

Up to Date on Which NOAC for Which Patient

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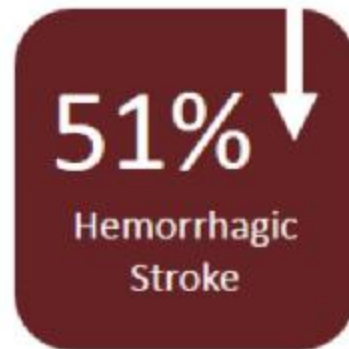
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Program Goals

- Increase knowledge regarding recent data on NOACs in subpopulations of patients with AF
- Improve competence related to the ability to select a NOAC for a patient based on patient characteristics and the pharmacologic profile

In Clinical Trials, NOACs Have Demonstrated Favorable Efficacy and Safety Profiles vs VKAs

Stroke prevention in AF^[a]



DVT/PE treatment^[b]



a. Ruff C, et al. *Lancet*. 2014;383:955-962.

b. Hirschl M, et al. *Vasa*. 2014;43:353-364.

Attributes of NOACs

- Once- or twice-daily dosing
- Do not require routine coagulation monitoring
- Very convenient to administer
- But -- they all have slightly different pharmacologic properties

Decision Process for Selecting OAC Therapy: VKA vs NOAC

- Reduction in intracranial hemorrhage
 - All 4 NOACs
- Reduction in major bleeding
 - Apixaban
 - Dabigatran
 - Edoxaban
- Reduction in all-cause mortality
- Difficulty in maintaining TTR (warfarin)

Contraindications for NOACs

- Moderate to severe mitral stenosis (usually of rheumatic origin)
- Mechanical prosthetic valve
- CrCl < 15 mL/min -- no official indication for use

All Major and Minor Bleeding Events on Warfarin

	Patients, %	
	Asians	Non-Asians
RE-LY	3.82	3.53
ROCKET	5.14	3.4
ARISTOTLE	3.84	3
ENGAGE	4.8	3.3

- When warfarin is used, Asian patients have a higher risk of stroke, major bleeding, and ICH compared with non-Asians, despite the average anticoagulation intensity of warfarin being lower in Asians.

Recommendations From Taiwan AF Guidelines

- Warfarin has not been extensively tested against placebo in large-scale RCTs in Asians
- Standard-dose NOACs are more effective and safer than warfarin in Asians, and should be recommended as first choice for stroke prevention in Asians

Balancing Safety and Efficacy

- Safety first
- Consider renal function
 - CrCl 15-30 mL/min -- preference is for a factor Xa NOAC (dabigatran not indicated)

Dose Reductions for NOACs

RE-LY ^[a]	ROCKET-AF ^[b]	ARISTOTLE ^[c]	ENGAGE-AF ^[d]
<ul style="list-style-type: none">• None	<ul style="list-style-type: none">• 20→15 mg/d for:<ul style="list-style-type: none">– CrCl < 30-49 mL/min	<ul style="list-style-type: none">• 5→2.5 mg BID for ANY 2 of:<ul style="list-style-type: none">– Age ≥ 80 years– Body weight ≤ 60 kg– SCr ≥ 1.5 mg/dL	<ul style="list-style-type: none">• 60→30 mg/d or 30→15 mg/d for:<ul style="list-style-type: none">– CrCl 30-50 mL/min– Body weight ≤ 60 kg– Use of quinidine, verapamil, or dronedarone

a. Connolly SJ, et al. *N Engl J Med.* 2009;361:1139-1151; b. Patel MR, et al. *N Engl J Med.* 2011;365:883-891; c. Granger CB, et al. *N Engl J Med.* 2011;365:981-992; d. Giugliano RP, et al. *N Engl J Med.* 2013;369:2093-2104.

Canadian Dose Reduction Recommendation

- Advanced age (≥ 75 years) is a clear risk factor for ischemic stroke and major hemorrhage
- In RE-LY, there was a significant interaction between age and choice of therapy
- Because the 150-mg dose of dabigatran may cause more major bleeding among patients aged > 75 years, it is prudent to prescribe dabigatran at 110 mg for those patients

ESC/EHRA Recommendation for Dose Reduction

Cockcroft-Gault formula

$$eCcr = \frac{(140 - \text{Age}) \times \text{Mass (in kilograms)} \times (0.85 \text{ if female})}{72 \times \text{Serum Creatinine (in mg/dL)}}$$

	Dabigatran (RE-LY)	Rivaroxaban (ROCKET-AF)	Apixaban (ARISTOTLE)	Edoxaban (ENGAGE AF-TIMI 48)
Dose adjustments with CKD	None	15 mg once daily if CrCL <30-49 mL/min	2.5 mg twice daily if 2 of the following: serum creatinine ≥ 1.5 mg/dL (133 μmol/L), age ≥80 years or weight ≤60 kg	30 mg (or 15 mg) once daily if any of the following: CrCl <50 mL/min, weight ≤60 kg, concomitant use of verapamil or quinidine or dronedarone

Cockcroft DW, et al. *Nephron*. 1976;6:31-41.

Kirchhof P, et al. *Eur Heart J*. 2016;37:2893-2962.

