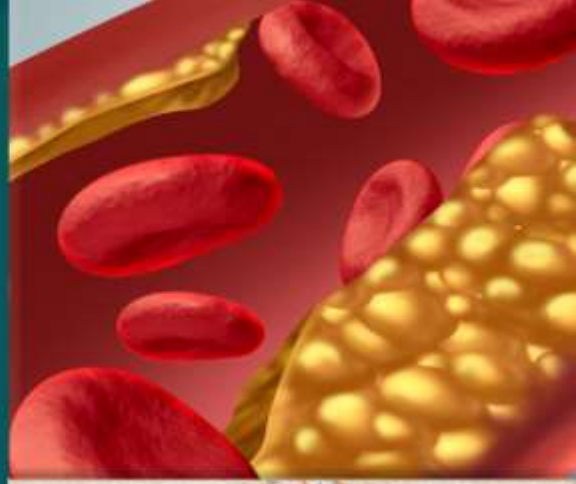
Anticoagulation in Polyvascular Disease: *Translating Data into Practice*



Online CME Activity

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Antithrombotic Therapy: Setting the Stage

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Burden of Thrombosis

THE FACTS

A blood clot that forms in the leg is called deep vein thrombosis (DVT). If the blood clot breaks loose and travels up to your lungs, it is called a pulmonary embolism (PE).

Together, they are known as venous thromboembolism (VTE).

THE NUMBERS

1 IN 4
people die from causes related to blood clots

1-3
top cardiovascular killers are linked to blood clots

#1
cause of preventable death in hospitals is VTE

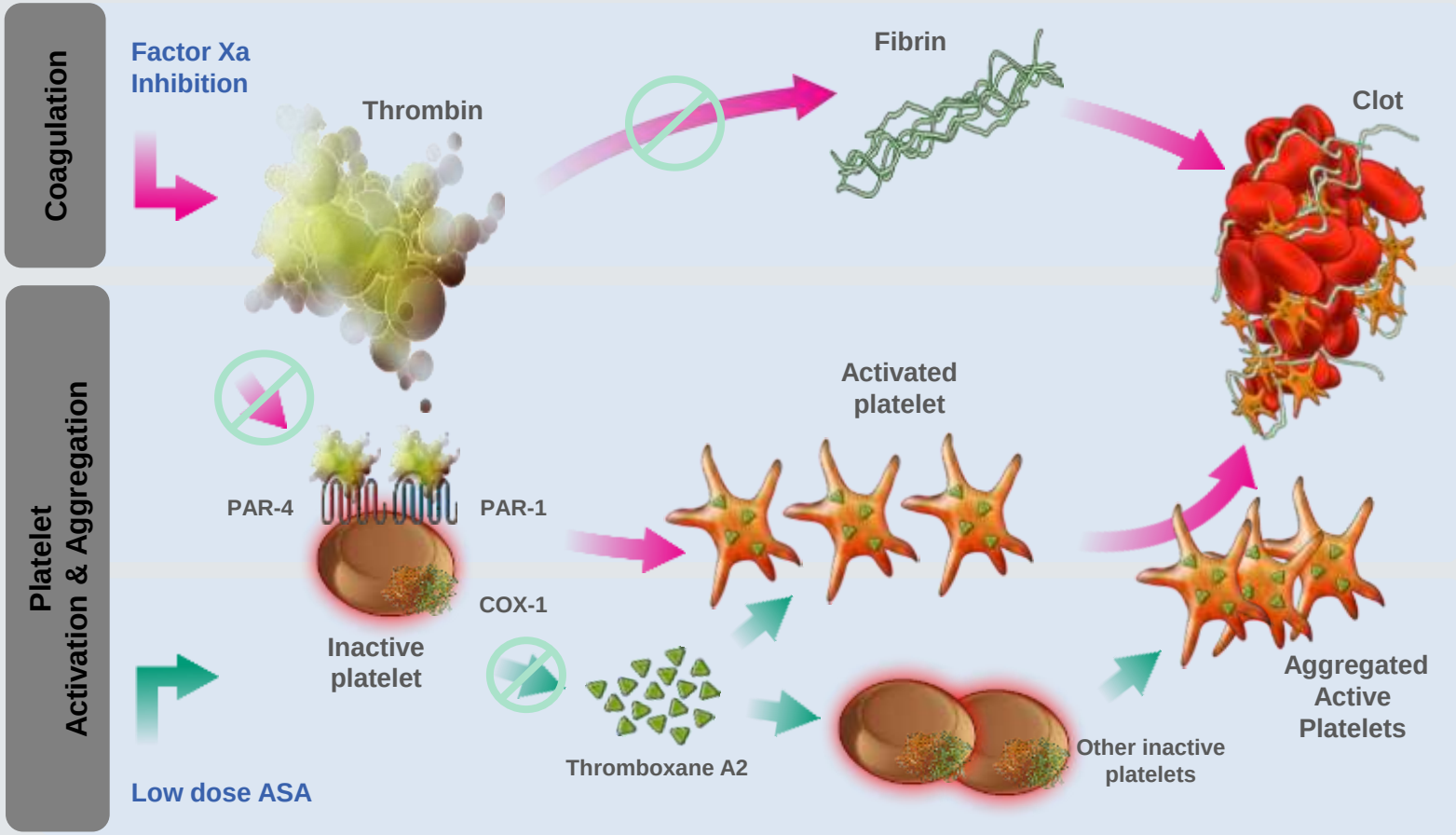
60%
of all VTE cases occur during or following hospitalization

Atherothrombosis

Cardiovascular disease affects 4% of global population (300 million persons)

Accounts for more than 300,000 deaths per week (17 million deaths each year)

Rationale for Dual Pathway Inhibition



Adapted from Angiolillo DJ et al. *Eur Heart J*. 2010;31:17-28. Mitchell JRA et al. *Br Med J*. 1981;282:590-4.

Studies of Dual Pathway Inhibition

Indication	Trial
CAD and/or PAD	COMPASS[1]
HF with reduced ejection fraction	COMMANDER HF[2]

[1]Eikelboom JW et al. *N Engl J Med.* 2017;377:1319-30.
[2]Zannad F et al. *N Engl J Med.* 2018;379:1332-42.

Thromboprophylaxis in Medically Ill Patients

Hospitalization increases the risk of VTE 6- to 13-fold

About 1.7% of medical patients develop VTE within 3 months of hospitalization

Up to 60% of patients with VTE have a history of recent hospitalization and 75% of fatal PE occur in medical patients

PE is the number one cause of preventable death in hospitalized patients

Heit JA et al. *Arch Intern Med* 2000;160:809-15. Edelsberg J et al. *J Thromb Haemost* 2007;5:1. Spencer FA et al. *Arch Intern Med* 2007;167:1471-5. Lindblad B et al. *Br J Surg.* 1991;78:849-52. Anderson FA Jr et al. *Arch Intern Med* 1991;151:933-8.

Putting COMPASS Into Perspective

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Chief, Division of Cardiology
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Durham, NC

Three messages

1. Stronger anti-platelet therapy does not improve outcomes
2. COMPASS Trial
3. World of PAD – polyvascular disease

Atherothrombotic Diseases in the US – The "Big 3"

	Prevalence (millions)	Incidence (millions)
Coronary heart disease	15.4	0.9
Cerebrovascular disease	6.8	0.8
PAD	8.5	—

Go AS et al. *Circulation*. 2013;127:e6-e245.

Evidence for the Anti-thrombotic Therapy for CAD

Select Clinical Studies in Patients With CAD

Regimen Comparison	Medications	Study	Population Size	Primary Efficacy Results	Primary Bleeding Results
Monotherapy vs Placebo	Aspirin vs Placebo	Meta-analysis[1]	87,654	Rate of nonfatal MI, nonfatal stroke, or vascular death OR (95% CI): 0.79 (0.76-0.83); *P*<0.0001	Major bleed rate OR (95% CI): 1.87 (1.51-2.32); *P*<0.0001
Monotherapy vs Monotherapy	Clopidogrel vs Aspirin	CAPRIE[2]	19,185	Rate of ischemic stroke, MI, or vascular death RRR (95% CI): 8.7% (0.3-16.5); *P*=0.043	Did not specifically evaluate bleeding events
Dual or Triple Antiplatelet Therapy vs Monotherapy	Clopidogrel + Aspirin vs Aspirin	CHARISMA[3]	15,603	Rate of MI, stroke, or CV death RR (95% CI): 0.93 (0.83-1.05); *P*=0.22	GUSTO severe bleed rate RR (95% CI): 1.25 (0.97-1.61); *P*=0.09
	Vorapaxar + Aspirin and/or Clopidogrel vs Aspirin and/or Clopidogrel*	TRA 2P—TIMI 50[4]	26,449	Rate of CV death, MI, or stroke HR (95% CI): 0.87 (0.80-0.94); *P*<0.001	GUSTO moderate or severe bleed rate HR (95% CI): 1.66 (1.43-1.93); *P*<0.001
	Ticagrelor + Aspirin vs Aspirin	PEGASUS[5]	21,162	Rate of CV death, MI, or stroke HR (95% CI): 0.84 (0.74-0.95); *P*=0.004 (60 mg) HR (95% CI): 0.85 (0.75-0.96); *P*=0.008 (90 mg)	TIMI major bleed rate HR (95% CI): 2.32 (1.68-3.21); *P*<0.001 (60 mg) HR (95% CI): 2.69 (1.96-3.70); *P*<0.001 (90 mg)
Anticoagulant Therapy + Aspirin vs Aspirin	Warfarin + Aspirin vs Aspirin	WARIS II[6]	3630	Rate of death, non-fatal reinfarction, or TE cerebral stroke RR (95% CI): 0.71 (0.60-0.83); *P*=0.001	Major non-fatal bleed rate *P*<0.001

*94% and 62% of patients received aspirin and thienopyridine, respectively. OR=odds ratio; RRR=relative risk ratio; HR=hazard ratio; CI=confidence interval; TE=thromboembolic; GUSTO=Global Use of Strategies to Open Occluded Coronary Arteries; TIMI=Thrombolysis In Myocardial Infarction.

1. Lièvre M, Cucherat M. *Fundam Clin Pharmacol*. 2010;24(3):385-391. **2.** CAPRIE Steering Committee. *Lancet*. 1996;348(9038):1329-1339. **3.** Bhatt DL et al. *J Am Coll Cardiol*. 2007;49(19):1982-1988. **4.** Morrow DA, et al. *N Engl J Med*. 2012;366(15):1404-1413. **5.** Bonaca MP et al. *N Engl J Med*. 2015;372(19):1791-1800. **6.** Hurlen M et al. *N Engl J Med*. 2002;347(13):969-974.

Guidelines for SIHD Chronic Management

ACC/AHA Guideline Recommendations for Antiplatelets in the Management of Stable Ischemic Heart Disease (SIHD)

Class	LOE	Recommendations
I	A	Treatment with **aspirin 75 to 162 mg daily** should be continued indefinitely in the absence of contraindications in patients with SIHD
I	B	Treatment with **clopidogrel** is reasonable when aspirin is contraindicated in patients with SIHD
IIb	B	Treatment with **aspirin 75 to 162 mg daily and clopidogrel 75 mg daily** might be reasonable in certain high-risk patients with SIHD

LOE A=data derived from multiple randomized clinical trials or meta-analyses; LOE B=data derived from a single randomized trial or nonrandomized studies.
ACC=American College of Cardiology; AHA=American Heart Foundation; LOE=level of evidence.
Fihn SD et al. *J Am Coll Cardiol*. 2012;60:e44-e164.

Evidence for Therapy for PAD

Select Clinical Studies in Patients With PAD

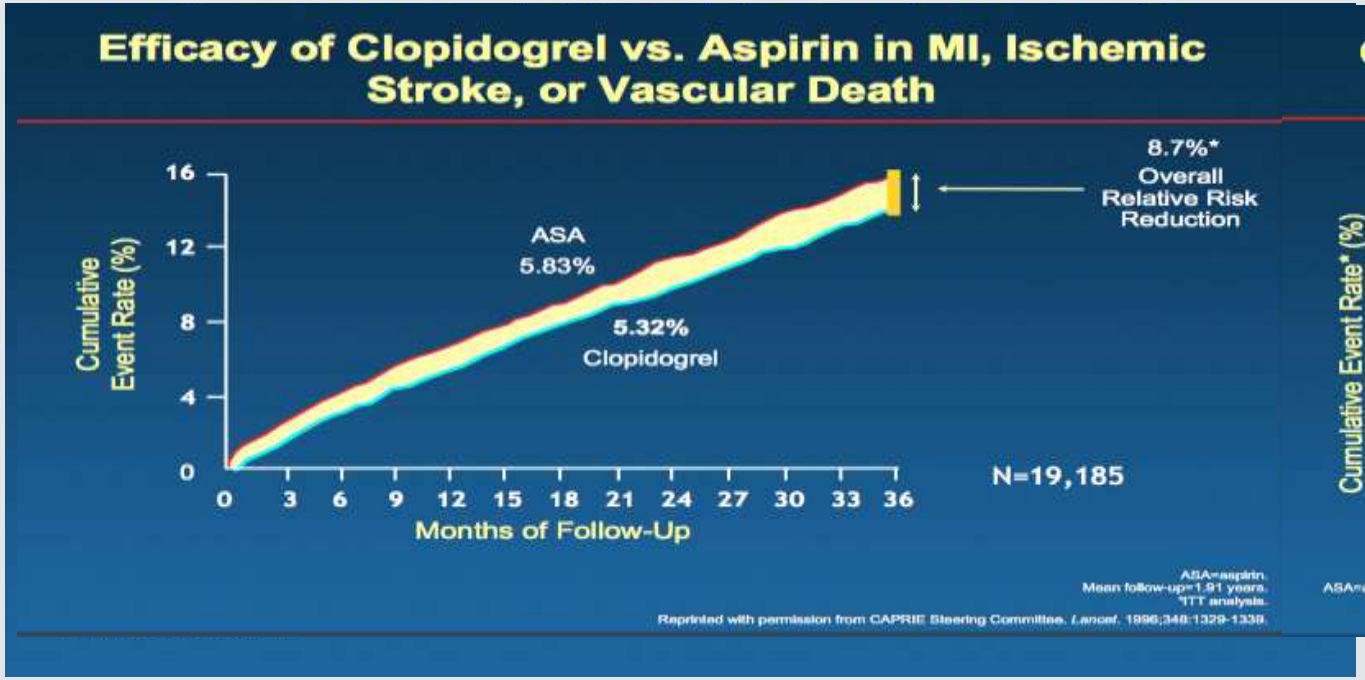
Regimen Comparison	Medications	Study	Population Size	Primary Efficacy Results	Primary Bleeding Results
Monotherapy vs Placebo	Aspirin vs Placebo	Meta-analysis[1]	87,654	Rate of nonfatal MI, nonfatal stroke, or vascular death OR (95% CI): 0.79 (0.76-0.83); *P*<0.0001	Major bleed rate OR (95% CI): 1.87 (1.51-2.32); *P*<0.0001
Monotherapy vs Monotherapy	Clopidogrel vs Aspirin	CAPRIE[2]	19,185	Rate of ischemic stroke, MI, or vascular death RRR (95% CI): 8.7% (0.3-16.5); *P*=0.043	Did not specifically evaluate bleeding events
	Ticagrelor vs Clopidogrel	EUCLID[3]	13,885	Rate of MI, ischemic stroke, or CV death HR (95% CI): 1.02 (0.92-1.13); *P*=0.65	TIMI major bleed rate HR (95% CI): 1.10 (0.84-1.43); *P*=0.49
Dual or Triple Antiplatelet Therapy vs Monotherapy	Clopidogrel + Aspirin vs Aspirin	CHARISMA[4]	15,603	Rate of MI, stroke, or CV death RR (95% CI): 0.93 (0.83-1.05); *P*=0.22	GUSTO severe bleed rate RR (95% CI): 1.25 (0.97-1.61); *P*=0.09
	Vorapaxar + Aspirin and/or Clopidogrel vs Aspirin and/or Clopidogrel*	TRA 2P—TIMI 50[5]	26,449	Rate of CV death, MI, or stroke HR (95% CI): 0.87 (0.80-0.94); *P*<0.001	GUSTO moderate or severe bleed rate HR (95% CI): 1.66 (1.43-1.93); *P*<0.001
Anticoagulant Therapy + Aspirin vs Aspirin	Warfarin + Aspirin vs Aspirin	WAVE[6]	2161	Rate of MI, stroke, or CV death RR (95% CI): 0.92 (0.73-1.16); *P*=0.48	Life-threatening bleed rate RR (95% CI): 3.41 (1.84-6.35); *P*<0.001 Moderate bleed rate RR (95% CI): 2.82 (1.43-5.58); *P*=0.002

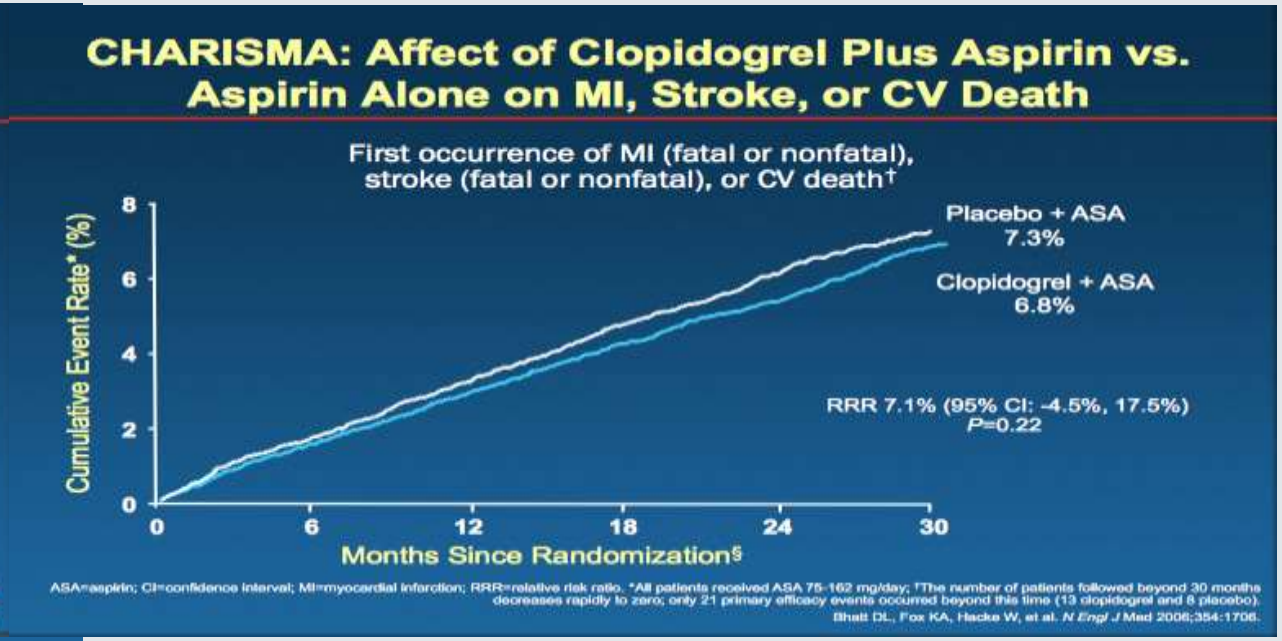
*94% and 62% of patients received aspirin and thienopyridine, respectively.

1. Lièvre M, Cucherat M. *Fundam Clin Pharmacol*. 2010;24(3):385-391. **2.** CAPRIE Steering Committee. *Lancet*. 1996;348(9038):1329-1339.
3. Hiatt WR et al. *N Engl J Med*. 2017;376(1):32-40. **4.** Cacoub PP et al. *Eur Heart J*. 2009;30(2):192-201.
5. Morrow DA, et al. *N Engl J Med*. 2012;366(15):1404-1413. **6.** Warfarin Antiplatelet Vascular Evaluation Trial Investigators. *N Engl J Med*. 2007;357(3):217-227.

Anti-platelet Therapy for PAD

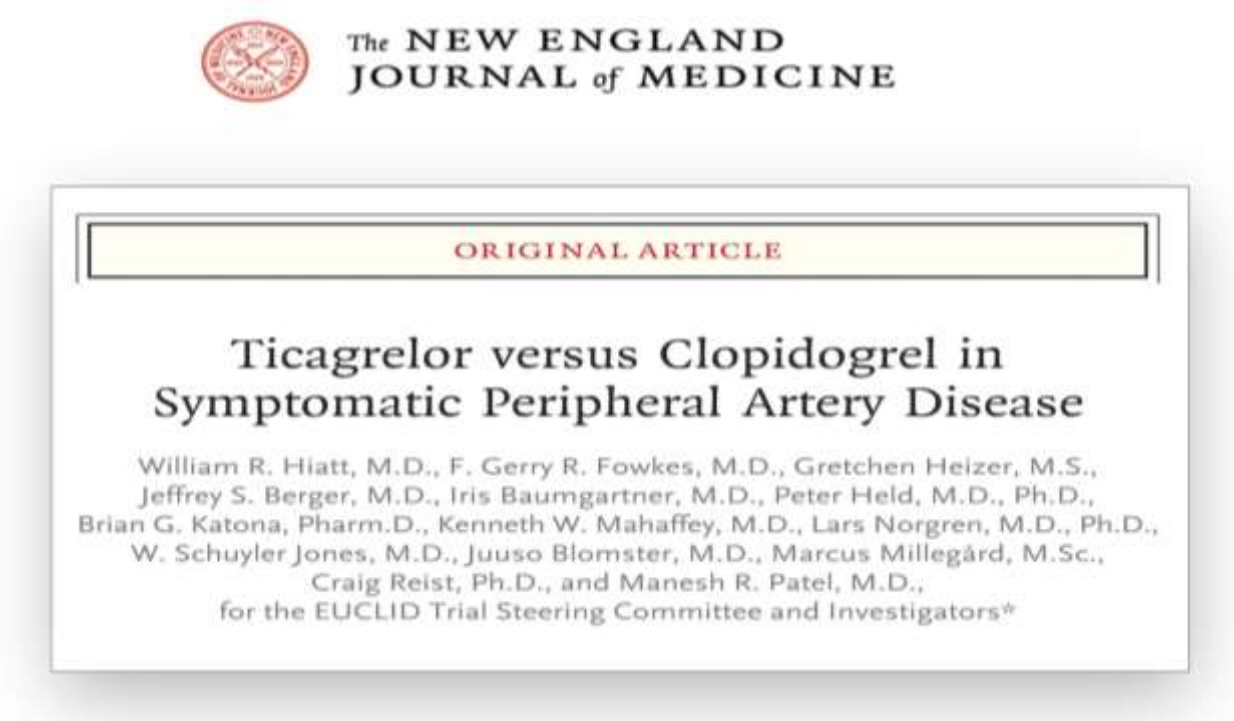
- ASA – mildly better than placebo (JAMA Meta-analysis)
- CAPRIE – Clopidogrel slightly better than ASA
- CHARISMA – DAPT not better than ASA

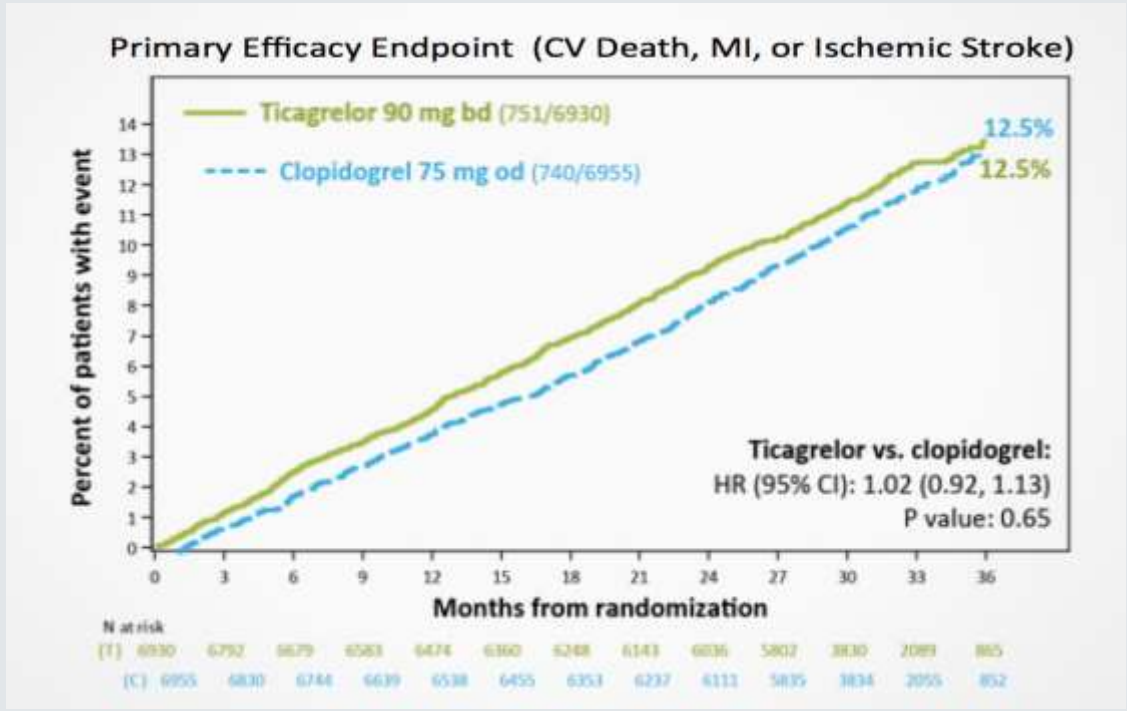




Anti-platelet Therapy for PAD

- ASA – mildly better than placebo (JAMA Meta-analysis)
- CAPRIE – Clopidogrel slightly better than ASA
- CHARISMA – DAPT not better than ASA
- EUCLID – Ticagrelor similar to Clopidogrel





