

MASTER CLASS Web Symposium  
**Controversies in Anticoagulation :  
Optimizing Outcome for GI Bleeding Risk**



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박 광 열

Patients with atrial fibrillation

NOAC trials

GI bleeding in trials of NOAC

Summary

## Cardioembolic stroke

- ▶ 비판막성 심방세동
- ▶ 인공판막
- ▶ 좌심실 혈전증
- ▶ 점액종
- ▶ 감염성 심뇌막염

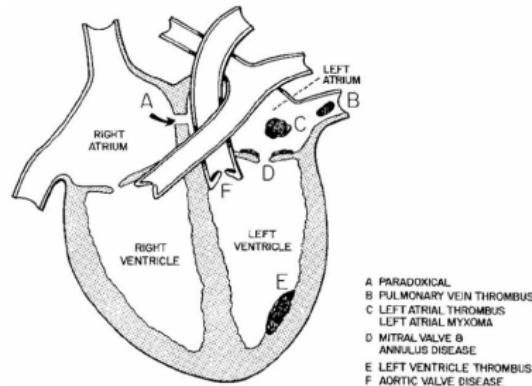
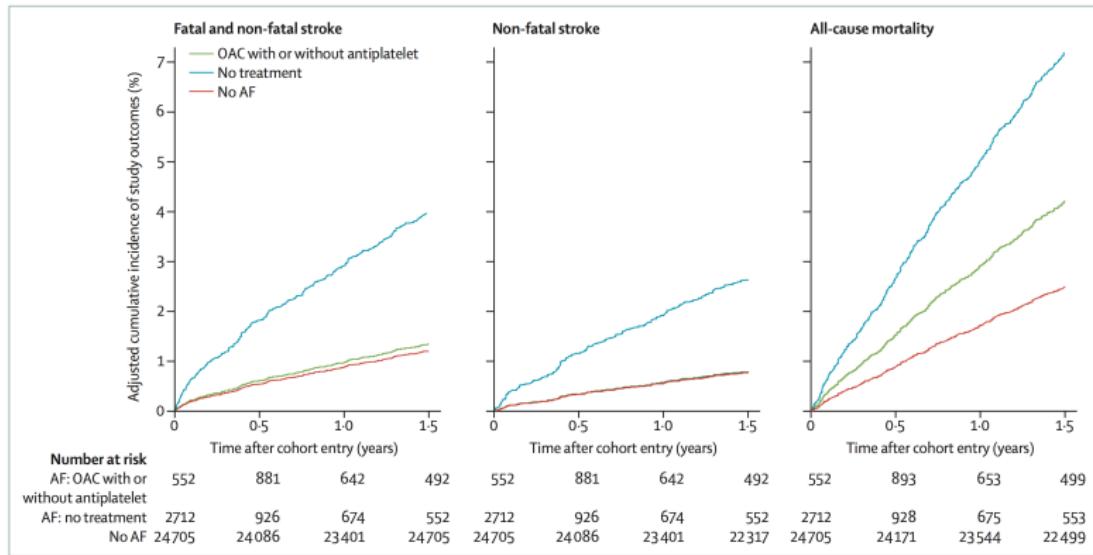
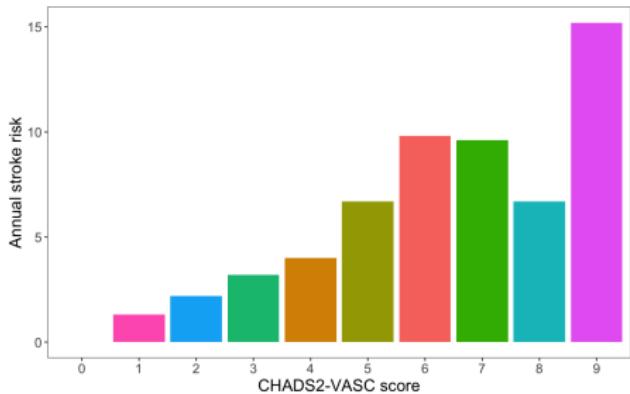