Baseline Characteristics in AF Trials

	RE-LY ^[a] (Dabigatran)	ARISTOTLE ^[b] (Apixaban)	ENGAGE AF-TIMI 48 ^[c] (Edoxaban)	ROCKET-AF ^[d] (Rivaroxaban)
Enrolled, n	18,113	18,201	21,105	14,264
Age, y	72 ± 9	70 (63-76)	72 (64-78)	73 (65-78)
Female, %	36	35	38	40
CHADS ₂ score ≥3, %	32	30	53	87
VKA naive, %	50	43	41	38
Paroxysmal AF, %	33	15	25	18
Prior stroke/TIA, %	20	19	28	55**
Diabetes, %	23	25	36	40
Prior CHF, %	32	35	58	62
Hypertension, %	79	87	94	90

*includes prior systemic embolism

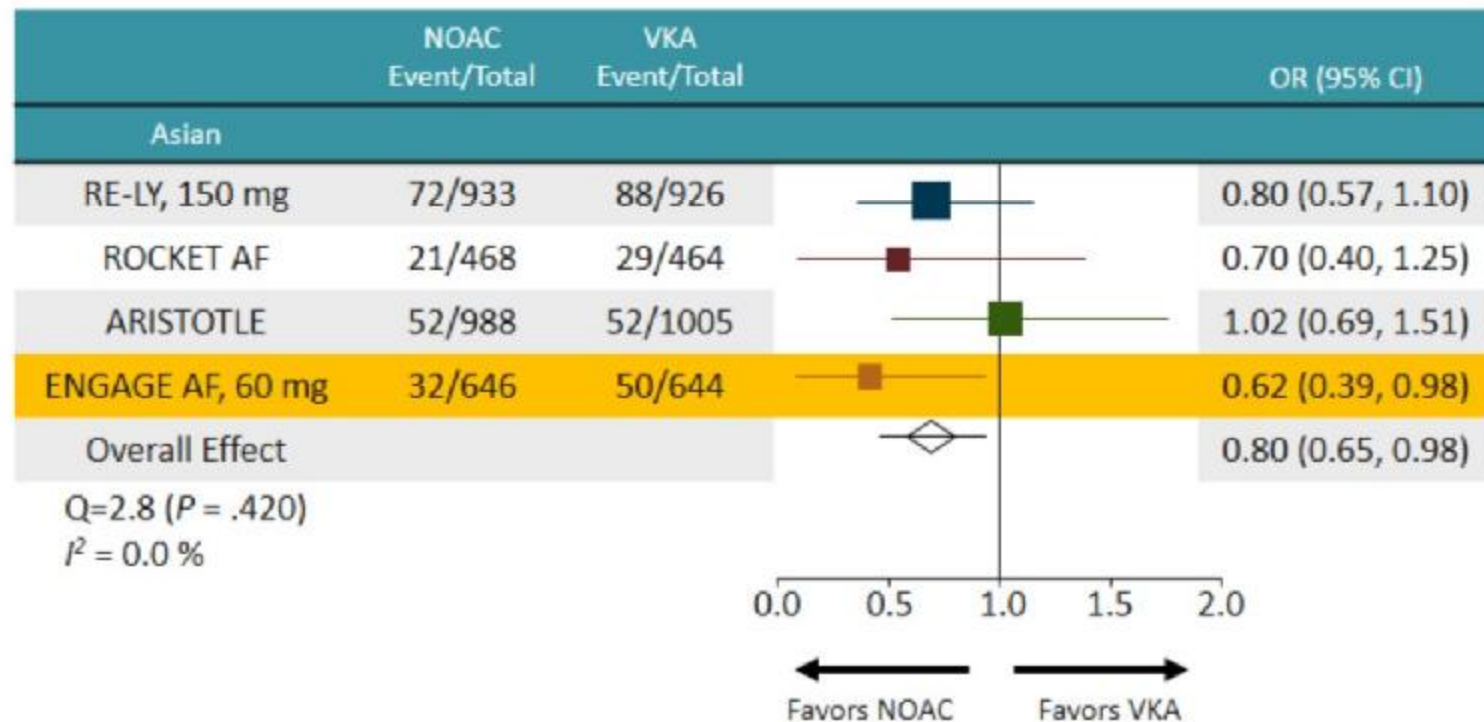
a. Connolly et al. *N Engl J Med.* 2009;361:1139-1151; b. Granger et al. *N Engl J Med.* 2011;365:981-992;

c. Giugliano RP et al. *N Engl J Med.* 2013;369:2093-2104; d. Patel et al. *N Engl J Med.* 2011;365:883-891.

