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Synergy of Dual Pathway Inhibition (DPI) in chronic cardiovascular disease

Robert C. Welsh, MD, FRCPC
Professor of Medicine, University of Alberta
Zone Clinical Department Head, Cardiac Sciences

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Robert C. Welsh, MD, FRCPC

Disclosures

- **Research and Clinical Trials:** Abbott Vascular, Astra Zeneca, Bayer, BMS, Boehringer Ingelheim, CIHR, CSL Behring LLC, Edwards Lifesciences, Eli Lilly, Jansen, Johnson and Johnson, Pfizer, Population Health Research Institute, University of Alberta Hospital Foundation
- **Consulting Fees/Honoraria:** Astra Zeneca, Bayer, Bristol Myers-Squibb/Pfizer, Canadian Cardiovascular Society
- **Other:** University of Alberta (employee), Alberta Health Services (Clinical privileges)

Canadian VIGOUR Centre
Bridging Hearts and Minds

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Objectives

1. Define ‘residual risk’ for patients with chronic atherosclerotic cardiovascular disease (ASCVD).
2. Review contemporary anti-thrombotic therapy in relationship to chronic ASCVD.
3. Discuss strategies to apply contemporary antithrombotic therapies to individual patients.

Mrs D.B.

- 66-year-old woman with HTN, dyslipidemia, diabetes mellitus and prior NSTEMI 20 months previously presents to outpatient clinic for routine follow up.
- Angiogram – 3.0 X 28 DES in mid LAD with diffuse moderate CAD (no residual lesion >60%)
- Transthoracic Echocardiogram 12 months post NSTEMI – normal LV dimensions and function, no significant valvular disease
- Current medical therapy
  - ASA 81 mg + ticagrelor 90 mg bid
  - Atorvastatin 80 mg daily
  - Bisoprolol 5 mg and perindopril 8 mg daily
  - Metformin 500 mg bid

Mrs D.B.

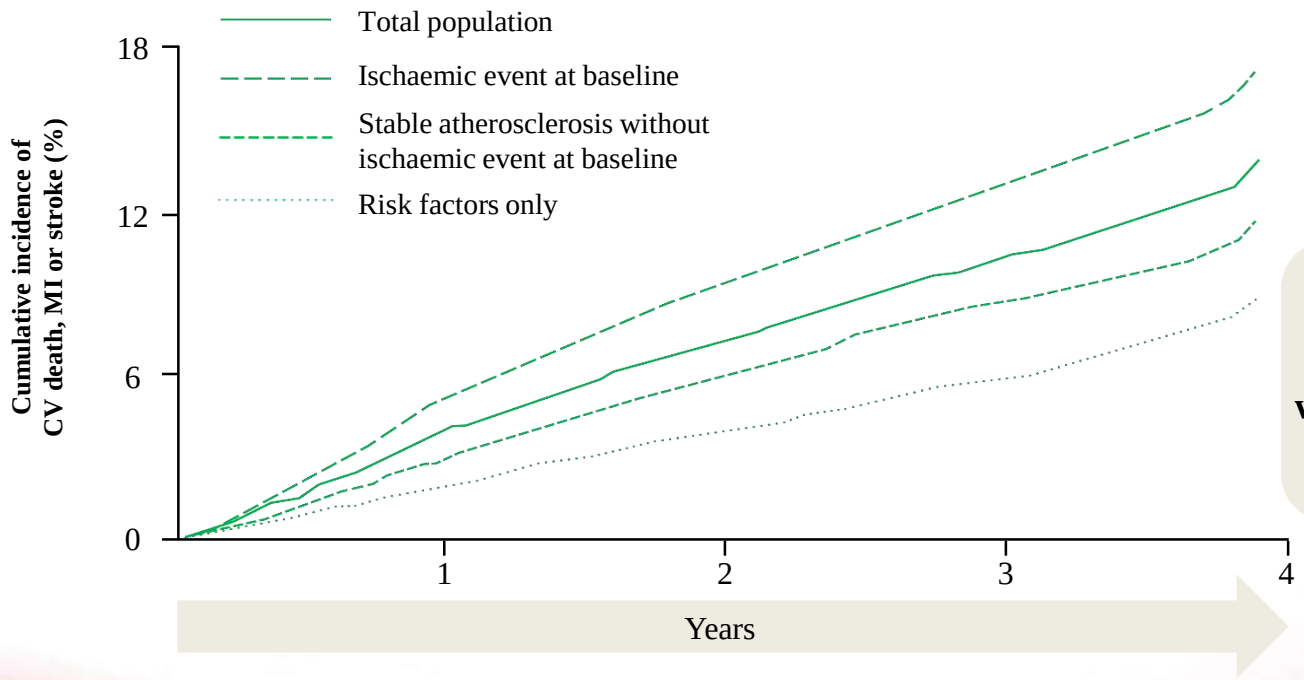
- Blood Pressure optimally controlled – BP 132/78
- Cholesterol profile – LDL 1.34, HDL 0.82, TG 1.79
- HbA1C – 6.7%
- Creatinine 73 (eGFR 74)
- Hemoglobin 110 (HCT 33)

What changes would you make to her current medical therapy?

1. Continue all current therapy?
2. Discontinue ticagrelor i.e transition to asa monotherapy?
3. Initiation therapy with rivaroxaban 2.5 mg bid + ASA 81 mg?

What is the Risk of this Patient Having Another Cardiovascular Event?

Incidence of MACE according to the history of ischaemic events in the REACH registry



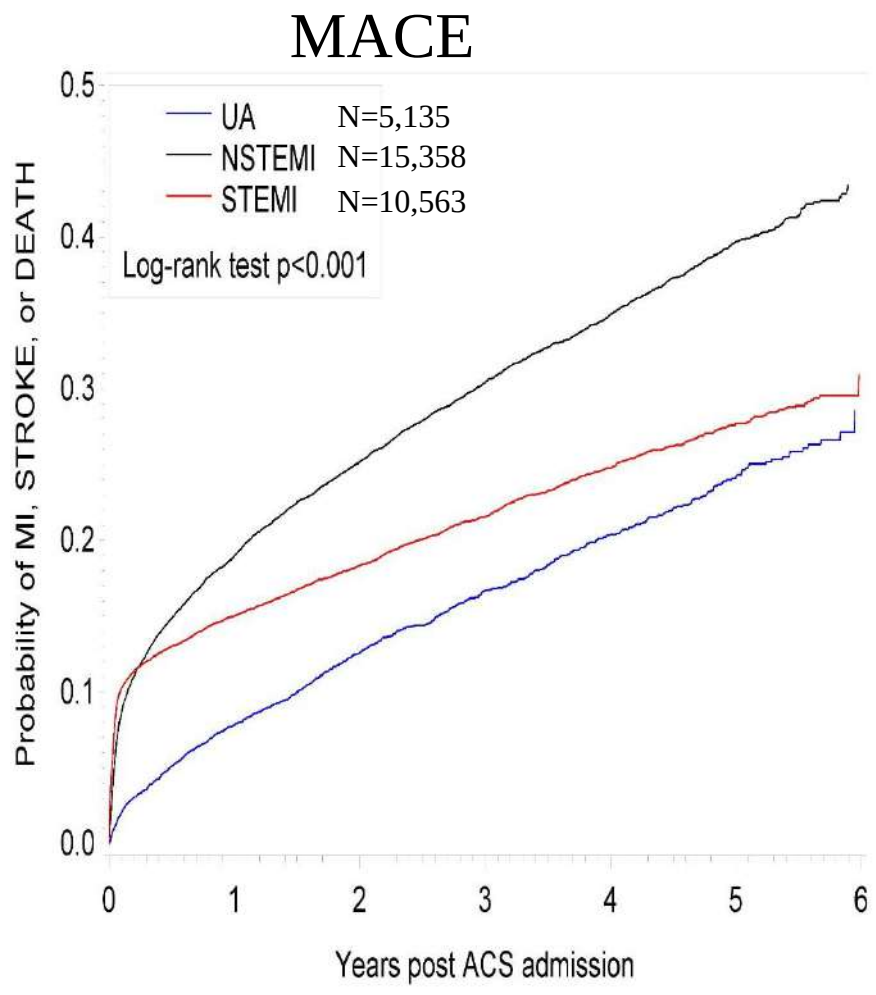
4-year incidence of MACE in patients with a prior ischaemic event: 18.3%

Despite guideline-recommended therapy, patients with previous ischaemic events are at high risk of recurrence

Bhatt *et al*, *JAMA* 2010;304:1350–1357

Defining the Residual Risk

Consecutive ACS Patients from Alberta Population Health Data



Major Adverse Cardiac Events
(MACE) (Death, MI, Stroke)

STEMI ≈ 3% yearly

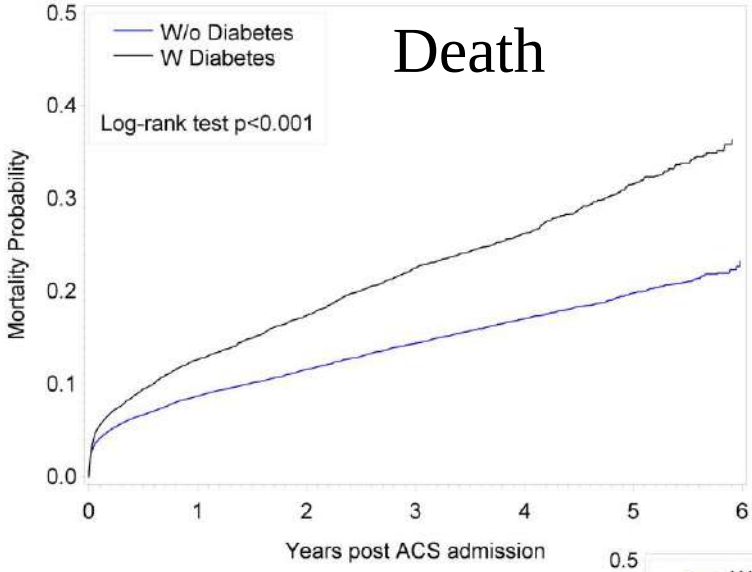
Unstable Angina ≈ 5% yearly

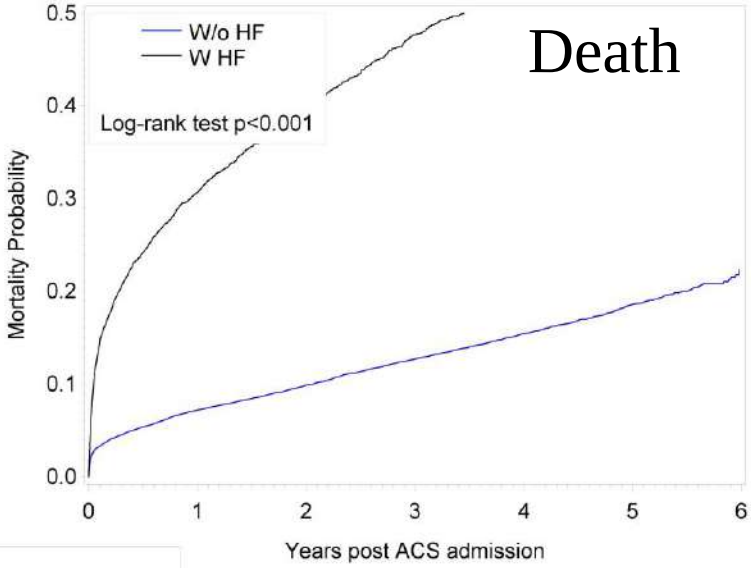
NSTEMI ≈ 8% yearly

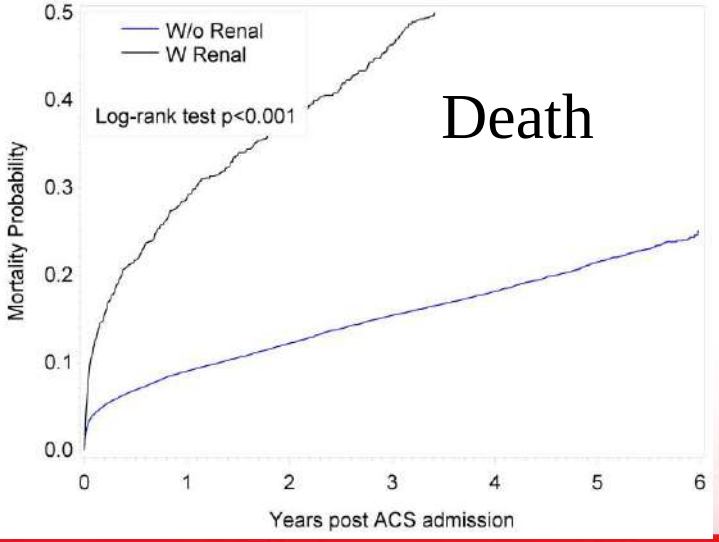
Welsh et al, ACC, 2019

Defining the Residual Risk

Consecutive ACS Patients from Alberta Population Health Data







Welsh et al, ACC, 2019

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ASSESSING DAPT IN STABLE CAD

Study design and patient characteristics

	CHARISMA (N = 15,603)	DAPT (N = 9961)	PEGASUS (N = 21,162)
Patient characteristics	Clinically evident CVD or multiple risk factors	Adults stable for 12 months on DAPT post-DES	≥50 years old MI 1–3 years prior
Treatment arms	Clopidogrel 75 mg QD + low-dose* ASA vs. placebo + ASA	Continued ASA + $P2Y_{12}$ inhibitor ASA + placebo	Ticagrelor 60 mg BID + low-dose* ASA vs. ticagrelor 90 mg BID + low-dose* ASA vs. placebo + low-dose ASA
Median follow-up	28 months	18 months	33 months
Primary efficacy outcome	MI + stroke + CV death	1) Definite / probable stent thrombosis 2) MI + stroke + CV death	MI + stroke + CV death
Primary safety outcome	Severe bleeding	Moderate or severe bleeding	TIMI major bleeding

*Low-dose ASA: 75-162 mg QD

ASA, acetylsalicylic acid; BID, twice daily; CAD, coronary artery disease; CV, cardiovascular; CVD, cardiovascular disease; DAPT, dual antiplatelet therapy; DES, drug-eluting stent; MI, myocardial infarction; TIMI, Thrombolysis in Myocardial Infarction; QD, once daily

Bhatt DL *et al. N Engl J Med* 2006; 354:1706-17. Mauri L *et al. N Engl J Med* 2014; 371: 2155-66. Bonaca MP *et al. N Engl J Med* 2015; 372:1791-800.