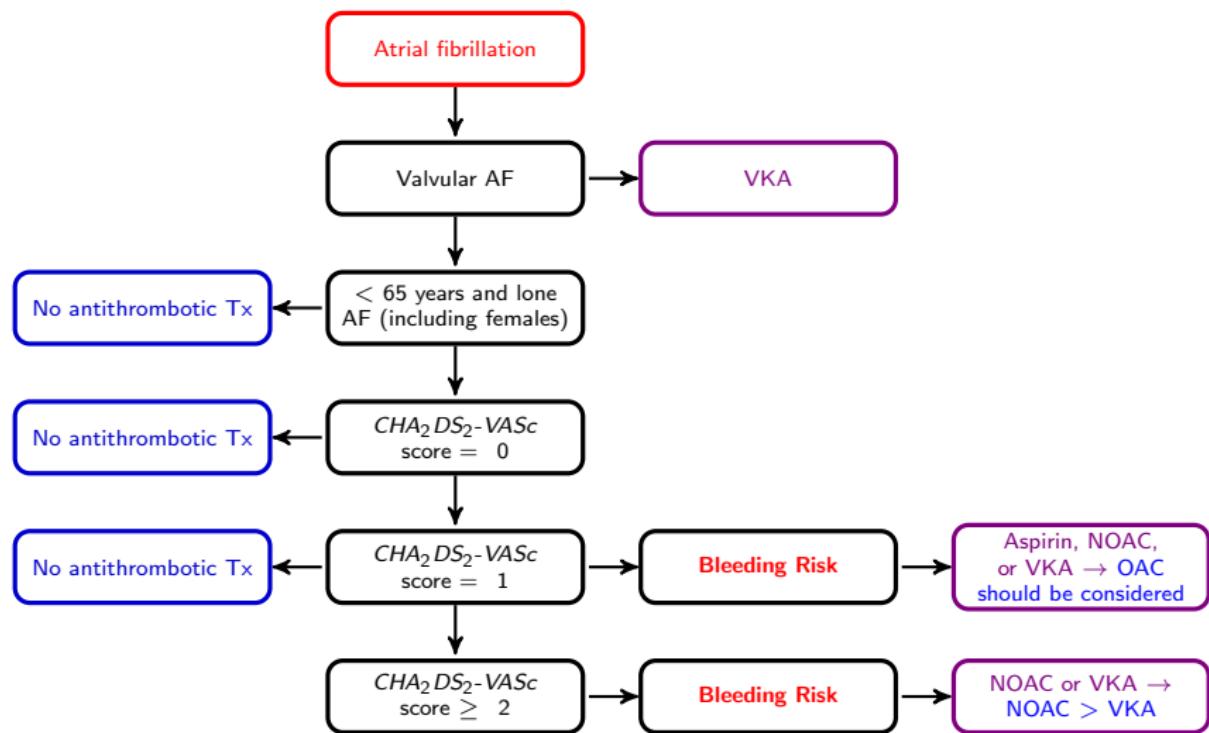
Figure 1. Cardiac causes of stroke (Adapted from Barnett et al)

**Figure 2: Effect of treatment on incidentally detected atrial fibrillation**AF=atrial fibrillation. OAC=oral anticoagulant. Reproduced with permission from Freedman and colleagues.<sup>21</sup>

# Thromboembolic risk of AF

<i>CHA<sub>2</sub>DS<sub>2</sub>-VASc</i> criteria	Score
CHF	1
Hypertension	1
Age $\geq$ 75 years	2
Diabetes mellitus	1
Stroke or TIA	2
Vascular disease	1
Age 65-74 years	1
Sex category (female)	1





# NOAC trials

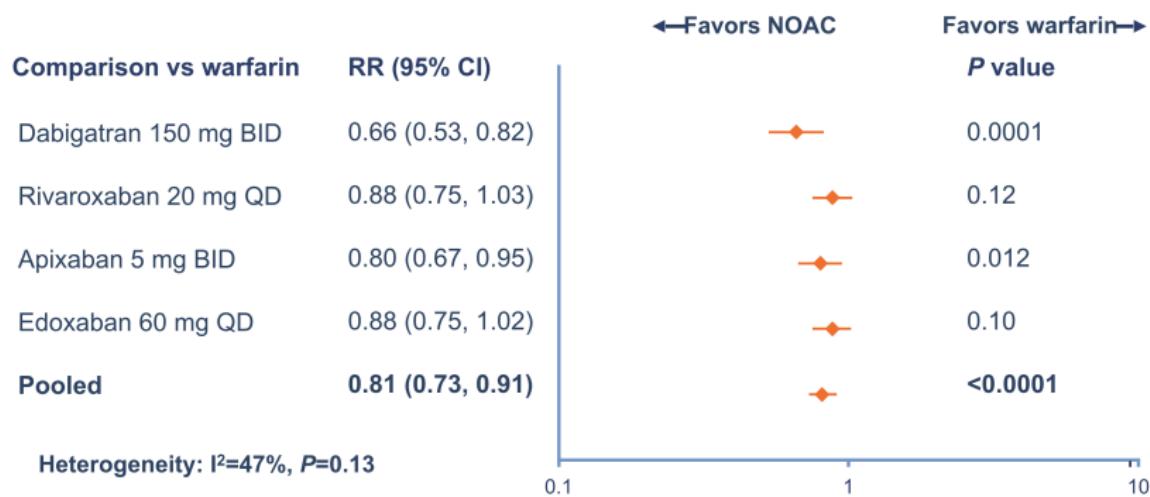
	RE-LY	ROCKET AF	ARISTOTLE	ENGAGE AF-TIMI 48
Number of Pts	18,113	14,264	18,201	21,105
Design	Blinded (dabigatran) Open-label (warfarin)	Double-blind, double-dummy	Double-blind, double-dummy	Double-blind, double-dummy
Treatments	<ul style="list-style-type: none"> <li>• Dabigatran: 110 mg/150 mg BID</li> <li>• Warfarin (INR target: 2–3)</li> </ul>	<ul style="list-style-type: none"> <li>• Rivaroxaban 20 mg OD 15 mg OD in selected patients<sup>†</sup></li> <li>• Warfarin (INR target: 2–3)</li> </ul>	<ul style="list-style-type: none"> <li>• Apixaban 5 mg BID 2.5mg BID in selected patients*</li> <li>• Warfarin (INR target: 2–3)</li> </ul>	<ul style="list-style-type: none"> <li>• Edoxaban 60 mg OD 30 mg OD in selected patients<sup>‡</sup></li> <li>• Warfarin (INR target: 2–3)</li> </ul>

<sup>†</sup>Patients with CrCl between 30–49 mL/min;