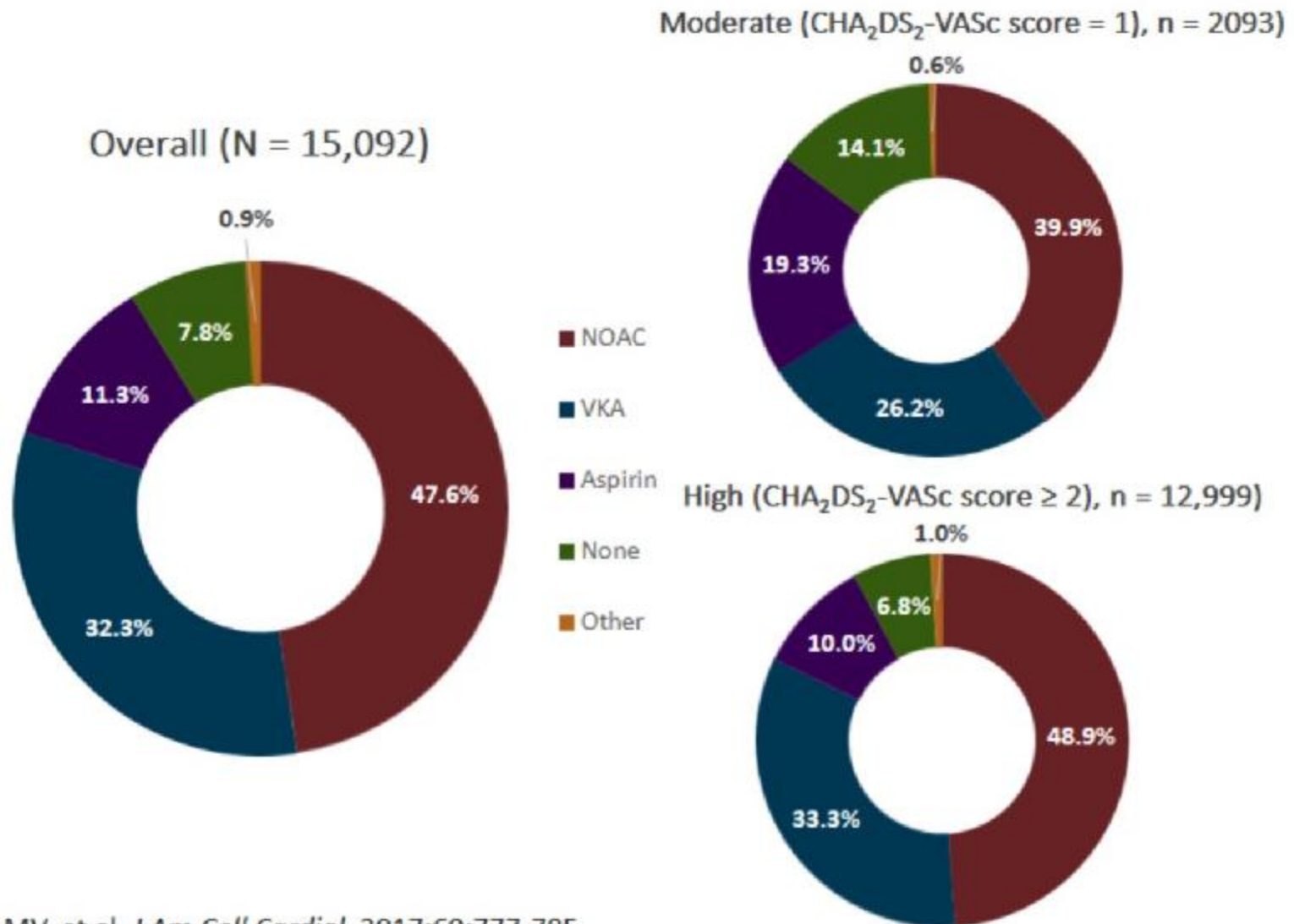
Efficacy of Once-Daily NOACs vs Warfarin in AF Trials: Asian Subgroup

Stroke or SEE	RR (95% CI)
ROCKET AF	0.77 (0.44, 1.34)
ENGAGE AF-TIMI 48	0.72 (0.47, 1.11)