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DAPT

Benefits of extended DAPT post-PCI

DAPT EFFICACY OUTCOMES				
Endpoint	**$P2Y_{12}$ + ASA (N = 5020)**	**Placebo + ASA (N = 4941)**	**RR (95% CI)**	***P* Value**
Coprimary efficacy endpoints: • **Stent thrombosis** • **MACE**	 0.4% 4.3%	 1.4% 5.9%	 0.29 (0.17–0.48) 0.71 (0.59–0.85)	 <0.001 <0.001
Primary safety endpoint – moderate or severe GUSTO bleeding	2.5%	1.6%	1.61 (1.21-2.16)	0.001

CONCLUSION

- ✓ Significant reduction in CV events
- ✓ Significant increase in the primary safety endpoint (moderate or severe bleeding); however, the rate of severe bleeding was similar between the groups

ASA, acetylsalicylic acid; CI, confidence interval; DAPT, dual antiplatelet agent; GUSTO, Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries; MACE, major adverse cardiac event; PCI, percutaneous coronary intervention; RR, relative risk

Mauri L *et al. N Engl J Med* 2014; 371: 2155-66.

All cause mortality

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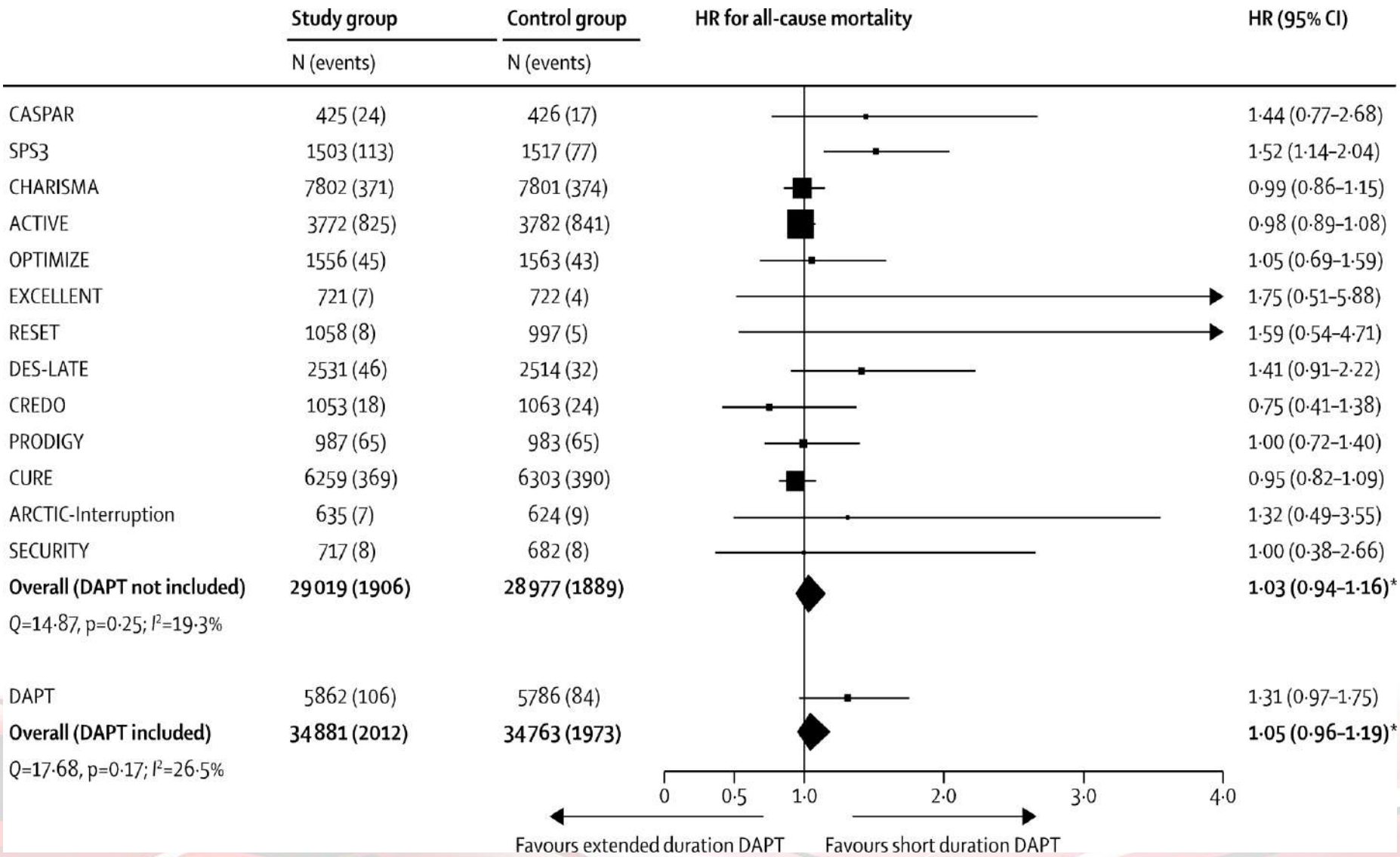
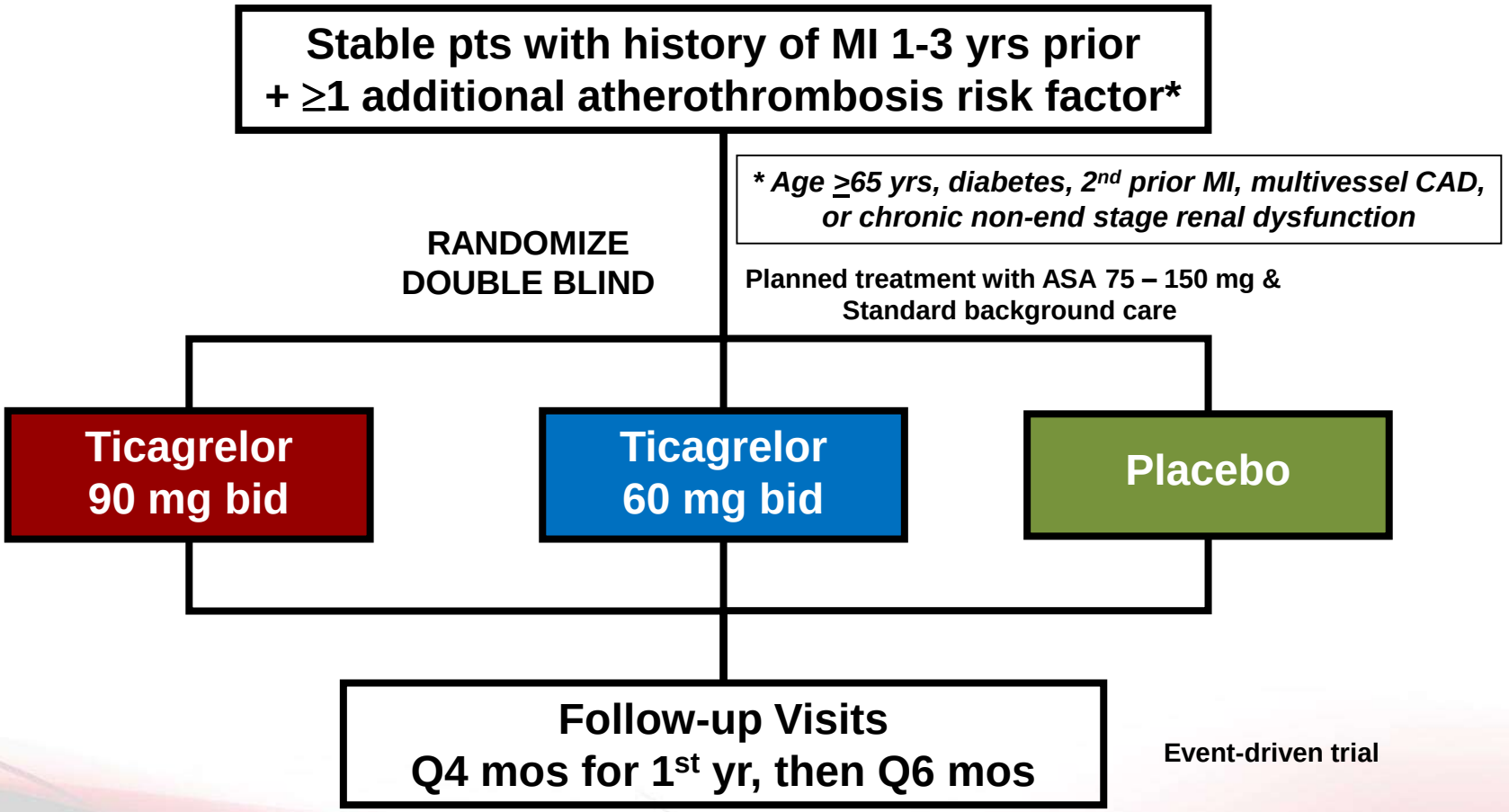


Extended duration dual antiplatelet therapy and mortality: a systematic review and meta-analysis

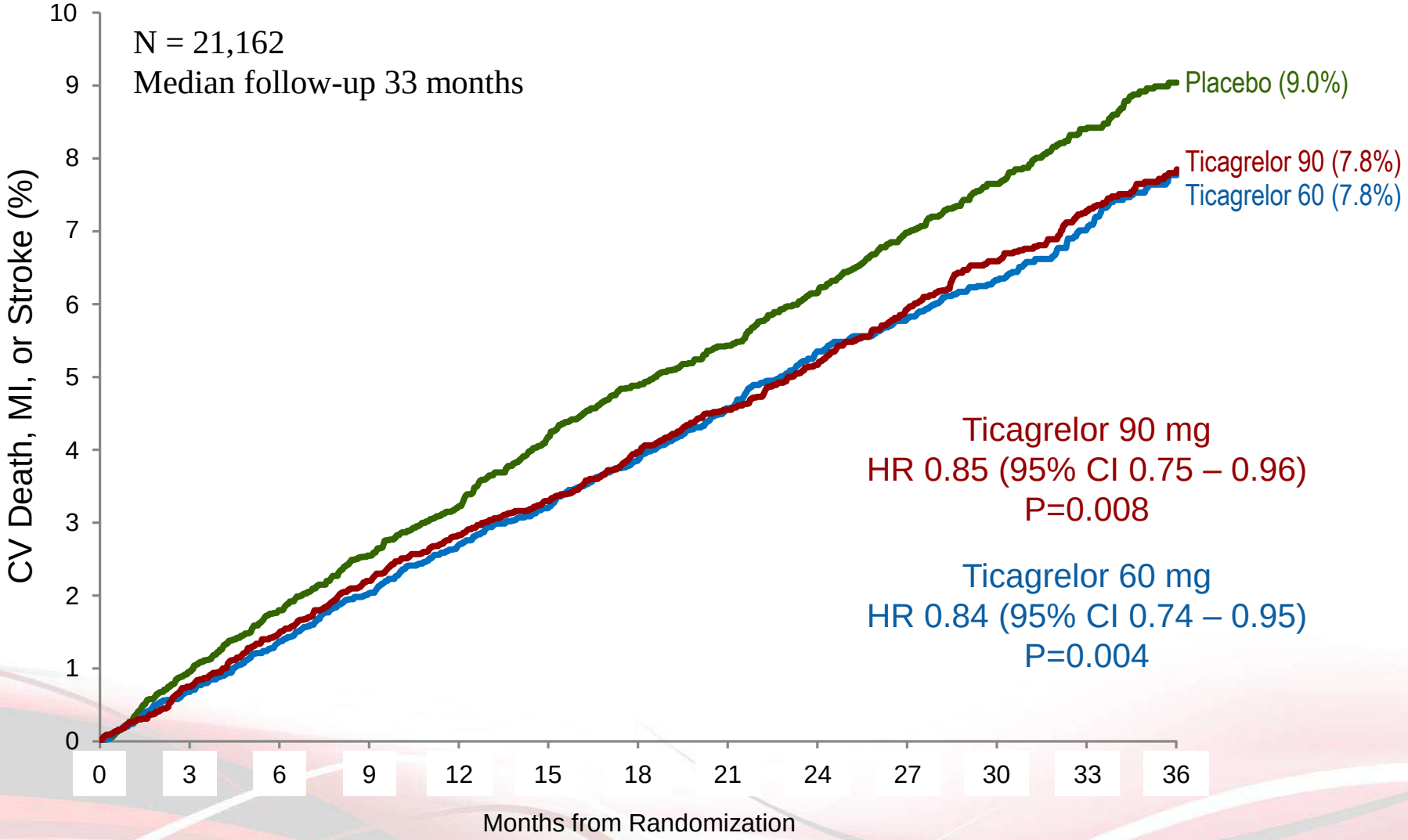
Sammy Elmariah , Laura Mauri et al; The Lancet, 2014