Guideline Recommendations for PAD

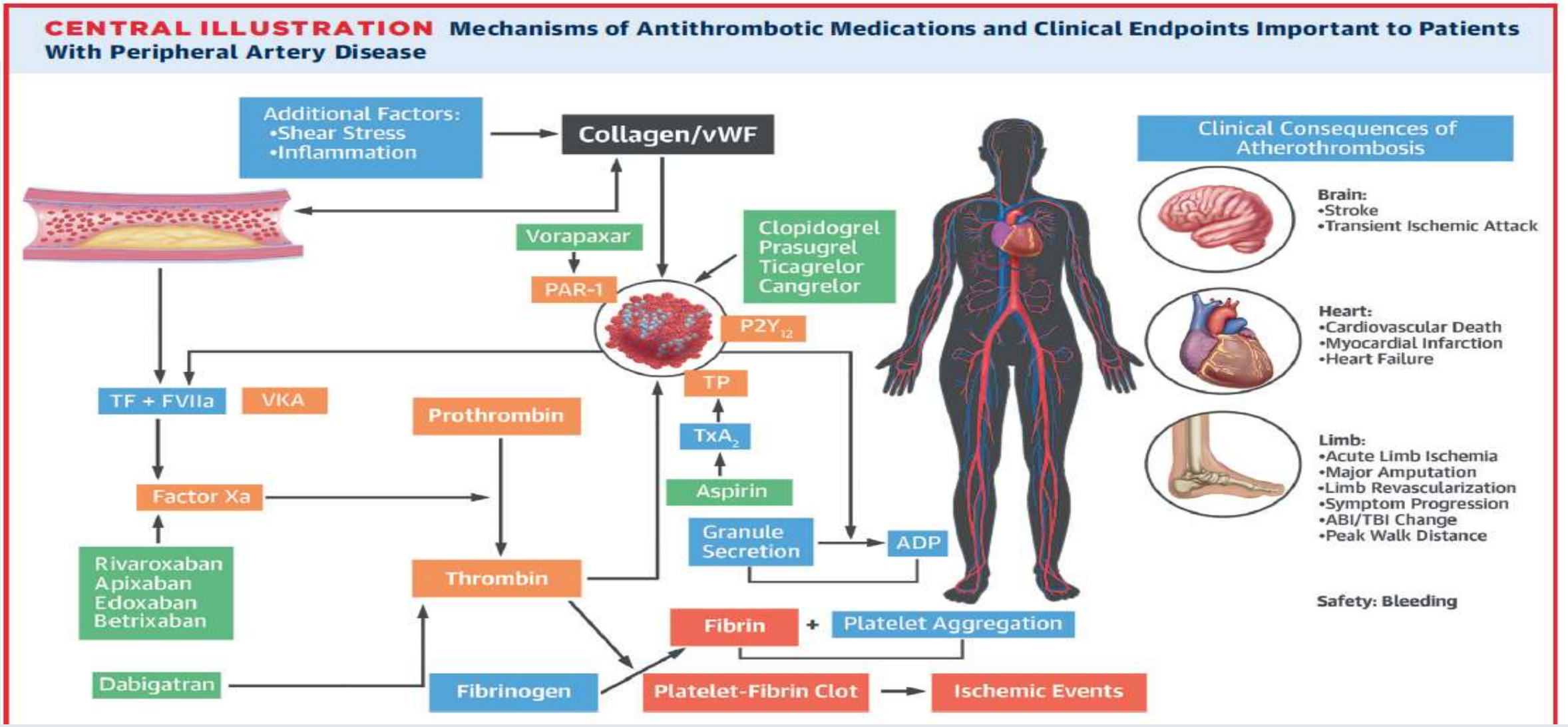
ACC/AHA Guideline on the Management of Patients With Lower Extremity PAD

Class	LOE	Recommendations
I	A	Antiplatelet therapy with **aspirin alone (range 75-325 mg per day) or clopidogrel alone (75 mg per day)** is recommended to reduce MI, stroke, and vascular death in patients with symptomatic PAD
IIa	C-EO	In asymptomatic patients with PAD (ABI ≤0.90), antiplatelet therapy is reasonable to reduce the risk of MI, stroke, or vascular death.
IIb	B-R	In asymptomatic patients with borderline ABI (0.91–0.99), the usefulness of antiplatelet therapy to reduce the risk of MI, stroke, or vascular death is uncertain
IIb	B-R	The effectiveness of **dual antiplatelet therapy (aspirin and clopidogrel)** to reduce the risk of cardiovascular ischemic events in patients with symptomatic PAD is not well established
IIb	C-LD	**Dual antiplatelet therapy (aspirin and clopidogrel)** may be reasonable to reduce the risk of limb-related events in patients with symptomatic PAD after lower extremity revascularization
IIb	B-R	The overall clinical benefit of **vorapaxar** added to existing antiplatelet therapy in patients with symptomatic PAD is uncertain

LOE A=high quality evidence from >1 randomized clinical trial (RCT), meta-analyses of high-quality RCTs, ≥1 RCTs corroborated by high-quality registry studies. LOE C-EO=consensus of expert opinion based on clinical experience. LOE B-R=moderate-quality evidence from ≥1 RCTs, meta-analyses of moderate-quality RCTs. LOE C-LD=randomized or nonrandomized observational or registry studies with limitations of design or execution, meta-analyses of such studies, physiological or mechanistic studies in human subjects.

Gerhard-Herman MD et al. *Circulation*. 2017;135(12):e686-e725.

Anti-thrombotic Therapy for Patients with CAD/PAD

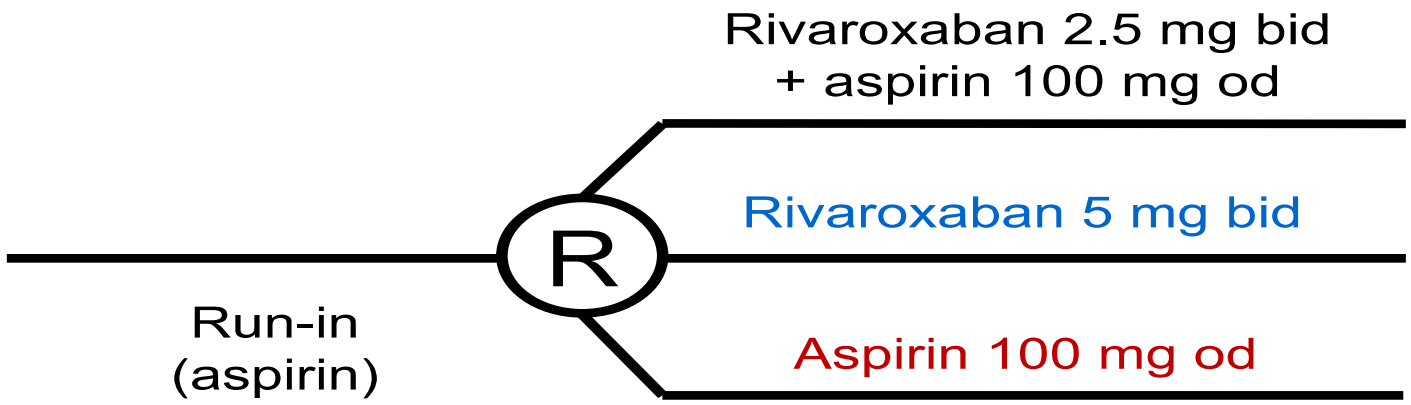


Jones WS and Patel MR. *J Am Coll Cardiol*. 2018;71:352-62.

COMPASS Design

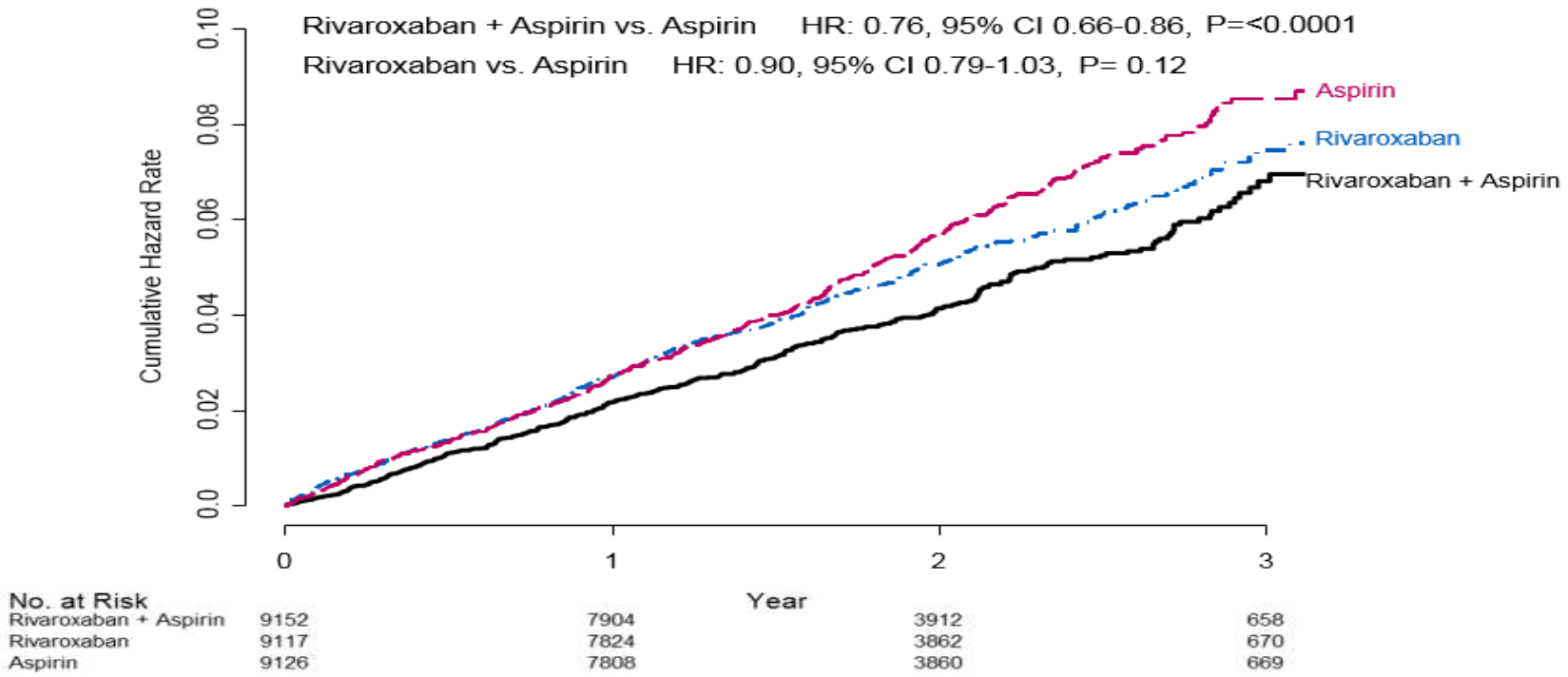
Population Health Research Institute
HEALTH THROUGH KNOWLEDGE

Stable CAD or PAD
2,200 with a primary outcome event



Expected follow up
3-4 years

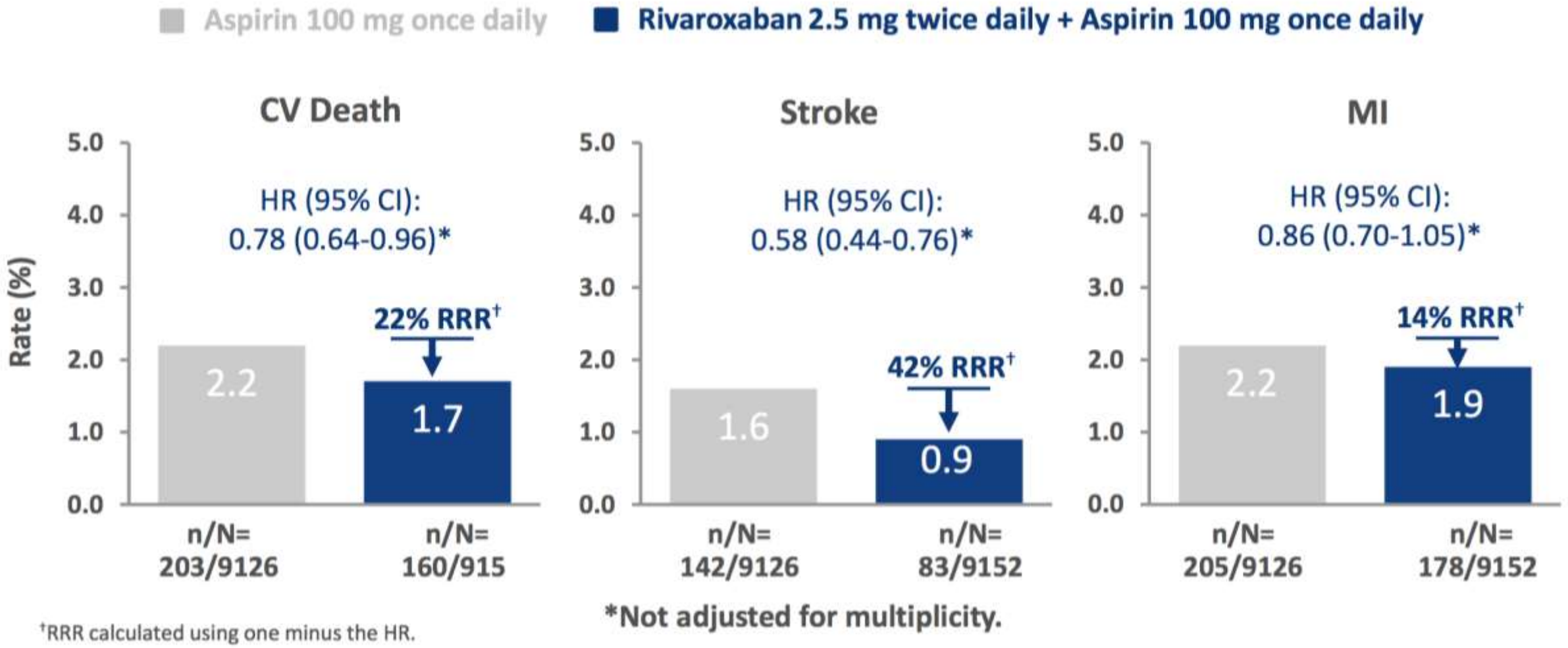
Primary: CV death, stroke, MI



Primary: CV death, stroke, MI

Outcome	R + A N=9,152	R N=9,117	A N=9,126	Rivaroxaban + aspirin vs. aspirin		Rivaroxaban vs. aspirin	
	N (%)	N (%)	N (%)	HR (95% CI)	p	HR (95% CI)	p
CV death, stroke, MI	379 (4.1%)	448 (4.9%)	496 (5.4%)	0.76 (0.66-0.86)	<0.0001	0.90 (0.79-1.03)	0.12

COMPASS: Components of Primary Endpoint



Eikelboom JW et al. *N Engl J Med*. 2017;377:1319-30.

Other Efficacy Endpoints – COMPASS

Outcome	HR (95% CI)	Rate, % (n/N) Rivaroxaban 2.5 mg twice daily + Aspirin 100 mg once daily	Rate, % (n/N) Aspirin 100 mg once daily
Ischemic stroke, myocardial infarction, ALI, or death from CHD	0.72 (0.63-0.83)	3.6 (329/9152)	4.9 (450/9126)
Ischemic stroke, myocardial infarction, ALI, or CV death	0.74 (0.65-0.85)	4.3 (389/9152)	5.7 (516/9126)
Death from any cause*	0.82 (0.71-0.96)	3.4 (313/9152)	4.1 (378/9126)

ALI=acute limb ischemia; CHD=coronary heart disease.

*Not adjusted for multiplicity.

Eikelboom JW et al. *N Engl J Med*. 2017;377:1319-30.

CAD and PAD

Population Health Research Institute
HEALTH THROUGH KNOWLEDGE

Subgroups for primary outcome

Outcome	R + A N=9,152	A N=9,126	Rivaroxaban + Aspirin vs. Aspirin
	N (%)	N (%)	HR (95% CI)
CAD	347 (4.2%)	460 (5.6%)	0.74 (0.65-0.86)
PAD	126 (5.1%)	174 (6.9%)	0.72 (0.57-0.90)

Major Bleeding

Population Health Research Institute
HEALTH THROUGH KNOWLEDGE

Outcome	R + A N=9,152	R N=9,117	A N=9,126	Rivaroxaban + Aspirin vs. Aspirin		Rivaroxaban vs. Aspirin	
	N (%)	N (%)	N (%)	HR (95% CI)	P	HR (95% CI)	P
Major bleeding	288 (3.1%)	255 (2.8%)	170 (1.9%)	1.70 (1.40-2.05)	<0.0001	1.51 (1.25-1.84)	<0.0001
Fatal	15 (0.2%)	14 (0.2%)	10 (0.1%)	1.49 (0.67-3.33)	0.32	1.40 (0.62-3.15)	0.41
Non fatal ICH*	21 (0.2%)	32 (0.4%)	19 (0.2%)	1.10 (0.59-2.04)	0.77	1.69 (0.96-2.98)	0.07
Non-fatal other critical organ*	42 (0.5%)	45 (0.5%)	29 (0.3%)	1.43 (0.89-2.29)	0.14	1.57 (0.98-2.50)	0.06

*Symptomatic.

Update on PAD Patients

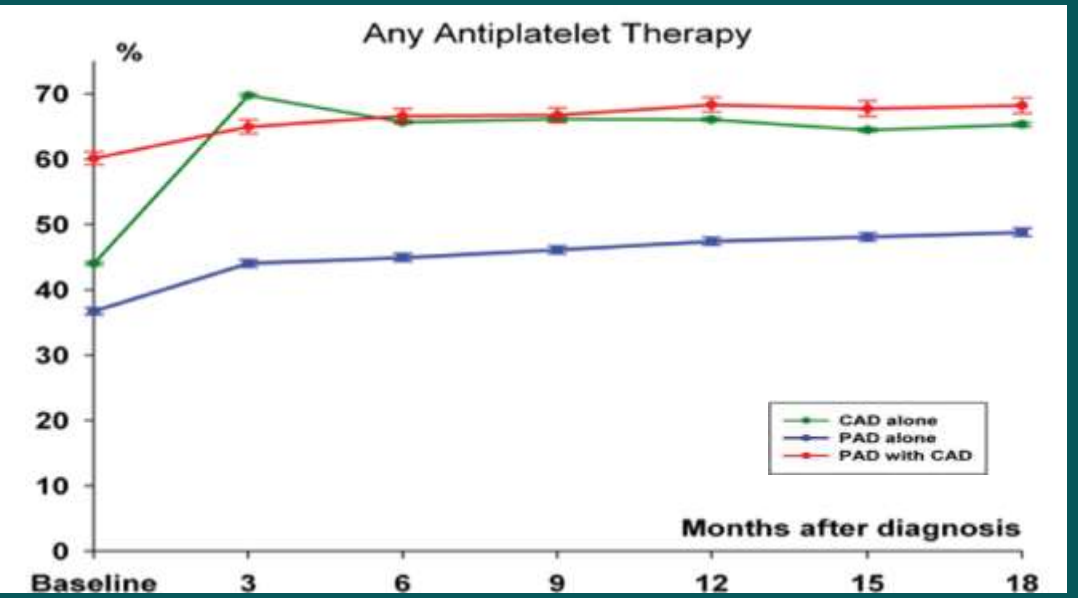
Epidemiology and Prevention

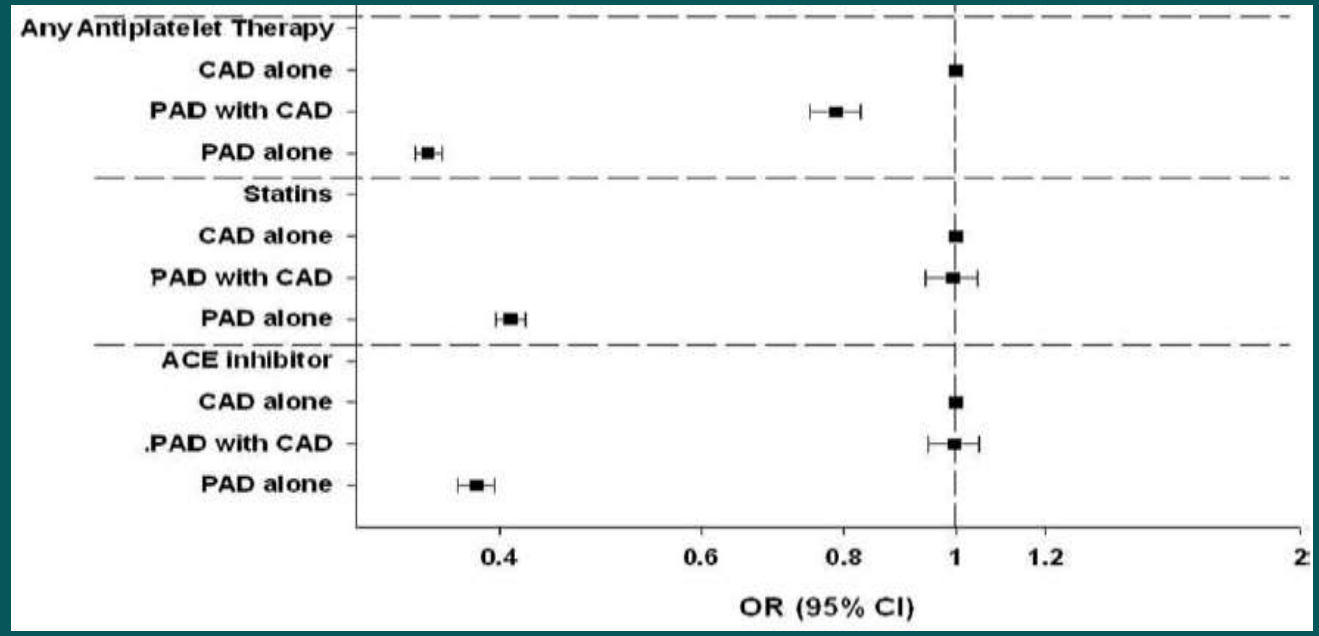
Missed Opportunities

Despite Improvement in Use of Cardioprotective Medications Among Patients With Lower-Extremity Peripheral Artery Disease, Underuse Remains

Sumeet Subherwal, MD, MBA; Manesh R. Patel, MD; Lars Kober, MD, DMSc; Eric D. Peterson, MD, MPH; William S. Jones, MD; Gunnar H. Gislason, MD, PhD; Jeffrey Berger, MD; Christian Torp-Pedersen, MD, DMSc; Emil L. Fosbol, MD, PhD

Wide variation and potentially significant underuse of anti-thrombotic therapy



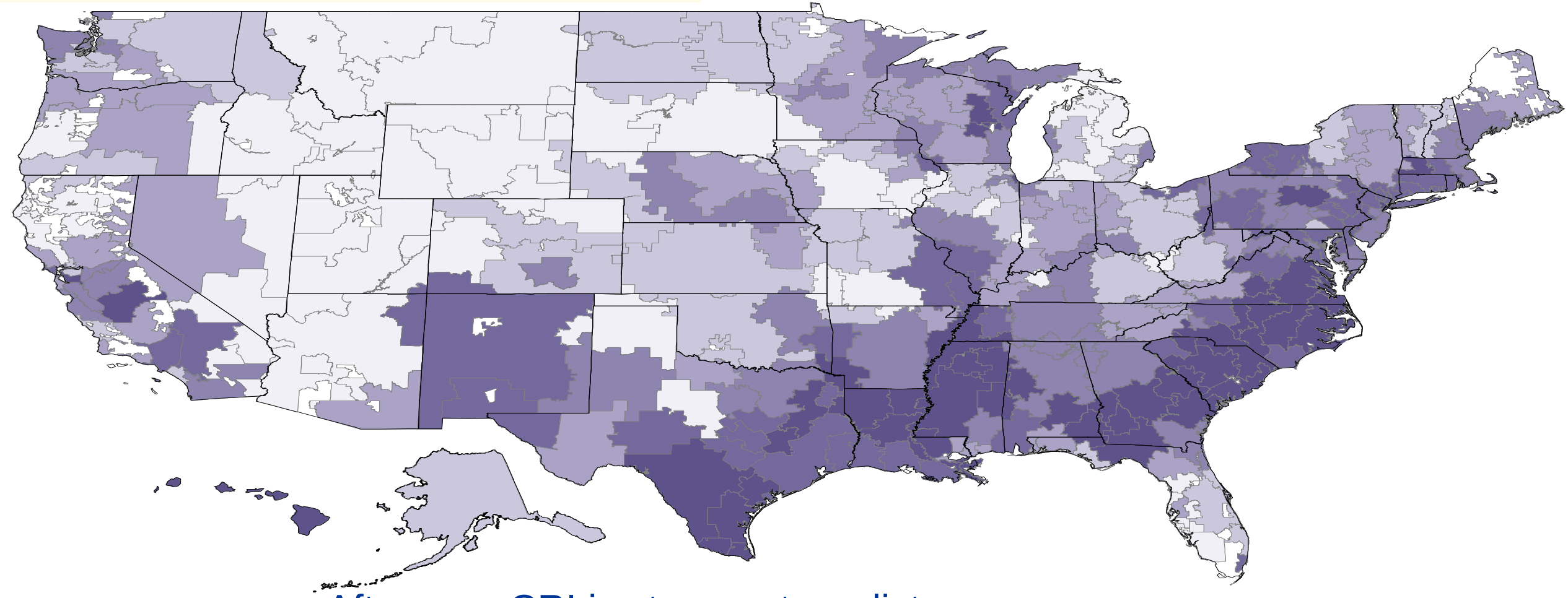


Subherwal S et al. *Circulation*. 2012;126:1345-54.