Reduction in All-Cause Mortality in Asians



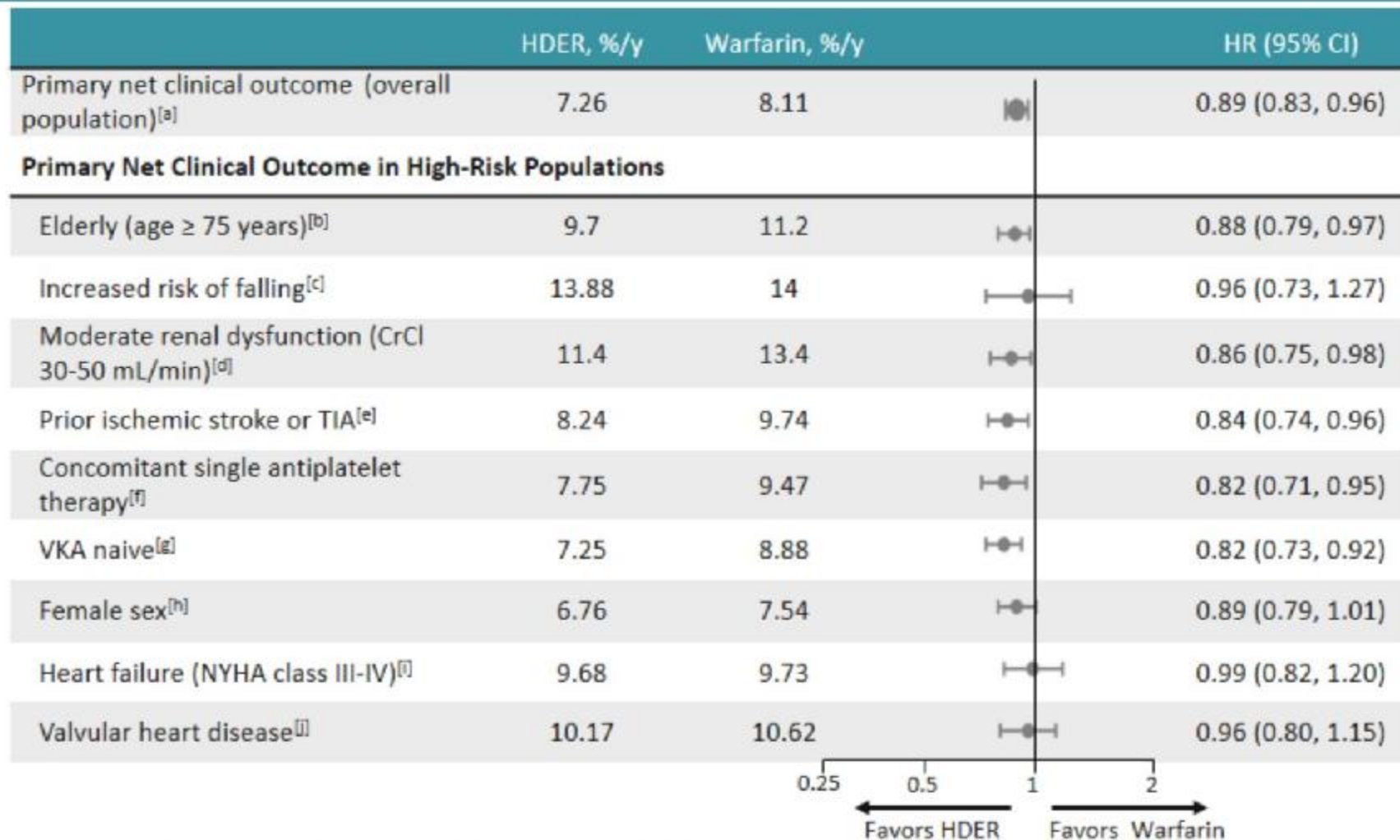
GLORIA: Antithrombotic Therapy by CHA₂DS₂-VASc Score



Risk-Benefit Profile of NOACs vs Warfarin in the Elderly

	Stroke/Systemic Thromboembolism, %/y	
	Age < 75 y	Age > 75 y
RE-LY		
Dabigatran 150 mg	0.9	1.4
Warfarin	1.4	2.1
ROCKET-AF		
Rivaroxaban	2	2.3
Warfarin	2.1	2.9
ARISTOTLE		
Apixaban	1.2	1.6
Warfarin	1.7	2.2
ENGAGE-TIMI 48		
Edoxaban -- higher dose	1.7	1.9
Warfarin	1.8	2.3

Net Clinical Outcome of HDER (60/30 mg) in High-Risk Populations



a. Giugliano et al. *N Engl J Med.* 2013; 369:2093-2104; b. Kato et al. *J Am Heart Assoc.* 2016;5:e003432; c. Steffel J, et al. *J Am Coll Cardiol.* 2016;68:1169-1178; d. Bohula EA, et al. *Circulation.* 2016; 134:24-36; e. Rost NS, et al. *Stroke.* 2016; 47:2075-2082; f. Xu H, et al. *J Am Heart Assoc.* 2016;5:e002587; g. O'Donoghue ML, et al. *Eur Heart J.* 2015;36:1470-1477; h. Giugliano RP, et al. Venice Arrhythmias 2015; i. Magnani G, et al. *Eur Heart J.* 2016; 18:1153-1161; j. De Caterina R, et al. *J Am Coll Cardiol.* 2017;69:1372-1382.

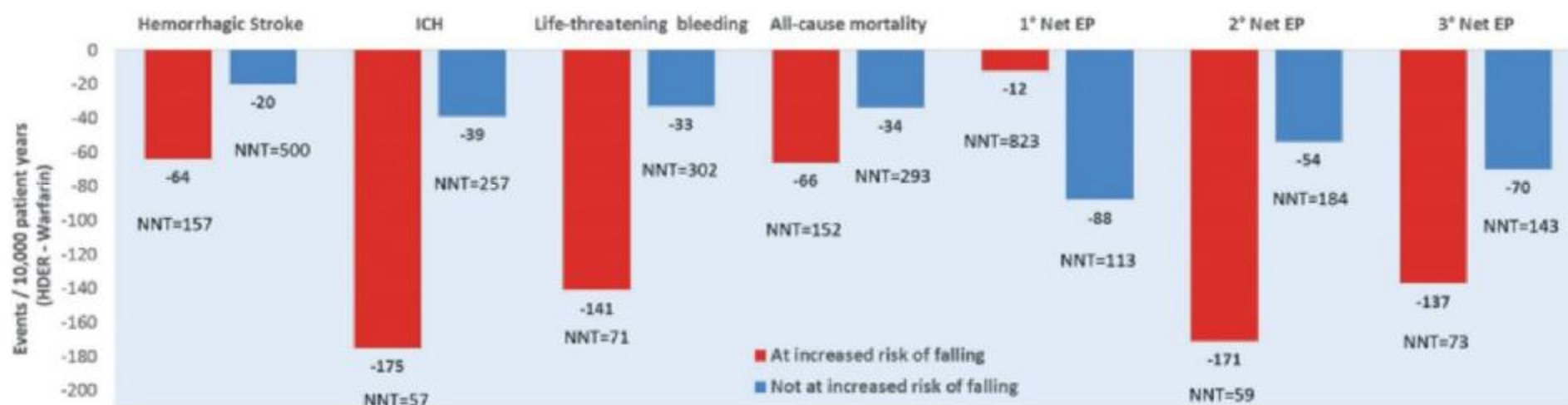
Risk-Benefit Profile of NOACs vs Warfarin in the Elderly