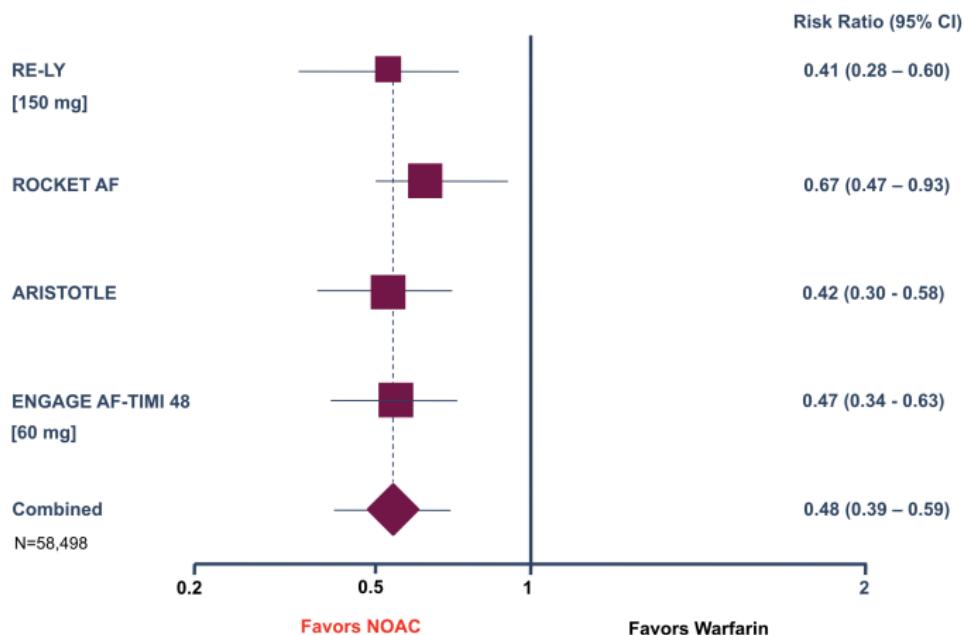
<sup>\*</sup>Patients with ≥2 of the following criteria: age ≥80 years, body weight ≤60 kg, or a serum creatinine level ≥1.5 mg/dL (133 µmol/L). Note: Per the apixaban SmPC, patients with the exclusive criterion of severe renal impairment (CrCl 15–29 mL/min) should also receive the lower dose of apixaban 2.5 mg BD. This criterion differs from the trial conduct.

<sup>‡</sup>Patients with any of the following: CrCl 30–50 mL/min, body weight ≤60 kg or concomitant use of specific P-gp inhibitors. Per the edoxaban SmPC, the recommended dose is 60 mg OD. A dose of 30 mg OD is recommended in selected patients. Please refer to the SmPC for further details.

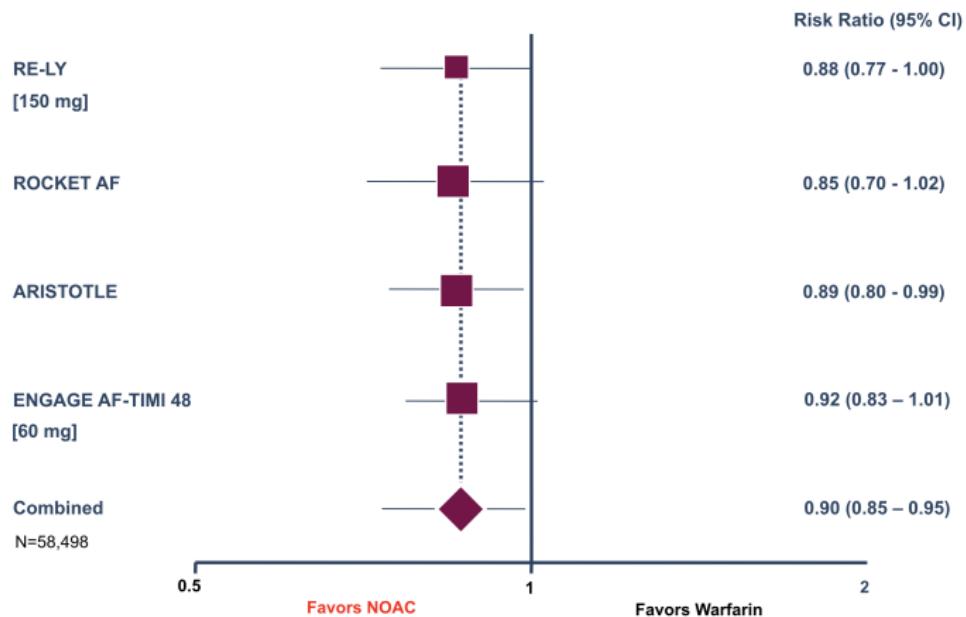
## NOAC trials: Systemic embolism/Stroke



