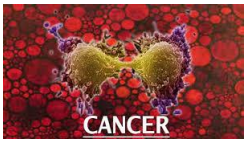
Liver Cirrhosis



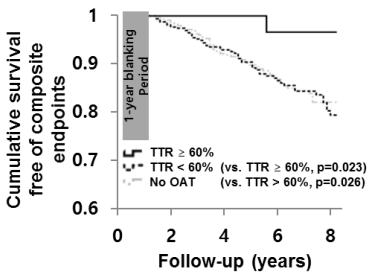


Lee SJ. Int J Cardiol 2015;180:185-191

Cancer



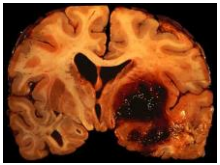
Lee YJ. Int J Cardiol 2015;203:372-8

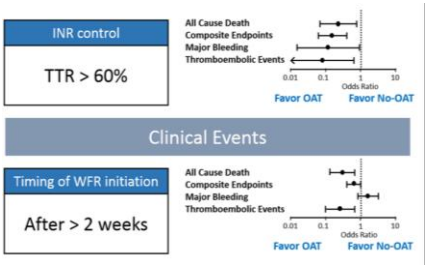


Number at risk

TTR≥60%	65	53	34	26	11
TTR<60%	498	403	261	156	44
OAT-	576	469	278	178	45

ICH

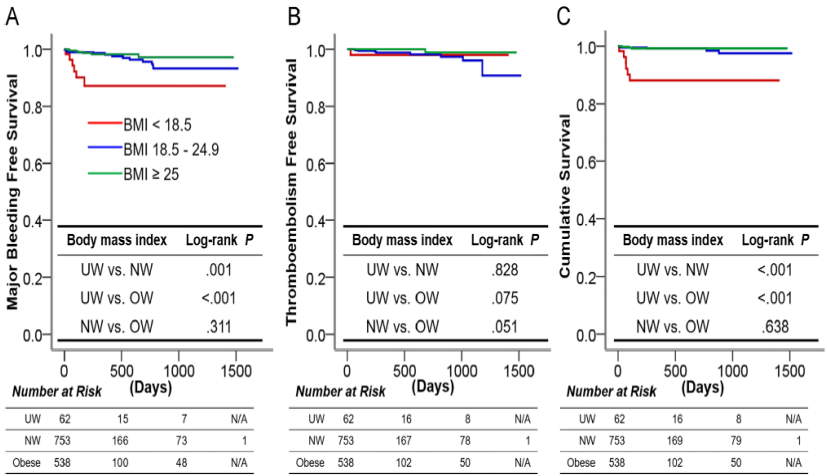




Park YH. Heart Rhythm 2016;13:1794-802

Association of body mass index (BMI) and major bleeding events

- analyzed 1353 AF patients who were prescribed NOACs according to their BMI



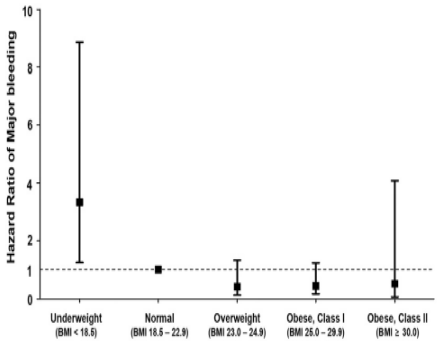
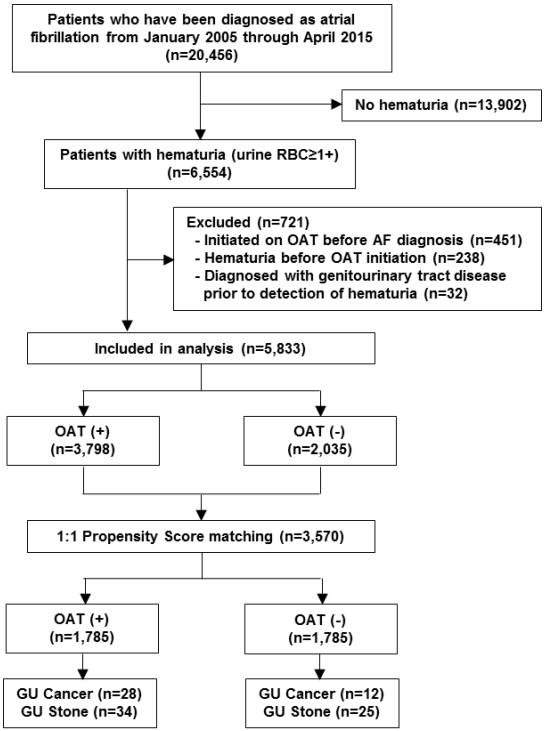


Figure 3 Association of body mass index (BMI) and major bleeding events. Patients were divided by obesity degree according to World Health Organization criteria. Risk on the y-axis is hazard ratio ± 95% confidence intervals using Cox regression model.

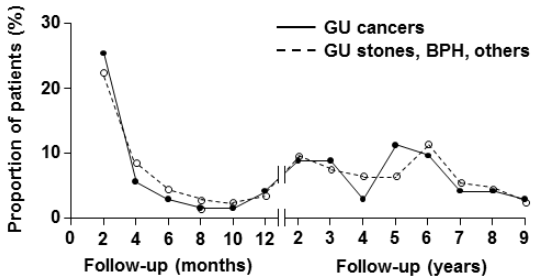
Park C, Choi E, et al. Heart rhythm 2017;14:501-507