Temporal Trends and Geographic Variation of Lower-Extremity Amputation in Patients With Peripheral Artery Disease

Results From U.S. Medicare 2000–2008

W. Schuyler Jones, MD,*† Manesh R. Patel, MD,*† David Dai, PHD,*
Sumeet Subherwal, MD, MBA,*† Judith Stafford, MS,* Sarah Calhoun, BS,*
Eric D. Peterson, MD, MPH*†
Durham, North Carolina



After age, CRI is strongest predictor

0.385-0.720 0.722-0.832 0.833-0.916
0.917-1.053 1.060-1.211 1.217-2.106

J Am Coll Cardiol. 2012;60:2230-6.

High mortality risks after major lower extremity amputation in Medicare patients with peripheral artery disease

W. Schuyler Jones, MD,[a,b] Manesh R. Patel, MD,[a,b] David Dai, PhD,[a] Sreekanth Vemulapalli, MD,[b] Sumeet Subherwal, MD, MBA,[a,b] Judith Stafford, MS,[a] and Eric D. Peterson, MD, MPH[a,b] *Durham, NC*

One year MACE rates remain high post amputation with PAD

Table II. Rate of death, MI, and stroke after major LE amputation during the study period

Event	From index procedure to event	All (n = 2,730,742) Rate (%)	95% Lower limit (%)	95% Upper limit (%)	PAD without LE amputation (n = 2,544,404) Rate (%)	95% Lower limit (%)	95% Upper limit (%)	PAD with LE amputation (N = 186,338) Rate (%)	95% Lower limit (%)	95% Upper limit (%)	*P* value, comparing PAD without LE amputation vs PAD with LE amputation
All-cause mortality	1 mo	7.4	7.4	7.4	6.9	6.9	7.0	13.5	13.3	13.6	<.001
	1 y	25.9	25.8	25.9	24.2	24.2	24.3	48.3	48.1	48.6	
	2 y	36.2	36.2	36.3	34.4	34.3	34.4	61.4	61.1	61.6	
	3 y	45.1	45.0	45.1	43.2	43.1	43.2	70.9	70.6	71.1	
MI	1 mo	1.9	1.9	1.9	1.9	1.9	1.9	1.2	1.1	1.2	<.001
	1 y	6.0	6.0	6.0	6.0	6.0	6.1	5.0	4.9	5.1	
	2 y	8.7	8.7	8.7	8.8	8.8	8.8	7.3	7.2	7.4	
	3 y	10.9	10.8	10.9	11.0	11.0	11.1	8.9	8.8	9.1	
Stroke	1 mo	1.7	1.7	1.7	1.8	1.8	1.8	1.0	0.9	1.0	<.001
	1 y	6.6	6.6	6.7	6.8	6.8	6.8	4.3	4.2	4.4	
	2 y	9.7	9.7	9.7	9.9	9.9	10.0	6.2	6.1	6.3	
	3 y	12.1	12.0	12.1	12.4	12.4	12.4	7.5	7.4	7.7	

Am Heart J. 2013;165:809-15.

Peripheral Arterial Testing Before Lower Extremity Amputation Among Medicare Beneficiaries, 2000 to 2010

Sreekanth Vemulapalli, MD; Melissa A. Greiner, MS; W. Schuyler Jones, MD; Manesh R. Patel, MD; Adrian F. Hernandez, MD, MHS; Lesley H. Curtis, PhD

Up to 30% of patients do not get arterial testing prior to amputation in US

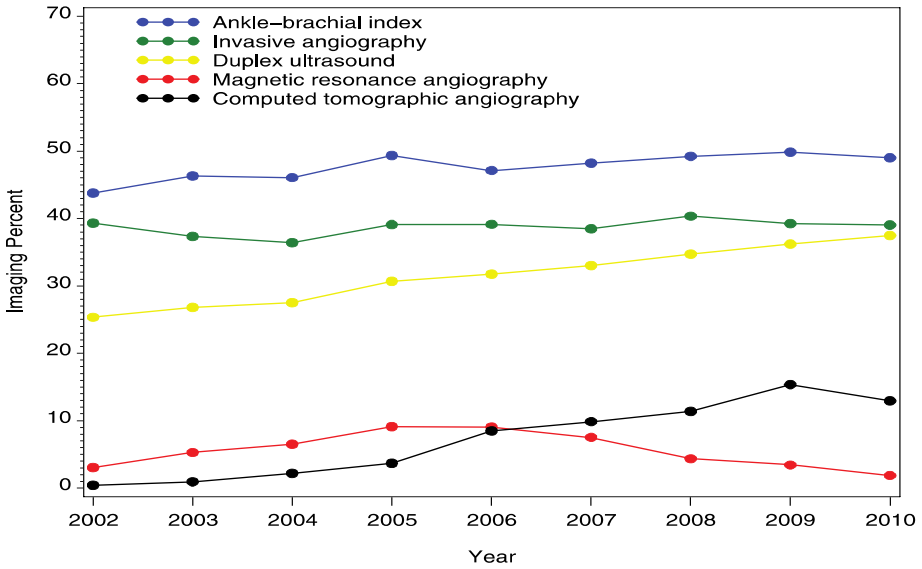


Figure 2. Trends in unadjusted rates of arterial testing before amputation by testing modality, 2002 to 2010.

Table 2. Use of Arterial Testing Before Amputation by Location of Amputation

Test	Location of Amputation, n (%)				*P* Value*
	All Patients (N=17 463)	Foot (n=7343)	Below Knee (n=4804)	Above Knee (n=5316)	
Any arterial testing	11 945 (68.4)	4589 (62.5)	3686 (76.7)	3670 (69.0)	<0.001
Ankle-brachial index	8293 (47.5)	3386 (46.1)	2542 (52.9)	2365 (44.5)	<0.001
Duplex ultrasound	5426 (31.1)	1959 (26.7)	1675 (34.9)	1792 (33.7)	<0.001
Computed tomographic angiography	1169 (6.7)	406 (5.5)	364 (7.6)	399 (7.5)	<0.001
Magnetic resonance angiography	974 (5.6)	391 (5.3)	342 (7.1)	241 (4.5)	<0.001
Invasive angiography	6750 (38.7)	2500 (34.0)	2362 (49.2)	1888 (35.5)	<0.001
Any arterial testing in the previous 2 y	12 512 (71.6)	4853 (66.1)	3820 (79.5)	3839 (72.2)	<0.001

*We tested for differences in patient characteristics by location (foot, below the knee, or above the knee) using χ^2 tests.

Circ Cardiovasc Qual Outcomes. 2014;7:142-50.

COMPASS-PAD

Rivaroxaban with or without aspirin in patients with stable peripheral or carotid artery disease: an international, randomised, double-blind, placebo-controlled trial

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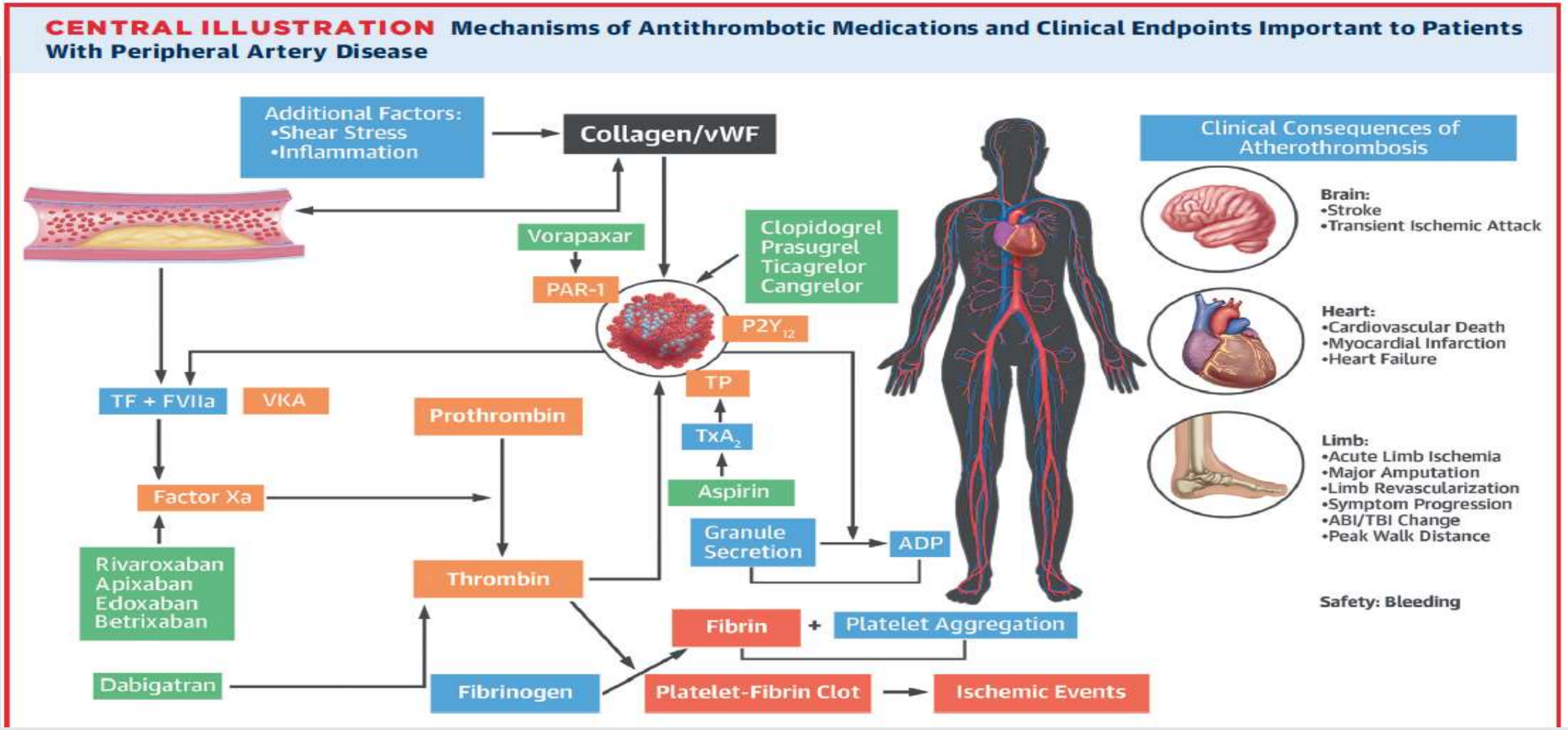
	Low-dose rivaroxaban plus aspirin (n=2492)	Rivaroxaban alone (n=2474)	Aspirin alone (n=2504)
History of PAD			
Previous aorta-femoral or lower extremity bypass surgery, PTA of iliac, or infrainguinal artery	668 (26·8)	703 (28·4)	674 (26·9)
History of intermittent claudication and ABI <0·90 or substantial peripheral arterial stenosis ≥50%	1142 (45·8)	1120 (45·3)	1140 (45·5)
Previous limb or foot amputation	116 (4·7)	107 (4·3)	112 (4·5)
Symptomatic PAD of lower extremities*	1409 (56·5)	1361 (55·0)	1359 (54·3)
Carotid artery disease†	617 (24·8)	622 (25·1)	680 (27·2)
Symptomatic PAD‡	2026 (81·3)	1983 (80·1)	2039 (81·4)
CAD and ABI <0·90§	466 (18·7)	491 (19·8)	465 (18·6)
ABI			
Normal ≥0·90	1226 (49·2)	1187 (48)	1191 (47·6)
0·70–0·90	979 (39·3)	949 (38·4)	984 (39·3)
≤0·70	211 (8·5)	268 (10·8)	249 (9·9)
eGFR <60 mL/min	688 (27·6)	681 (27·5)	706 (28·2)

Limb Outcomes

Outcome	R + A N=2492	R N=2474	A N=2504	Riva + aspirin vs aspirin		Riva vs aspirin	
	N (%)	N (%)	N (%)	HR (95% CI)	P	HR (95% CI)	P
MALE	30 (1.2)	35 (1.4)	56 (2.2)	0.54 (0.35-0.84)	0.005	0.63 (0.41-0.96)	0.03
Major amputation	5 (0.2)	8 (0.3)	17 (0.7)	0.30 (0.11-0.80)	0.01	0.46 (0.20-1.08)	0.07

Anand SS et al. *Lancet*. 2018;391:219-29.

Anti-thrombotic Therapy for Patients with PAD



Jones WS and Patel MR. *J Am Coll Cardiol*. 2018;71:352-62.

Conclusions – Emerging Medical Tx with CAD/PAD

- Anti-platelet therapy alone may not be as effective as we once thought
- (Dual pathway inhibition) Rivaroxaban 2.5 mg BID + ASA reduced MACE, MALE+ Amputation
- PAD patients (polyvascular patients) high risk and derive benefit
- Voyager PAD ongoing – for post PVI patients

Factor Xa Inhibitors in Patients with Heart Failure, Sinus Rhythm, and Coronary Disease

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COMMANDER HF

COMMANDER HF: Oversight Committees

Steering Committee Members	Independent Data Monitoring Committee Members
Faiez Zannad, Barry Greenberg, Co-Chairs Stefan D. Anker, William M. Byra, John G.F. Cleland, Mihai Gheorghiade (deceased), Carolyn S.P. Lam, Mandeep R. Mehra, James Neaton, Dirk J. van Veldhuisen	W. Douglas Weaver, Henry J. Dargie, Marc Klapholz, Bertram Pitt, Stuart J. Pocock, Yoshihiko Seino

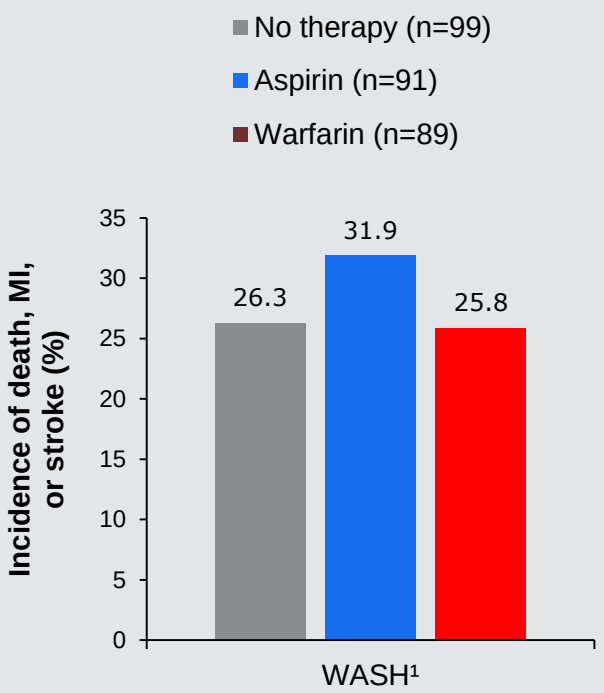
Background and Rationale (1/4)

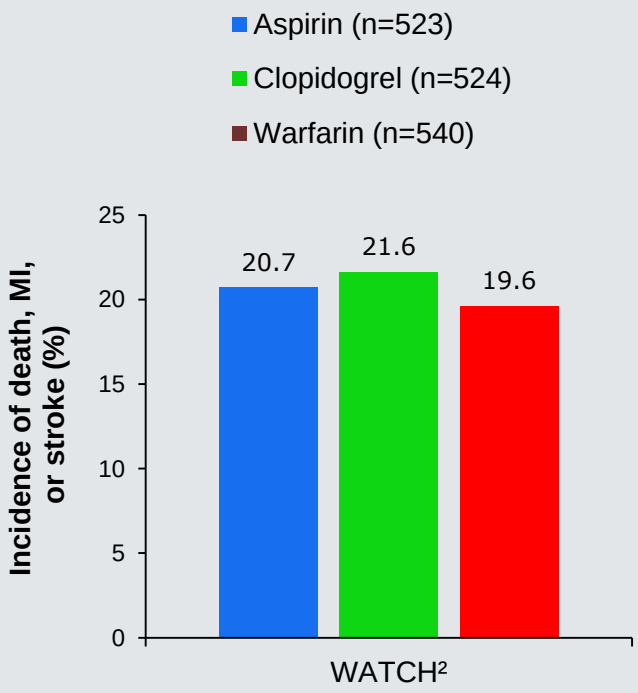
- Despite the remarkable progress in treating chronic HFrEF, following an episode of worsening chronic heart failure, rates of readmission and death remain high.[1,2]
- Trials in worsening HF of a large number of therapies targeting a variety of mechanisms have failed so far to improve outcome.
- Activation of thrombin-related pathways may contribute to disease progression by inducing inflammation, endothelial dysfunction, and arterial and venous thrombosis.[3]

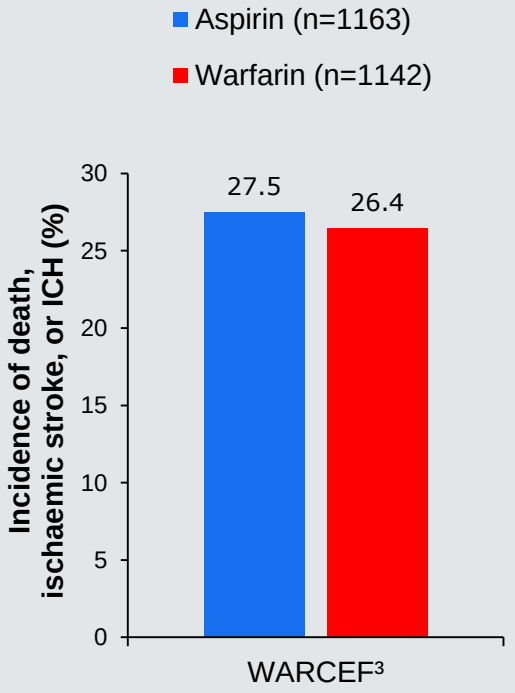
1. Maggioni AP et al. *Eur J Heart Fail.* 2013;15:808-17.
2. Solomon SD et al. *Circulation.* 2007;116:1482-7.
3. Borissoff JI et al. *Cardiovas Res.* 2009;82:392-403.

Background and Rationale (2/4)

Warfarin has not improved outcomes for patients with HFrEF who are in sinus rhythm, and is associated with an increase in bleeding complications.







1. Cleland JGF et al. *Am Heart J.* 2004;148:157-64. 2. Massie BM et al. *Circulation.* 2009;119:1616-24. 3. Homma S et al. *N Engl J Med.* 2012;366:1859-69. Zannad F et al. *Eur J Heart Fail.* 2015;17:735-42.

Background and Rationale (3/4)

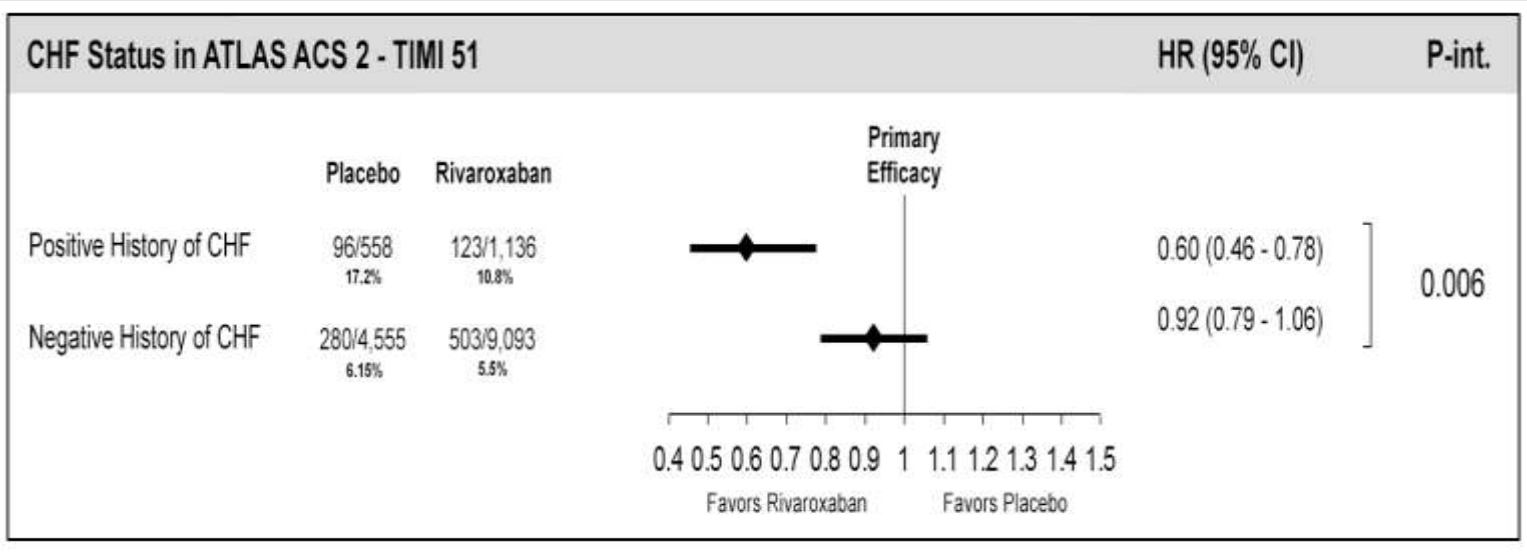
- Unlike warfarin, rivaroxaban directly targets thrombin generation
- In doses of 10 to 20 mg daily, approved for
  - Prevention and treatment of venous thromboembolism, and
  - the prevention of stroke or systemic embolism in patients with AF
- Lower doses of rivaroxaban (2.5 mg twice daily), in combination with antiplatelet agents, have been found to reduce cardiovascular mortality, MI, and stroke
  - in patients with acute coronary syndromes (ATLAS ACS TIMI 51)
  - or stable coronary artery disease (COMPASS)

Background and Rationale (4/4)

Rivaroxaban significantly reduced morbidity and mortality in patients with history of HF and:

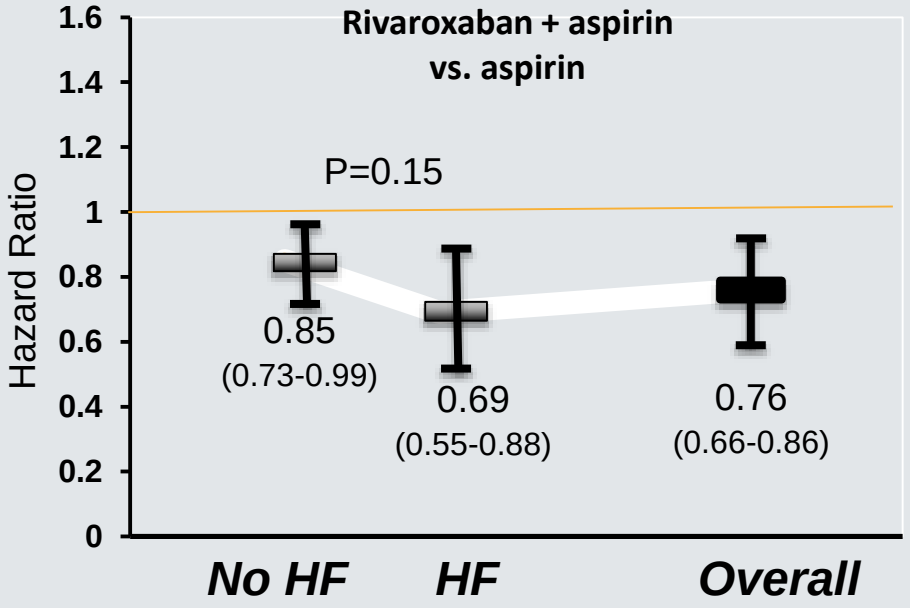
Recent ACS
ATLAS ACS 2-TIMI 51

Primary efficacy endpoint among subjects with history of CHF vs patients w/o prior history of CHF



Korjian S et al. *Am J Cardiology*. (in press).