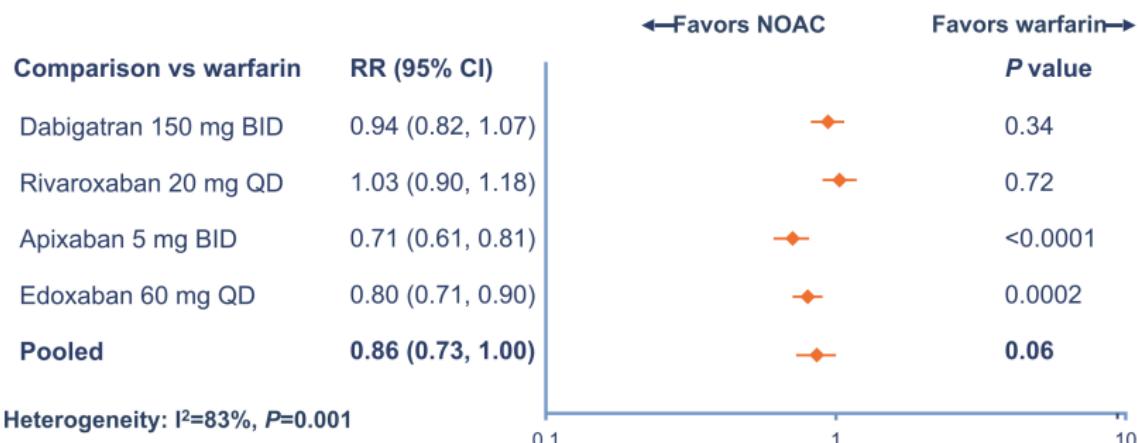
## NOAC trials: ICH



## NOAC trials: total death

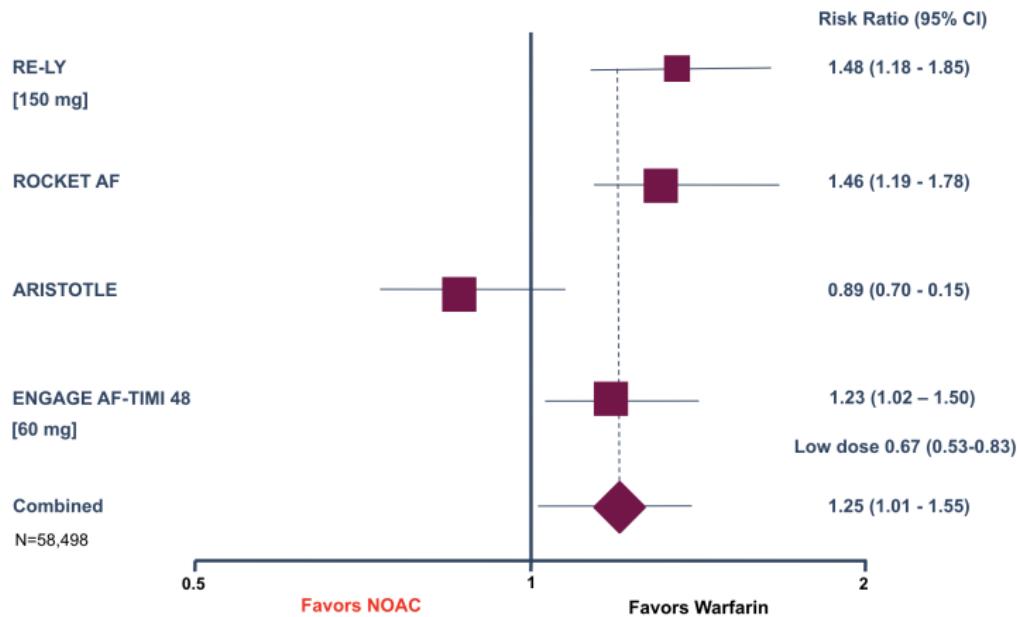


## NOAC trials: Major bleeding



High  $I^2$  percentage for major bleeding indicates significant amount of heterogeneity across trials.

## NOAC trials: GI bleeding



**Table:** Exclusion criteria due to hemorrhagic risk

	RE-LY	ROCKET	ARISTOTLE	ENGAGE
GI bleeding	Within 1y	Within 6m		Within 1y
GI ulcer	Within 1m	Within 6m		Within 1y
History of bleeding	Exclude	Exclude	Exclude	Exclude
Chronic hemorrhagic dis	Exclude	Exclude		Exclude
Intracranial neoplasm		Exclude		
Intracranial aneurysm		Exclude		
Major surgery or trauma	Exclude	Exclude	Exclude	Exclude
Thrombocytopenia or anemia	Exclude	Exclude	Exclude	Exclude
Uncontrolled HTN	Exclude	Exclude	Exclude	Exclude

## GI bleeding during anticoagulation

- ▶ Warfarin increases the risk of major GI bleeding approximately three-fold compared with placebo.
- ▶ The addition of anti-platelet agents to warfarin increases the risk of major GI bleeding approximately two-fold (compared with warfarin alone).
- ▶ Compared with warfarin, rivaroxaban and dabigatran 150, edoxaban 60mg increase the risk of major GI bleeding approximately 1.5 fold.
- ▶ Compared with warfarin, apixaban and dabigatran 110mg does not significantly alter the risk of major GI bleeding.