PEGASUS Trial Design



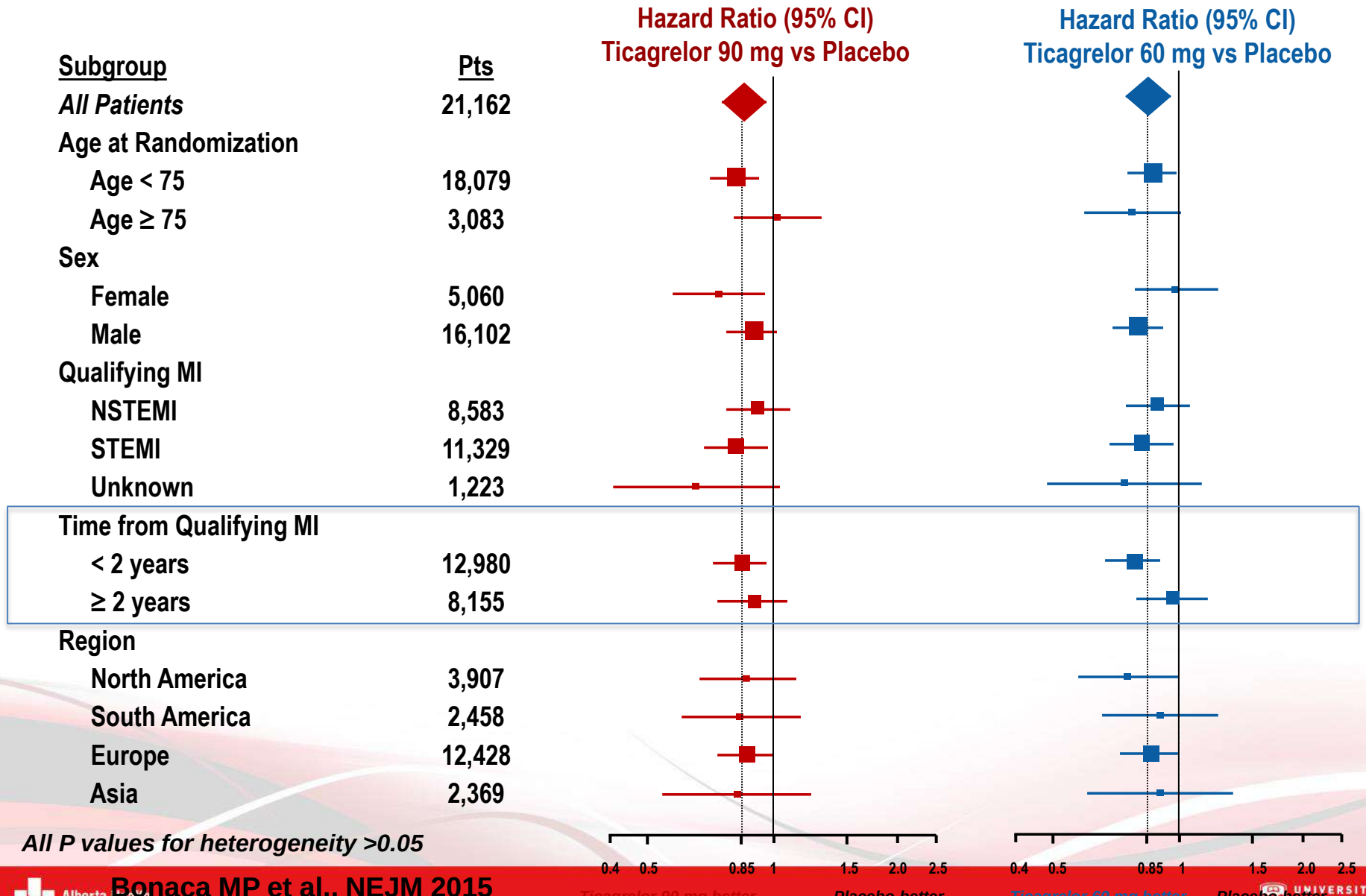
Bonaca MP et al., NEJM 2015

DAPT Ticagrelor + ASA vs. ASA
Primary Endpoint



Bonaca MP et al., NEJM 2015

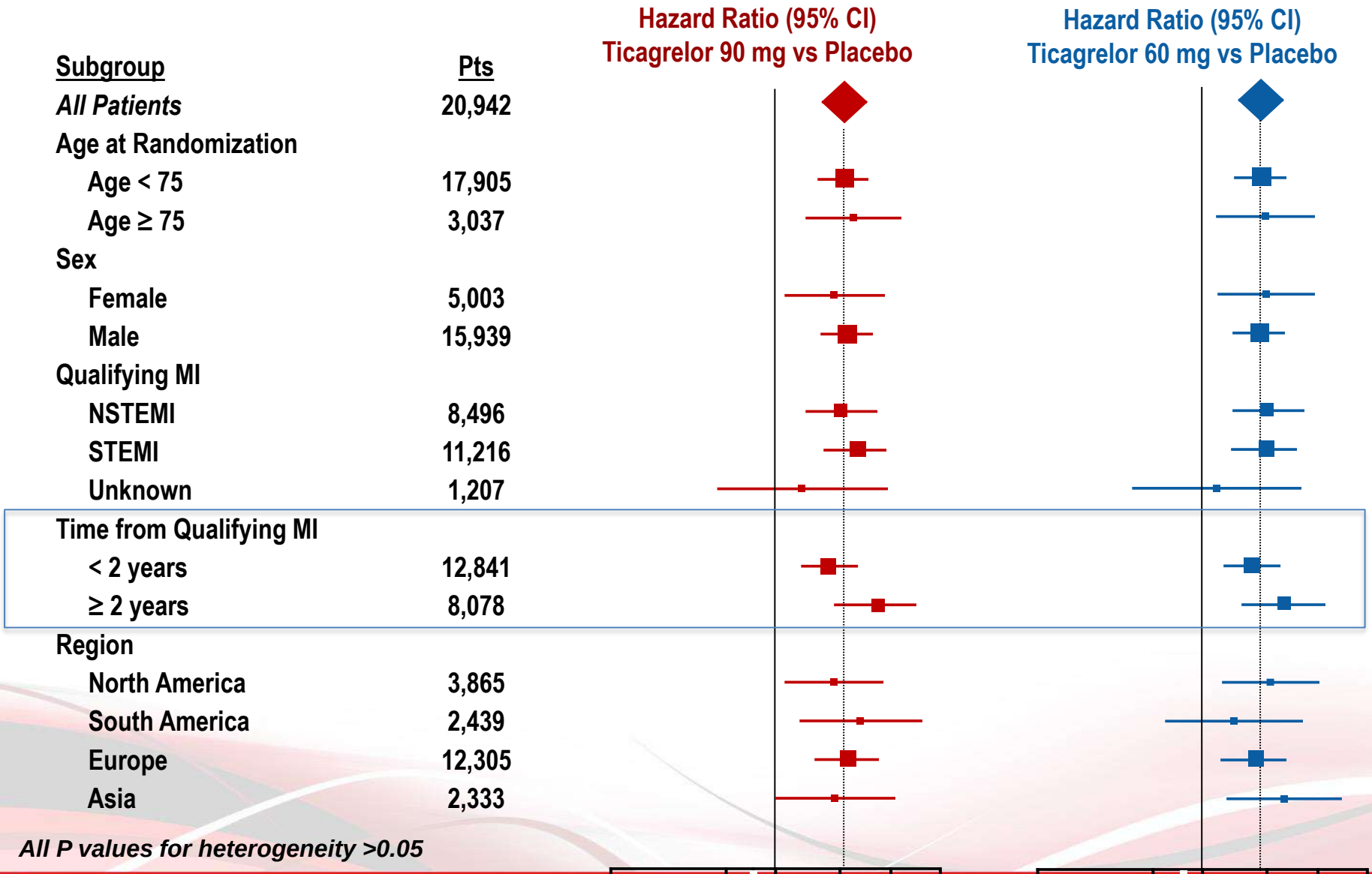
Efficacy in Subgroups



All P values for heterogeneity >0.05

Bonaca MP et al., NEJM 2015

Safety in Subgroups



All P values for heterogeneity >0.05

Bonaca MP et al., NEJM 2015

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Ticagrelor Effects Stratified by Time from index MI

Supplemental Table 2 – Efficacy and Safety of Ticagrelor 60 mg by Time from MI at

Endpoint (subgroup)	Placebo KM%	Ticagrelor 60 mg KM %	HR (95% CI)	p-interaction
CV Death, Myocardial infarction, Stroke				
< 2 years N=8664	9.7	7.8	0.77 (0.66 – 0.90)	0.09
≥ 2 years N=5428	7.9	7.8	0.96 (0.79 – 1.17)	
CV Death				
< 2 years N=8664	3.7	2.5	0.68 (0.53 – 0.89)	0.019
≥ 2 years N=5428	2.8	3.3	1.12 (0.81 – 1.54)	

These slides have been provided, on request, by Astrazeneca Scientific Affairs

Alberta Health Services

Bonaca MP et al. *J Am Coll Cardiol.* 2017; 70(11): 1368-1375

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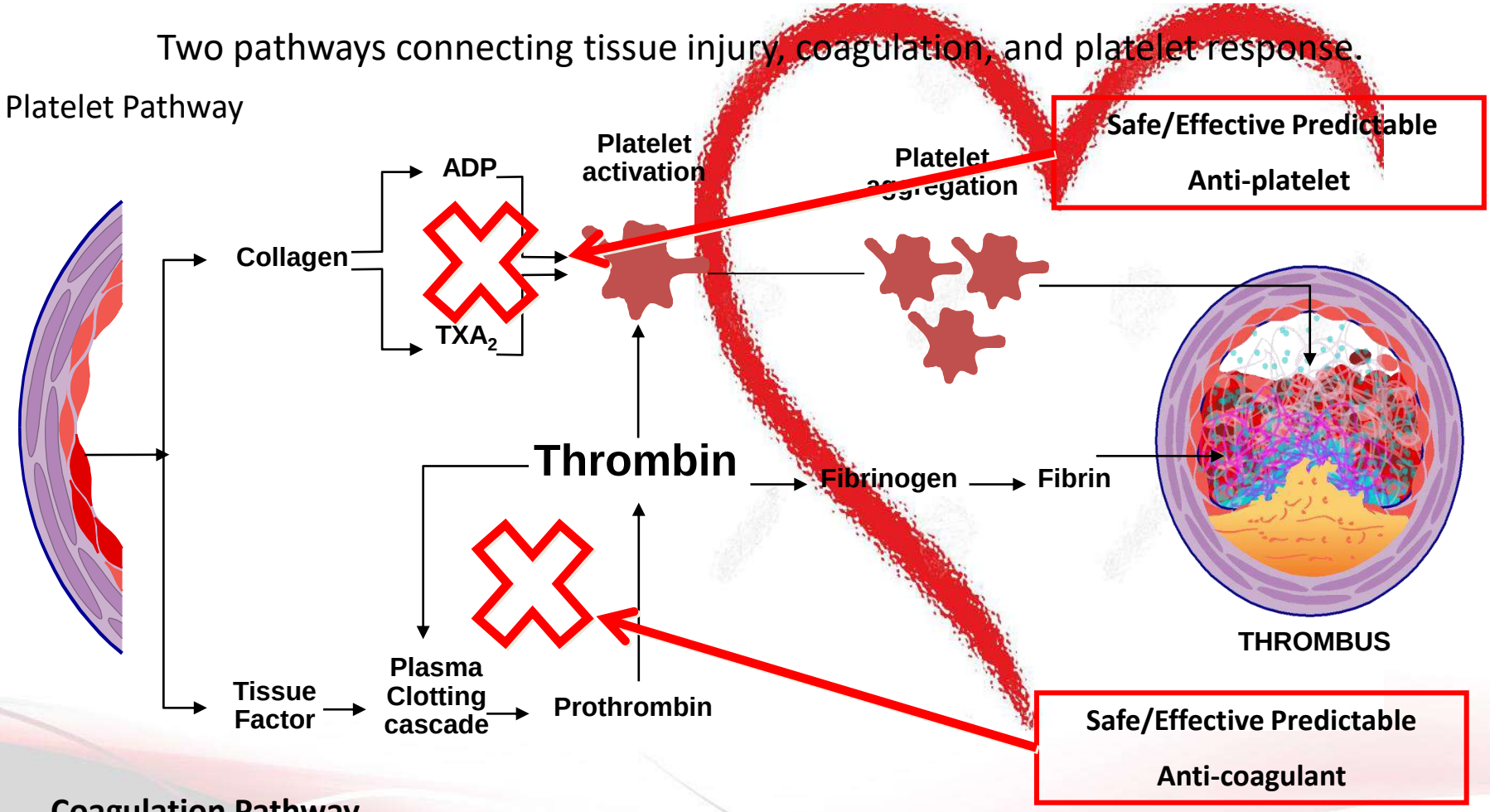
Contemporary Secondary Prevention

Inhibition of Pathways For Thrombus Formation

Two pathways connecting tissue injury, coagulation, and platelet response.



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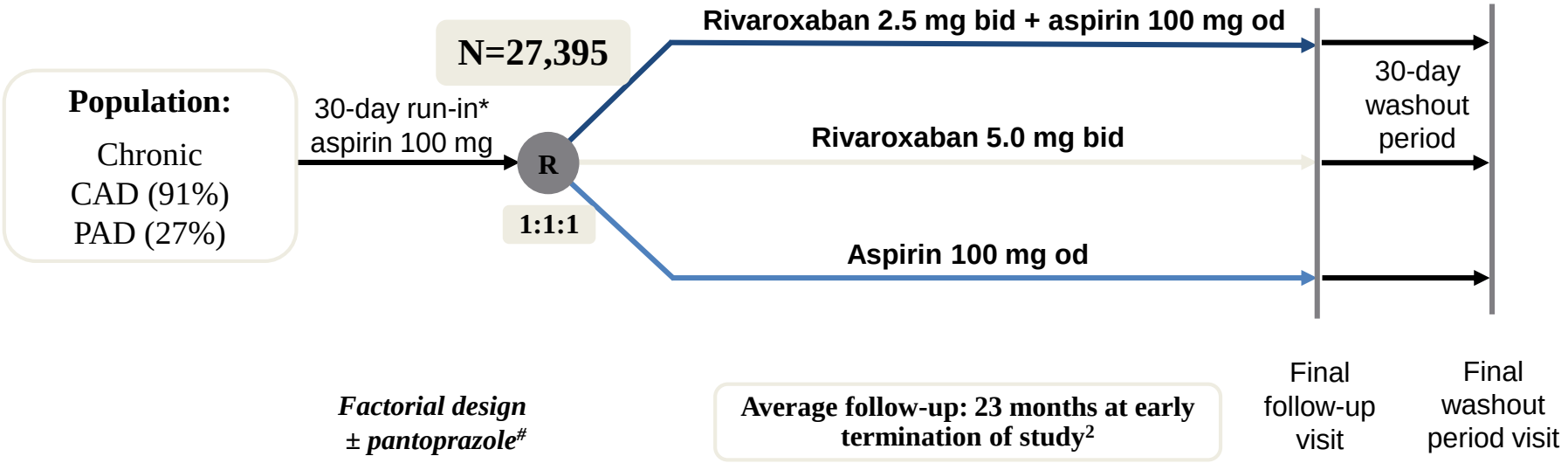
A Dual Pathway Approach Targeting Chronic Patients with CAD or PAD was Investigated in COMPASS

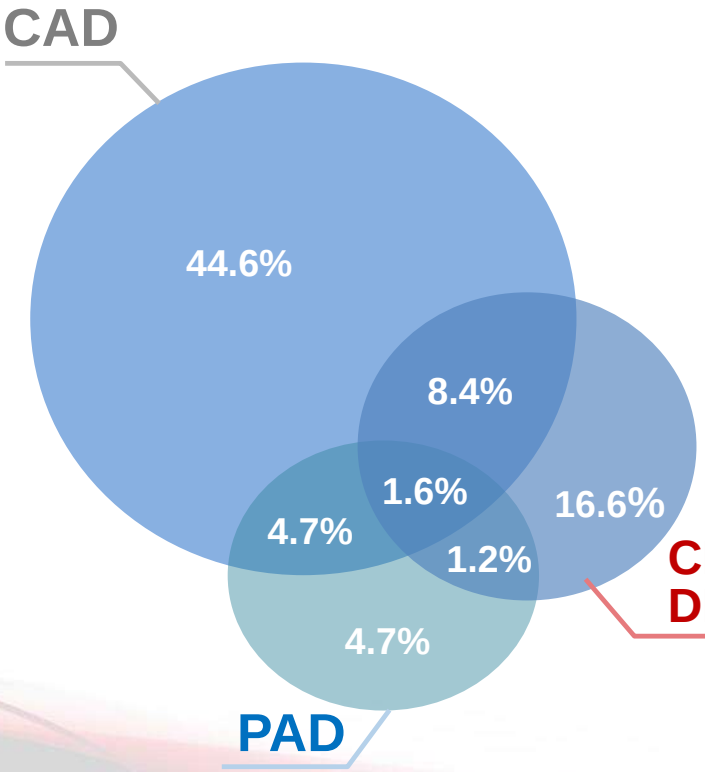
Objective: To determine the efficacy and safety of vascular dose rivaroxaban plus aspirin compared with aspirin alone for the prevention of MI, stroke and cardiovascular death in chronic CAD or PAD



Antithrombotic investigations‡ were stopped 1 year ahead of expectations in February 2017 due to overwhelming efficacy in the rivaroxaban 2.5 mg bid + aspirin arm[2]

*The CAD analysis includes 1448 patients who entered COMPASS immediately post-CABG (with no run-in)[3]; #Patients who were not receiving a proton pump inhibitor (PPI) were randomized to pantoprazole or placebo (partial factorial design); ‡1. Bosch J *et al*, *Can J Cardiol* 2017;33:1027–1035; 2. Eikelboom JW *et al*, *N Engl J Med* 2017;377:1319-1330;
3. Connolly SJ *et al*, *Lancet* 2017; doi:10.1016/S0140-6736(17)32816-7

Prevalence of disease in arterial beds (REACH Registry)



Atherothrombosis

Prevalence of >1 vascular bed involved (REACH Registry, N = 67,888):

- 25% of patients with CAD
- 40% of patients with cerebrovascular disease
- 61% of patients with PAD

Percentages are calculated from the total population included in the REACH Registry.