Chronic CAD
COMPASS



Branch K et al. ESC HFA, Vienna.

Objectives

The COMMANDER HF trial was designed to test the hypothesis that, compared with placebo, rivaroxaban 2.5 mg twice daily added to background antiplatelet therapy could reduce rates of death and cardiovascular events in patients with recent worsening of chronic HF, reduced ejection fraction, CAD, and no AF.

Inclusion and Exclusion Criteria

Key Inclusion Criteria	Key Exclusion Criteria
• Chronic HF (>3mths) with reduced LVEF (≤40%) • Within 21 days after an episode of hospitalization for worsening HF • Elevated plasma BNP (≥200 pg/mL) or NT-proBNP (≥800 pg/mL) during the index event • CAD (Hx MI, Revasc, angiogram, ECG+Echo) • Receiving appropriate guidelines medical treatment* • No anticoagulation	• Bleeding risk, AF, acute MI • Planned cardiac surgery within 28 days (eg, PCIs and EP devices) • History of severe valvular disease, chronic episodes of ventricular tachycardia, severe peptic ulcer disease, or HIV • eGFR <20 mL/min • Prior stroke (within 90 days) • Anemia (Hb<8 g/dL) or severe thrombocytopenia (platelets <50,000/μL)

*The dose of ASA was to be 100 mg or less per day, unless not clinically appropriate.
Dual antiplatelet therapy (ie, ticagrelor, clopidogrel, ticlopidine, prasugrel) was allowed where indicated.

Study Outcomes

Primary Efficacy Outcome

- Composite of all-cause mortality, MI, or stroke following an index event

Principal Safety Outcome

- Composite of fatal bleeding, or bleeding into a critical space (intracranial, intraspinal, intraocular, pericardial, intra-articular, retroperitoneal, intramuscular with compartment syndrome) with a potential for permanent disability

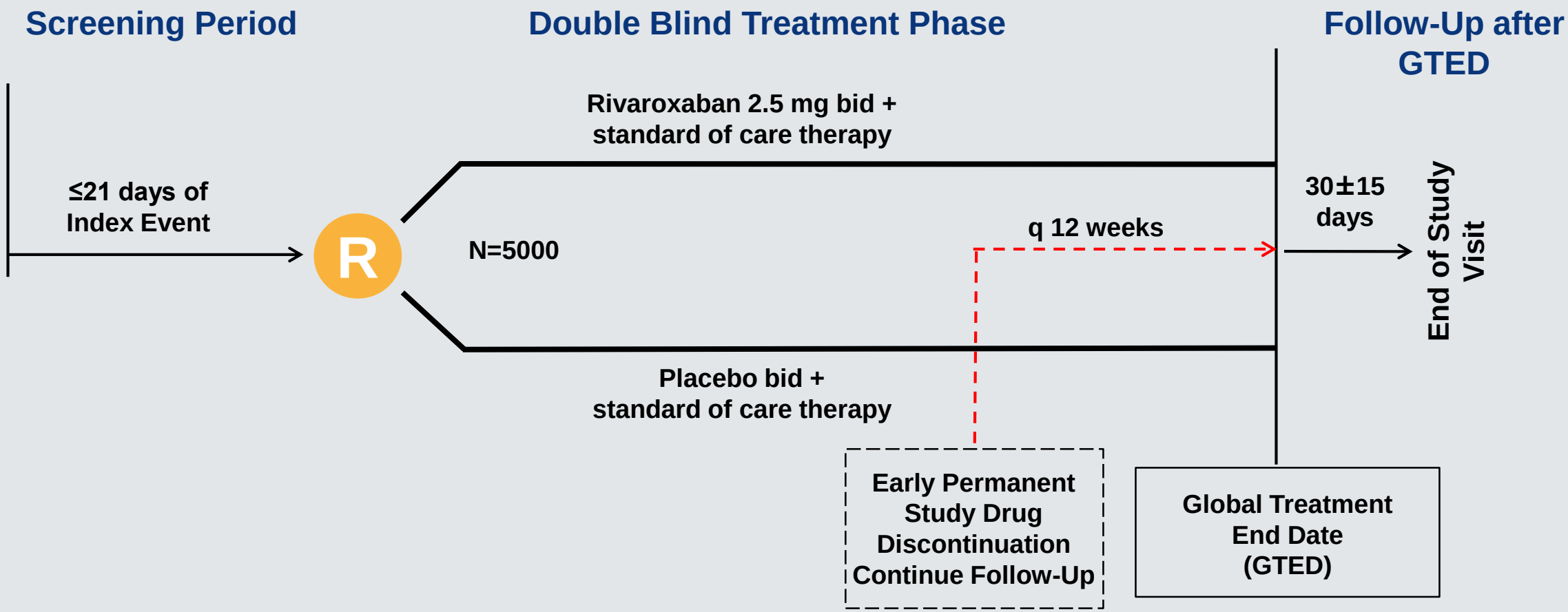
Secondary Efficacy Outcomes

- Composite of CV mortality or rehospitalization for worsening of HF
- CV mortality
- Rehospitalization for worsening of HF
- Rehospitalization for CV events

Other Safety Outcomes

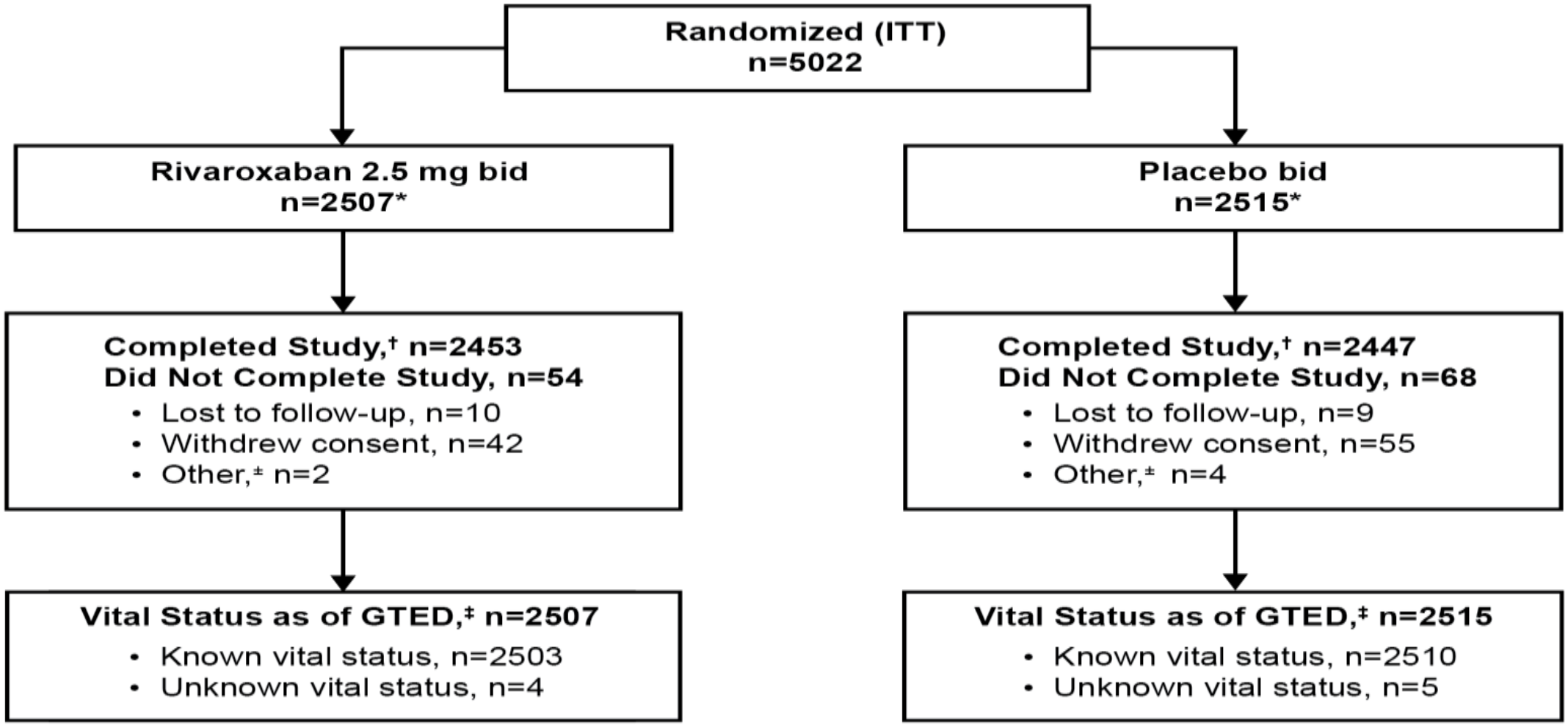
- Bleeding events requiring hospitalization
- Major bleeding events using the International Society on Thrombosis and Haemostasis (ISTH) bleeding criteria

Study Design



Zannad F et al. *Eur J Heart Fail*. 2015:17:735-42.

Randomization



Median Follow-up Time: 21.1 Months

*Three patients, 1 in the rivaroxaban 2.5 mg bid group and 2 in the placebo group, were randomized twice; only the 1st randomization was counted.
†Completed study: patients who died or were followed according to the visit schedule until the End of Study Visit.
±Other category primarily includes patients at sites in Ukraine and Turkey affected by local military action.
‡Vital status was collected as of the GTED (March 5, 2018), which included all sources allowed by regulations.
GTED=Global Treatment End Date.

Key Baseline Characteristics (ITT)

Characteristic	Rivaroxaban (N=2507)	Placebo (N=2515)
Age, yr	66.5±10.1	66.3±10.3
Female sex, n (%)	551 (22.0)	599 (23.8)
Race, n (%)		
White	2063 (82.3)	2065 (82.1)
Black or African American	29 (1.2)	36 (1.4)
Asian	362 (14.4)	365 (14.5)
Other	53 (2.1)	49 (1.9)
Region, n (%)		
Eastern Europe	1610 (64.2)	1614 (64.2)
North America	74 (3.0)	75 (3.0)
Asia Pacific	367 (14.6)	366 (14.6)
Latin America	229 (9.1)	229 (9.1)
Western Europe and South Africa	227 (9.1)	231 (9.2)
Body mass index (kg/m^2)	27.6±5.1	27.8±5.3
eGFR (mL/min/1.73 m^2), n (%)		
<30	81 (3.2)	82 (3.3)
30 to <60	884 (35.3)	898 (35.7)
60 to <90	1101 (43.9)	1137 (45.2)
≥90	441 (17.6)	398 (15.8)

Key Baseline Characteristics (ITT) (cont.)

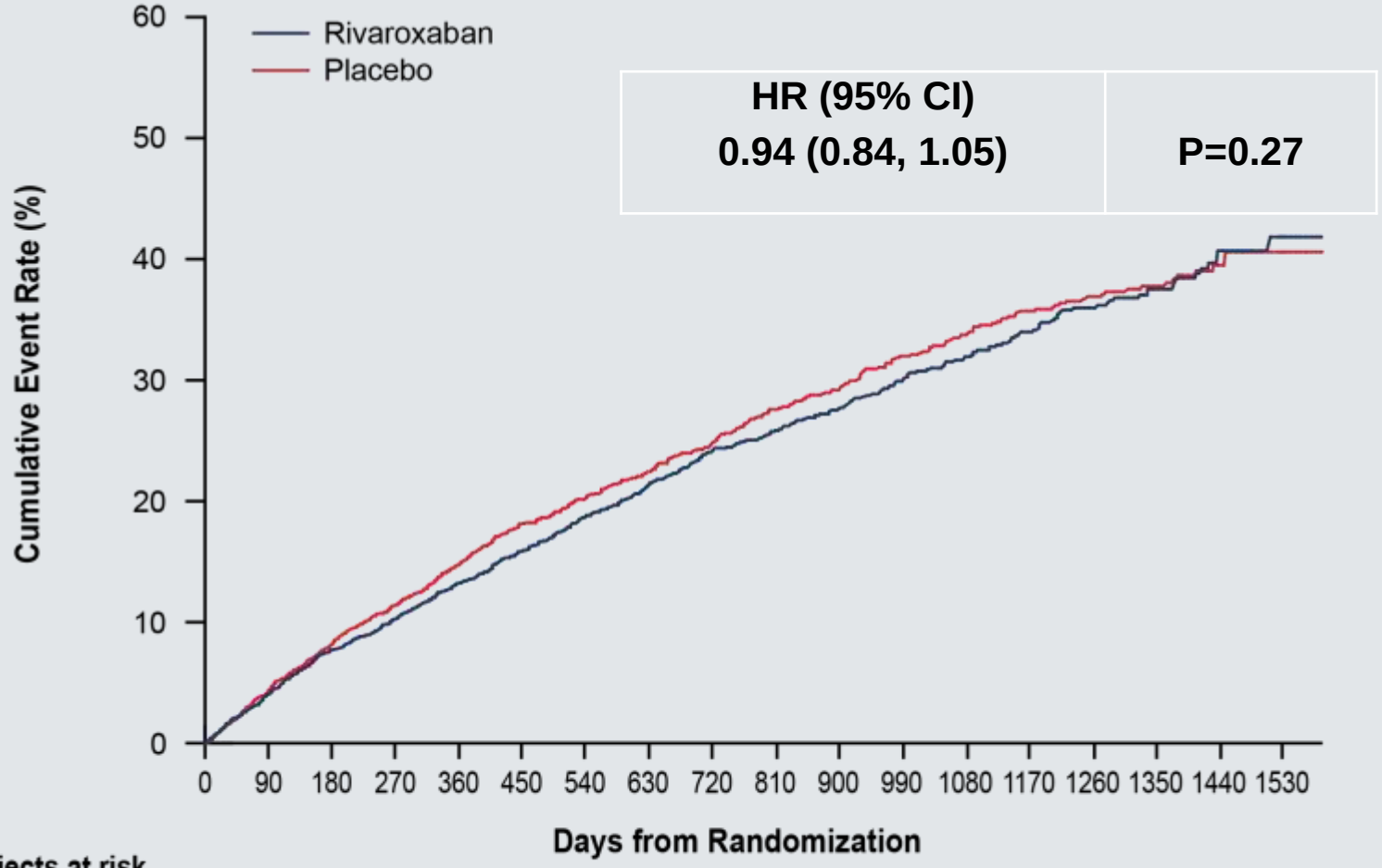
Characteristic	Rivaroxaban (N=2507)	Placebo (N=2515)
Clinical features of HF		
BNP (pg/mL) (IQR)	702.0 (403.4-1237.0)	695.5 (380.0-1266.3)
NT-proBNP (pg/mL) (IQR)	2840.0 (1537.0-6394.0)	2900.0 (1520.0-6270.5)
D-dimer (ug/L) (IQR)	360 (215-680)	360 (215-650)
Ejection fraction (IQR) (%)	35 (28-38)	34 (27-38)
New York Heart Association classification, n (%)		
I	80 (3.2)	69 (2.7)
II	1122 (44.8)	1096 (43.6)
III	1208 (48.2)	1254 (49.9)
IV	96 (3.8)	96 (3.8)
Medical history, n (%)		
MI	1911 (76.2)	1892 (75.2)
Stroke	208 (8.3)	245 (9.7)
Diabetes	1024 (40.8)	1028 (40.9)
Hypertension	1897 (75.7)	1886 (75.0)

Baseline Therapies (ITT)

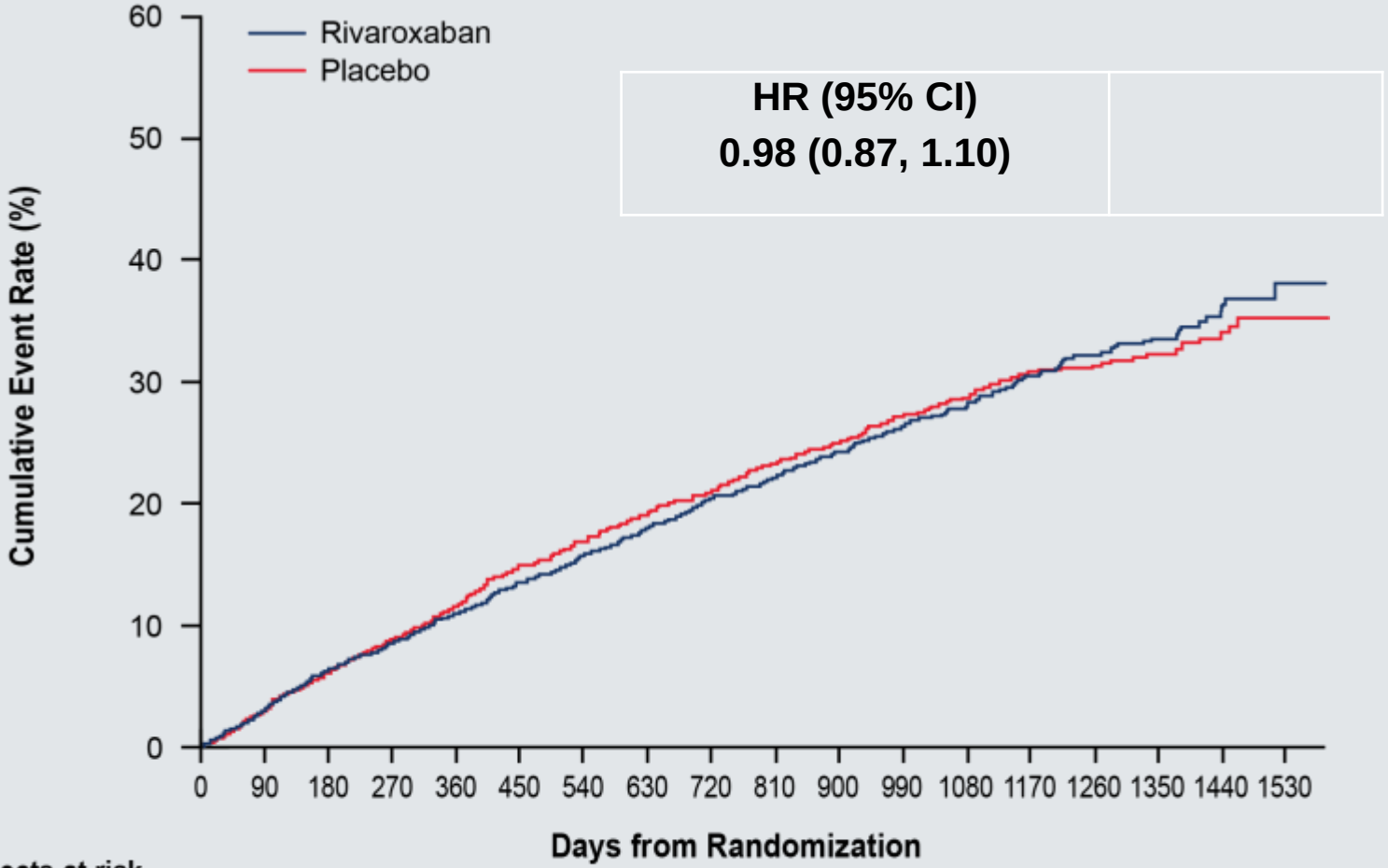
	Rivaroxaban (N=2507)	Placebo (N=2515)
Diuretic use, n (%)	2495 (99.5)	2504 (99.6)
Angiotensin-converting enzyme inhibitor use, n (%)	1813 (72.3)	1779 (70.7)
Angiotensin receptor blocker use, n (%)	544 (21.7)	541 (21.5)
Angiotensin receptor-neprilysin inhibitor use, n (%)	18 (0.7)	23 (0.9)
Angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use, n (%)	2346 (93.6)	2314 (92.0)
Nitrate use, n (%)	528 (21.1)	480 (19.1)
Hydralazine use, n (%)	24 (1.0)	31 (1.2)
Beta blocker use, n (%)	2300 (91.7)	2342 (93.1)
Mineralocorticoid Receptor Antagonist use, n (%)	1918 (76.5)	1922 (76.4)
Digoxin use, n (%)	223 (8.9)	210 (8.3)
Aspirin use, n (%)	2329 (92.9)	2346 (93.3)
Thienopyridine use, n (%)	1043 (41.6)	972 (38.6)
Aspirin vs. dual antiplatelet use, n (%)		
Aspirin alone	1422 (56.7)	1507 (59.9)
Thienopyridine alone	136 (5.4)	133 (5.3)
Dual antiplatelet therapy	907 (36.2)	839 (33.4)
None	42 (1.7)	36 (1.4)
Cardiac Devices	345 (13.8)	316 (12.6)

Results

Primary Efficacy Outcome (ITT, All-cause mortality, MI, or stroke)



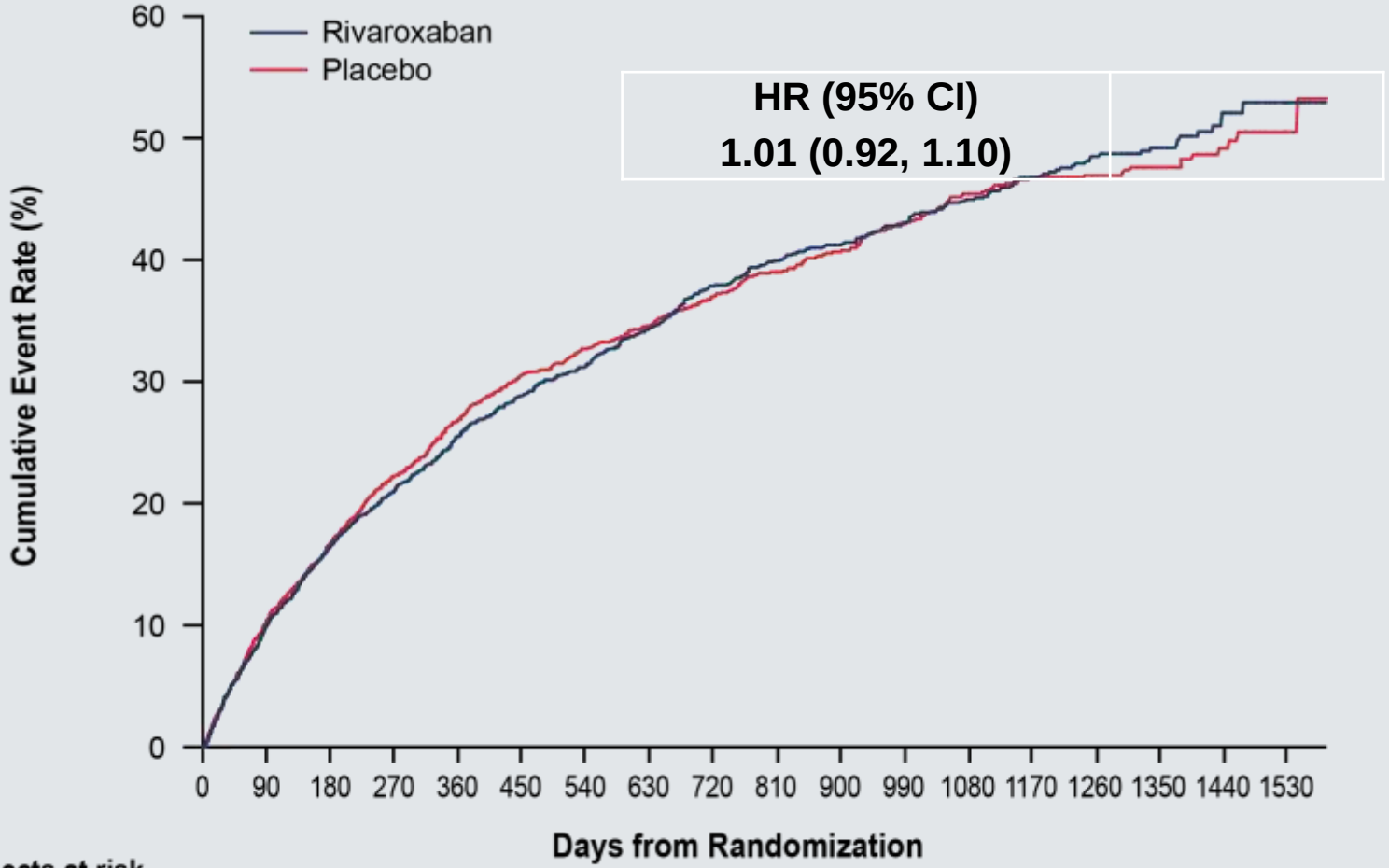
All-Cause Mortality (ITT)