## GI bleeding on NOAC: Proposed pathophysiology

Non-absorbed, active anticoagulant drug within the GI tract lumen promotes GI bleeding

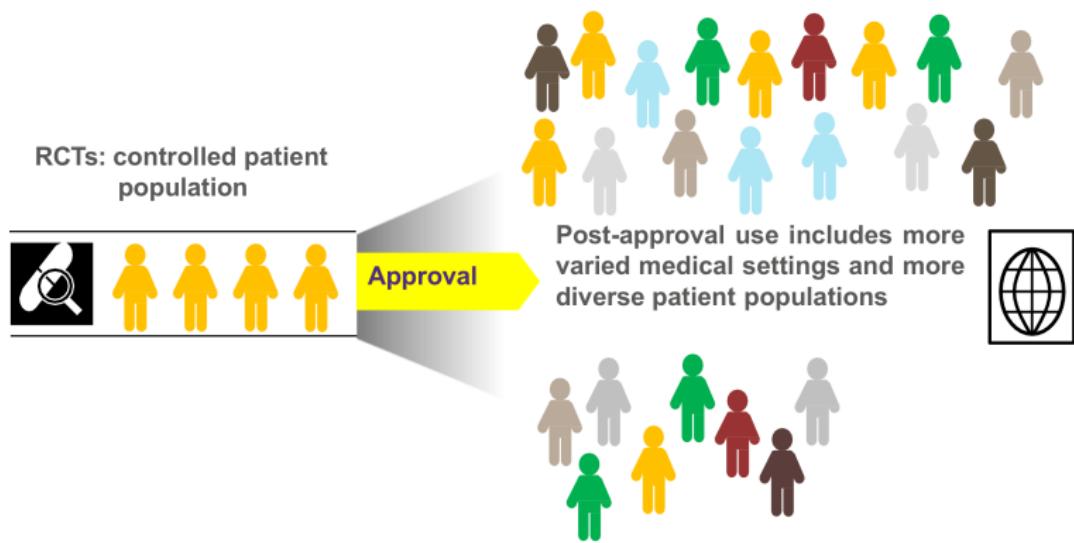
TABLE 2. Comparison of the absorption and elimination of warfarin, apixaban, dabigatran, and rivaroxaban

	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

## GI bleeding on NOAC: Proposed pathophysiology

- ▶ Major GI bleeding associated with VKAs, aspirin, and NSAIDs: preponderantly from the upper GI tract.
- ▶ Major GI bleeding associated with dabigatran: In RE-LY, 47 % of patients taking dabigatran have experienced lower GI bleeding. (25% in warfarin group)
- ▶ Rivaroxaban is dosed once daily, thereby leading to higher peak-to-trough anticoagulant activity than apixaban, which is dosed twice daily

## Randomized Clinical Trial Versus Real-World Evidence



## Eligibility and Preference of New Oral Anticoagulants in Patients With Atrial Fibrillation

### Comparison Between Patients With Versus Without Stroke

Chang Hyo Yoon, MD; Yoon Kyung Park, MD; Suk Jae Kim, MD; Mi-ji Lee, MD;  
Sookkyung Ryoo, MD; Gyeong-Moon Kim, MD, PD; Chin-Sang Chung, MD, PhD;  
Kwang Ho Lee, MD, PhD; June Soo Kim, MD, PhD; Oh Young Bang, MD, PhD

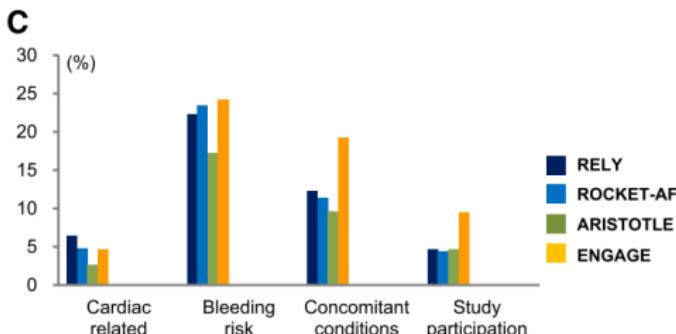
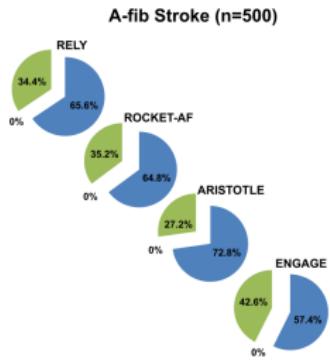
**Background and Purpose**—Recent randomized clinical trials (RCTs) have evaluated the benefit of new oral anticoagulants in reducing the risk of vascular events and bleeding complications in patients with atrial fibrillation (AF). However, abundant and strict enrollment criteria may limit the validity and applicability of results of RCTs to clinical practice. We estimated the eligibility for participation in RCTs of an unselected group of patients with AF. In addition, we compared features favoring new oral anticoagulant use between patients with versus without stroke. Randomized Evaluation of Long-Term Anticoagulation Therapy

**Methods**—We applied enrollment criteria of 4 RCTs (RE-LY, ROCKET-AF, ARISTOTLE, and ENGAGE-AF-TIMI 48) to 695 patients with AF taking warfarin, prospectively and consecutively collected at a university medical center; 500 patients with and 195 patients without stroke. Time in therapeutic range and bleeding risk scheme (anticoagulation and risk factors in atrial fibrillation) were also measured.

**Results**—The proportions of patients fulfilling the trial enrollment criteria varied, ranging from 39% to 72.8%, depending on the differences in indications/contraindications among studies and presence/absence of stroke. The main reasons for ineligibility for RCTs were hemorrhagic risk (anticoagulation and risk factors in atrial fibrillation [ATRIA] score) (10.8%–40.5%) and planned cardioversion (5.1%–7.7%) for nonstroke patients, and a low creatinine clearance (5.6%–9.2%) and higher risk of bleeding (15.2%–20.8%) for patients with stroke. When compared with nonstroke patients, patients with stroke showed a lower time in therapeutic range (54.4±42.8% versus 65.4±34.9%, especially with severe disability) and a high hemorrhagic risk (ATRIA score) (3.06±2.30 versus 2.18±2.16) ( $P<0.05$  in both cases).