CAD, coronary artery disease; PAD, peripheral artery disease

Bhatt DL *et al*. *JAMA* 2006; 295:180-9.

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COMPASS TRIAL

Baseline characteristics were consistent across treatment arms

Typical COMPASS patient:

- Age 68 years
- 90% had CAD
- 62% prior MI
  - Median time from prior MI: 7.1 years
- 27% had PAD
- 4% had prior stroke
- 38% had diabetes
- Mean total cholesterol: 4.2 mmol/L

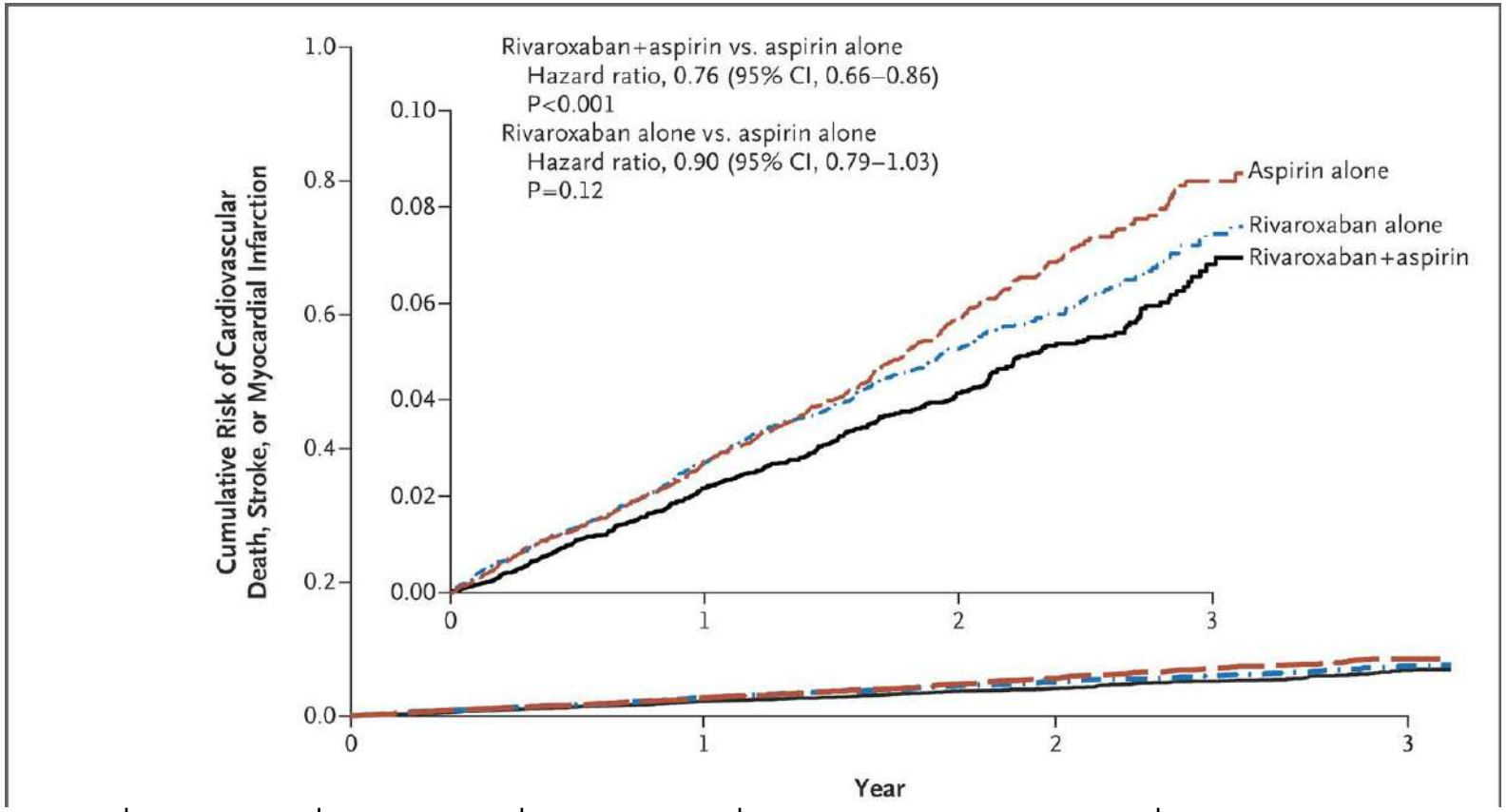
Optimally managed for secondary prevention:

- ✓ 90% were on lipid-lowering therapy
- ✓ 71% were on ACEIs/ARBs

Rivaroxaban no está comercializado para la prevención de eventos aterotrombóticos en pacientes con EAC o EAP en España

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin-receptor blocker; CAD, coronary artery disease; MI, myocardial infarction; PAD, peripheral artery disease

Primary Outcome - CV death, stroke, MI



Outcome	R + A N=9,152	Riva N=9,117	Aspirin N=9,126	Riva + 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)	0.11

Eikelboom JW *et al*, *N Engl J Med* 2017;377:1319-1330

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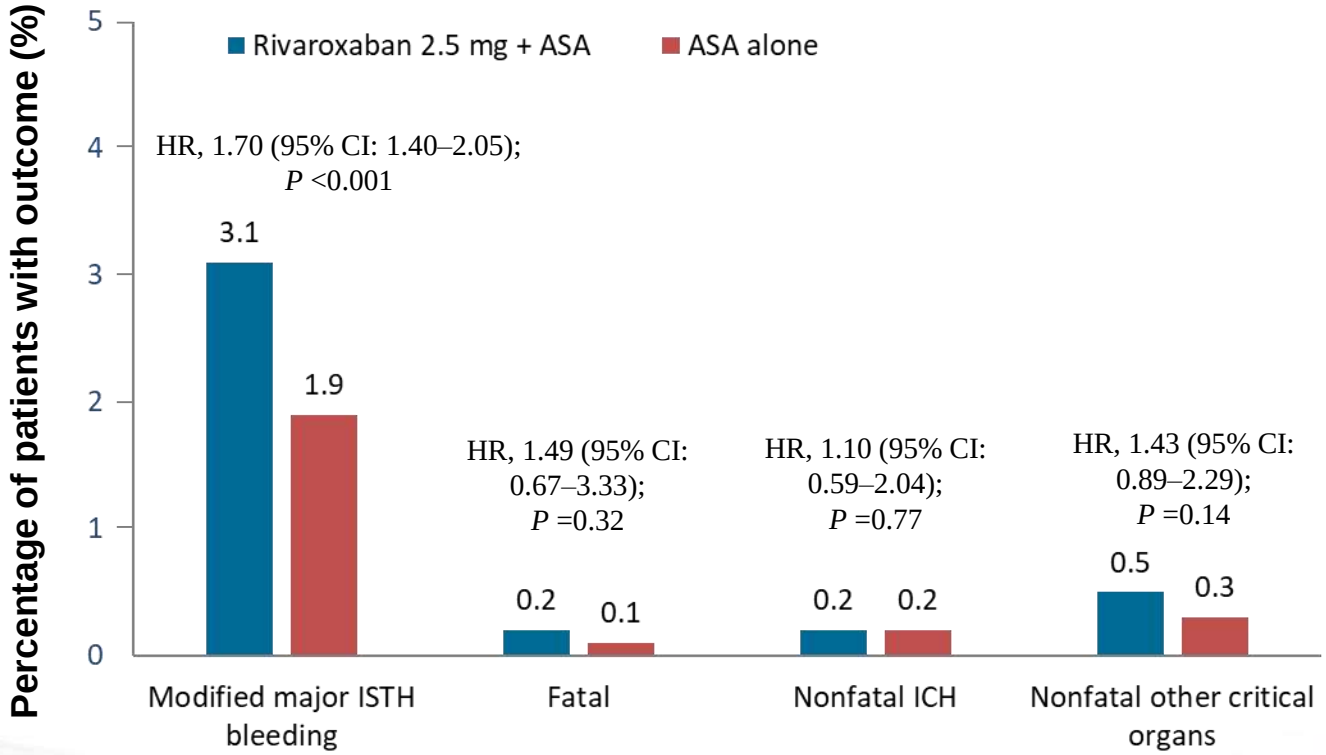
Components of primary outcome

	R + A N=9,152	**Aspirin** N=9,126	**Riva + aspirin vs. aspirin**	
	N (%)	**N (%)**	**HR (95% CI)**	**p**
CV death	160 (1.7)	203 (2.2)	0.78 (0.64-0.96)	0.02
Stroke	83 (0.9)	142 (1.6)	0.58 (0.44-0.76)	<0.001
MI	178 (1.9)	205 (2.2)	0.86 (0.70-1.05)	0.14

Eikelboom JW *et al*, *N Engl J Med* 2017;377:1319-1330

COMPASS TRIAL: MAJOR BLEEDING RATES



ASA, acetylsalicylic acid; CI, confidence interval; HR, hazard ratio; ICH, intracerebral hemorrhage; ISTH, International Society on Thrombosis and Haemostasis

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

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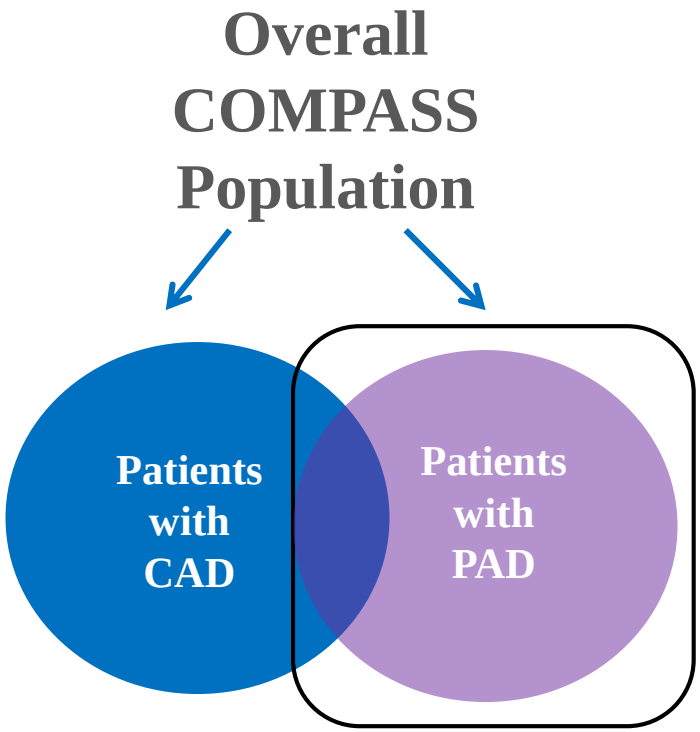
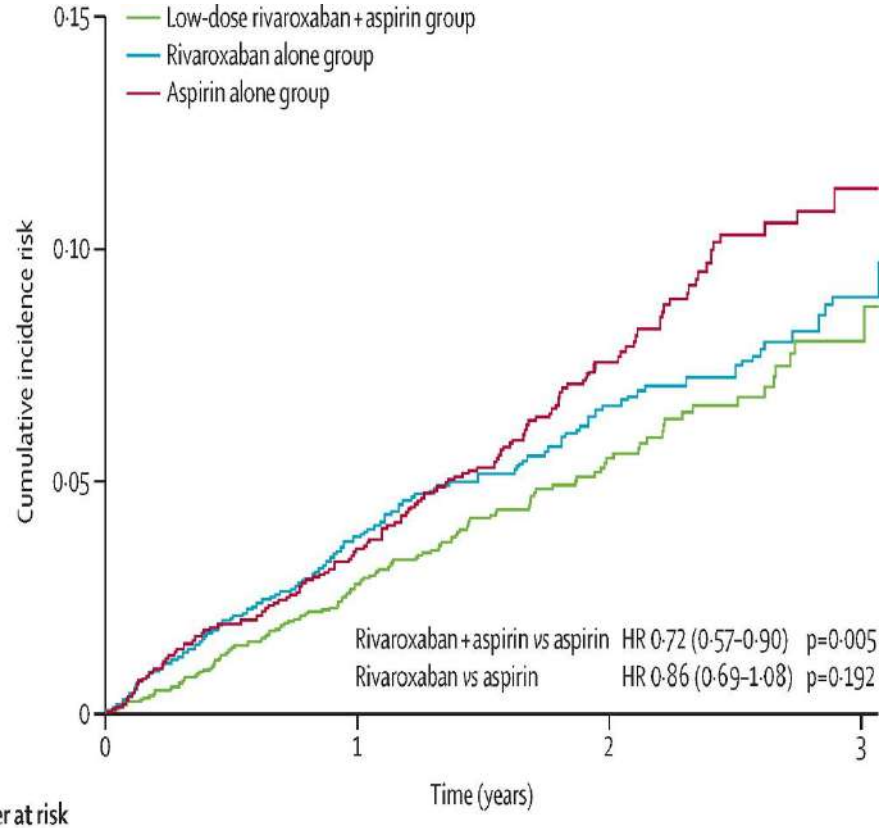
COMPASS: Focus on PAD Patients