High risk AF patients & OAC

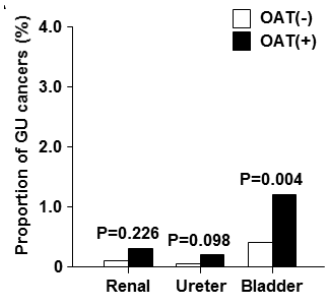
GU cancer and hematuria



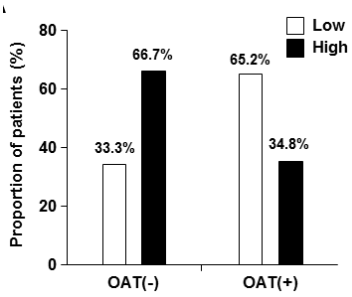
Hematuria detection time after OAT



Location of genitourinary cancers

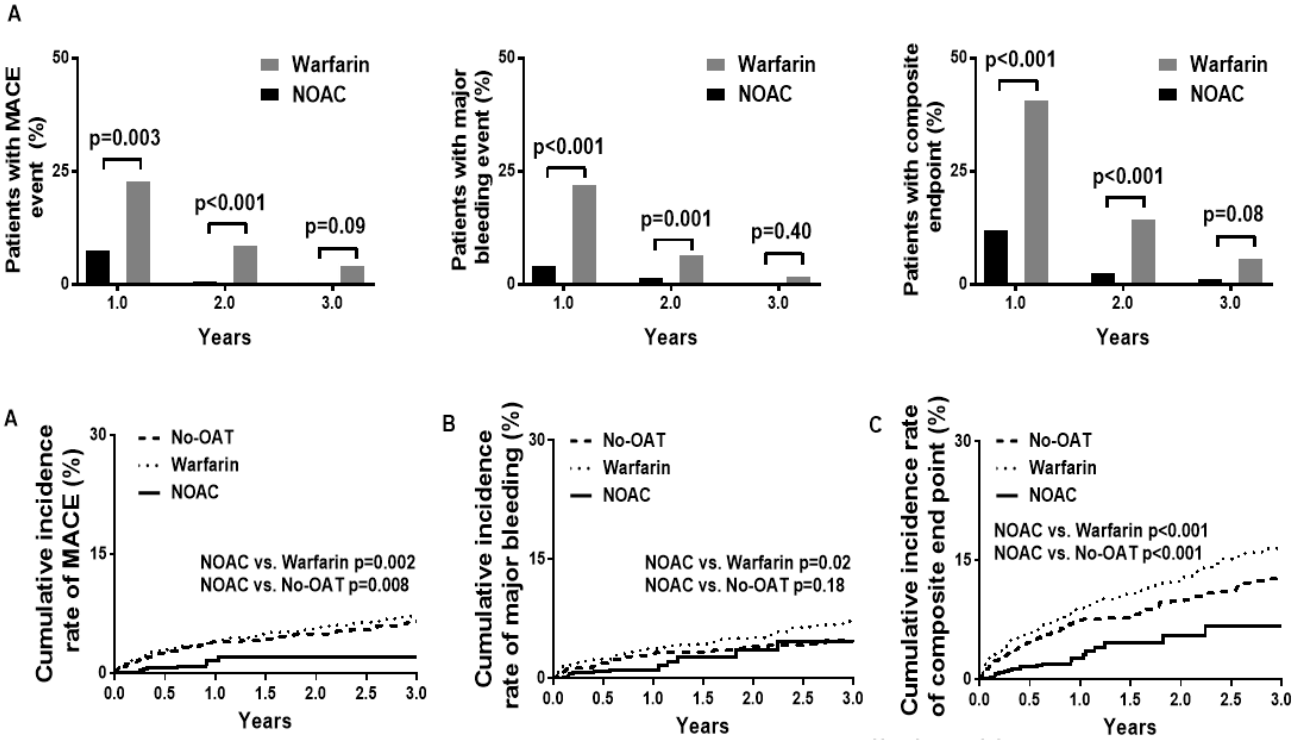


Pathologic grade of bladder cancer



Yu HT, et al. Circ J. 2017;81:158-164

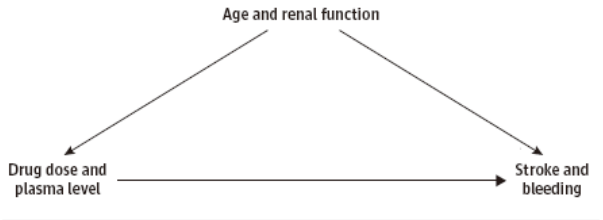
Proportion of patients with events according to the duration after cancer diagnosis for the PS matched population.



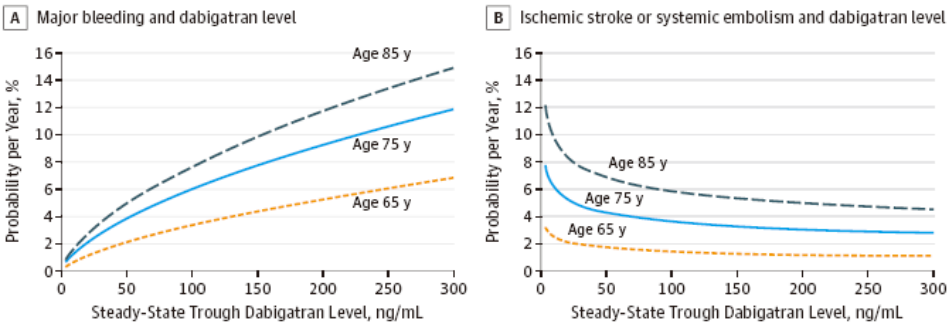
Kim K. AHA 2016

Old Age and Renal function: Laboratory monitoring of NOAC

Figure 2. Challenge in Defining a Therapeutic Range for Individual Non–Vitamin K Antagonist Oral Anticoagulants



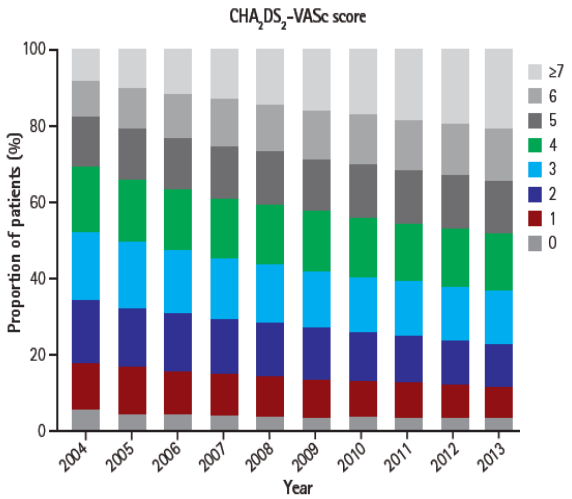
The association between drug dose and plasma level is confounded by clinical characteristics, especially age and renal function.