Subjects at risk

Rivaroxaban	2507	2429	2342	2200	1928	1683	1433	1236	1018	854	698	616	532	447	346	252	130	48
Placebo	2515	2437	2353	2204	1919	1653	1415	1219	1007	850	703	622	539	457	359	257	137	48

Secondary Efficacy Outcome (CV Death or Rehospitalization for Worsening of HF) (ITT)



Subjects at risk

Rivaroxaban	2507	2252	2077	1877	1585	1353	1145	971	773	650	531	475	406	341	259	184	94	29
Placebo	2515	2249	2075	1860	1557	1313	1100	946	766	644	532	473	403	346	267	187	96	36

Secondary and Exploratory Efficacy Outcomes (ITT)

	Rivaroxaban		Placebo		Rivaroxaban vs Placebo
Outcomes	n (%)	Event Rate/ (100 pt-yr)	n (%)	Event Rate/ (100 pt-yr)	HR (95% CI)
CV death or RHHF	932 (37.2)	23.32	929 (36.9)	23.46	0.99 (0.91, 1.09)
CV death	453 (18.1)	9.46	476 (18.9)	9.96	0.95 (0.84, 1.08)
RHHF	689 (27.5)	17.24	691 (27.5)	17.45	0.98 (0.89, 1.09)
RHCV	543 (21.7)	13.30	572 (22.7)	14.04	0.95 (0.84, 1.07)
All-cause mortality or RHHF (composite)	993 (39.6)	24.84	973 (38.7)	24.57	1.01 (0.92, 1.10)
Symptomatic deep vein thrombosis	5 (0.2)	0.10	7 (0.3)	0.15	0.71 (0.23, 2.24)
Symptomatic pulmonary embolism	11 (0.4)	0.23	9 (0.4)	0.19	1.23 (0.51, 2.96)

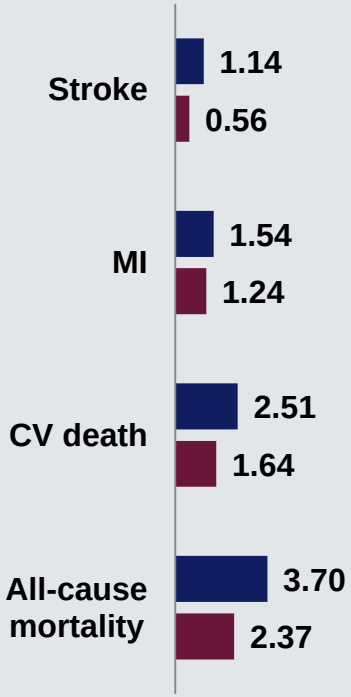
Safety Outcome

	Rivaroxaban (N=2499)		Placebo (N=2509)		Rivaroxaban vs Placebo	P value
Outcomes	n (%)	Event Rate/ (100 pt-yr)	n (%)	Event Rate/ (100 pt-yr)	HR (95% CI)	Log-rank P value
Principal safety (composite)	18 (0.7)	0.44	23 (0.9)	0.55	0.80 (0.43, 1.49)	0.484
Fatal bleeding	9 (0.4)	0.22	9 (0.4)	0.22	1.03 (0.41, 2.59)	0.951
Bleeding in critical space with potential for permanent disability	13 (0.5)	0.32	20 (0.8)	0.48	0.67 (0.33, 1.34)	0.253
ISTH major bleeding	82 (3.3)	2.04	50 (2.0)	1.21	1.68 (1.18, 2.39)	0.003
ISTH: HGB decreases ≥2 g/dL	55 (2.2)	1.37	30 (1.2)	0.73	1.87 (1.20, 2.91)	0.005
ISTH: transfusions ≥2 Units	31 (1.2)	0.77	18 (0.7)	0.43	1.74 (0.98, 3.12)	0.058
ISTH: critical bleeding sites	25 (1.0)	0.62	23 (0.9)	0.56	1.12 (0.63, 1.97)	0.699
ISTH: fatal outcome	3 (0.1)	0.07	7 (0.3)	0.17	0.45 (0.12, 1.72)	0.228
Bleeding requiring hospitalization	61 (2.4)	1.52	48 (1.9)	1.16	1.30 (0.89, 1.90)	0.170

Conclusion

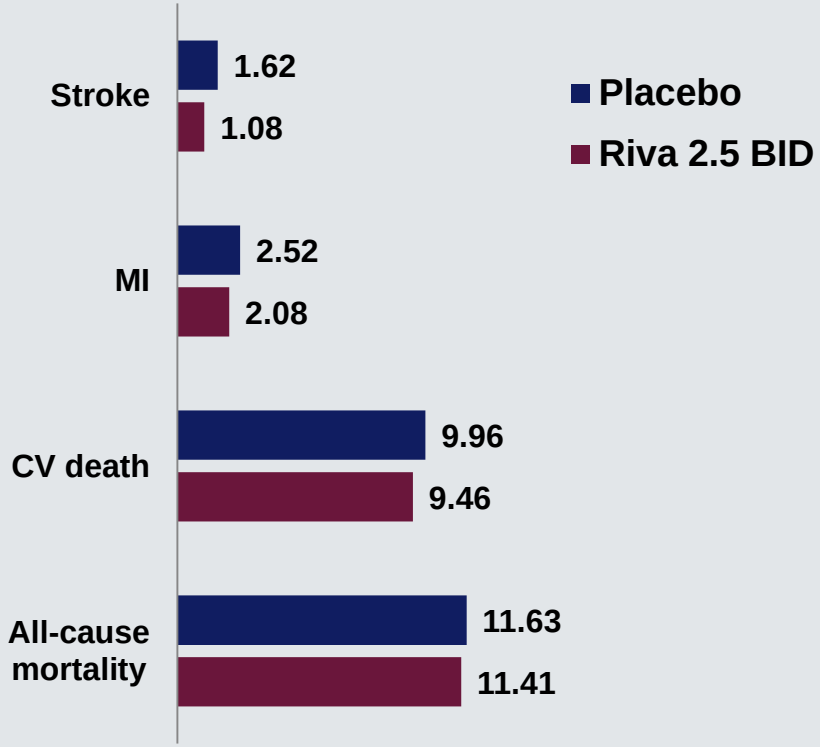
In patients with recent worsening of chronic HF and reduced ejection fraction who also have underlying CAD and are not in AF, low-dose rivaroxaban, when added to guideline-based therapy, does not improve the composite of all-cause mortality, MI, or stroke, nor does it favorably influence HF rehospitalization

COMPASS
Chronic stable HF subgroup



Event rate for 100 pt-yr

COMMANDER HF
Post HF hospitalization



- COMMANDER HF enrolled HF patients at high risk, after recent HF hospitalization.
- It is likely that in this specific population, HF deaths, rather than deaths mediated by atherothrombotic events, contributed to a substantial proportion of all deaths.

Not intended for direct comparison.

Zannad F et al. *N Engl J Med*. (in press). Branch K, presented at Heart Failure 2018, abstract 1591, data on file with permission from author.

Analysis of Thromboembolic Events

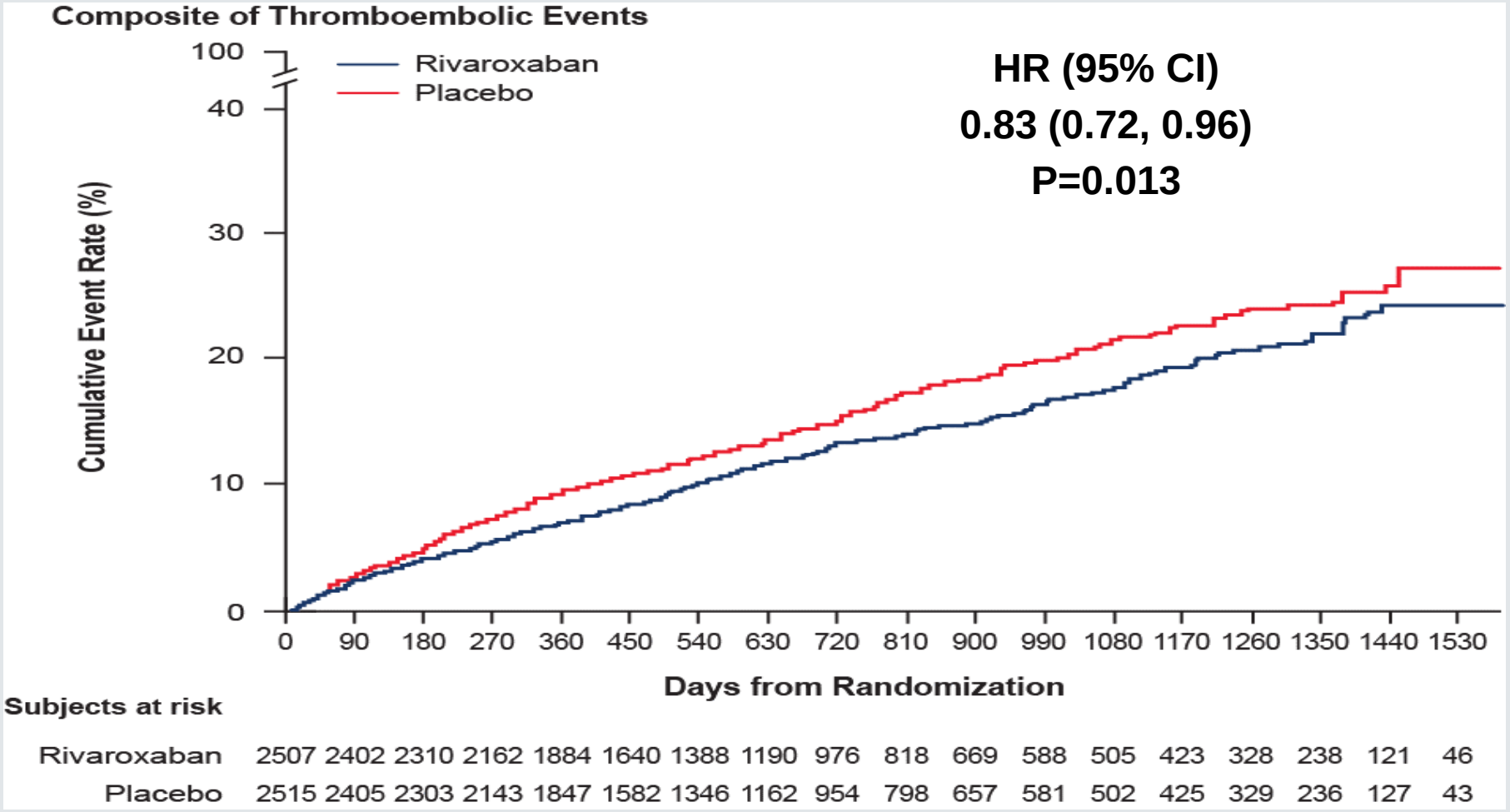
- An effect of rivaroxaban in reducing risk of thrombotic events might have been masked by the preponderance of pump failure-related events

- Would low-dose rivaroxaban be superior to placebo in reducing the risk of ongoing thrombotic events in patients enrolled in COMMANDER HF?

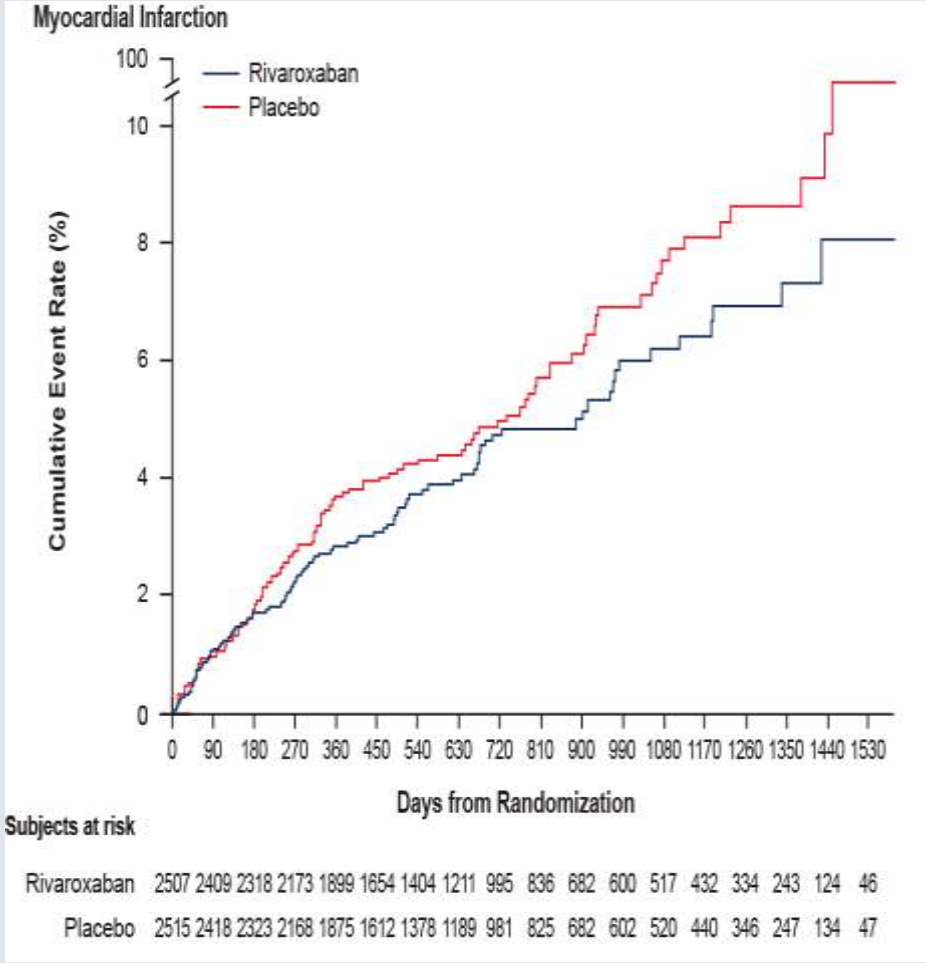
Analysis of Thromboembolic Events

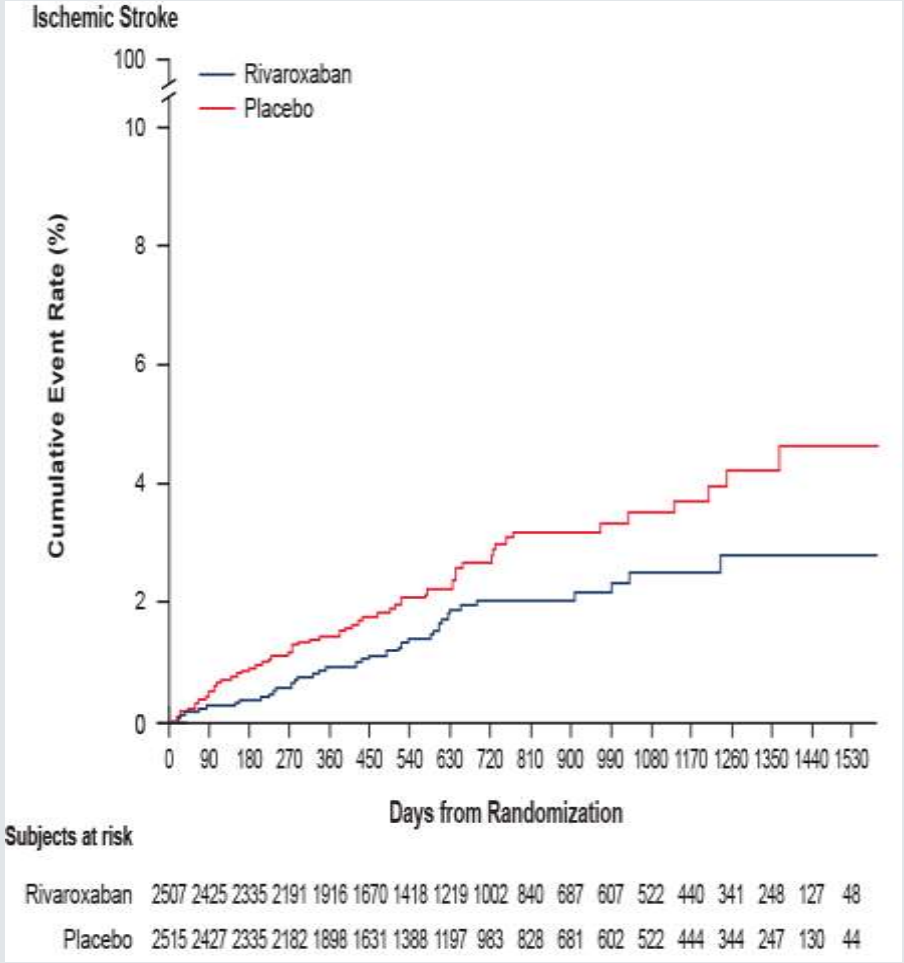
- Although post hoc, this analysis focused on pre-defined events
- The thromboembolic composite endpoint included: MI, ischemic stroke, sudden or unwitnessed death, symptomatic pulmonary embolism and symptomatic deep venous thrombosis
  - Overall, 14.6% of patients experienced such a thromboembolic event over a mean follow-up of 19.6 months

KM Estimates for the Thromboembolic Event Composite



KM Curves for MI and Stroke





Extended Thromboprophylaxis in Medically Ill Patients: The MARINER Trial

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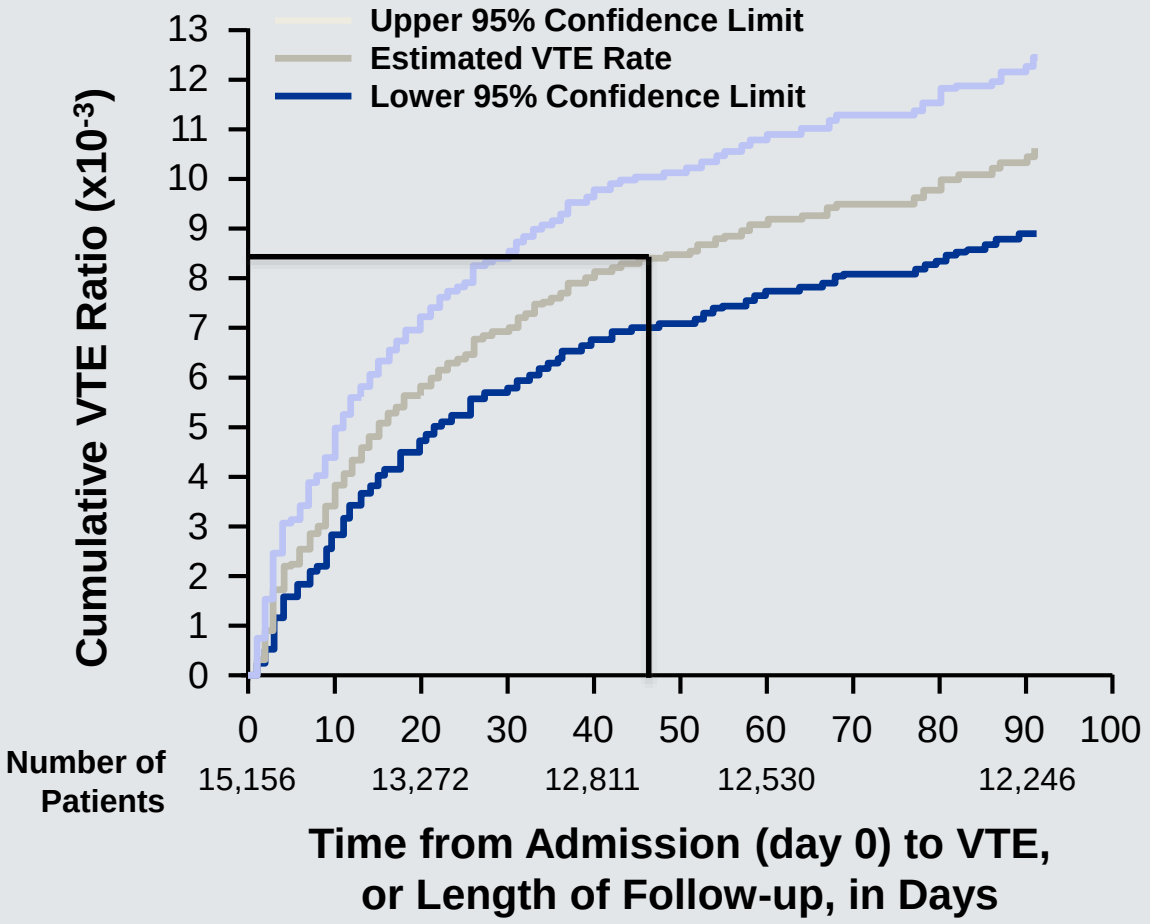
Scope of the Problem in Hospitalized Medical Patients

- An estimated 8 million acutely ill medical patients at risk of VTE are hospitalized annually in the US[1]
  - The number is approximately 12 million in the European Union[2]
- Significant unmet medical need exists for VTE prevention for the acutely ill medical population, especially post-hospital discharge
  - 50 – 70% of symptomatic VTEs and 70-80% of fatal PEs occur in acute medically ill non-surgical patients[3,4]
  - In subgroups, the risk of symptomatic venous thromboembolism, including fatal pulmonary embolism, may present in 3% of patients, accounting for >400,000 VTE and fatal PE events
  - Rate of symptomatic VTE more than doubles over the first 21 days post-discharge and is associated with a five-fold increase of fatal PE within 45 days[5]

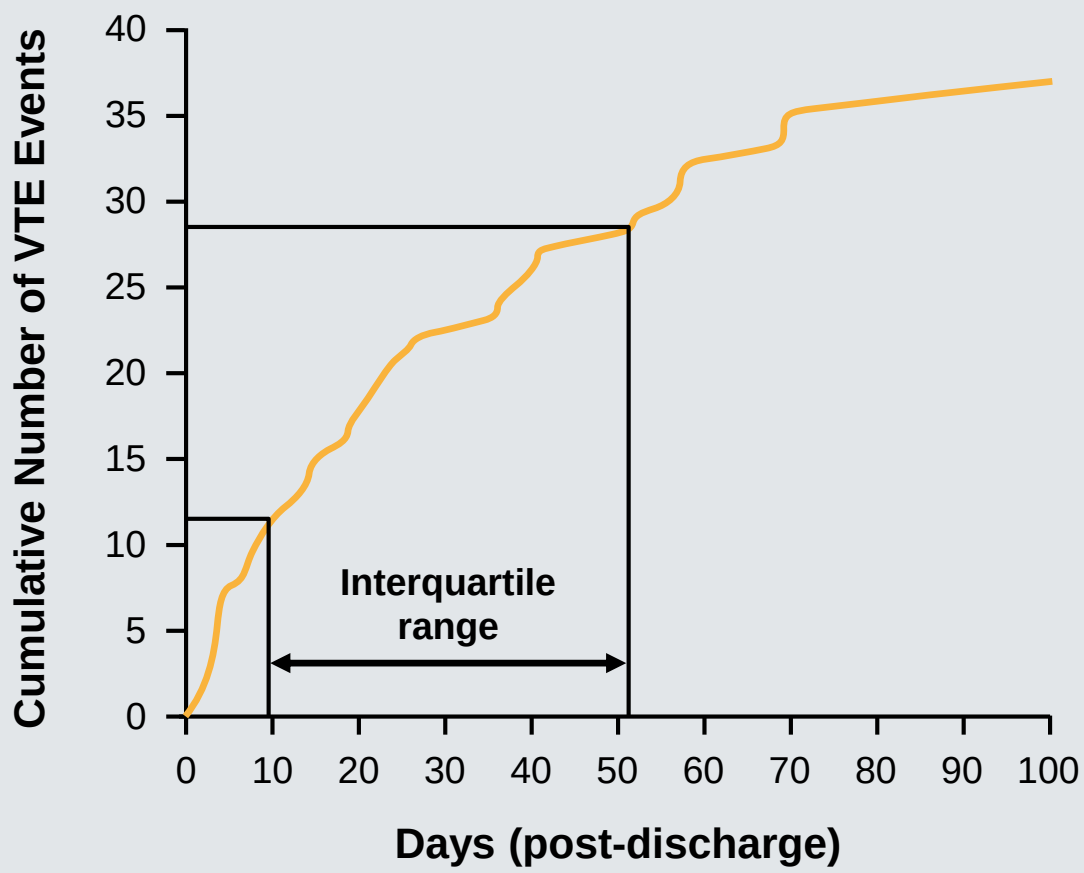
1. Anderson FA et al. *Am J Hematol*. 2007;82:777-82. 2. Cohen AT et al. *Thromb Haemost*. 2007;98:756-64. 3. Goldhaber SZ et al. *Chest*. 2000;118:1680-4.
4. Kahn SR et al. *Chest*. 2012;141(2 Suppl):e195S-e226S. 5. Spyropoulos AC et al. *Chest*. 2011;10.1378;10-19.