	Stroke/Systemic Thromboembolism, %/y		Major Bleeding	
	Age < 75 y	Age > 75 y	Age < 75 y	Age > 75 y
RE-LY				
Dabigatran 150 mg	0.9	1.4	2.1	5.1
Warfarin	1.4	2.1	3.0	4.4
ROCKET-AF				
Rivaroxaban	2	2.3	2.7	4.9
Warfarin	2.1	2.9	2.8	4.4
ARISTOTLE				
Apixaban	1.2	1.6	2.0	3.3
Warfarin	1.7	2.2	2.8	5.2
ENGAGE-TIMI 48				
Edoxaban -- higher dose	1.7	1.9	2.5	4.0
Warfarin	1.8	2.3	3.3	4.8

Edoxaban vs Warfarin in Patients With an Increased Risk of Falls

	Fall Risk (n = 900, 4%)	No Fall Risk (n = 20205, 96%)	P value
Male gender	51%	62%	< .001
Age (years)	77	72	< .001
CHADS ₂ score (mean)	3.3	2.8	< .001
CHA ₂ DS ₂ -VASc score (mean)	5.1	4.3	< .001
CHADS ₂ score > 3	39%	22%	< .001
History of Stroke (or TIA)	41%	28%	< .001
CrCl (mL/min, median)	58	71	< .001
TTR (warfarin arm, median)	67	69	.15

Absolute Risk Reduction of Edoxaban vs Warfarin in Patients With an Increased Risk of Falls



Reprinted from *J Am Coll Cardiol*, 68, Steffel J, et al. Edoxaban Versus Warfarin in Atrial Fibrillation Patients at Risk of Falling: ENGAGE AF-TIMI 48 Analysis, 1169-1178, Copyright 2016, with permission from Elsevier.

Drug-Drug Interactions With NOACs

Drug	Avoid Use	No Specific Recommendations	No Adjustment Needed	CrCl 30 to 50 mL/min	Dose Reduction
Carbamazepine	A D R	E			
Clarithromycin		E	D R		A 2.5 mg twice daily*
Dronedarone		A R	E	D 75 mg twice daily	
Itraconazole	R	E	D		A 2.5 mg twice daily*
Ketoconazole	A R	E		D 75 mg twice daily	A 2.5 mg twice daily*
Phenytoin	A D R	E			
Rifampin	A D E R				
Ritonavir	R	E	D		A 2.5 mg twice daily*
St. John's wort	A D R	E			