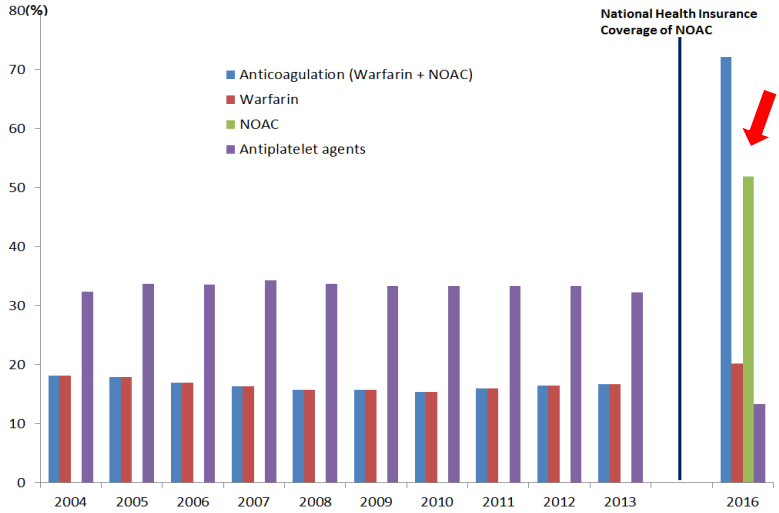


JAMA Cardiology 2017

Optimal NOAC dosage in Asian AF patients

CHA_2DS_2-VASc score and Anticoagulation Rate: The impact of the insurance of NOAC