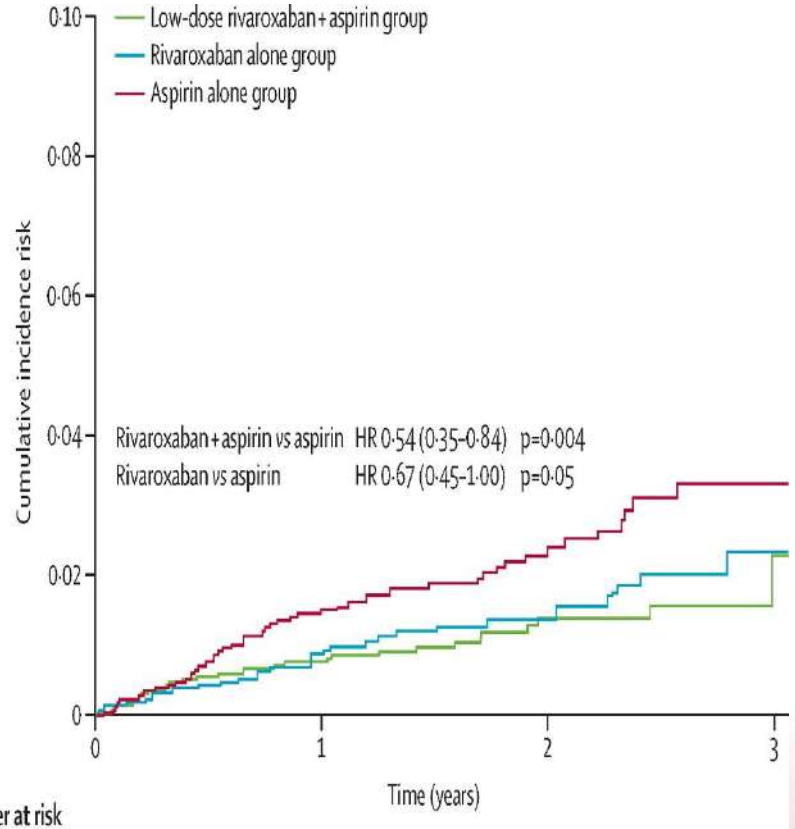
Rivaroxaban with or without aspirin in patients with stable peripheral or carotid artery disease: an international, randomised, double-blind, placebo-controlled trial

Primary Endpoint – CV Death, MI and Stroke



Number at risk				
Rivaroxaban+aspirin	2492	2086	907	127
Rivaroxaban	2474	2044	870	147
Aspirin	2504	2065	930	119

MALE and Amputations



Number at risk				
Rivaroxaban+aspirin	2492	2099	919	129
Rivaroxaban	2474	2071	902	151
Aspirin	2504	2072	951	120

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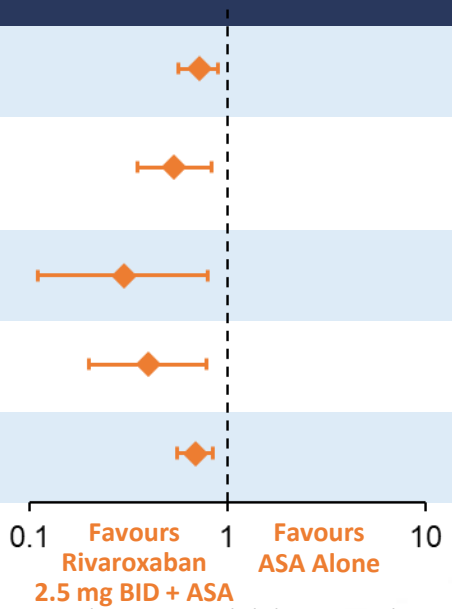
RIVAROXABAN 2.5 MG BID + ASA SIGNIFICANTLY REDUCES CV AND LIMB EVENTS VS. ASA

Pre-specified PAD outcomes*	Rivaroxaban vascular dose 2.5 mg BID + ASA N=2492 n (%)	ASA N=2474 n (%)	HR (95% CI)	HR	95% CI
MACE (CV death, stroke, MI)	126 (5)	174 (7)		0.72	0.57-0.90
MALE (acute or chronic limb ischemia and major amputations†)	30 (1)	56 (2)		0.54	0.35-0.84
Major Amputation	5 (0.2)	17 (0.7)		0.30	0.11-0.80
All Vascular Amputations	11 (0.4)	28 (1)		0.40	0.20-0.79
MACE or MALE, or Major Amputation	157 (6)	225 (9)		0.69	0.56-0.85



*Crude incidence over mean follow-up of 21 months; †includes major amputations due to a vascular event not included in acute or chronic limb ischemia.
Rivaroxaban no está comercializado para la prevención de eventos aterotrombóticos en pacientes con EAC o EAP en España.
ASA: acetylsalicylic acid; CI: confidence interval; CV: cardiovascular; HR: hazard ratio; MACE: major adverse cardiovascular event; MALE: major adverse limb event; MI: myocardial infarction.

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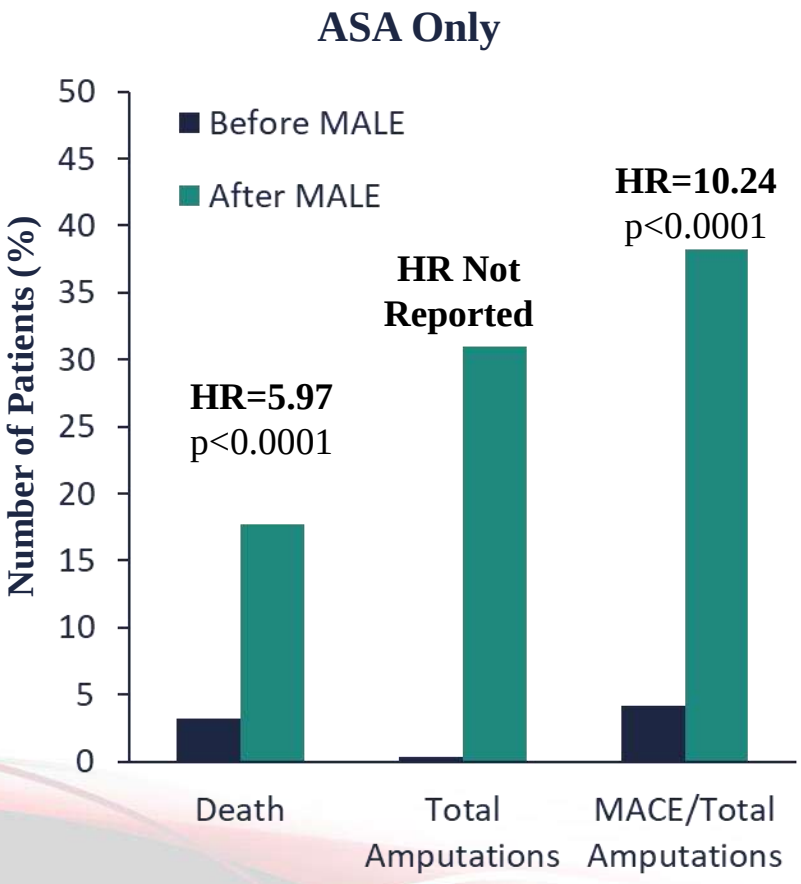
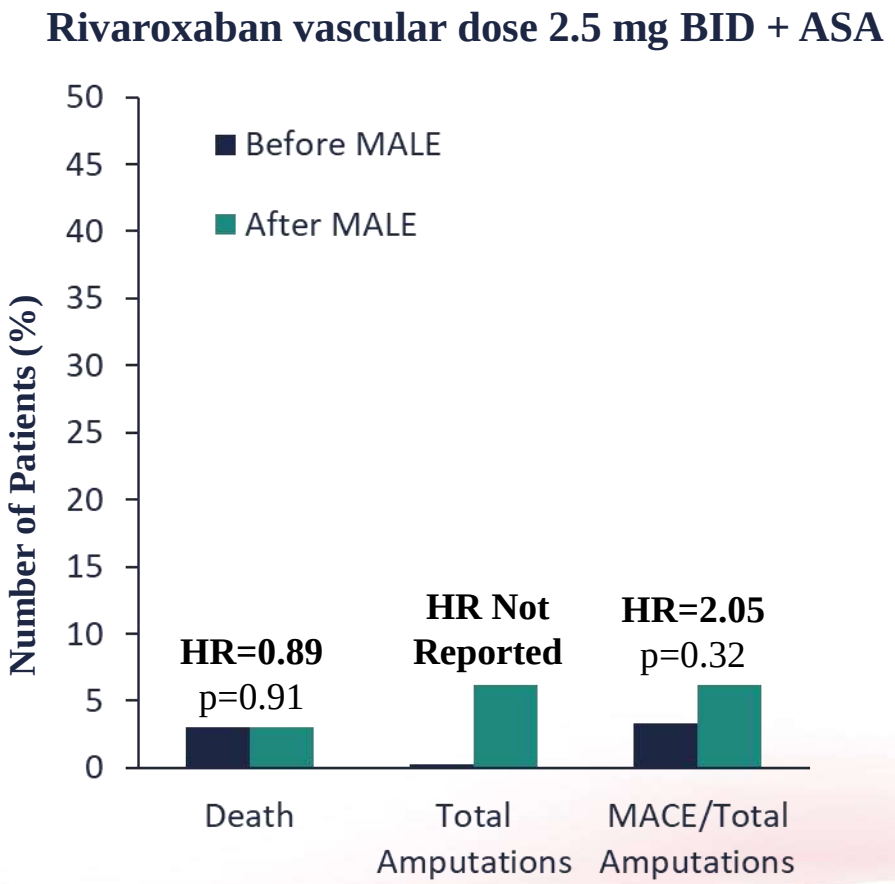
PROGNOSIS OF MALE BY RANDOMIZED TREATMENT





Rivaroxaban no está comercializado para la prevención de eventos aterotrombóticos en pacientes con EAC o EAP en España
ASA: acetylsalicylic acid; HR: hazard ratio; MACE: major adverse cardiovascular event; MALE: major adverse limb event.

Anand, ACC 2018 presentation; Anand et al. J Am Coll Cardiol. 2018;71:2306-15.

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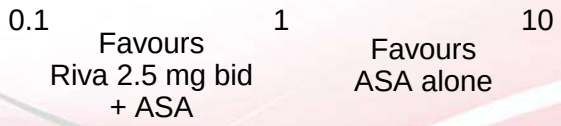
ANALYSIS INDICATES POTENTIAL IMPROVEMENT IN BENEFIT-RISK OVER TIME: EFFICACY MAINTAINED, BLEEDING RISK REDUCED

Time from Randomization	Rivaroxaban 2.5 mg BID + ASA n/N (%)		ASA Alone n/N (%)		HR (95% CI)	HR (95% CI)
MACE						
<1 year	176/8313	(2)	221/8261	(3)		0.79 (0.65–0.96)
1–<2 years	113/7228	(2)	169/7125	(2)		0.66 (0.52–0.83)
>2 years	58/3655	(2)	70/3621	(2)		0.82 (0.58–1.16)
Major bleeding						
<1 year	163/8313	(2)	70/8261	(1)		2.32 (1.75–3.07)
1–<2 years	70/7189	(1)	59/7183	(1)		1.19 (0.84–1.68)
>2 years	30/3626	(1)	29/3694	(1)		1.05 (0.63–1.75)
All deaths						
<1 year	117/8313	(1)	145/8261	(2)		0.80 (0.63–1.02)
1–<2 years	93/7323	(1)	120/7242	(2)		0.77 (0.59–1.01)
>2 years	52/3743	(1)	74/3762	(2)		0.70 (0.49–1.00)



ASA, acetylsalicylic acid; BID, twice daily; CI, confidence interval; HR, hazard ratio; MACE, major adverse cardiac event; Riva, rivaroxaban

Connolly *SJ et al. Lancet* 2017. doi: 10.1016/S0140-6736(17)32458-3.

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Consistent efficacy benefits of rivaroxaban 2.5 mg bid between ATLAS ACS 2 TIMI 51 and the COMPASS CAD subanalysis

Outcome (%*)	ATLAS ACS 2 TIMI 51[1] Patients with recent ACS			COMPASS CAD substudy[2] Patients with chronic CAD		
	Placebo plus SOC[#]	Rivaroxaban 2.5 mg bid plus SOC[#]	HR (95% CI)	Placebo plus aspirin	Rivaroxaban 2.5 mg bid plus aspirin	HR (95% CI)
MACE	10.7	9.1	0.84 (0.72–0.97)	5.6	4.2	0.74 (0.65–0.86)
MI	6.6	6.1	0.90 (0.75–1.09)	2.4	2.0	0.86 (0.70–1.05)
Stroke	1.2	1.4	1.13 (0.74–1.73)	1.6	0.9	0.56 (0.42–0.75)
CV death	4.1	2.7	0.66 (0.51–0.86)	2.2	1.7	0.75 (0.60–0.93)
All-cause death	4.5	2.9	0.68 (0.53–0.87)	4.1	3.2	0.77 (0.65–0.90)
Major bleeding[‡]	0.6	1.8	3.46 (2.08–5.77)	1.9	3.2	1.66 (1.37–2.03)
Fatal bleeding	0.2	0.1	0.67 (0.24–1.89)	0.1	0.2	1.55 (0.67–3.58)
ICH[§]	0.2	0.4	2.83 (1.02–7.86)	0.2	0.2	0.99 (0.52–1.87)

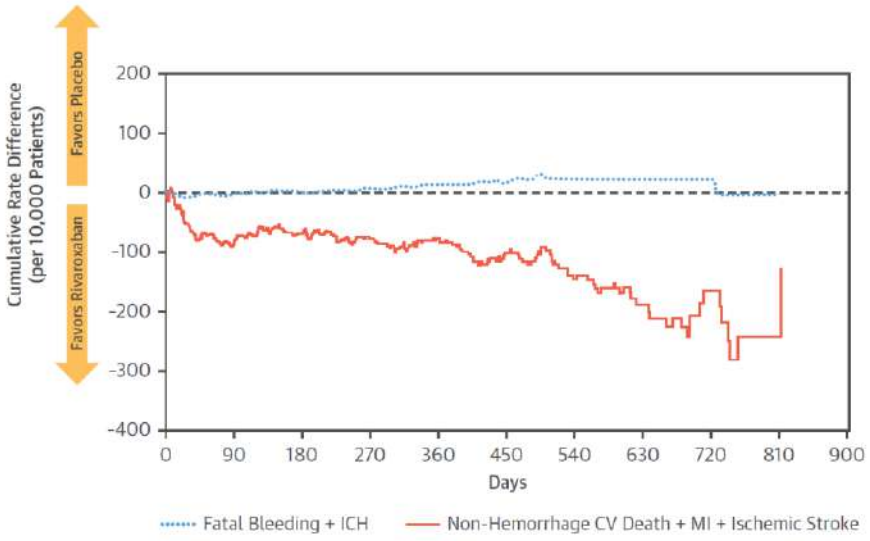
- Direct comparison between trials should be avoided because of different patient risk profiles, treatment regimens and bleeding definitions

*ATLAS ACS 2 TIMI 51 outcomes: 2-year Kaplan–Meier estimates. COMPASS CAD subanalysis outcomes: incidence proportions after a mean follow-up of 1.95 years; [#]aspirin plus thienopyridine (~93%) or aspirin alone (~7%); [‡]ATLAS ACS 2 TIMI 51: TIMI non-CABG major bleeding. COMPASS: Modified ISTH major bleeding; [§]COMPASS: non-fatal symptomatic ICH. ACS, acute coronary syndrome; bid, twice daily; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CI, confidence interval; CV, cardiovascular; HR, hazard ratio; ICH, intracranial haemorrhage; ISTH, International Society on Thrombosis and Haemostasis; MACE, major adverse cardiovascular events; MI, myocardial infarction; SOC, standard of care; TIMI, Thrombolysis In Myocardial Infarction.