*If on 2.5 mg twice daily, discontinue apixaban

Apixaban

Dabigatran

Edoxaban

Rivaroxaban

NOAC Administration: With or Without Food

Apixaban

Can be taken with or without food

Dabigatran

Yes -- may lessen risk of dyspepsia

Edoxaban

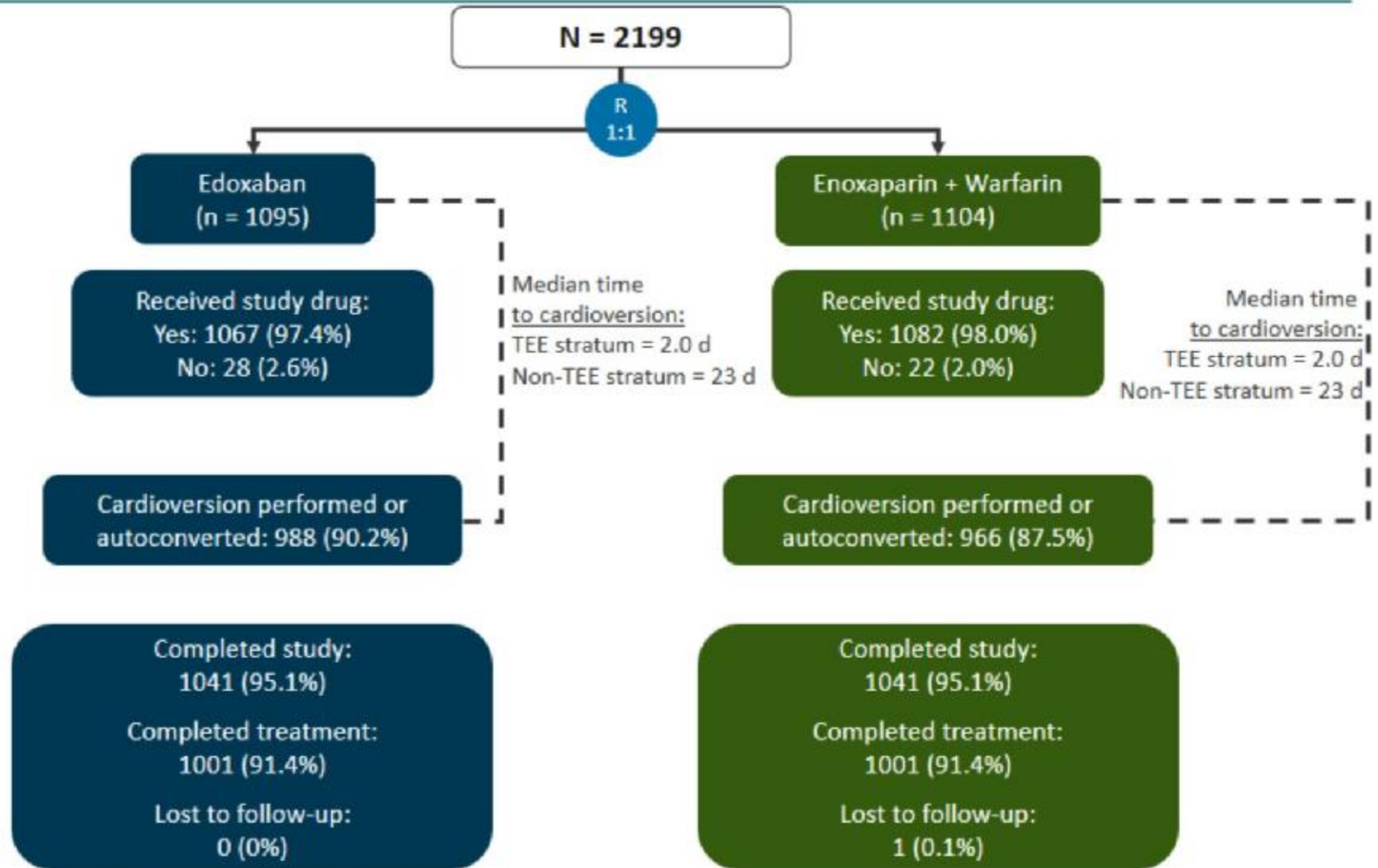
Can be taken with or without food

Rivaroxaban

Yes -- should be taken with a meal

- Requirement to take with food might have a negative influence on adherence

ENSURE-AF: Study Design



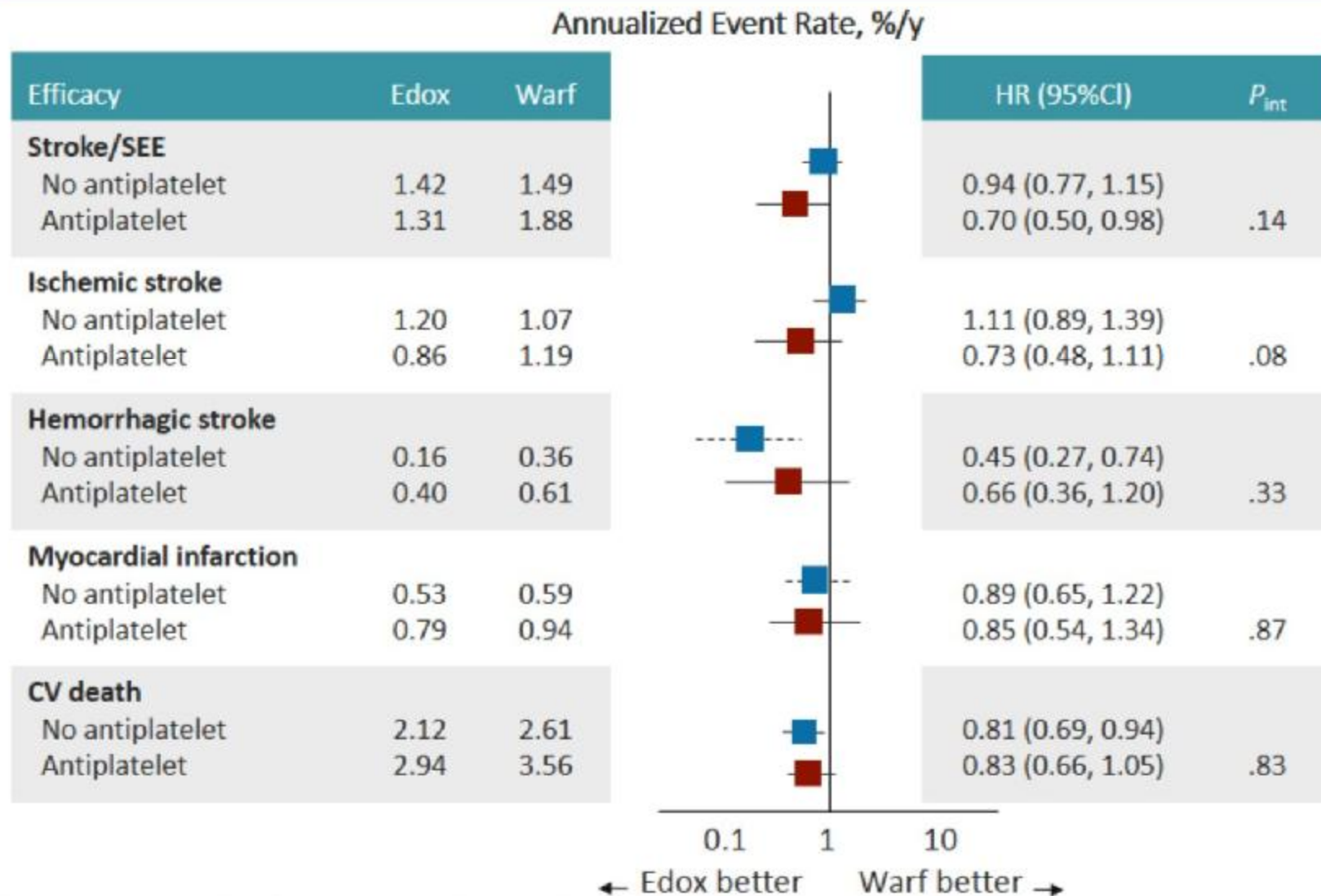
Concomitant Use of Aspirin With OAC

- Make sure the patient has an indication for both agents
- Consider the specifics of each patient because combination therapy increases the overall bleeding risk