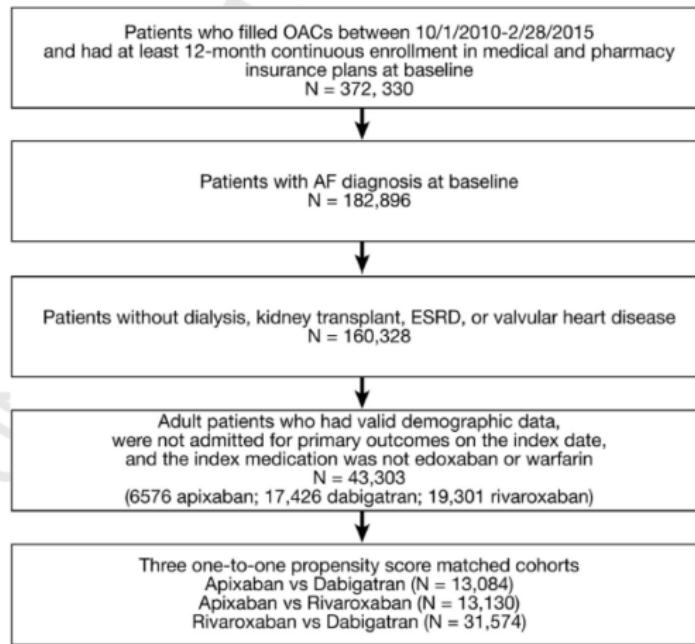
**Conclusions**—Patients enrolled in RCTs are partly representative of patients with AF in clinical practice. When time in therapeutic range and bleeding tendency with warfarin use were considered, the use of new oral anticoagulants was preferred in patients with stroke than in nonstroke patients, but they were more likely to be excluded in RCTs. (*Stroke*. 2014;45:2983–2988.)

- Eligible
- Not indicated
- Contraindicated



The main reasons for ineligibility for RCTs were a low creatinine clearance (5.6%-9.2%) and higher risk of bleeding (15.2%-20.8%) for patients with stroke.

## Gastrointestinal Safety of Direct Oral Anticoagulants: A Large Population-Based Study



## GI Bleeding of 3 NOACs

Table 4. Stratified Analysis in Propensity Score Matched Rivaroxaban vs Dabigatran Users

Variable	Rivaroxaban (n= 15,787)		Dabigatran (n= 15,787)		Rivaroxaban vs dabigatran (n= 31,574)	
	Events, n	IR	Events, n	IR	HR (95% CI)	P for interaction
Overall	222	2.74	215	2.02	1.20 (1.00 – 1.45)	
Age						.10
18 - 64 y	26	1.05	14	0.46	2.03* (1.06 – 3.90)	
65 - 74 y	66	2.54	54	1.56	1.44* (1.00 – 2.06)	
≥ 75 y	130	4.29	147	3.54	1.06 (0.84 – 1.34)	

NOTE. P value in the table is for interaction: \*p &lt; .05.

IR, incidence rate per 100 person-years.

Table 5. Stratified Analysis in Propensity Score Matched Apixaban vs Dabigatran Users

Variable	Apixaban (n= 6,542)		Dabigatran (n= 6,542)		Apixaban vs dabigatran (n= 13,084)	
	Events, n	IR	Events, n	IR	HR (95% CI)	P for interaction
Overall	33	1.38	121	2.73	0.39*** (0.27 – 0.58)	
Age						.54
18 - 64 y	2	0.34	7	0.73	0.38 (0.08 – 1.84)	
65 - 74 y	5	0.69	29	2.12	0.25* (0.10 – 0.65)	
≥ 75 y	26	2.43	85	4.06	0.45*** (0.29 – 0.71)	

NOTE. P value in the table is for interaction: \*\*p &lt; .01; \*\*\*p &lt; .001 indicates significance for the HR.

IR, incidence rate per 100 person-years.

Table 6. Stratified Analysis in Propensity Score-Matched Apixaban vs Rivaroxaban Users

Variable	Apixaban (n= 6,565)		Rivaroxaban (n= 6,565)		Apixaban vs rivaroxaban (n= 13,130)	
	Events, n	IR	Events, n	IR	HR (95% CI)	P for interaction
Overall	32	1.34	116	3.54	0.33*** (0.22 – 0.49)	
Age						.36
18 - 64 y	2	0.34	6	0.81	0.38 (0.08 – 1.89)	
65 - 74 y	5	0.69	32	3.24	0.18*** (0.07 – 0.47)	
≥ 75 y	25	2.32	78	5.05	0.39*** (0.25 – 0.61)	

NOTE. P value in the table is for interaction: \*\*\*p &lt; .001 indicates significance for the HR.

IR, incidence rate per 100 person-years.