1. Mega JL *et al*, *N Engl J Med* 2012;366:9–19; 2. Connolly SJ *et al*, *Lancet* 2018;391:205–218.

Temporal impact of bleeding and ischemic events

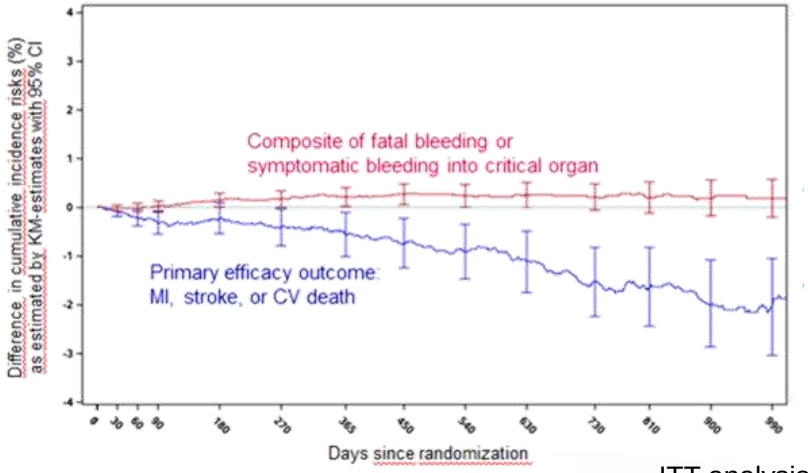
ATLAS ACS 2 TIMI 51: Balance of efficacy and safety over time[1]



COMPASS CAD analysis: Efficacy and safety over time[2]

Stable absolute risk increase in bleeding outcome after 1 year

Increasing absolute risk reduction for primary efficacy outcome



ITT analysis

ACS, acute coronary syndrome; CAD, coronary artery disease; CV, cardiovascular; ICH, intracranial haemorrhage; ITT, intention to treat; KM, Kaplan–Meier; MI, myocardial infarction.

1. Gibson CM *et al*, *J Am Coll Cardiol* 2018;72:129–136; 2. COMPASS – data on file (manuscript in preparation)

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Components of primary outcome

	R + A N=9,152	**Aspirin** N=9,126	**Riva + aspirin vs. aspirin**	
	N (%)	**N (%)**	**HR (95% CI)**	**p**
CV death	160 (1.7)	203 (2.2)	0.78 (0.64-0.96)	0.02
Stroke	83 (0.9)	142 (1.6)	0.58 (0.44-0.76)	<0.001
MI	178 (1.9)	205 (2.2)	0.86 (0.70-1.05)	0.14

Eikelboom JW *et al*, *N Engl J Med* 2017;377:1319-1330

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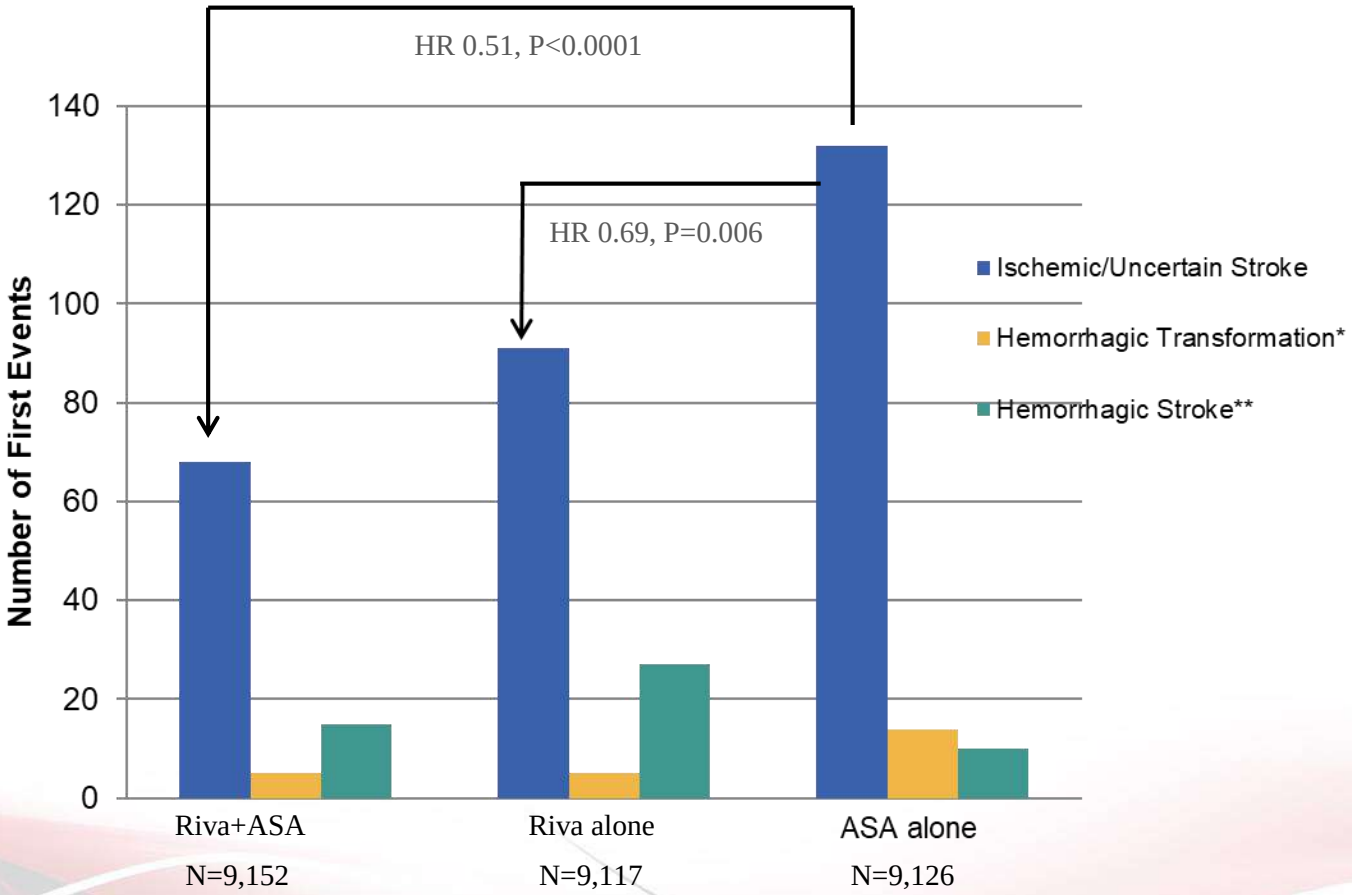
Ischemic/Uncertain Strokes Reduced by Nearly Half with Rivaroxaban + ASA vs. ASA Alone



*Incidence of hemorrhagic strokes was significantly increased by Riva alone vs ASA alone (HR=2.70, P=0.005), but not by Riva+ASA vs. ASA alone (HR=1.49, P=0.33). ** Hemorrhagic transformation of ischemic stroke was reduced in both the Riva+ASA and Riva alone arms vs. ASA alone (HR=0.35, P=0.04 and HR=0.36,P=0.04, respectively)

Sharma M *et al.* Circulation 2019 Feb 26;139(9):1134-1145.

Previous Stroke Status and Outcomes

Outcome	Rivaroxaban plus Aspirin (N=9152)		Aspirin (N=9126)		Rivaroxaban plus Aspirin vs. Aspirin		
	N Pts	%/yr	N Pts	%/yr	HR (95% CI)	P	P inter
Stroke							0.40
No Previous Stroke	8801	0.4	8791	0.7	0.60 (0.45-0.80)	0.0006	
Previous Stroke	351	0.7	335	3.4	0.42 (0.19-0.92)	0.03	
Ischemic or uncertain stroke							0.28
No Previous Stroke	8801	0.4	8791	0.7	0.54 (0.40-0.74)	0.0001	
Previous Stroke	351	1.1	335	3.4	0.33 (0.14-0.77)	0.01	

Previous stroke ARR = 2.7%

NNT = 37

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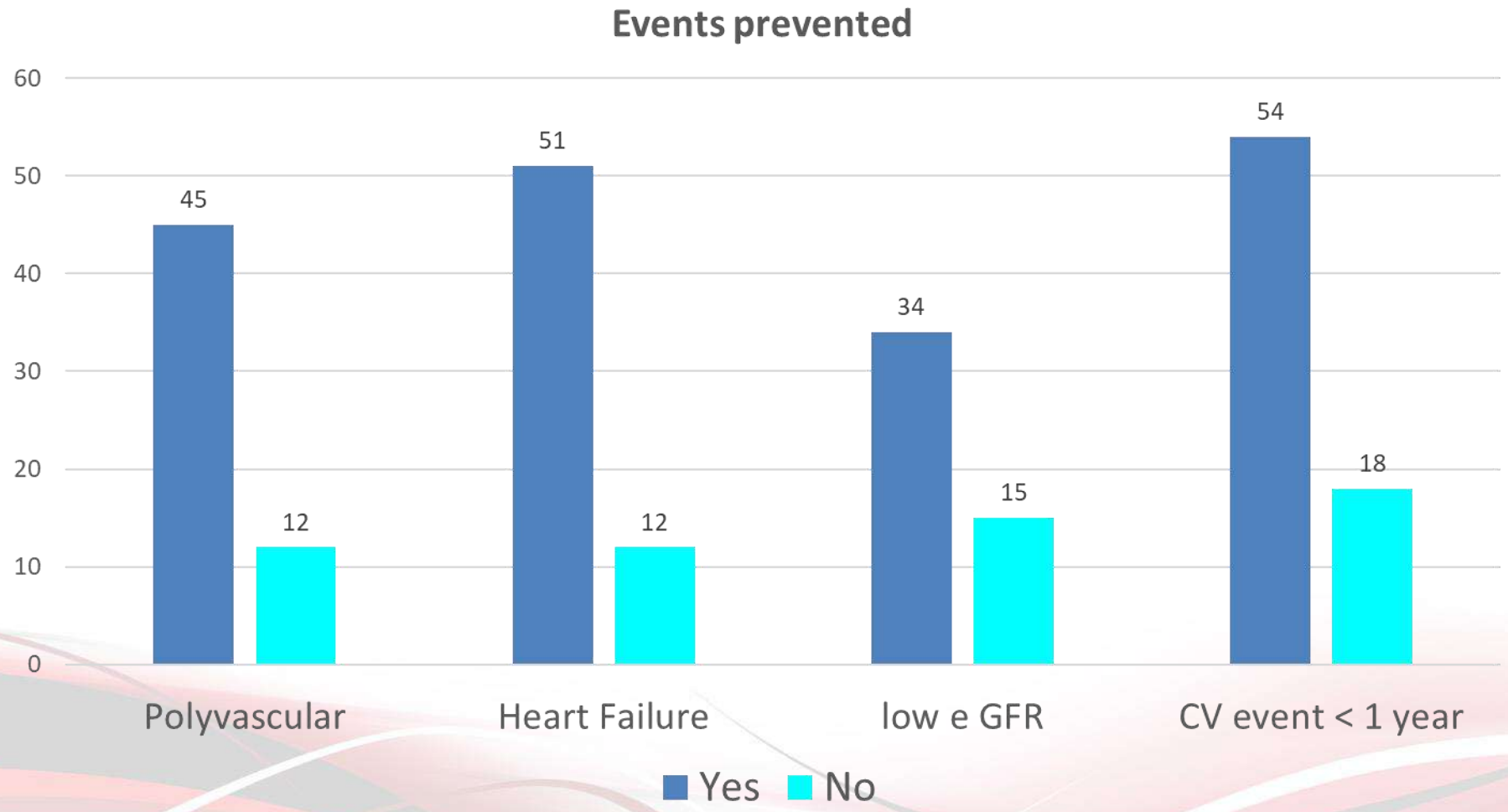
Strategies to apply contemporary antithrombotic therapies to individual patients

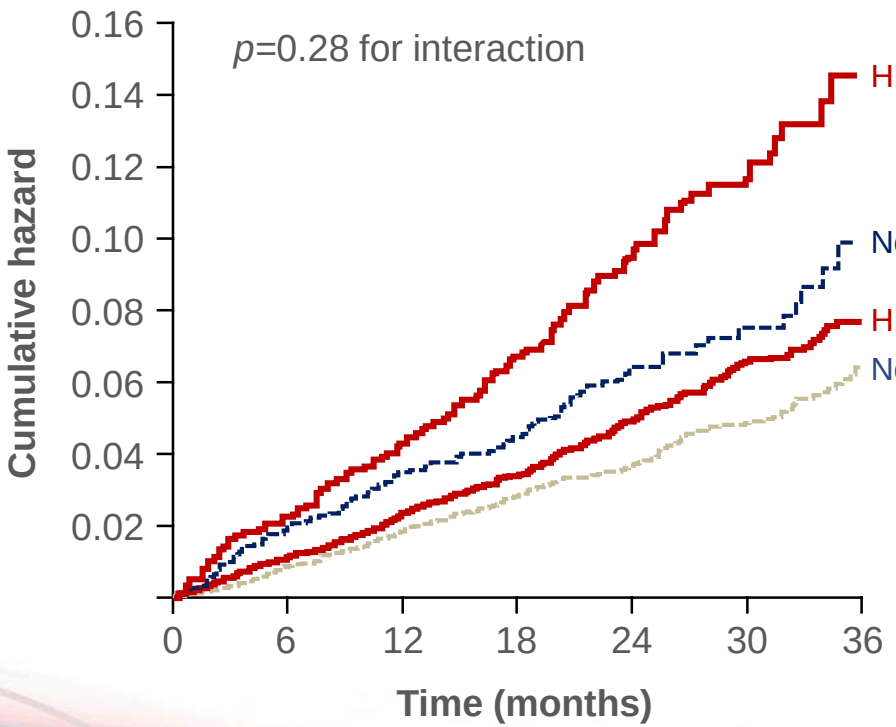
Identifying patients with chronic Atherosclerotic Cardiovascular Disease who could benefit most in clinical practice.