- Antiplatelet therapy is the standard management for CAD to reduce the risk of coronary events
- Long-term antithrombotic management of patients presenting with AF and CAD is often challenging, and combination therapy carries an increased risk of bleeding

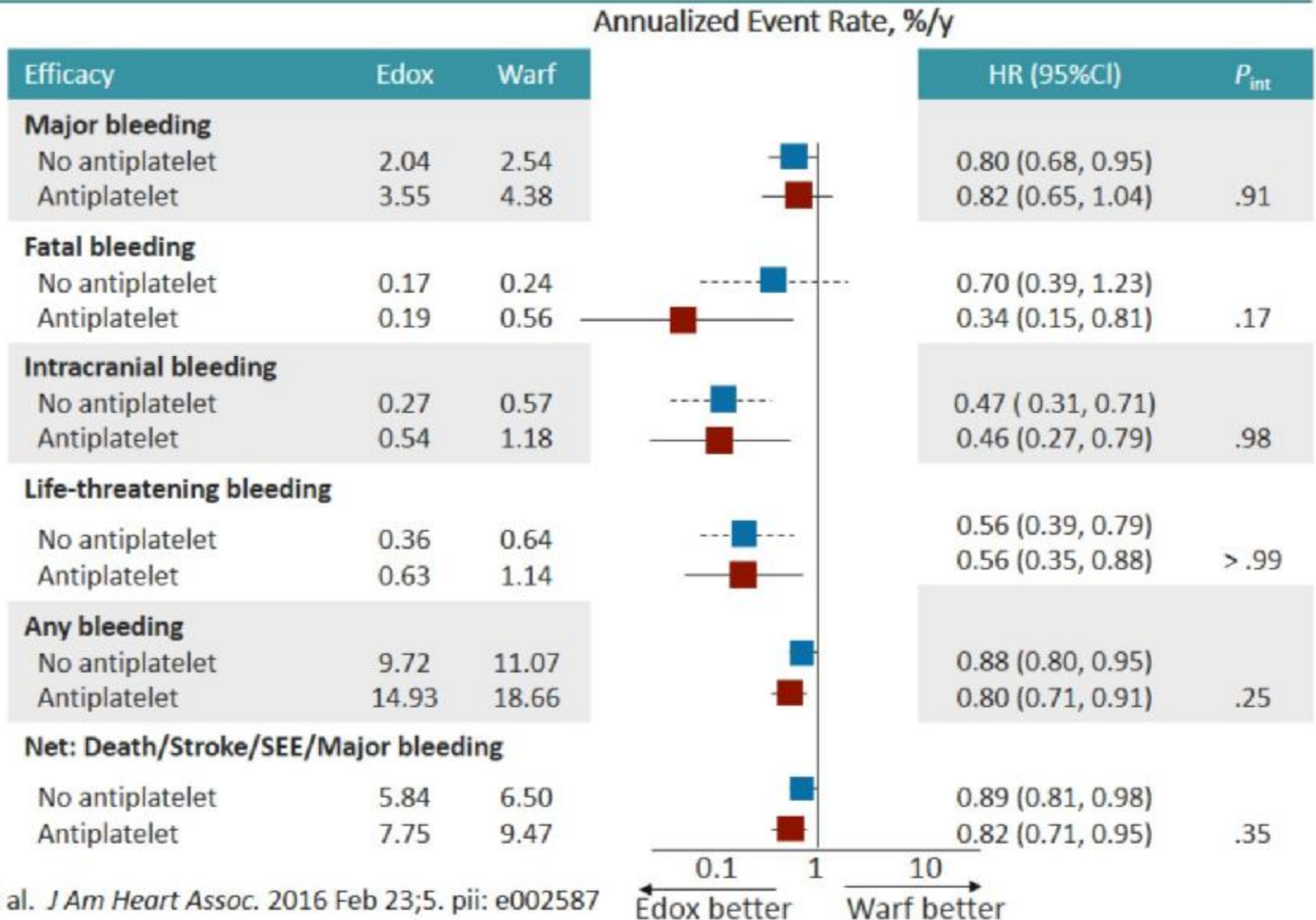
Platelet -- All Trials

	RE-LY			ROCKET-AF		ARISTOTLE		ENGAGE AF-TIMI 48			Combined	
	Dabigatran 150 mg (n = 6076)	Dabigatran 110 mg (n = 6015)	Warfarin (n = 6022)	Rivaroxaban (n = 7131)	Warfarin (n = 7133)	Apixaban (n = 9120)	Warfarin (n = 9081)	Edoxaban 60 mg (n = 7035)	Edoxaban 30 mg (n = 7034)	Warfarin (n = 7036)	NOAC (n = 42,411)	Warfarin (n = 29,272)
Aspirin at baseline, %	39	40	41	36	37	31	31	29	29	30	34	34