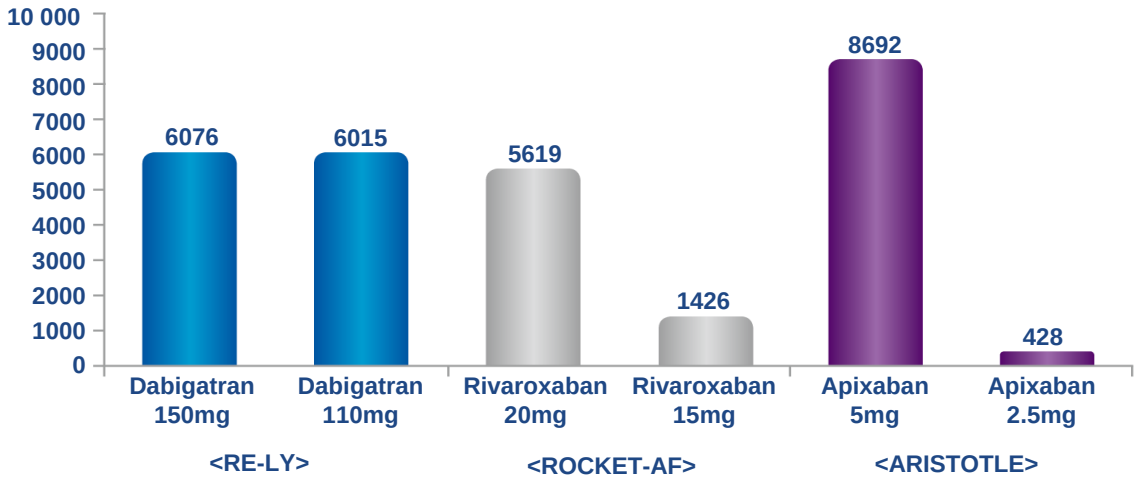




Lee H, Kim TH, et al. Korean Circ J 2017;47:56-64,
Kim TH, unpublished

Discrepancy between trials and clinical practice : Randomized controlled trials

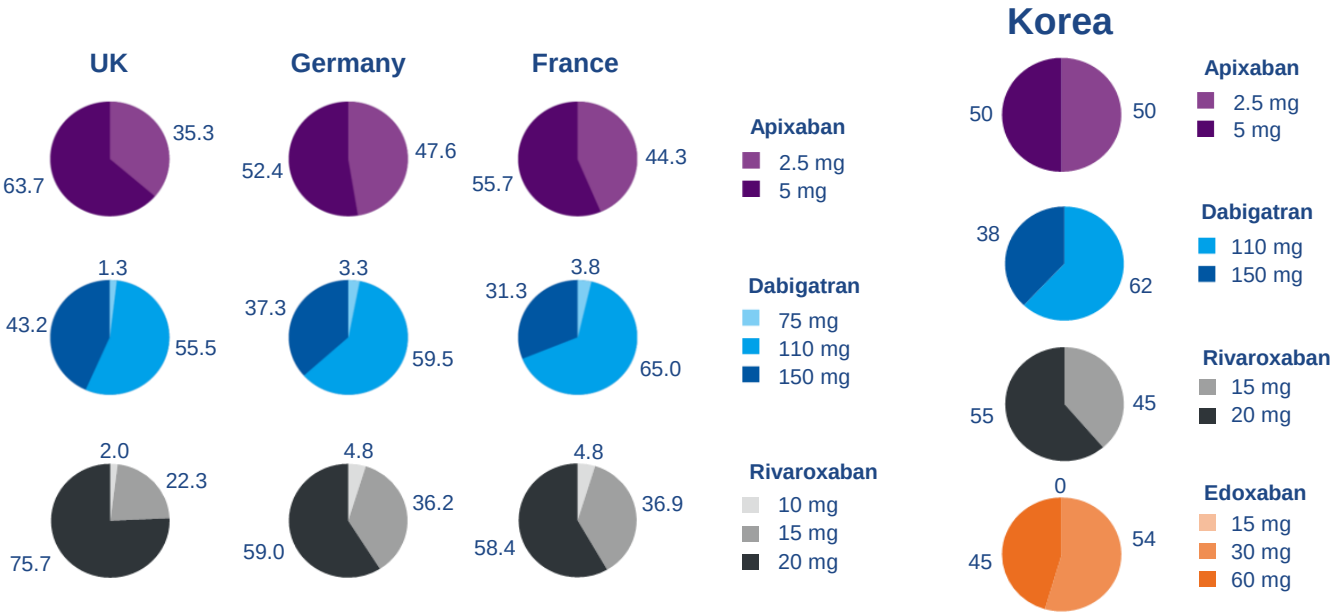
Academic centres



Connolly et al. N Engl J Med 2009;361:1139-51, Patel et al. N Engl J Med 2011;365:883-91, Granger et al. N Engl J Med 2011;365:981-92

Reduced dose NOAC usage in clinical practice

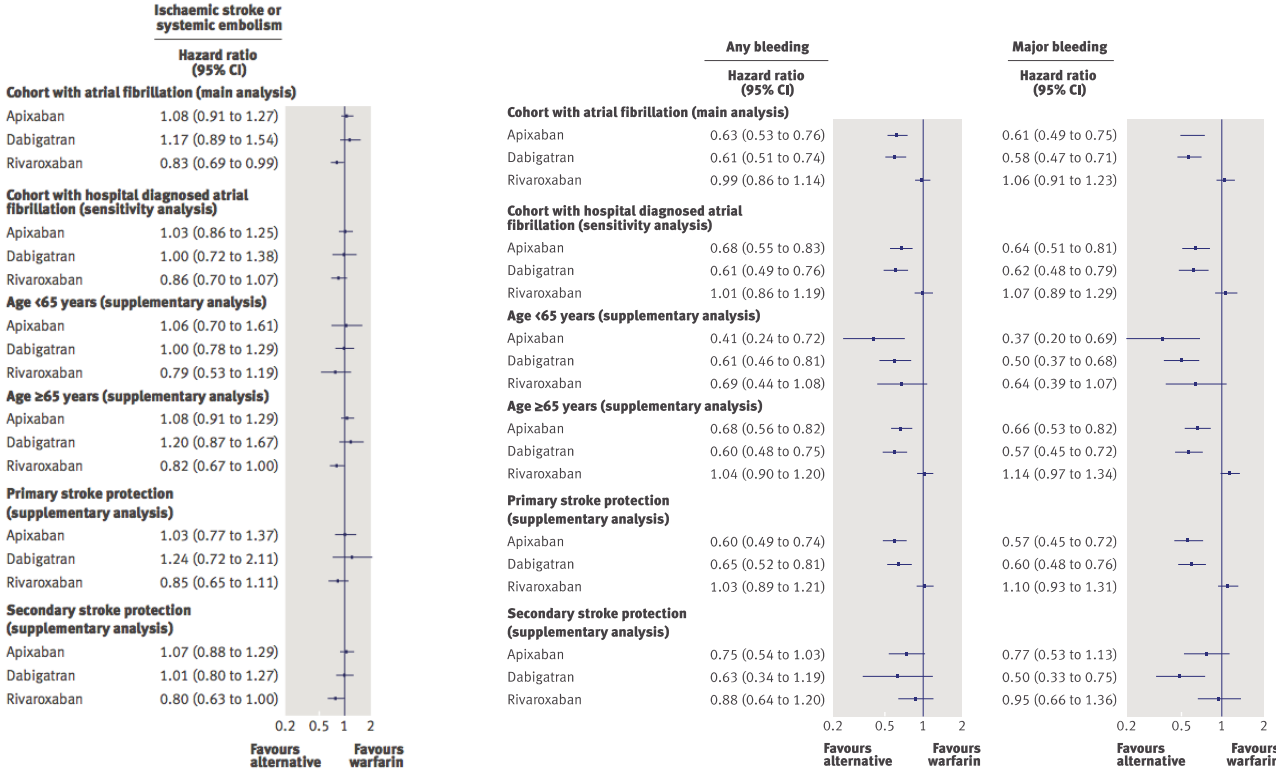
Academic centres



Fay et al. ESC Poster P2597; Aug 2016

Source:UBIST(Jan-Dec 2016)

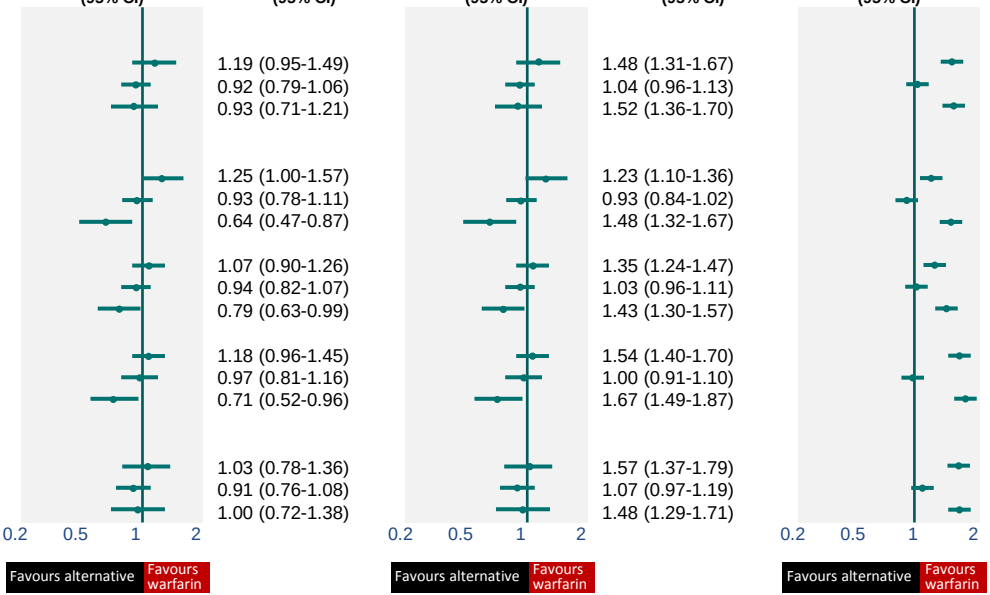
Effectiveness and safety of NOAC and warfarin in patients with AF: Danish cohort study