VTE Risk Extends Beyond Hospitalization in Medical Patients

Medically Ill Patients

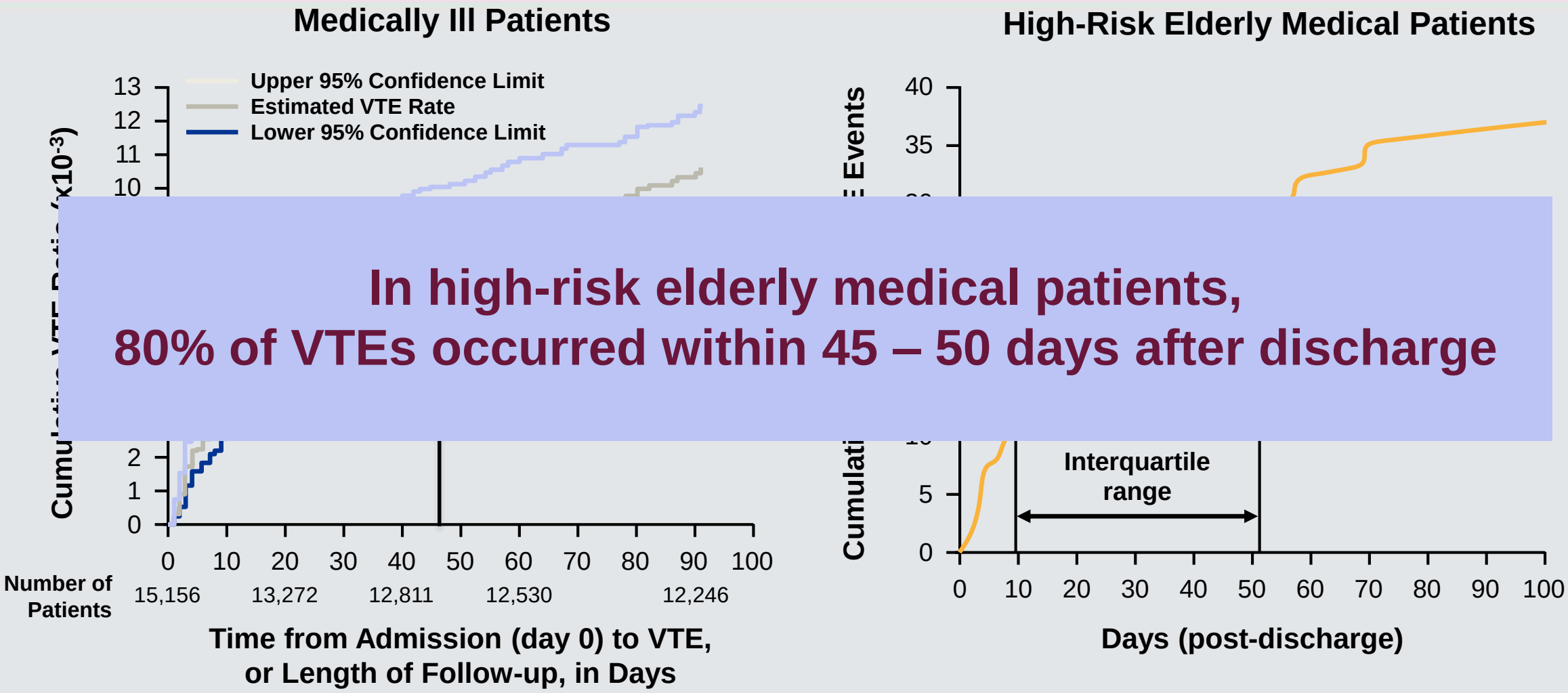


High-Risk Elderly Medical Patients



Spyropoulos AC et al. *Chest*. 2011;140:706-14. Hull RD et al. *Clin Appl Thromb Hemost*. 2013;19:357-62.

VTE Risk Extends Beyond Hospitalization in Medical Patients



In high-risk elderly medical patients,
80% of VTEs occurred within 45 – 50 days after discharge

Spyropoulos AC et al. *Chest*. 2011;140:706-14. Hull RD et al. *Clin Appl Thromb Hemost*. 2013;19:357-62.

Characteristics of VTE among Hospitalized Medical and Nonmedical Patients

Characteristics	Hospitalized Med Patients (No., %)	Hospitalized Nonmed Patients (No., %)	P Value
PE	488 (22.2)	241 (15.5)	<0.001
Proximal lower extremity & calf DVT	1065 (40.9)	594 (30.4)	<0.001
Proximal lower extremity DVT w/o calf involvement	1064 (40.8)	708 (36.3)	0.002
Calf DVT	335 (12.9)	391 (20)	<0.001
Upper extremity DVT	215 (8.3)	329 (16.9)	<0.001

	Medical Patients (N=756)	Surgical Patients (N=884)	OR (95% CI)	P Value
Fatal PE	27 (3.6)	8 (0.9)	4.1 (1.8,9.0)	<0.001

Hospitalized medical patients have more severe forms of VTE than their surgical counterparts and more VTE-related deaths

Piazza G et al. *Chest*. 2007;132:554-61. Monreal M et al. *J Thromb Haemost*. 2004;2:1892-8.

Inpatient Thromboprophylaxis Trials in Medically Ill Patients

Average duration 7 – 14 days

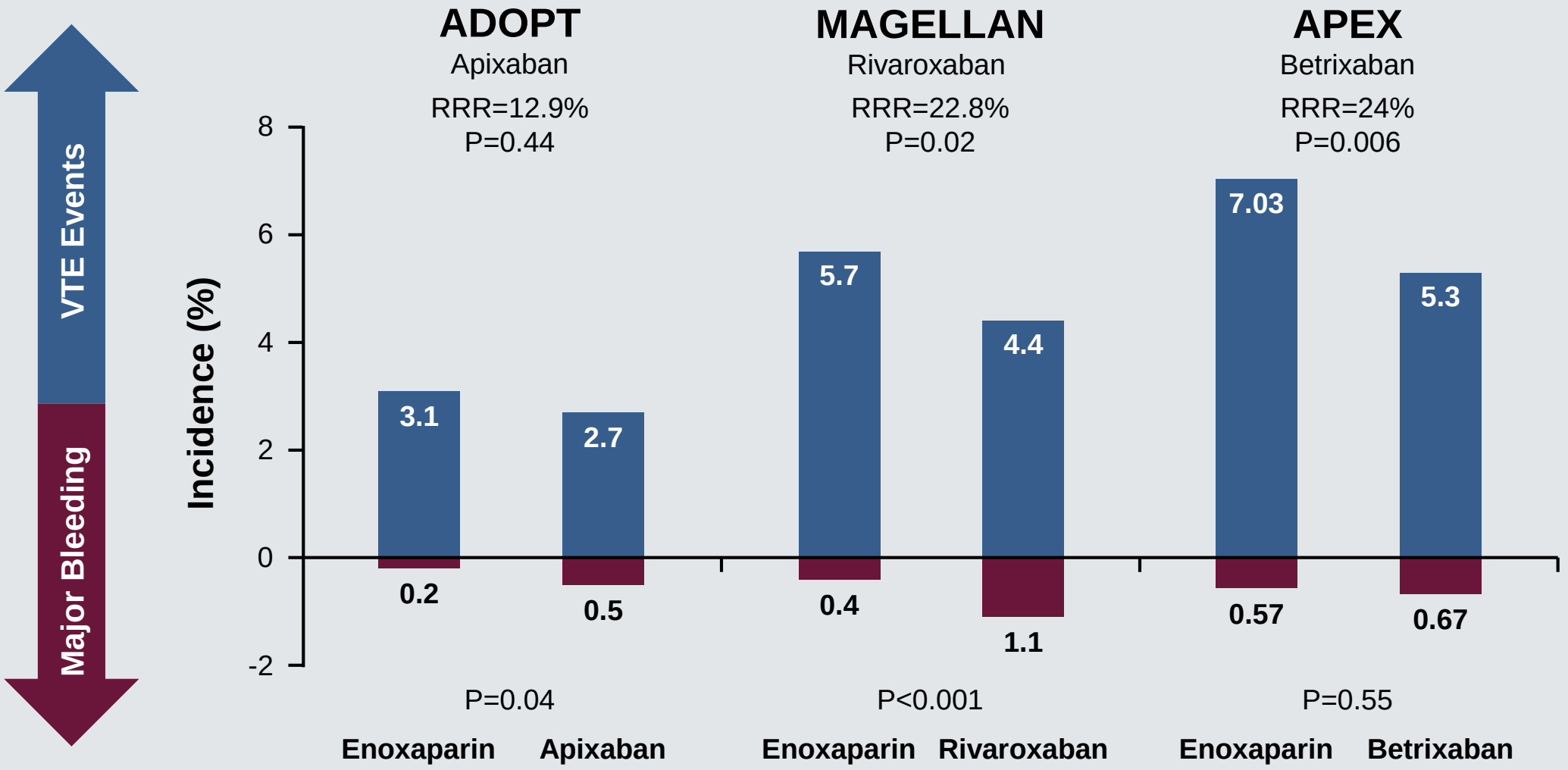
Study	RRR	Thromboprophylaxis	Patients with VTE (%)
MEDENOX[1] N=1102	**63%** P<0.001	Placebo Enoxaparin 40 mg daily	**14.9*** **5.5**
PREVENT[2] N=3706	**49%** P=0.0015	Placebo Dalteparin 5000 IU daily	**5.0*** **2.8**
ARTEMIS[3] N=849	**47%** P=0.029	Placebo Fonda 2.5 mg daily	**10.5†** **5.6**

***VTE at day 14; †VTE at day 15.**

RRR = relative risk reduction.

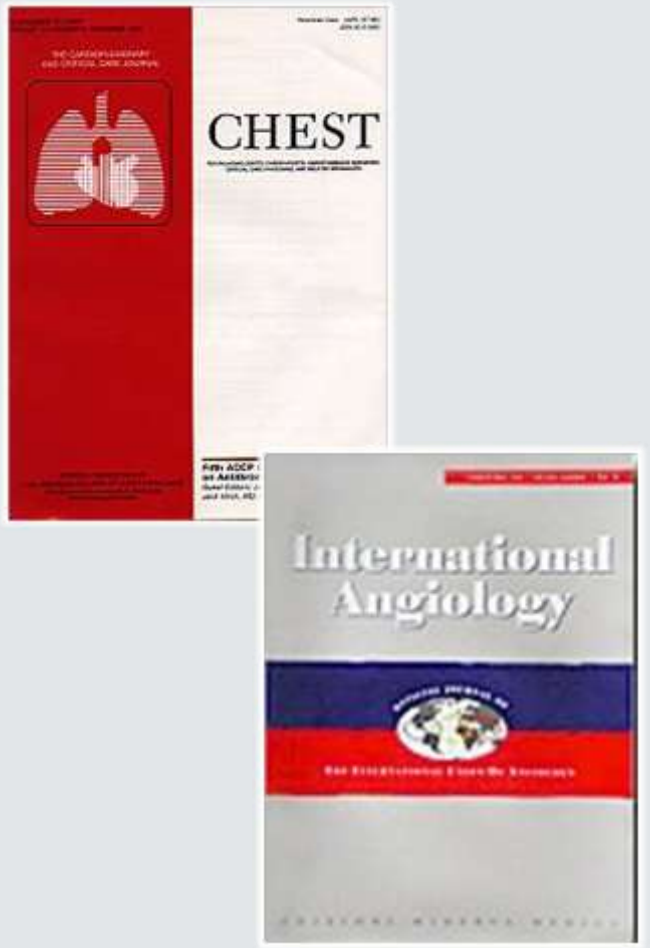
1. Samama MM et al. N Engl J Med. 1999;341:793-800. 2. Leizorovicz A et al. Circulation. 2004;110:874-9. 3. Cohen AT et al. BMJ. 2006;332:325-9.

Comparison of Direct Oral Anticoagulant Trials of Extended Thromboprophylaxis in Acute Medically Ill Patients



9th 2012 ACCP and 2013 IUA Recommendations: Extended Thromboprophylaxis in Medical Patients

- *"2.8. For acutely ill hospitalized medical patients who receive an initial course of thromboprophylaxis, we suggest against extending the duration of thromboprophylaxis beyond the period of patient immobilization or acute hospital stay (Grade 2B)"*
- *"Extended duration of thromboprophylaxis may be considered in female patients, patients older than 75 years, or severe immobility but should be determined on an individual basis"*



IUA=International Union of Angiology.

Kahn SR et al. *Chest*. 2012;141(2 Suppl):e195S-e226S. Nicolaides A et al. *Clin Appl Thromb Haemost.* 2013;19:163-71.

VTE Risk Assessment Models: Padua and IMPROVE*

Baseline Features	Score
Active cancer	3
Previous VTE (with the exclusion of superficial vein thrombosis)	3
Reduced mobility	3
Already known thrombophilic condition	3
Recent (≤1 month) trauma and/or surgery	2
Elderly age (≥70 years)	1
Heart and/or respiratory failure	1
Acute MI or ischemic stroke	1
Acute infection and/or rheumatic disorder	1
Obesity (BMI ≥30)	1
Ongoing hormonal treatment	1

VTE Risk Factor	Points for the Risk Score
Previous VTE	3
Thrombophilia	2
Lower limb paralysis	2
Current cancer	2
ICU/CCU stay	1
Immobilization ≥7 days	1
Age >60 years	1

Low risk for VTE: 0–1 points
Intermediate risk for VTE: 2–3 points
High risk for VTE: ≥4 points

*IMPROVEDD Score with elevated Dd (2 points)

Low risk for VTE: <4 points. High risk for VTE: ≥4 points.

Barbar S et al. *J Thromb Haemost.* 2010;8:2450-7. Spyropoulos AC et al. *Chest*. 2011;140:706-14.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Rivaroxaban for Thromboprophylaxis after Hospitalization for Medical Illness

Alex C. Spyropoulos, M.D., Walter Ageno, M.D., Gregory W. Albers, M.D., C. Gregory Elliott, M.D., Jonathan L. Halperin, M.D., William R. Hiatt, M.D., Gregory A. Maynard, M.D., P. Gabriel Steg, M.D., Jeffrey I. Weitz, M.D., Eunyoung Suh, Ph.D., Theodore E. Spiro, M.D., Elliot S. Barnathan, M.D., and Gary E. Raskob, Ph.D., for the MARINER Investigators*

Spyropoulos AC et al. *N Engl J Med*. 2018;379:1118-27 .

Objectives

Primary Objective

Prevention of symptomatic venous thromboembolism (VTE: lower extremity deep vein thrombosis [DVT] and non-fatal pulmonary embolism [PE])

and

VTE-related death (death due to PE or death in which PE cannot be ruled out as the cause)

Secondary Objectives

- VTE-related death
- Symptomatic VTE
- The composite of symptomatic VTE and all-cause mortality
- The composite of symptomatic VTE, myocardial infarction, non-hemorrhagic stroke and CV death
- All-cause mortality

Principal Safety Objective

Major bleeding using International Society of Thrombosis and Haemostasis (ISTH) bleeding criteria

Secondary Safety Objective

Non-major clinically relevant bleeding

Key Inclusion and Exclusion Criteria

Key inclusion criteria*

- Patients ≥40 years hospitalized for 3–10 days with thromboprophylaxis (LMWH or UFH) prior to randomization for one of the following acute medical conditions
  - Heart failure
  - Acute respiratory insufficiency or acute exacerbation of COPD
  - Acute ischemic stroke
  - Acute infectious diseases
  - Inflammatory diseases, including rheumatic disease
- Total modified IMPROVE VTE Risk Score ≥4 OR total modified IMPROVE VTE Risk Score 2 or 3 and D dimer >2x ULN during index hospitalization

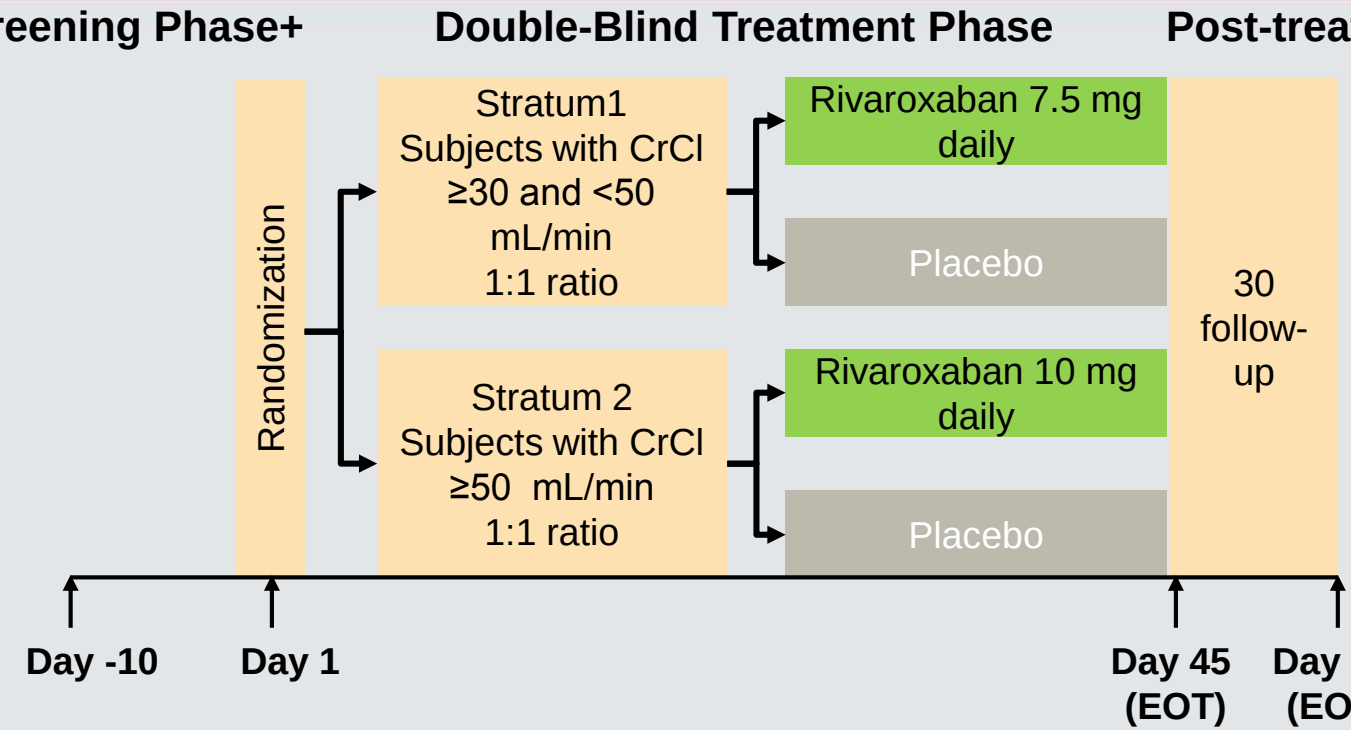
Key exclusion criteria*

- Bleeding Risks
  - Any bleeding within 3 months
  - Surgery, biopsy, or trauma 4 weeks prior or planned
  - Active gastroduodenal ulcer
  - Active cancer
- Required anticoagulation after discharge
- Use of dual antiplatelet therapy during the index hospitalization
- Concomitant Medications
  - Combined P-gp and strong CYP3A4 inhibitors
  - Combined P-gp and strong CYP3A4 inducers

* Reflects I/E Criteria as of INT-7.

MARINER Study Design

Randomized double blind placebo controlled event driven trial



Acute medical condition plus:

1. Total IMPROVE VTE Risk Score ≥4
   or
2. Total IMPROVE VTE Risk Score of 2 or 3 and elevated D-dimer (>2x ULN)

Primary Efficacy Endpoint: Composite of symptomatic VTE **or VTE-related death**
Secondary Efficacy Endpoint: **VTE-related death** (hierarchical design)
Primary Safety Endpoint: Major bleeding (ISTH Definition)

Estimated Sample Size – Event Driven Study

Sample size	Placebo	RRR	Events	Power for superiority	2 sided α
12,000	2.5%	40%	161	90%	5%

Raskob GE, Spyropoulos AC, et al. *Thromb Haemost.* 2016;115:1240-8.

Baseline Characteristics (1)

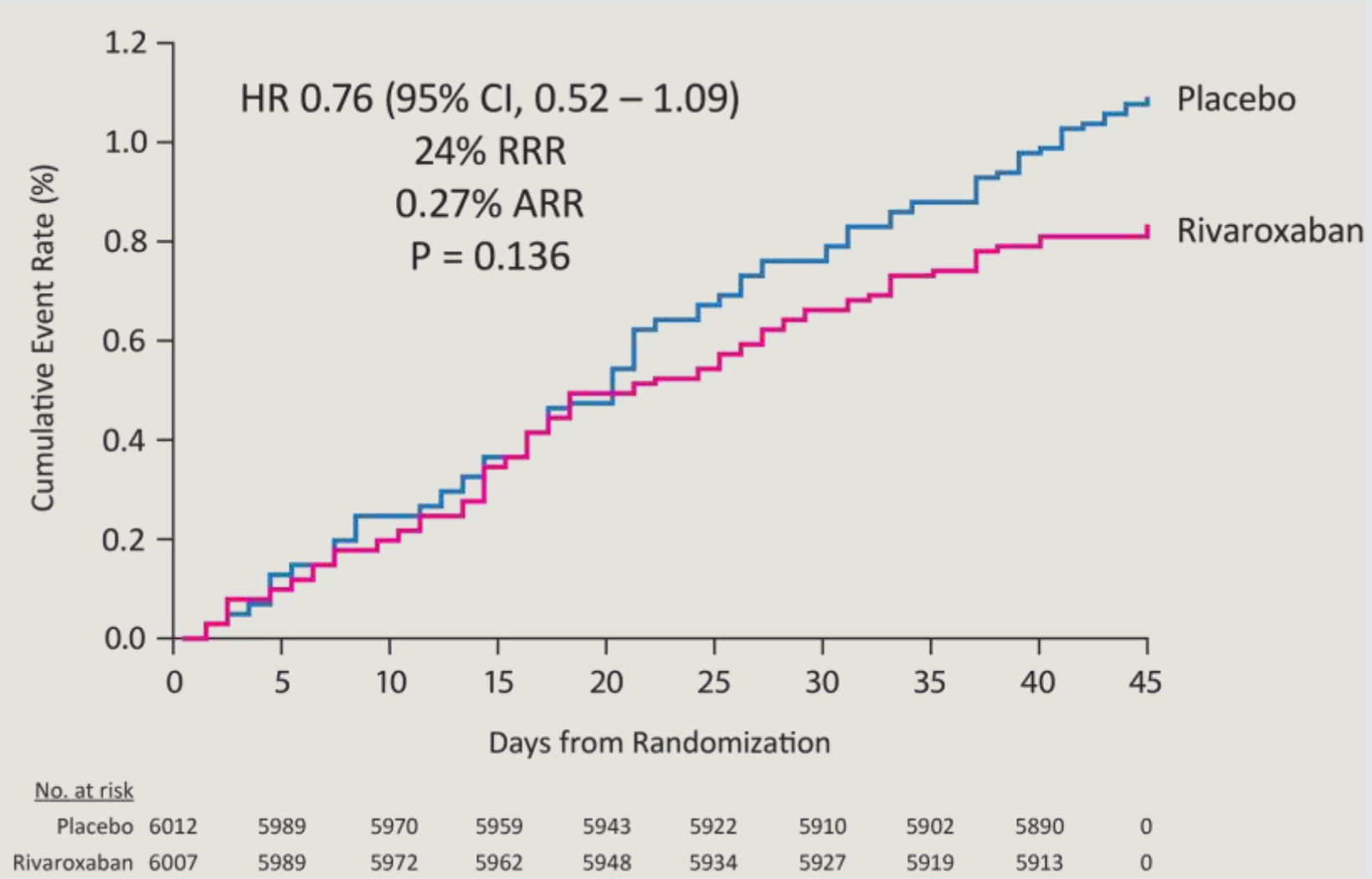
Characteristic	Rivaroxaban (n=6007)	Placebo (n=6012)
Age (Mean-yr)	69.7	69.7
≥75 yr (%)	35.9	35.6
Male Sex (%)	52.1	52.5
Race (% White)	96.3	96.6
Weight (mean kg)	80.8	80.6
Creatinine Clearance (mL/min)		
30 to <50 (%); 7.5 mg Dose Stratum	18.3	18.3
≥50 (%); 10 mg Dose Stratum	81.7	81.7
Diabetes (%)	29.1	27.9
History of Cancer (%)	8.1	8.9
Baseline aspirin use (%)	52.6	50.7

Spyropoulos AC et al. *N Engl J Med*. 2018;379:1118-27 .