Efficacy of Edoxaban vs Warfarin in Patients With AF on Antiplatelet Therapy



Safety of Edoxaban vs Warfarin in Patients With AF on Antiplatelet Therapy



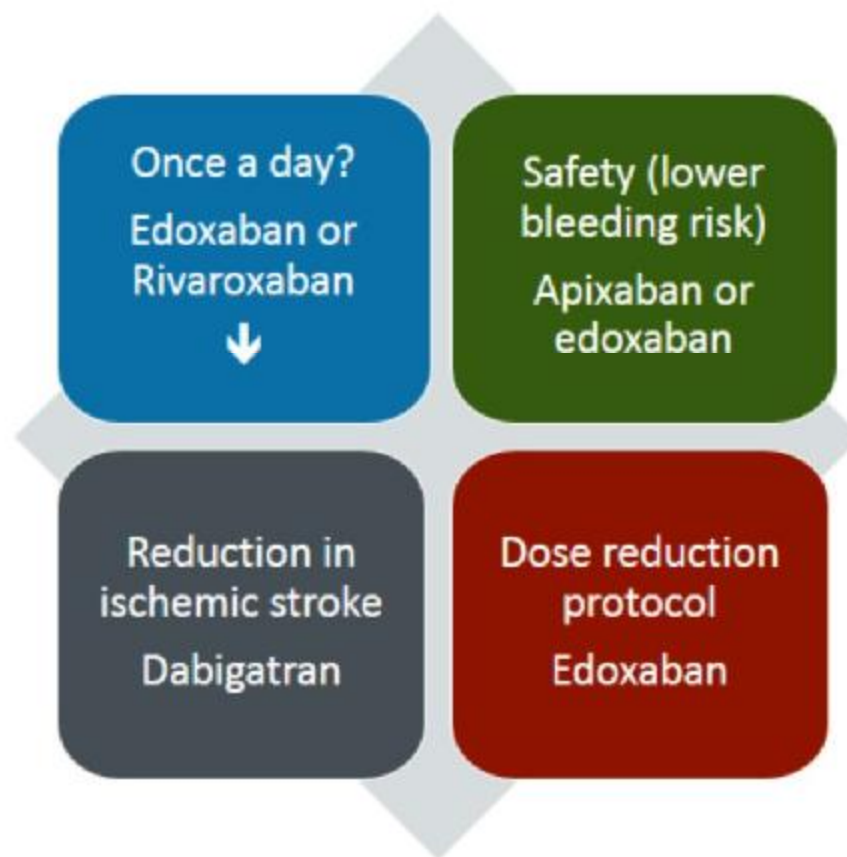
Risk of GI Bleeding

- May consider avoiding dabigatran
- Xa inhibitors may be safer
- In ENGAGE, there was no increase in very severe major forms of GI bleeding
- Asian patients may be different; only edoxaban and dabigatran have been evaluated, and there was no signal of increased GI bleeding with either
- If a patient has a GI bleed, investigate the cause and treat it; then the patient can be restarted on a NOAC

Which NOAC for Which Patient?

Factors to Consider

- Measure renal function at least once yearly
- Avoid underdosing -- dose appropriately



*Compared with warfarin.

Connolly SJ, et al. *N Engl J Med.* 2009;361:1139-1151; Patel MR, et al. *N Engl J Med.* 2011;365:883-891; Granger CB, et al. *N Engl J Med.* 2011;365:981-992; Giugliano RP, et al. *N Engl J Med.* 2013;369:2093-2104.

Abbreviations

AF = atrial fibrillation

BID = twice daily

CAD = coronary artery disease

CHADS2 = congestive heart failure, hypertension, age, diabetes, stroke

CHF = congestive heart failure

CKD = chronic kidney disease

CrCl = creatinine clearance

CV = cardiovascular

DVT = deep vein thrombosis

Edox = edoxaban

EHRA = European Heart Rhythm Association

ESC = European Society of Cardiology

GI = gastrointestinal

HDER = high-dose edoxaban regimen

HR = hazard ratio

ICH = intracranial hemorrhage

Abbreviations (cont)

NOAC = non-vitamin K antagonist oral anticoagulant

NYHA = New York Heart Association

OAC = oral anticoagulant

OR = odds ratio

PE = pulmonary embolism

RCT = randomized controlled trial

RR = relative risk

SCr = serum creatinine

SE = systemic embolism

SEE = systemic embolic event

TEE = transesophageal echocardiography

TIA = transient ischemic attack

TTR = time in therapeutic range

VKA = vitamin K antagonist

VTE = venous thromboembolism

Warf = warfarin