Larsen et al. BMJ 2016;353:i3189

Effectiveness and safety of reduced dose NOAC and warfarin in patients with AF: Danish cohort study

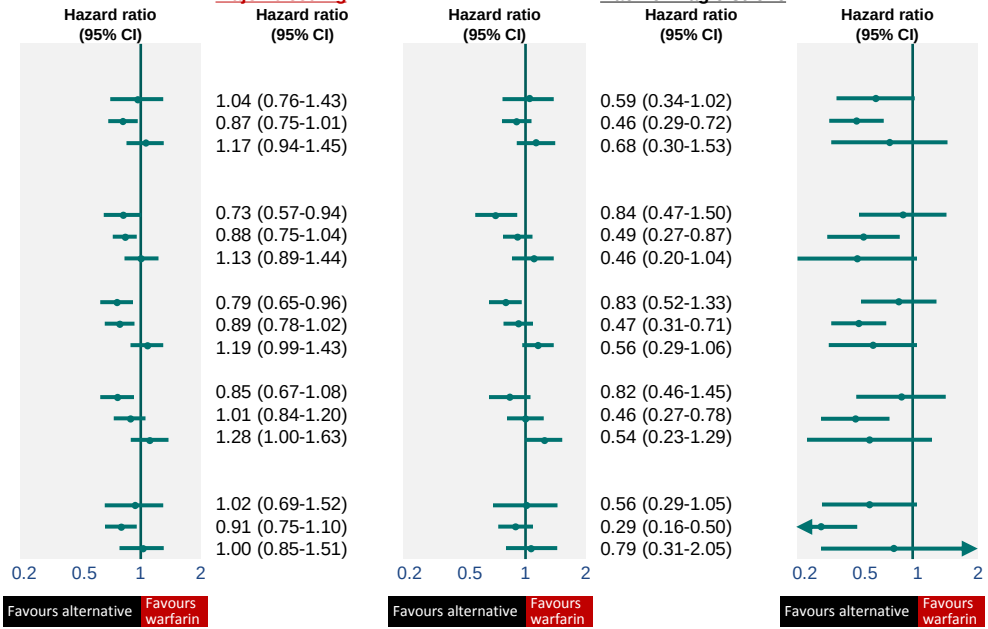
Study	Ischaemic stroke/SE Hazard ratio (95% CI)	Ischaemic stroke Hazard ratio (95% CI)	Death Hazard ratio (95% CI)
Entire cohort, analysis weighted for inverse probability of treatment			
Apixaban	**1.19 (0.95-1.49)**	1.19 (0.95-1.49)	1.48 (1.31-1.67)
Dabigatran	**0.89 (0.77-1.03)**	0.92 (0.79-1.06)	1.04 (0.96-1.13)
Rivaroxaban	**0.89 (0.69-1.16)**	0.93 (0.71-1.21)	1.52 (1.36-1.70)
Indication for reduced dose (additional analysis)			
Apixaban	1.24 (1.00-1.55)	1.25 (1.00-1.57)	1.23 (1.10-1.36)
Dabigatran	0.93 (0.79-1.10)	0.93 (0.78-1.11)	0.93 (0.84-1.02)
Rivaroxaban	0.63 (0.47-0.85)	0.64 (0.47-0.87)	1.48 (1.32-1.67)
Entire cohort (adjusted analysis)			
Apixaban	1.07 (0.91-1.26)	1.07 (0.90-1.26)	1.35 (1.24-1.47)
Dabigatran	0.94 (0.82-1.07)	0.94 (0.82-1.07)	1.03 (0.96-1.11)
Rivaroxaban	0.78 (0.63-0.97)	0.79 (0.63-0.99)	1.43 (1.30-1.57)
Age ≥80 (sensitivity analysis)			
Apixaban	1.15 (0.94-1.41)	1.18 (0.96-1.45)	1.54 (1.40-1.70)
Dabigatran	0.98 (0.82-1.17)	0.97 (0.81-1.16)	1.00 (0.91-1.10)
Rivaroxaban	0.71 (0.52-0.95)	0.71 (0.52-0.96)	1.67 (1.49-1.87)
Cohort with atrial fibrillation diagnosed in hospital (sensitivity analysis)			
Apixaban	1.06 (0.81-1.40)	1.03 (0.78-1.36)	1.57 (1.37-1.79)
Dabigatran	0.91 (0.77-1.07)	0.91 (0.76-1.08)	1.07 (0.97-1.19)
Rivaroxaban	0.98 (0.71-1.34)	1.00 (0.72-1.38)	1.48 (1.29-1.71)