COMPASS

Events prevented per 1000 patients treated over 36 months of therapy



COMPASS HF Subgroup: Primary MACE Outcome by HF Status



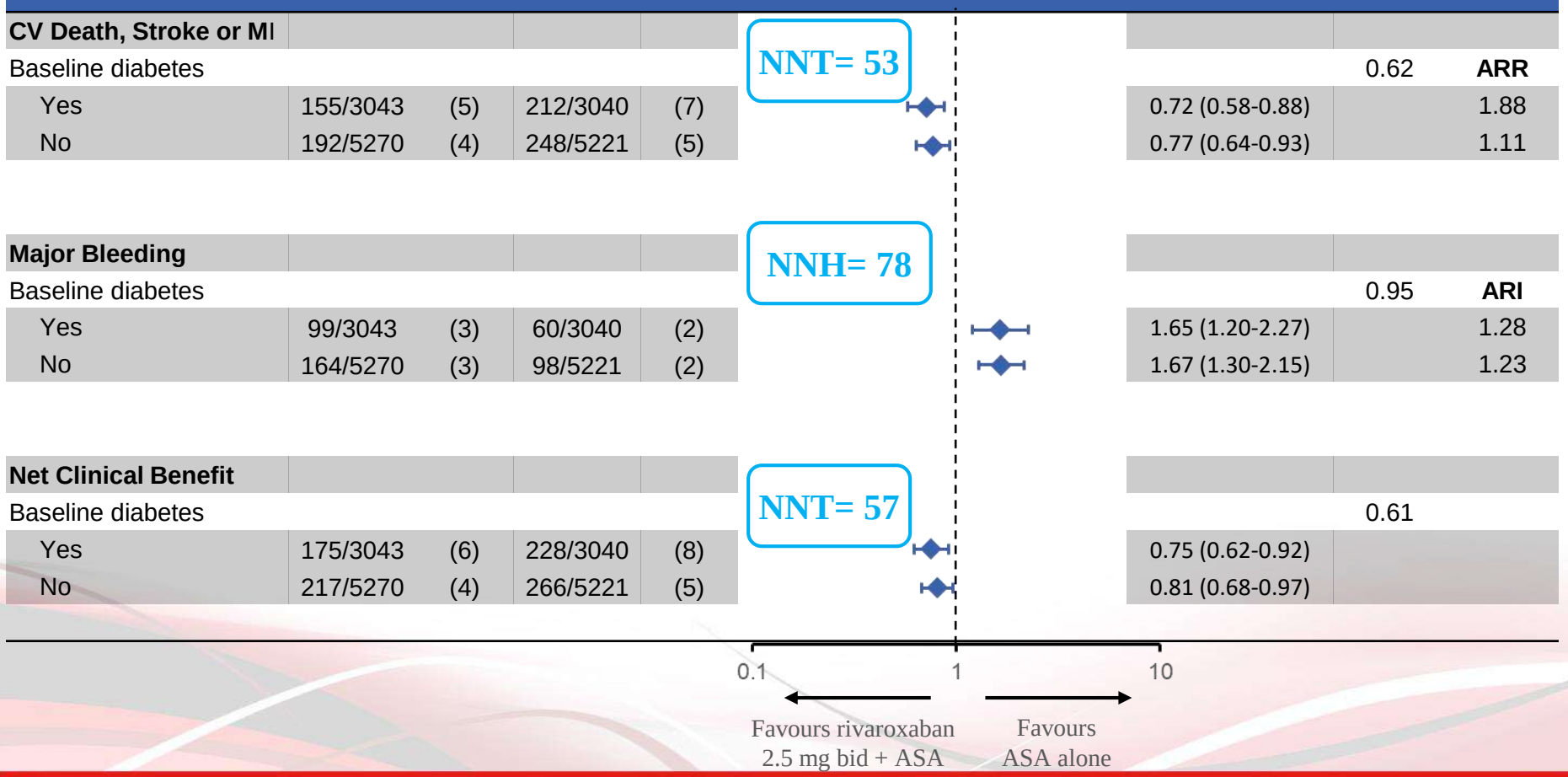
HR=0.68
(95% CI 0.53–0.86)
ARR=2.4%
NNT=42

HR=0.79
(95% CI 0.68–0.93)
ARR=0.9%
NNT=111

Branch K, *et al.* Presented at ESC-HF. clinicaltrialresults.org [accessed Aug 2018]

Consistent Benefit of Dual Pathway Inhibition with Rivaroxaban Vascular Dose 2.5 mg bid + ASA in CAD Patients with Diabetes

Subgroup	Rivaroxaban 2.5 mg bid + ASA n/N (%)		ASA alone n/N (%)		HR (95% CI)	HR (95% CI)	p-value (intx)	ARR/ ARI
CV Death, Stroke or MI					NNT= 53			
Baseline diabetes							0.62	**ARR**
Yes	155/3043	(5)	212/3040	(7)		0.72 (0.58-0.88)		1.88
No	192/5270	(4)	248/5221	(5)		0.77 (0.64-0.93)		1.11
Major Bleeding					NNH= 78			
Baseline diabetes							0.95	**ARI**
Yes	99/3043	(3)	60/3040	(2)		1.65 (1.20-2.27)		1.28
No	164/5270	(3)	98/5221	(2)		1.67 (1.30-2.15)		1.23
Net Clinical Benefit					NNT= 57			
Baseline diabetes							0.61	
Yes	175/3043	(6)	228/3040	(8)		0.75 (0.62-0.92)		
No	217/5270	(4)	266/5221	(5)		0.81 (0.68-0.97)		



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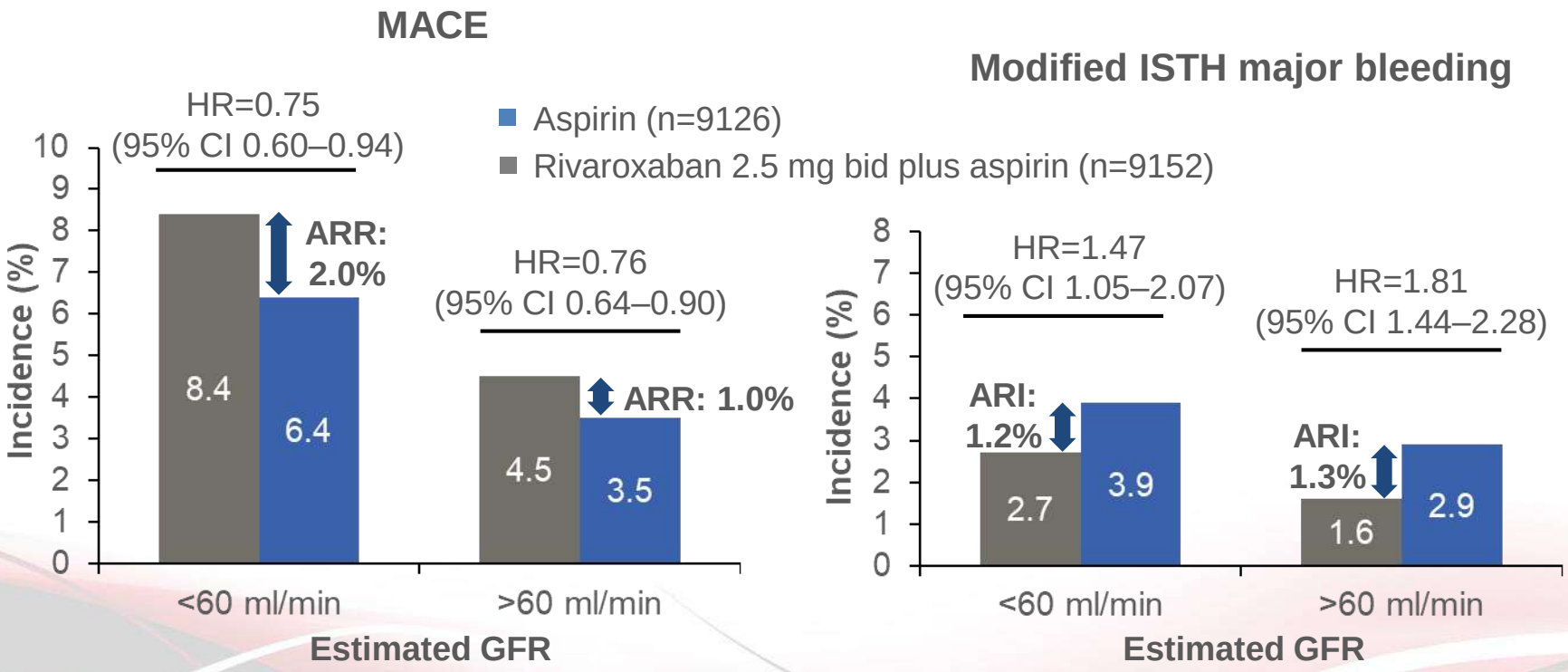
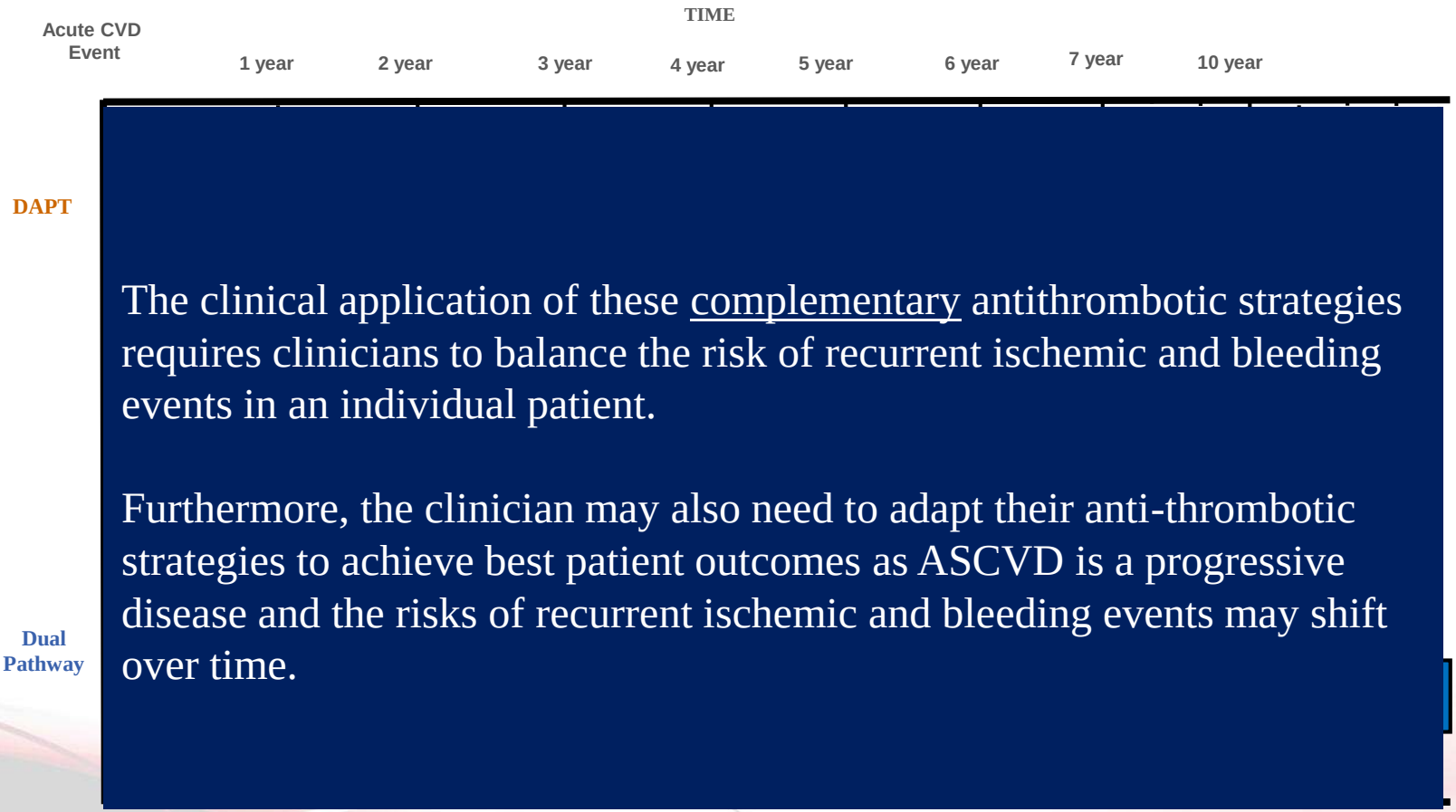
Rivaroxaban 2.5 mg bid plus Aspirin Significantly Reduced the Risk of MACE in Patients with CAD or PAD and Renal Impairment

Incidence of the primary efficacy and safety outcomes according to eGFR in COMPASS



Eikelboom JW *et al*, *N Engl J Med* 2017; 377:1319–1330

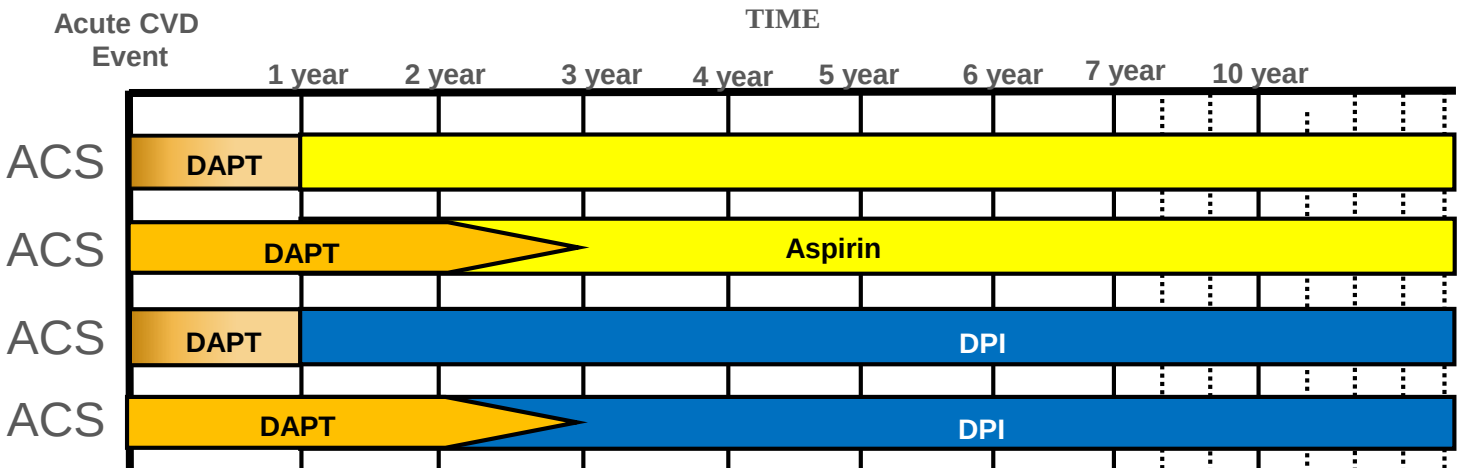
Antithrombotic trial populations and enrolment periods



The clinical application of these complementary antithrombotic strategies requires clinicians to balance the risk of recurrent ischemic and bleeding events in an individual patient.