Direct Head-to-Head trials among NOACs do not exist. Conclusions about the relative efficacy and safety of any the NOACs cannot be drawn from these data

Research

JAMA Cardiology | Original Investigation

# Effectiveness and Safety of Standard-Dose Nonvitamin K Antagonist Oral Anticoagulants and Warfarin Among Patients With Atrial Fibrillation With a Single Stroke Risk Factor A Nationwide Cohort Study

Gregory Y. H. Lip, MD; Flemming Skjøth, MSc, PhD; Peter Brønnum Nielsen, MSc, PhD; Jette Nordstrøm Kjældgaard, BSc; Torben Bjerregaard Larsen, MD, PhD

+ Supplemental content

**IMPORTANCE** The randomized clinical trials comparing nonvitamin K antagonist oral anticoagulants (NOACs) vs warfarin largely focused on recruiting high-risk patients with atrial fibrillation with more than 2 stroke risk factors, with only the trials testing dabigatran or apixaban including few patients with 1 stroke risk factor. Despite this, regulatory approvals of all NOACs have been based on stroke prevention for patients with atrial fibrillation with 1 or more stroke risk factors.

# Optimizing Outcome for GI Bleeding Risk

## └ GI bleeding in trials of NOAC

**Table 1. Participant Characteristics at Treatment Initiation According to Treatment**

Characteristic	No. (%)	Apixaban	Dabigatran	Rivaroxaban	Warfarin	All
No. of patients	1470	3272	1604	7674	14 020	
Women	589 (40.1)	1160 (35.5)	609 (38.0)	2793 (36.4)	5151 (36.7)	
Age, median (IQR)	67.4 (62.5-70.9)	66.2 (61.3-69.8)	67.2 (62.4-70.7)	66.2 (60.5-70.4)	66.5 (61.1-70.4)	
Heart failure or LVD	31 (2.1)	90 (2.8)	17 (1.1)	232 (3.0)	370 (2.6)	
Hypertension	411 (28.0)	1134 (34.7)	471 (29.4)	2430 (31.7)	4446 (31.7)	
65≤ age <75 y	963 (65.5)	1884 (57.6)	1037 (64.7)	4435 (57.8)	8319 (59.3)	
Diabetes	44 (3.0)	96 (2.9)	41 (2.6)	271 (3.5)	452 (3.2)	
Vascular disease	21 (1.4)	68 (2.1)	38 (2.4)	306 (4.0)	433 (3.1)	
Prior AF diagnosis	1042 (70.9)	2300 (70.3)	1037 (64.4)	4114 (53.6)	8489 (60.5)	
Cancer	206 (14.0)	345 (10.5)	217 (13.5)	1079 (14.1)	1847 (13.2)	
HAS-BLED score, mean (SD) <sup>a</sup>	1.5 (0.6)	1.5 (0.6)	1.5 (0.6)	1.5 (0.7)	1.5 (0.7)	
Hepatic dysfunction	<0.3 (<5)	<0.1 (<5)	0.3 (5)	0.4 (29)	0.3 (39)	
Alcohol	38 (2.6)	83 (2.5)	55 (3.4)	264 (3.4)	440 (3.1)	
CPD	128 (8.7)	237 (7.2)	115 (7.2)	665 (8.7)	1145 (8.2)	
Previous bleeding	128 (8.6)	224 (6.8)	128 (8.0)	521 (6.8)	999 (7.1)	
Aspirin	342 (23.3)	960 (29.3)	437 (27.2)	2316 (30.2)	4055 (28.9)	
Ticagralor	<0.3 (<5)	0.4 (12)	<0.2 (<5)	0.4 (31)	0.3 (49)	
Clopidogrel	28 (1.9)	55 (1.7)	34 (2.1)	181 (2.4)	298 (2.1)	
β-blockers	914 (62.2)	2175 (66.5)	931 (58.0)	4408 (57.4)	8428 (60.1)	
NSAIDs	339 (23.1)	806 (24.6)	386 (24.1)	2053 (26.8)	3584 (25.6)	
Statins	359 (24.4)	817 (25.0)	387 (24.1)	2053 (26.8)	3616 (25.8)	
ACE/ARB inhibitors	396 (26.8)	1000 (30.6)	430 (26.8)	2118 (26.8)	3944 (28.1)	
Loop diuretics	97 (6.6)	200 (6.1)	94 (5.9)	680 (8.9)	1071 (7.6)	

# Optimizing Outcome for GI Bleeding Risk

## └ GI bleeding in trials of NOAC

**Table 3. Number of Events and Crude and Weighted Event Rates at 1-Year Follow-up According to Treatment for Main End Points and Selected Study Cohorts<sup>a</sup>**

End Point/Cohort	Apixaban			Dabigatran			Rivaroxaban			Warfarin		
	Events	Crude	Weighted	Events	Crude	Weighted	Events	Crude	Weighted	Events	Crude	Weighted
<b>Ischemic Stroke/SE</b>												
Main analysis cohort	10	0.86	0.83	22	0.70	0.65	14	1.09	1.20	57	0.79	0.81
Cohort hospitalized with AF	9	1.01	1.07	17	0.69	0.66	11	1.25	1.29	41	0.94	0.96
Low mortality cohort	9	1.00	1.00	19	0.75	0.79	10	0.97	0.92	38	0.68	0.70
<b>All-Cause Death</b>												
Main analysis cohort	19	1.62	1.52	51	1.62	1.84	26	2.01	1.67	249	3.45	3.11
Cohort hospitalized with AF	14	1.56	1.40	36	1.46	1.60	15	1.69	1.50	107	2.44	2.33
Low mortality cohort	11	1.21	0.96	26	1.02	1.14	6	0.58	0.50	69	1.24	1.24
<b>Any Bleeding</b>												
Main analysis cohort	8	0.68	0.57	23	0.74	0.73	17	1.33	1.38	109	1.52	1.53
Cohort hospitalized with AF	8	0.90	0.79	18	0.74	0.72	12	1.36	1.24	69	1.58	1.59
Low mortality cohort	5	0.55	0.44	15	0.59	0.58	11	1.06	1.02	70	1.26	1.32