Nielsen et al. BMJ 2017;356:j510

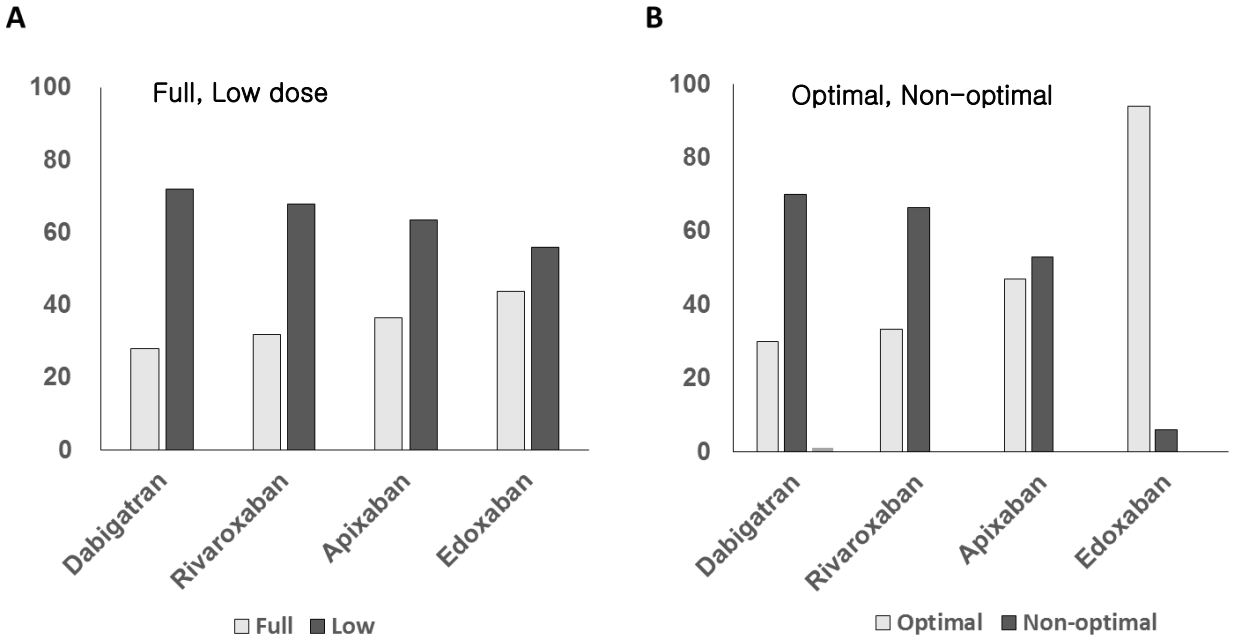
Effectiveness and safety of reduced dose NOAC and warfarin in patients with AF: Danish cohort study

Study	Any bleeding Hazard ratio (95% CI)	Major bleeding Hazard ratio (95% CI)	Haemorrhagie stroke Hazard ratio (95% CI)
Entire cohort, analysis weighted for inverse probability of treatment			
Apixaban	**0.96 (0.73-1.27)**	1.04 (0.76-1.43)	0.59 (0.34-1.02)
Dabigatran	**0.80 (0.70-0.92)**	0.87 (0.75-1.01)	0.46 (0.29-0.72)
Rivaroxaban	**1.06 (0.87-1.29)**	1.17 (0.94-1.45)	0.68 (0.30-1.53)
Indication for reduced dose (additional analysis)			
Apixaban	0.78 (0.61-0.99)	0.73 (0.57-0.94)	0.84 (0.47-1.50)
Dabigatran	0.81 (0.69-0.94)	0.88 (0.75-1.04)	0.49 (0.27-0.87)
Rivaroxaban	1.00 (0.81-1.24)	1.13 (0.89-1.44)	0.46 (0.20-1.04)
Entire cohort (adjusted analysis)			
Apixaban	0.76 (0.64-0.90)	0.79 (0.65-0.96)	0.83 (0.52-1.33)
Dabigatran	0.81 (0.72-0.91)	0.89 (0.78-1.02)	0.47 (0.31-0.71)
Rivaroxaban	1.07 (0.91-1.26)	1.19 (0.99-1.43)	0.56 (0.29-1.06)
Age ≥80 (sensitivity analysis)			
Apixaban	0.78 (0.63-0.96)	0.85 (0.67-1.08)	0.82 (0.46-1.45)
Dabigatran	0.89 (0.76-1.04)	1.01 (0.84-1.20)	0.46 (0.27-0.78)
Rivaroxaban	1.13 (0.91-1.40)	1.28 (1.00-1.63)	0.54 (0.23-1.29)
Cohort with atrial fibrillation diagnosed in hospital (sensitivity analysis)			
Apixaban	0.95 (0.68-1.33)	1.02 (0.69-1.52)	0.56 (0.29-1.05)
Dabigatran	0.81 (0.68-0.96)	0.91 (0.75-1.10)	0.29 (0.16-0.50)
Rivaroxaban	1.05 (0.81-1.36)	1.00 (0.85-1.51)	0.79 (0.31-2.05)



Nielsen et al. BMJ 2017;356:j510

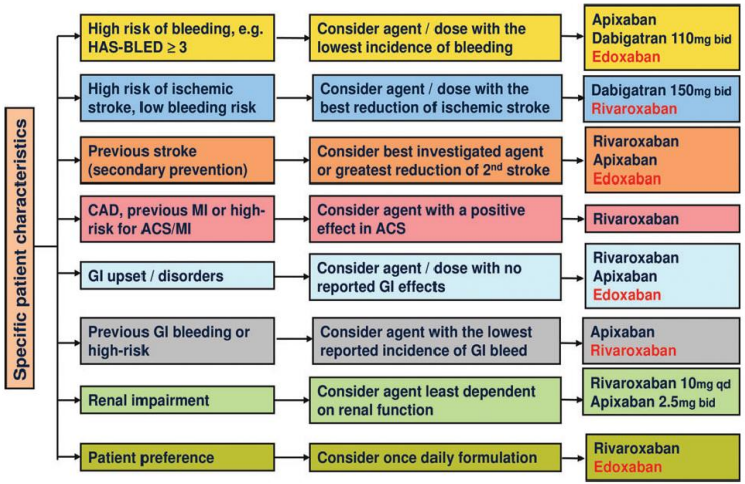
Choice of NOAC for Korean patients with nonvalvular AF: analysis of a multicenter registry (COmparision study of Drugs for symptom control and complication prEvention of Atrial Fibrillation; CODE-AF registry)