Baseline Characteristics (2)

Characteristic	Rivaroxaban (n=6007)	Placebo (n=6012)
Reason for Index Hospitalization (%)		
Heart Failure	40.6	39.9
Acute Resp Insuff or Exac of COPD	26.2	26.8
Acute Infectious Disease	17.5	17.4
Acute Ischemic Stroke	14.3	14.4
Inflammatory Disease	1.4	1.5
Duration of Index Hosp. (days, mean)	6.7	6.7
Duration of thromboprophylaxis (days, mean)	6.2	6.2
Modified IMPROVE Risk Score (%)		
2	34.9	35.8
3	31.4	29.6
≥4	33.6	34.5
D-Dimer >2x Upper Limit of Normal (%)	70.4	70.5

Primary Efficacy Outcome up to Day 45



N=66
1.10%

N=50
0.83%

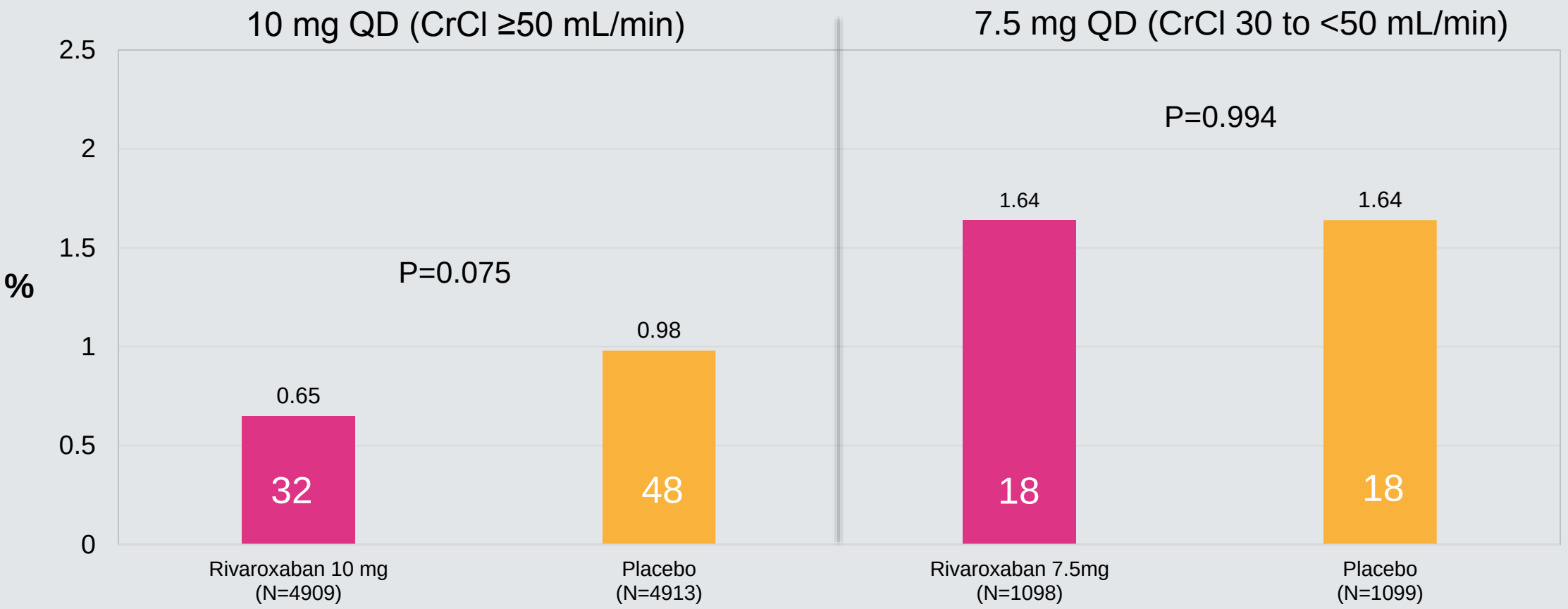
Components of the Primary Efficacy Outcome up to Day 45

	Rivaroxaban (n=6007)	Placebo (n=6012)	Rivaroxaban vs Placebo	
Outcomes	**n (%)**	**n (%)**	**Hazard Ratio (95% CI) [1]**	**P-value [2]**
Primary efficacy outcome (Sx VTE and VTE-related death)	**50 (0.83)**	**66 (1.10)**	**0.76 (0.52, 1.09)**	**0.136**
Symptomatic lower extremity DVT	4 (0.07)	13 (0.22)	0.31 (0.10, 0.94)	0.039
Symptomatic non-fatal PE	7 (0.12)	15 (0.25)	0.47 (0.19, 1.14)	0.096
VTE-related death	43 (0.72)	46 (0.77)	0.93 (0.62, 1.42)	0.751
Death (PE)	3 (0.05)	5 (0.08)	0.60 (0.14, 2.51)	0.485
Death (PE cannot be ruled out)	40 (0.67)	41 (0.68)	0.98 (0.63, 1.51)	0.912

[1] Hazard ratio (95% CI) and P-value are from the Cox proportional hazard model, stratified by baseline creatinine clearance (CrCl) (30 to <50 mL/min vs ≥50 mL/min), with treatment as the only covariate.
[2] P-value (two-sided) for superiority of rivaroxaban vs placebo from the Cox proportional hazard model.

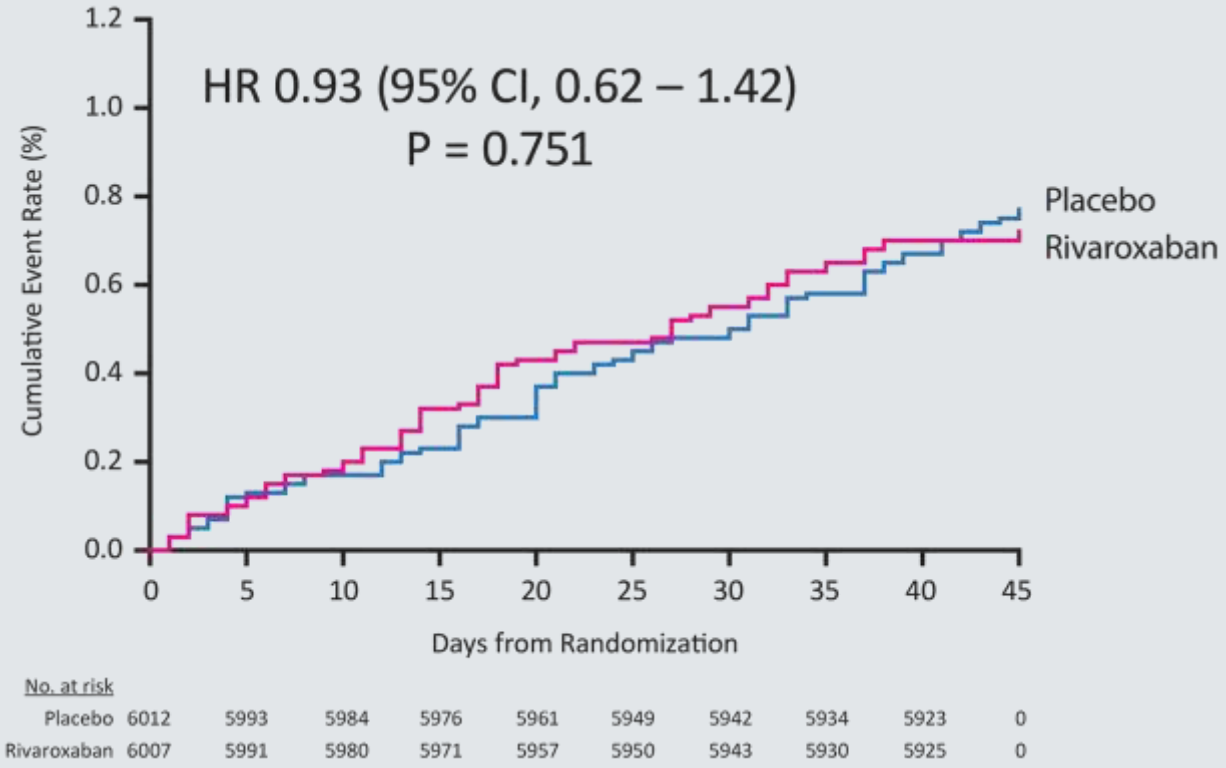
Primary Efficacy Outcome: By Dose Stratum/Baseline Renal Function

Symptomatic VTE and VTE Death up to Day 45

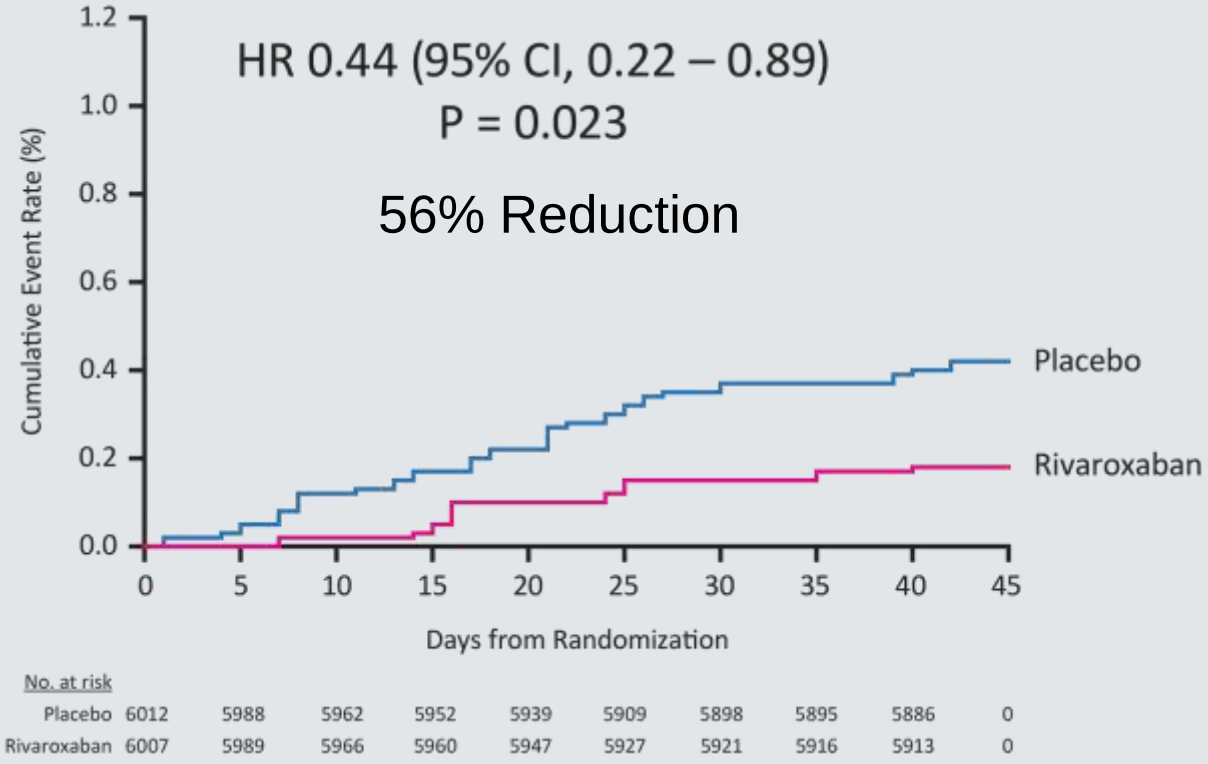


Secondary Efficacy Outcomes up to Day 45

VTE-related Death



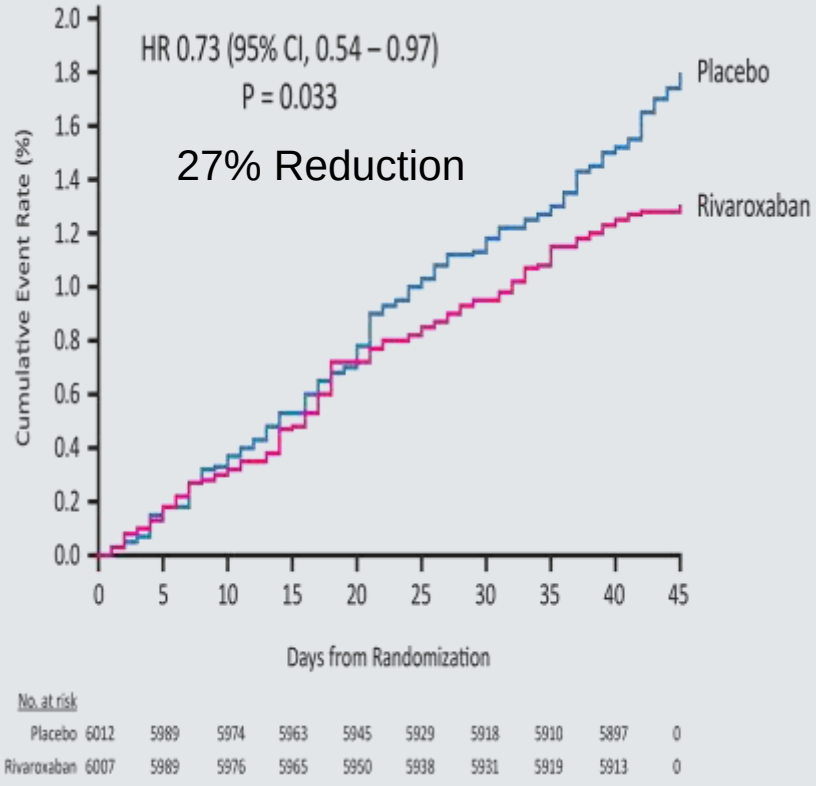
Symptomatic VTE



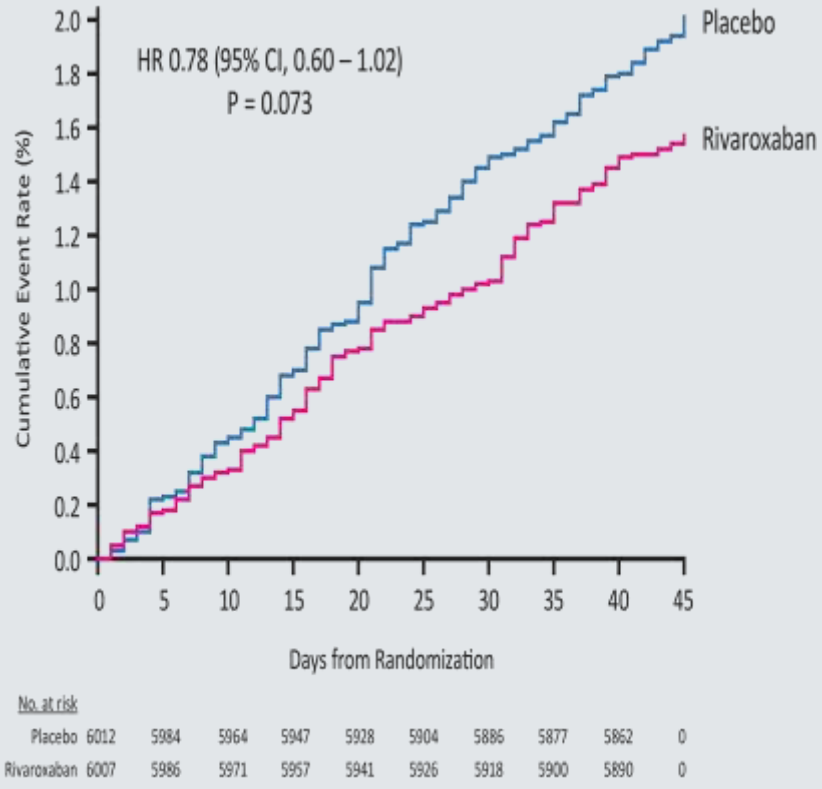
Spyropoulos AC et al. *N Engl J Med*. 2018;379:1118-27.

Secondary Efficacy Outcomes up to Day 45

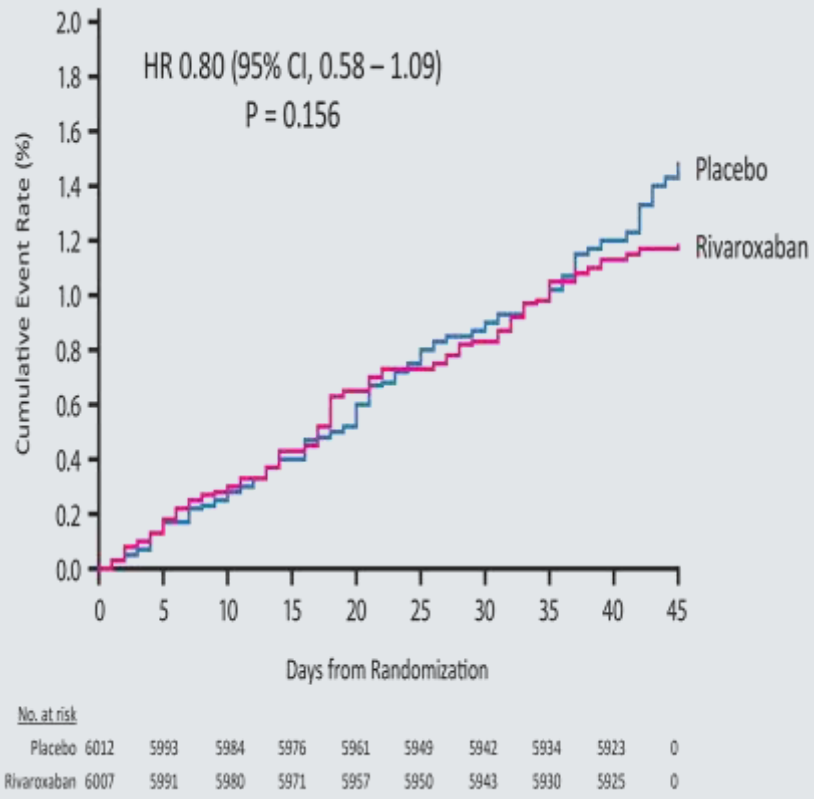
Symptomatic VTE and All-Cause Mortality



Symptomatic VTE, MI, Ischemic Stroke and CV Death



All-Cause Mortality



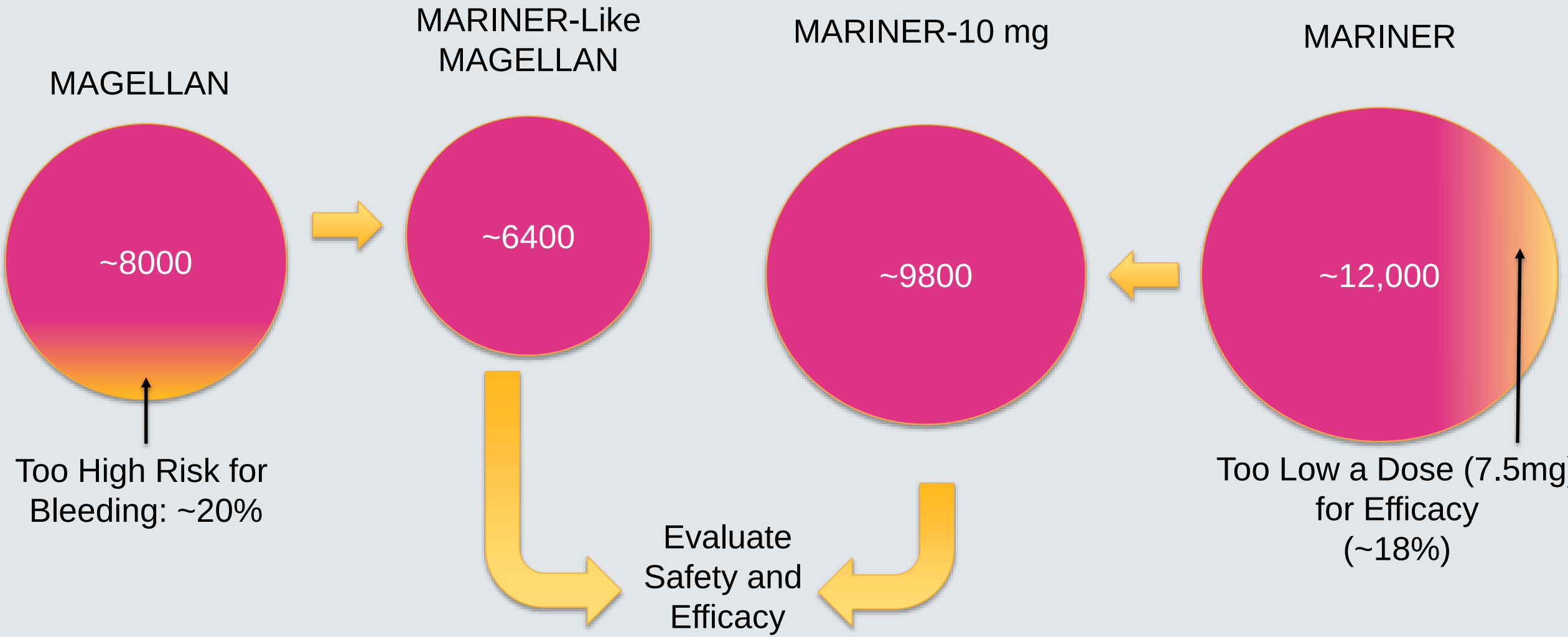
Spyropoulos AC et al. *N Engl J Med*. 2018;379:1118-27.

Bleeding Outcomes (On Treatment + 2 Days)

	Rivaroxaban (n=5982)	Placebo (n=5980)	Rivaroxaban vs Placebo	
	n (%)	n (%)	Hazard Ratio (95% CI) [1]	P-value [2]
Major bleeding	**17 (0.28)**	**9 (0.15)**	**1.88 (0.84, 4.23)**	**0.124**
A fall in hemoglobin of ≥2 g/dL	14 (0.23)	6 (0.10)	2.33 (0.89, 6.05)	0.084
A transfusion of ≥2 units of packed RBC	11 (0.18)	3 (0.05)	3.66 (1.02, 13.10)	0.047
A critical site	3 (0.05)	2 (0.03)	1.50 (0.25, 8.97)	0.657
A fatal outcome	2 (0.03)	0 (0.0)	N/A	
Non-major clinically relevant bleeding	**85 (1.42)**	**51 (0.85)**	**1.66 (1.17, 2.35)**	**0.004**

[1] Hazard ratio (95% CI) and P-value are from the Cox proportional hazard model, stratified by baseline creatinine clearance (CrCl) (30 to <50 mL/min vs ≥50 mL/min), with treatment as the only covariate.
[2] P-value (two-sided) for superiority of rivaroxaban vs placebo from the Cox proportional hazard model.