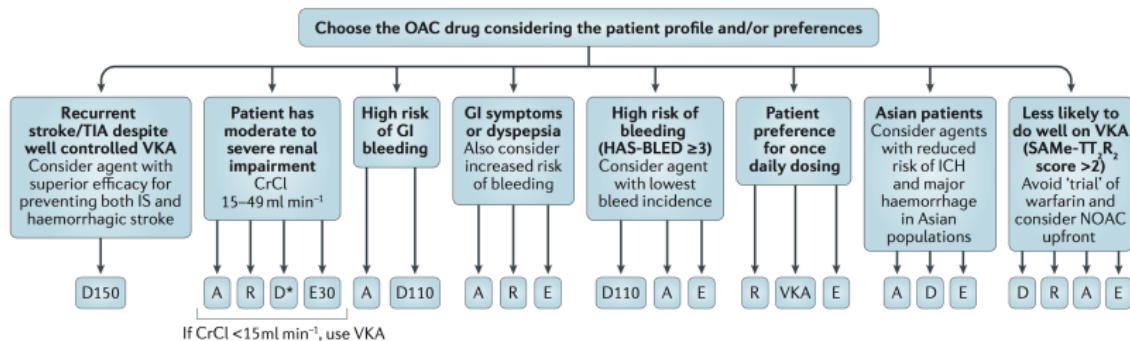
Abbreviations: AF, atrial fibrillation; IPTW, inverse probability of treatment weighted; SE, systemic embolism.

<sup>a</sup> Crude rates are events divided by person time per 100 years; weighted rates are based on IPTW population and express population mean treatment rates per 100 years.

**Table 4: NOACs and GI bleeding: prevention strategies.**

- |  |
|--|
| 1. Confirm that NOAC indication is appropriate and that there are no absolute contra-indications to NOAC administration.   |
| 2. Confirm that NOAC dosage is appropriate (e.g. dose dabigatran as indicated by creatinine clearance).  |
| 3. Screen all patients for presence of on-going GI bleeding by history (history of recent melena or rectal bleeding) and physical exam (digital rectal exam). Consider screening with laboratory testing (faecal occult blood testing, haemoglobin evaluation and evaluation of iron stores). If GI bleeding is suggested, consider GI investigation prior to initiating NOAC treatment. |
| 4. Assess for history of previous GI bleeding and consider diagnostic interventions (e.g. endoscopy) or therapeutic interventions (e.g. concomitant administration of a PPI) where indicated.  |
| 5. Assess for co-administration of drugs such as anti-platelet agents or NSAIDs which increase the risk of NOAC related GI bleeding.   |
| 6. If patient is concurrently taking anti-platelet medication, weigh the risks, benefits, and alternatives of continuing NOAC plus anti-platelet agent.  |
| 7. If patient is taking chronic NSAIDs, consider alternative therapies and/or co-administration of a gastroprotective agent such as a PPI.   |
| 8. Consider non-medication risk factors such as alcohol intake, and encourage risk factor modification.  |
| 9. Assess creatinine clearance and institute renal protective measures as indicated (especially in patients receiving dabigatran).   |
| 10. Counsel the patient regarding the potential for increased risk of GI bleeding in the setting of dehydration, concomitant illness, or concomitant medication use, and the recommended measures in these settings (e.g. seeking prompt medical attention, maintaining hydration, performing laboratory assessments of renal function).   |

# Choice of NOAC



**Figure 8 | Selection of oral anticoagulant drugs.** A schematic representation of decision making in the selection of an oral anticoagulant (OAC) drug based on patient and drug characteristics using illustrative examples. A, apixaban; CrCl, creatinine clearance; D, dabigatran (D75, dabigatran 75 mg two times per day, available in the United States only; D110, dabigatran 110 mg, not available in the United States for AF; D150, dabigatran 150 mg); E, edoxaban (E30, edoxaban 30 mg); GI, gastrointestinal; ICH, intracranial haemorrhage; IS, ischaemic stroke; NOAC, non-vitamin K antagonist oral anticoagulant; R, rivaroxaban; TIA, transient ischaemic attack; VKA, vitamin K antagonist. \*D110 for patients with a CrCl 30–49 ml min<sup>-1</sup> (most countries); in the United States only, D75 for patients with CrCl 15–29 ml min<sup>-1</sup> (and only 150 mg b.i.d. dose available in the United States, for CrCl >30 ml min<sup>-1</sup>). Figure adapted with permission from REF. 250, Wiley.

## Take-Home Message

- ▶ Compared with warfarin, apixaban and dabigatran 110mg bid are not associated with increased risk of major GI bleeding.
- ▶ GI bleeding associated with NOAC occurs more from a source in the lower GI tract.
- ▶ In a population-based study, GI bleeding events among patient taking NOACs increased with age; the risk was greatest among older persons. Apixaban had the most favorable GI safety profile among all age groups.