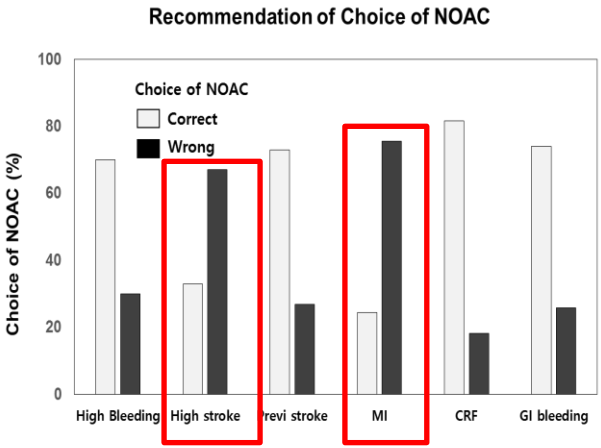
CODE-AF investigators, Sung M, et al. (Unpublished)

The Choice of NOAC

Choice of NOAC for Korean patients with nonvalvular AF: analysis of a multicenter registry (COmparision study of Drugs for symptom control and complication prEvention of Atrial Fibrillation; CODE-AF registry)



Okumura K, et al. Clin Cardiol 2017



CODE-AF investigators, Sung M, et al. (Unpublished)

Clinical outcome according to NOAC: Yonsei

Total (n=5702)	Warfarin (n =4990)	NOAC (n = 5702)	p-value	Dabigatran	Apixaban	Ribaroxaban
MACE, n (%)	63 (1.3)	29 (0.5)	<0.001	7 (0.4)	14 (0.7)	8 (0.5)
%/year	0.96	0.53	0.001	0.38	0.77	0.50
Stroke, n (%)	52 (1.0)	19 (0.3)	<0.001	5 (0.3)	8 (0.4)	6 (0.4)
%/year	0.79	0.35	<0.001	0.27	0.44	0.38
Systemic embolism	9 (0.2)	2 (0.04)	0.042	0 (0)	1 (0.1)	1 (0.1)
%/year	0.14	0.04	0.051	0	0.05	0.06
Major bleeding	96 (1.9)	41 (0.7)	<0.001	10 (0.6)	11 (0.6)	19 (1.2)
%/year	1.47	0.75	<0.001	0.54	0.60	1.20
GI system	50 (1.0)	25 (0.4)	0.001	5 (0.3)	9 (0.5)	10 (0.6)
%/year	0.77	0.46	0.013	0.27	0.49	0.63
CNS system	33 (0.7)	12 (0.2)	0.001	4 (0.2)	1 (0.1)	7 (0.4)
%/year	0.51	0.22	0.004	0.22	0.05	0.44
Follow up (median, day)	362 (100, 752)	286 (105, 550)	<0.001	298 (106, 580)	305 (107, 560)	314 (102, 570)

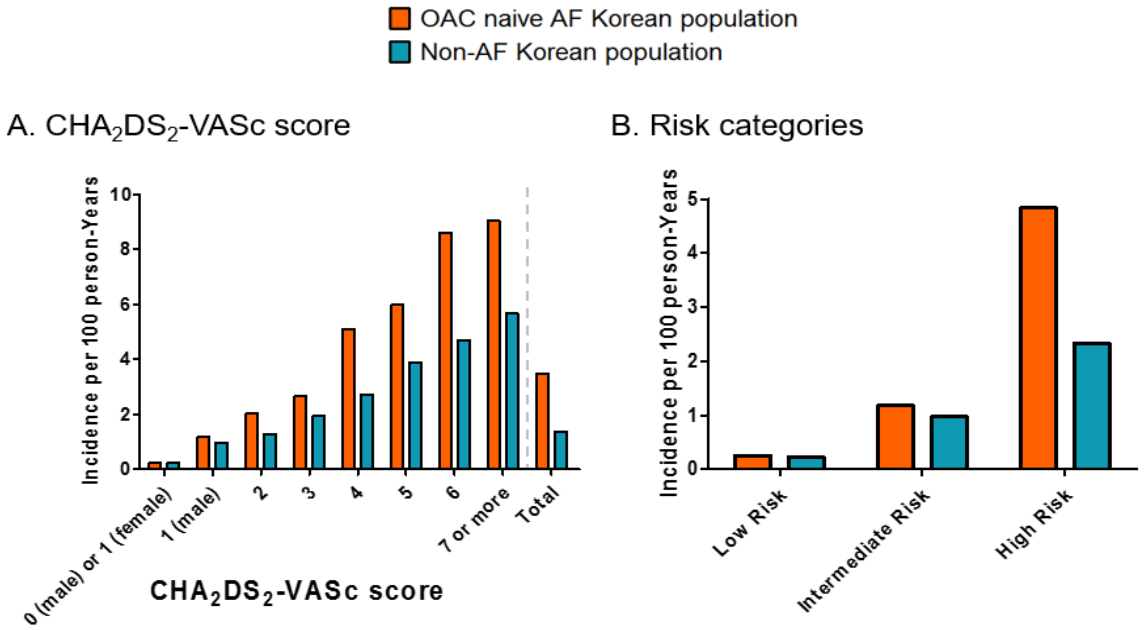
Kim K, et al. unpublished

Conclusion

- **NOAC은 RCT 결과 아시아인에서 효과적이다.**
- **아시아 국가간 뇌졸중률의 차이가 존재할 수 있다.**
- **아시아인에서 적절한 NOAC 용량에 대한 추가 자료가 필요하다.**
- **Real world data에서 NOAC의 효과에 대한 추가 자료가 필요하다.**

경청해주셔서 감사합니다!