The MAGELLAN / MARINER Puzzle: Next Steps



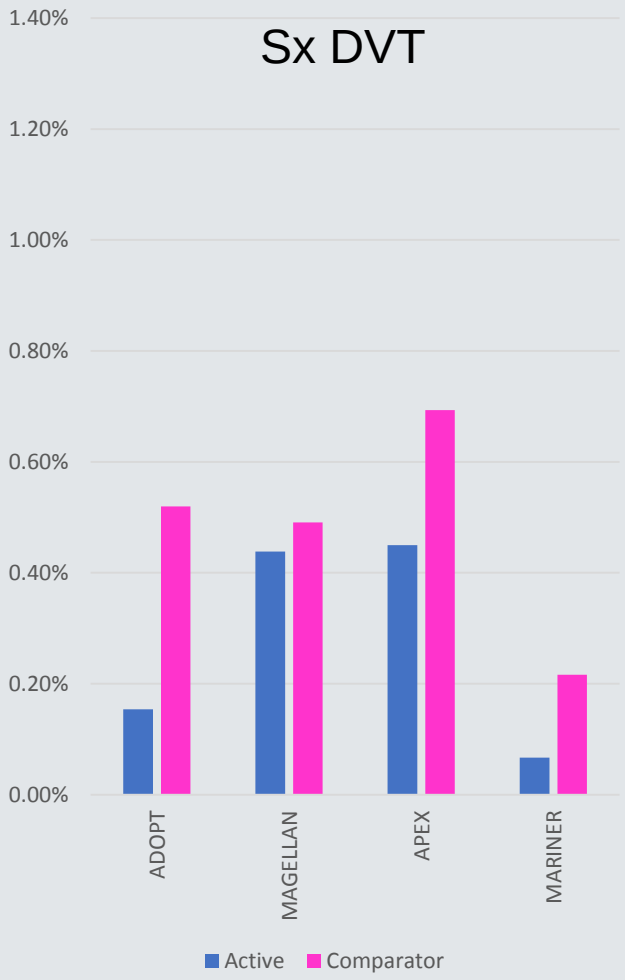
MARINER-like Subpopulation from MAGELLAN: Safety A Analysis

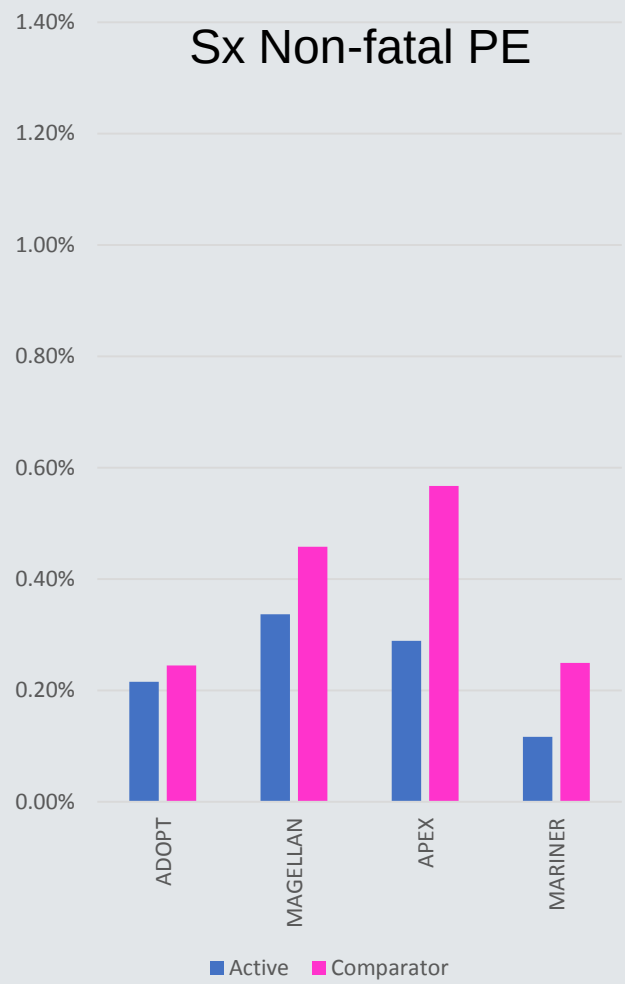
	MAGELLAN			MAGELLAN Subpopulation		
Safety Population*	**Rivaroxaban N=3997**	**Enoxaparin N=4001**	**RR (95% CI)**	**Rivaroxaban N=3218**	**Enoxaparin N=3229**	**RR (95% CI)**
Rivaroxaban-enoxaparin/placebo treatment phase (Day 1 to 35)*						
Clinically relevant bleeding	164 (4.1%)	67 (1.7%)	2.455 (1.854, 3.251)	114 (3.5%)	49 (1.5%)	2.345 (1.685, 3.264)
Major bleeding	43 (1.1%)	15 (0.4%)	2.867 (1.596, 5.149)	22 (0.7%)	15 (0.5%)	1.480 (0.771, 2.842)
Clinically relevant non-major bleeding	124 (3.1%)	52 (1.3%)		93 (2.9%)	34 (1.1%)	
Fatal bleeding	7 (0.2%	1 (<0.1%)		3 (<0.1%)	1 (<0.1%)	
Rivaroxaban-enoxaparin treatment phase (Day 1 to 10)*						
Clinically relevant Bleeding	111 (2.8%)	49 (1.2%)	2.272 (1.628, 3.171)	80 (2.5%)	35 (1.1%)	2.306 (1.556, 3.418)
Major bleeding	24 (0.6%)	11 (0.3%)	2.181 (1.070, 4.445)	13 (0.4%)	11 (0.3%)	1.191 (0.535, 2.651)
Clinically relevant non-major bleeding	88 (2.2%)	38 (0.9%)		67 (2.1%)	24 (0.7%)	
Fatal Bleeding	5 (0.1%)	1 (<0.1%)		1 (<0.1%)	1 (<0.1%)	

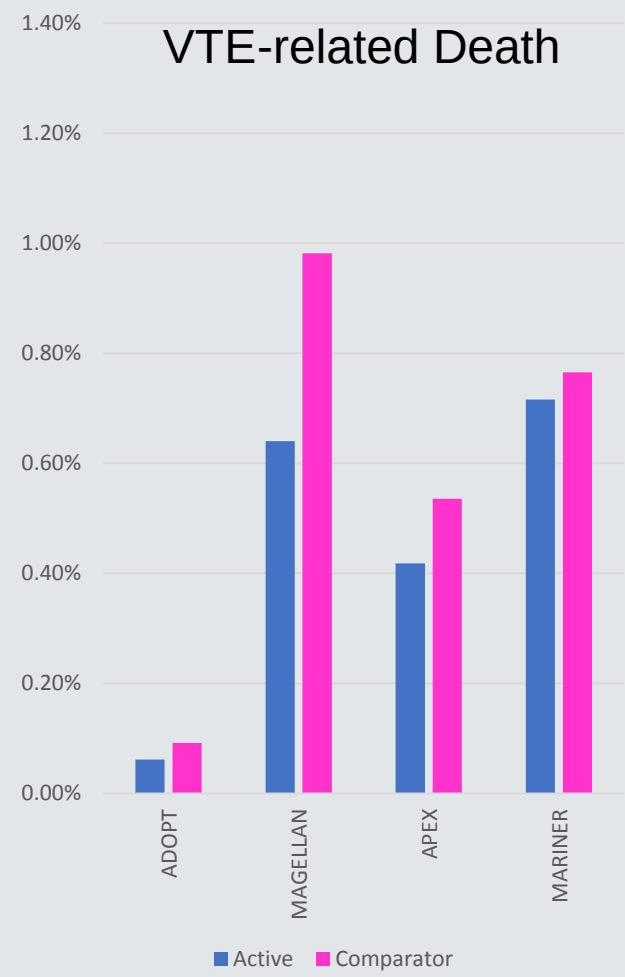
The risk of major bleeding associated with rivaroxaban was reduced in both treatment phases in the MAGELLAN Subpopulation

* On treatment +2 days

Extended DOAC Thromboprophylaxis Trials (Efficacy)

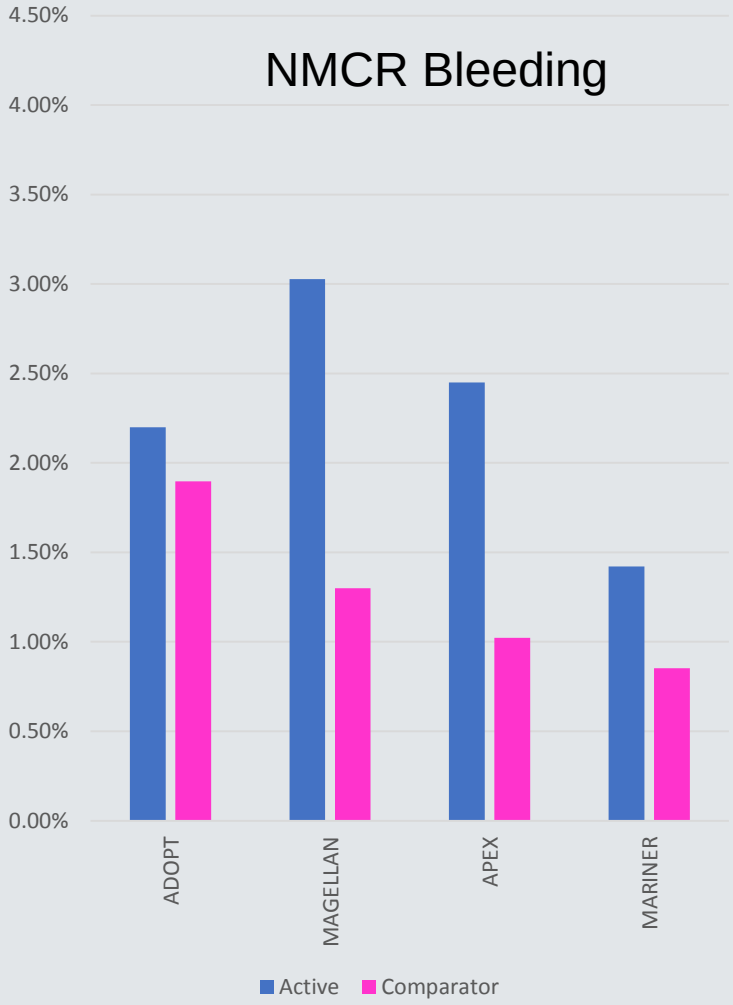






*Results from ADOPT, MAGELLAN, and APEX adapted from Al Yami MS et al. *J Blood Med*. 2018;9:25-34.

Extended DOAC Thromboprophylaxis Trials (Safety)



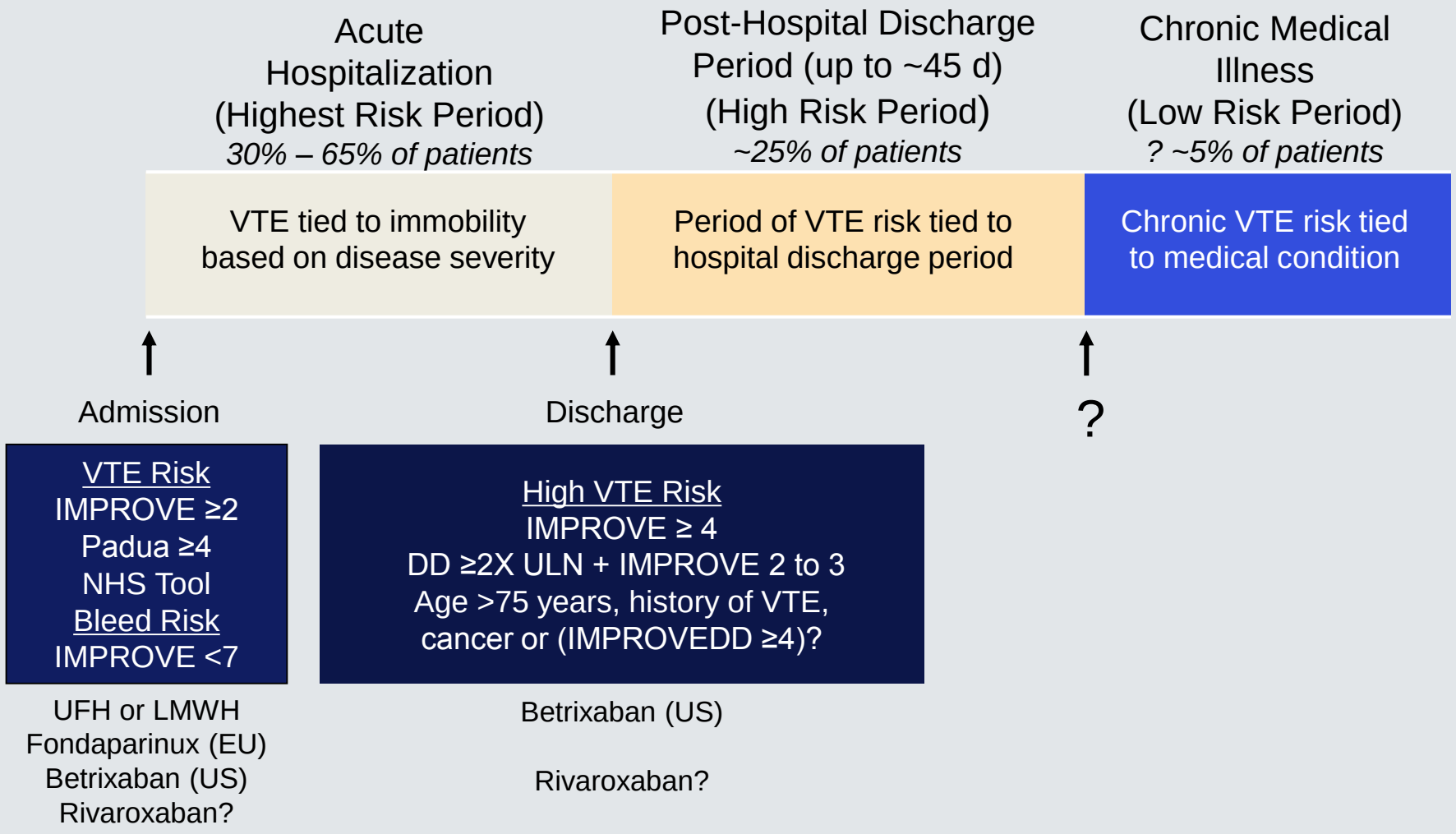
*Results from ADOPT, MAGELLAN, and APEX adapted from Al Yami MS et al. *J Blood Med*. 2018;9:25-34.

Benefit-Risk

Using 10 mg dose of rivaroxaban and a clinically important 1.0% incidence of symptomatic VTE applied to ~30% of patients in US/EU by modeling assumptions (6 million at risk patients):

- Prevent 2 non-fatal PEs and VTE-related death at the cost of almost no critical site/fatal bleeds per 1000 patients = 12,000 patients (NNT 500/NNH 2000000)
- Prevent 4 major or fatal thrombotic events (symptomatic VTE, MI, stroke, CV death) at the cost of almost no critical site/fatal bleeds per 1000 patients = 24,000 patients (NNT 260/NNH 2000000)

New Paradigm in Medically Ill Thromboprophylaxis: Individualized (Patient-Level)



Spyropoulos AC, Raskob GE. *Thromb Haemost*. 2017;117:1662-70.

Challenging Cases

Patient Case

- ACS is 76-year-old man hospitalized for heart failure and is immobile. He has a history of a lower leg distal DVT.
- Medications on admission:
  - Furosemide (60 mg PO bid)
  - Enalapril (5 mg PO qd)
  - Carvedilol (3.125 mg PO bid)
  - Spironolactone (25 mg PO qd)
- After 4 days of treatment, discharge is pending

Questions to consider:

- What is the risk of VTE?
  - What VTE prophylaxis should be considered for this patient on admission?
- Is the risk of VTE limited to the hospital stay?
- How best can I prevent VTE in this patient?
  - What, if any, VTE prophylaxis should be considered for this patient on discharge?

Case 1 (Part A)

A 68-year-old woman is due for routine colonoscopy next week. She is taking apixaban (5 mg twice daily) for stroke prevention on the background of paroxysmal atrial fibrillation. Other medical problems include well controlled hypertension and type 2 diabetes mellitus.

How would you manage her apixaban prior to her colonoscopy?

1. No need to stop
2. Hold for 3 days prior to procedure and in the morning of the day of the procedure
3. Hold for 2 days prior to procedure and in the morning of the day of the procedure
4. Hold for 1 day prior to procedure and in the morning of the day of the procedure

How would you manage her apixaban prior to her colonoscopy?

1. No need to stop
2. Hold for 3 days prior to procedure and in the morning of the day of the procedure
3. Hold for 2 days prior to procedure and in the morning of the day of the procedure
4. **Hold for 1 day prior to procedure and in the morning of the day of the procedure**

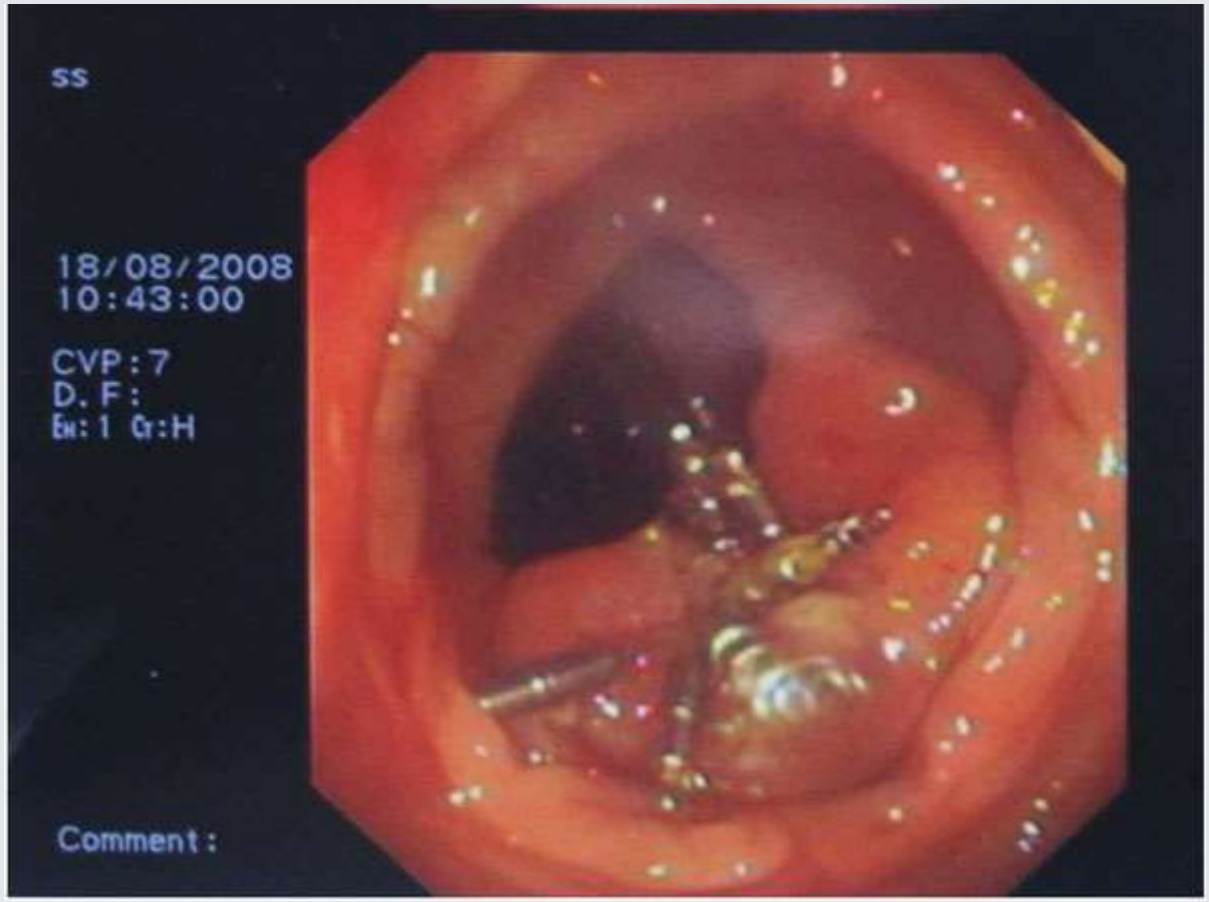
For procedures with low risk of bleeding, holding apixaban for 24 hours prior to the procedure is sufficient to ensure that there will be minimal bleeding should there be a need for biopsy or polyp removal.

Case 1 (Part B)

The colonoscopy was performed and a large sessile polyp was removed and endoclips were applied.

How soon after the colonoscopy would you re-start apixaban?

1. At least 48 hours after the colonoscopy
2. Immediately after the colonoscopy
3. In the evening of the day of the colonoscopy
4. In the morning of the day after the colonoscopy

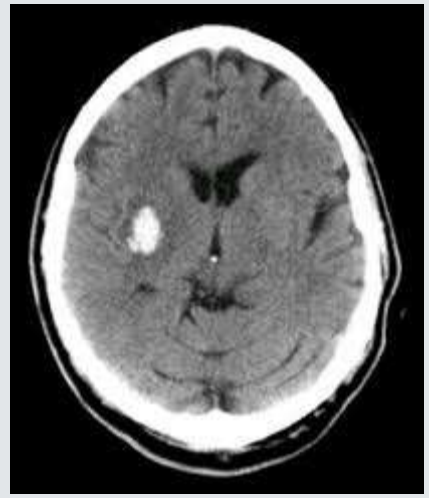


How soon after the colonoscopy would you re-start apixaban?

1. **At least 48 hours after the colonoscopy**
2. Immediately after the colonoscopy
3. In the evening of the day of the colonoscopy
4. In the morning of the day after the colonoscopy

Apixaban has a rapid onset of action since peak blood concentrations are achieved within 1 to 3 hours of its administration. Therefore, there is a risk of bleeding from the site of polyp removal if apixaban is given too soon after the procedure. Bleeding can occur even if endoclips are applied. Therefore, apixaban should be delayed for 48 hours after the procedure.

Case 2 (Part A)



A 70-year-old man presents to the emergency department with headache and right sided weakness. He is taking rivaroxaban (20 mg once daily) for stroke prevention on the background of permanent atrial fibrillation. Other problems include hypertension, type 2 diabetes mellitus, and a history of a transient ischemic attack. The CT scan reveals an intracerebral hemorrhage.

The last dose of rivaroxaban was taken about 12 hours ago. Which of the following would you use for reversal of the anticoagulant effects of rivaroxaban?

1. Idarucizumab
2. Andexanet alfa
3. 4-factor prothrombin complex concentrate
4. Activated prothrombin complex concentrate

Which of the following would you use for reversal of the anticoagulant effects of rivaroxaban?

1. Idarucizumab
2. **Andexanet alfa**
3. 4-factor prothrombin complex concentrate
4. Activated prothrombin complex concentrate

Andexanet alfa is a recombinant analog of human factor Xa that sequesters circulating rivaroxaban or other oral factor Xa inhibitors. It is licensed in the United States but is not widely available. If andexanet was unavailable, it would be reasonable to administer 4-factor prothrombin complex concentrate. Although activated prothrombin complex concentrate could also be used, it is more expensive and its use is associated with a higher risk of thromboembolic complications. Idarucizumab is the reversal agent for dabigatran.

Case 2 (Part B)

Which dose regimen of andexanet alfa would you give?

1. High dose (800 mg intravenous bolus followed by a 960 mg infusion over 2 hours)
2. Low dose (400 mg intravenous bolus followed by a 480 mg infusion over 2 hours)

Which dose regimen of andexanet alfa would you give?

1. High dose (800 mg intravenous bolus followed by a 960 mg infusion over 2 hours)
2. **Low dose (400 mg intravenous bolus followed by a 480 mg infusion over 2 hours)**

Low dose andexanet alfa is given for reversal of apixaban (except if the patient was taking 10 mg twice daily) and for reversal of rivaroxaban provided that the last dose was taken more than 8 hours prior to reversal. If the last dose was taken within 8 hours, then the higher dose should be given.

Case 2 (Part C)

Which reversal agent would you give if the patient was taking dabigatran instead of rivaroxaban?

1. Idarucizumab
2. Andexanet alfa
3. 4-factor prothrombin complex concentrate
4. Activated prothrombin complex concentrate

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Idarucizumab, the specific reversal agent for dabigatran, is widely available and rapidly reverses the anticoagulant effects of dabigatran.