Incidence rates of ischemic stroke/systemic embolism according to each CHA_2DS_2-VASc scores (A) and risk categories as stratified by low (score 0 or 1 in female), intermediate (1 in male), and high risk (≥2) (B).



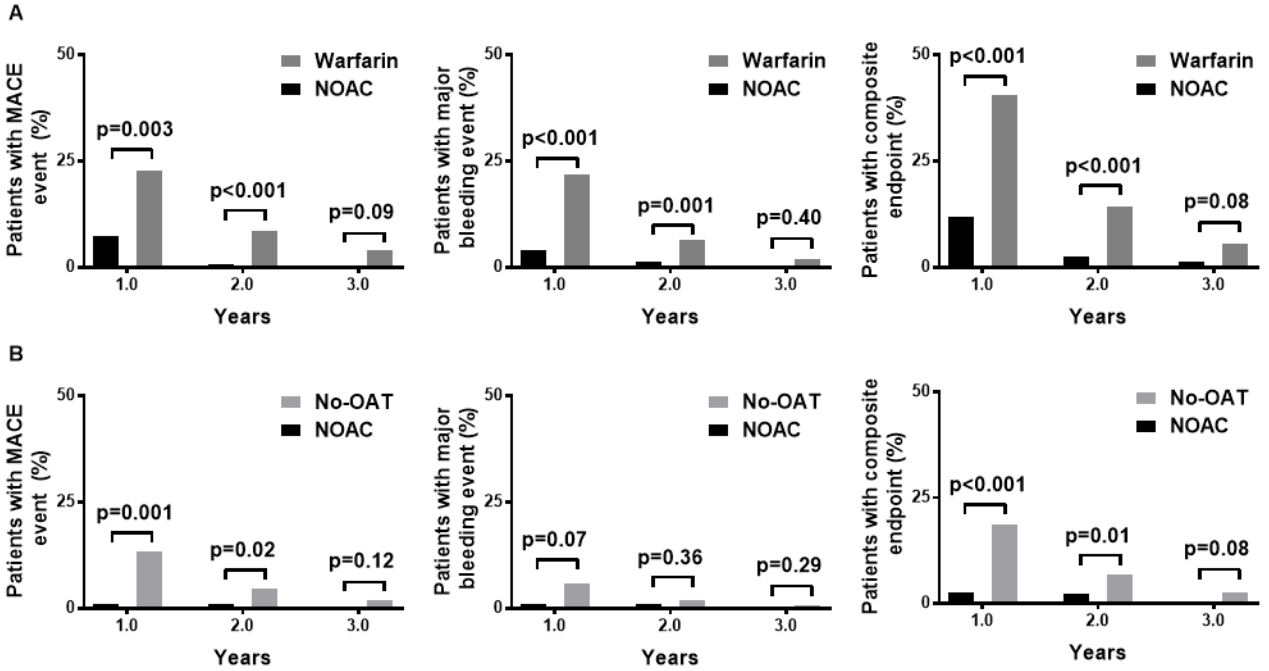
Kim TH, Yang PS, Joung B, Lip G et al. Stroke 2017 (In press)

Clinical outcome according to NOAC: Yonsei

Total (n=5702)	Dabigatran (n=1,772)	Apixaban (n=1,964)	Ribaroxaban (n=1,599)	Edoxaban (n=367)	p-value
MACE, n (%)	7 (0.4)	14 (0.7)	8 (0.5)	0 (0)	0.267
%/year	0.38	0.77	0.50	0	0.309
Stroke, n (%)	5 (0.3)	8 (0.4)	6 (0.4)	0 (0)	0.620
%/year	0.27	0.44	0.38	0	0.677
Systemic embolism	0 (0)	1 (0.1)	1 (0.1)	0 (0)	0.745
%/year	0	0.05	0.06	0	0.771
Major bleeding	10 (0.6)	11 (0.6)	19 (1.2)	1 (0.3)	0.064
%/year	0.54	0.60	1.20	0.50	0.103
Gastrointestinal system	5 (0.3)	9 (0.5)	10 (0.6)	1 (0.3)	0.472
%/year	0.27	0.49	0.63	0.50	0.484
Central nervous system	4 (0.2)	1 (0.1)	7 (0.4)	0 (0)	0.069
%/year	0.22	0.05	0.44	0	0.081
Follow up (median, day)	298 (106, 580)	305 (107, 560)	314 (102, 570)	193 (90, 290)	<0.001

Kim K, et al. unpublished

Figure 5


A
Patients with MACE event (%)
Warfarin
NOAC
p=0.003
p<0.001
p=0.09
Years
Patients with major bleeding event (%)
p<0.001
p=0.001
p=0.40
Patients with composite endpoint (%)
p<0.001
p<0.001
p=0.08
B
No-OAT
p=0.001
p=0.02
p=0.12
p=0.07
p=0.36
p=0.29
p<0.001
p=0.01
p=0.08
1.0
2.0
3.0
0
25
50

World-Wide AF Cohorts and RCTs, by Region, Publication Year,
Number of Subjects off Anticoagulation, and Annual Stroke Rate

Study Name	Midpoint Year	Subjects	Annual Stroke Rate (95% CI)
TOTAL NORTH AMERICAN COHORTS		46,574	1.30 (1.24 – 1.26)
TOTAL EUROPEAN COHORTs		254,576	4.14 (4.07 – 4.21)
TOTAL ASIAN COHORTS		204,469	3.64 (3.60 – 3.69)
TOTAL MIDDLE EASTERN COHORTS		38,234	3.00 (2.83 – 3.19)
TOTAL PROSPECTIVE COHORTS		50,391	1.22 (1.17 – 1.28)
TOTAL RETROSPECTIVE COHORTS		493,462	3.80 (3.76 – 3.83)
TOTAL RANDOMIZED CONTROLLED TRIALS		7,578	3.45 (3.14 – 3.79)

Quinn et al. Circulation 2017