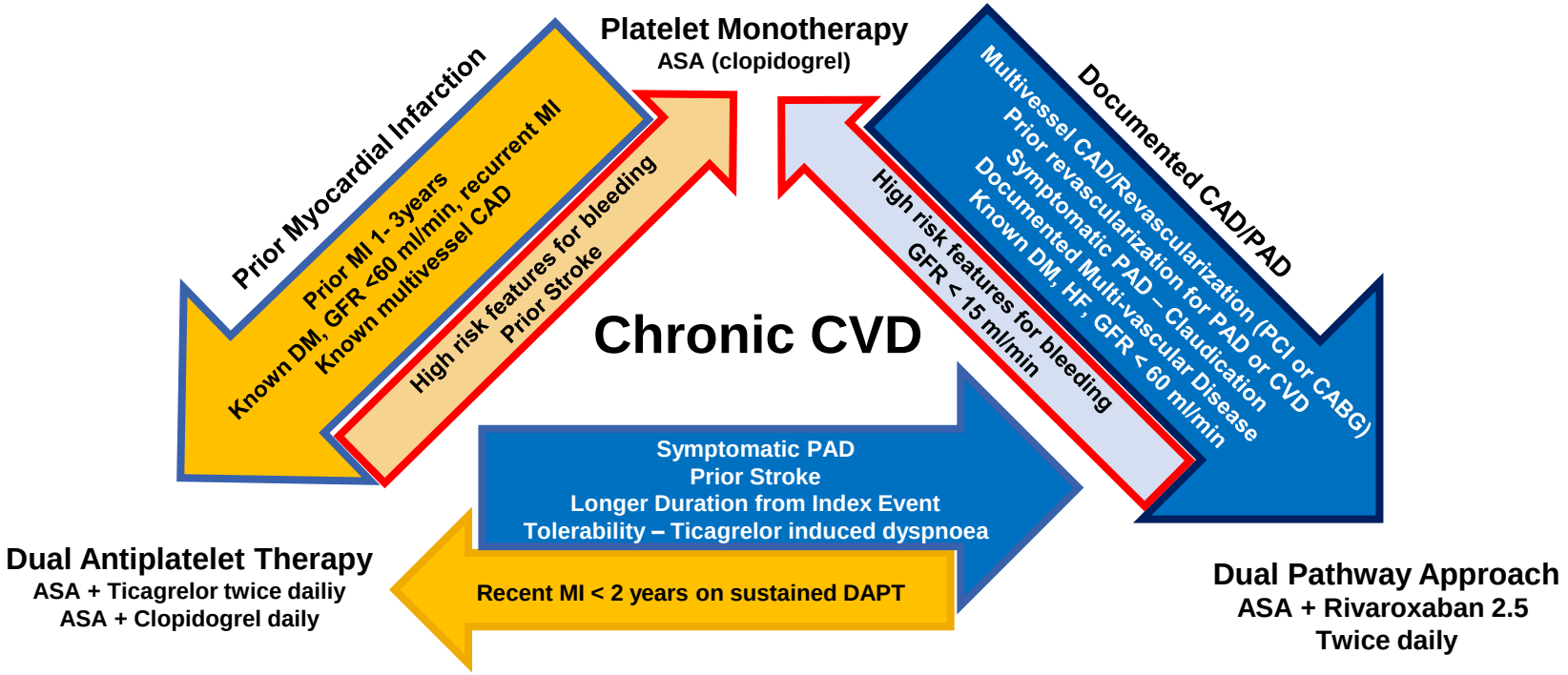
Furthermore, the clinician may also need to adapt their anti-thrombotic strategies to achieve best patient outcomes as ASCVD is a progressive disease and the risks of recurrent ischemic and bleeding events may shift over time.

Clinical Scenarios
Anti-thrombotic strategies from acute to chronic ASCVD



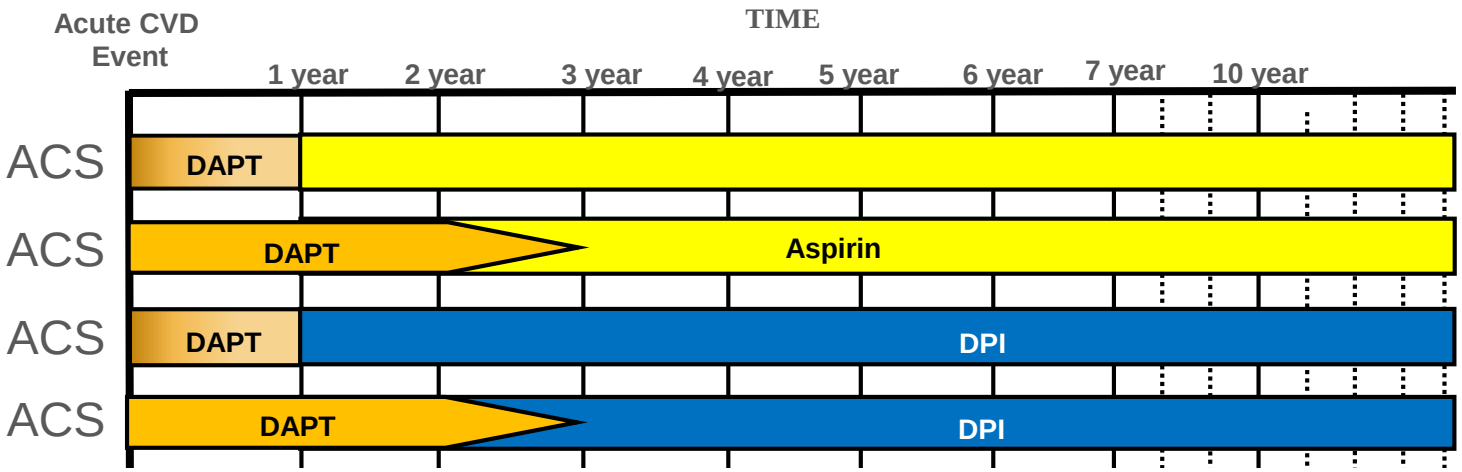
Welsh R. et al, under review.

Applying antithrombotic strategies in clinical practice



Welsh R. et al, under review.

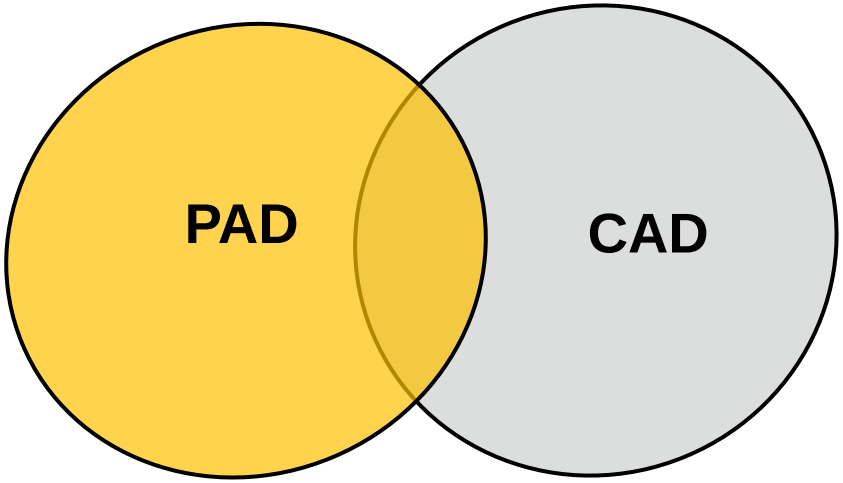
Clinical Scenarios
Anti-thrombotic strategies from acute to chronic ASCVD



Welsh R. et al, under review.

Patient populations with largest absolute benefit

RIVAROXABAN 2.5 MG BID + ASA REDUCES VASCULAR EVENTS* AND DEATH IN CAD and PAD PATIENTS#



Largest Patient Benefit

- Poly-vascular disease (CAD and PAD)
- CKD (eGFR <60 ml/min)
- Heart failure (ejection fraction >30%)
- Diabetes
- CV event within one year
- Multi-vessel CAD or revascularization

Avoid in patients with eGFR <15 ml/min and/or high bleeding risk

*Reduced MACE, stroke, CV death, MALE and amputations; #Symptomatic PAD or revascularization, CAD patients aged <65 years require additional risk factors; Patients not requiring DAPT or anticoagulation for AF/VTE/mechanical valve; Encouraging optimal guideline adherent secondary prevention

Welsh R. et al, under review.

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COMPASS IN CONTEXT

Proven secondary prevention therapies

	ACEI[1,2]	Lipid lowering (1 mmol/L)[3]	DAPT (PEGASUS; ticagrelor 60 mg BID)[4,5]	BP lowering (10 mmHg)[6]	COMPASS Rivaroxaban vascular dose 2.5 mg BID + ASA[7,8]
Composite of efficacy outcomes	–18%	–21%	–16%	–20%	–24%
Death	–14%	–9%*	–11%*	–13%	–18%
Stroke	–23%	–15%*	–25%	–27%	–42%
MI	–18%	–24%	–16%	–17%	–14%*
MALE	–11%*	–	–19%*	–	–46%

The relative reductions in adverse ischemic outcomes, including death, were indirectly comparable (or greater) with rivaroxaban 2.5 mg BID + ASA relative to other established secondary prevention therapies

*Not significant

Rivaroxaban no está comercializado para la prevención de eventos aterotrombóticos en pacientes con EAC o EAP en España

ACEI, angiotensin-converting-enzyme inhibitor; ASA, acetylsalicylic acid; BID, twice daily; BP, blood pressure; DAPT, dual antiplatelet therapy; MALE, major adverse limb event; MI, myocardial infarction

1. Ostergren *J, et* al. *Eur Heart J* 2004; 25:17-24. 2. Dagenais GR *et al. Lancet* 2006; 368:581-8. 3. CTT Collaboration. *Lancet* 2015; 385:1397-405. 4. Bonaca MP *et al. N Engl J Med* 2015; 372:1791-800. 5. Bonaca MP *et al. J Am Coll Cardiol* 2016; 67:2719-28. 6. Ettehad D *et al. Lancet* 2016; 387:957-67. 7. Eikelboom JW *et al. N Engl J Med* 2017; 377:1319-30; 8. Anand SS et al. *Lancet* 2017; 391: 219-29

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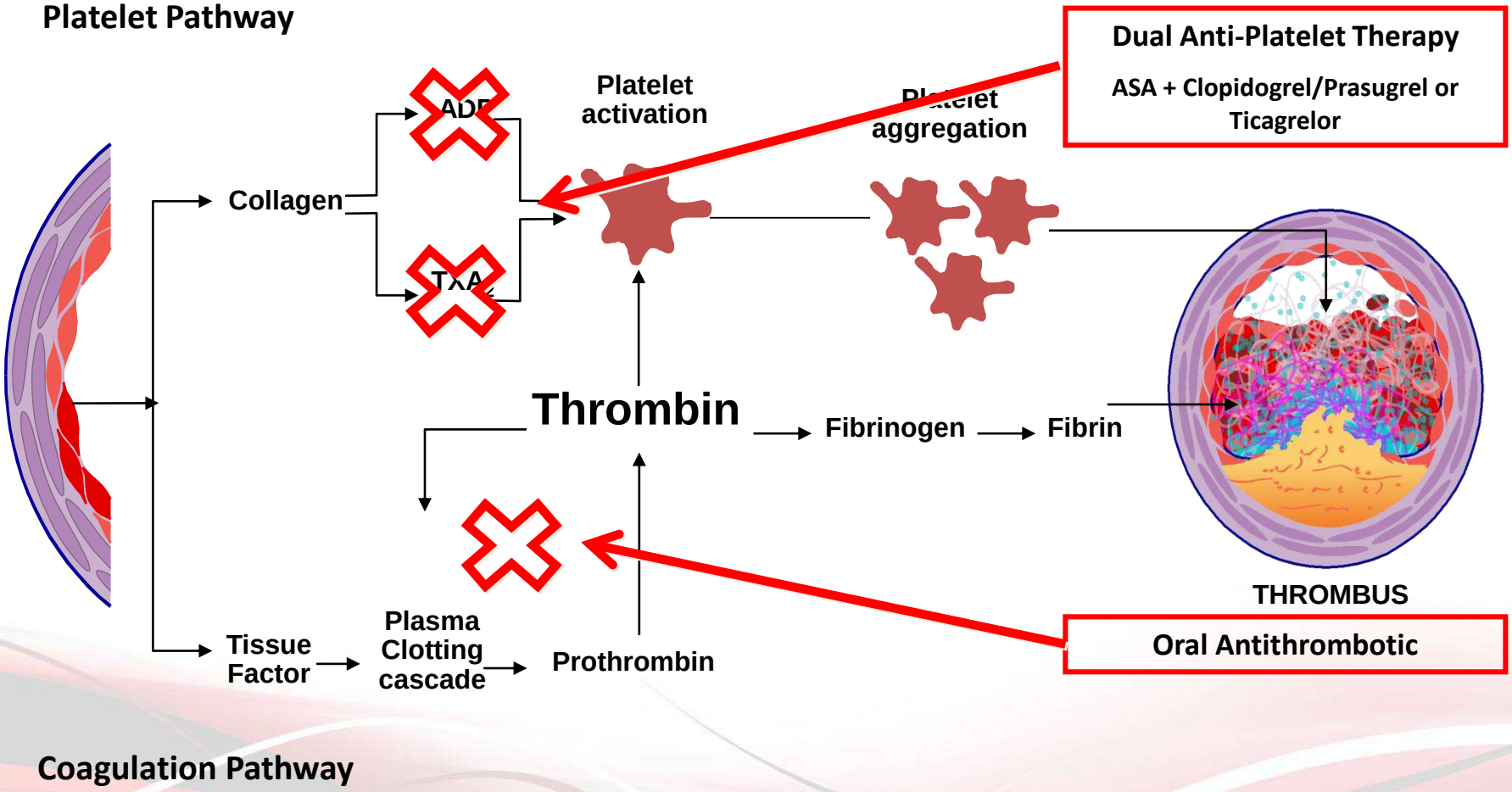
Synergy of Dual Pathway Inhibition (DPI) in chronic cardiovascular disease

Robert C. Welsh, MD, FRCPC
Professor of Medicine, University of Alberta
Zone Clinical Department Head, Cardiac Sciences

Experimental treatment of ACS

Pathways For Thrombus Formation

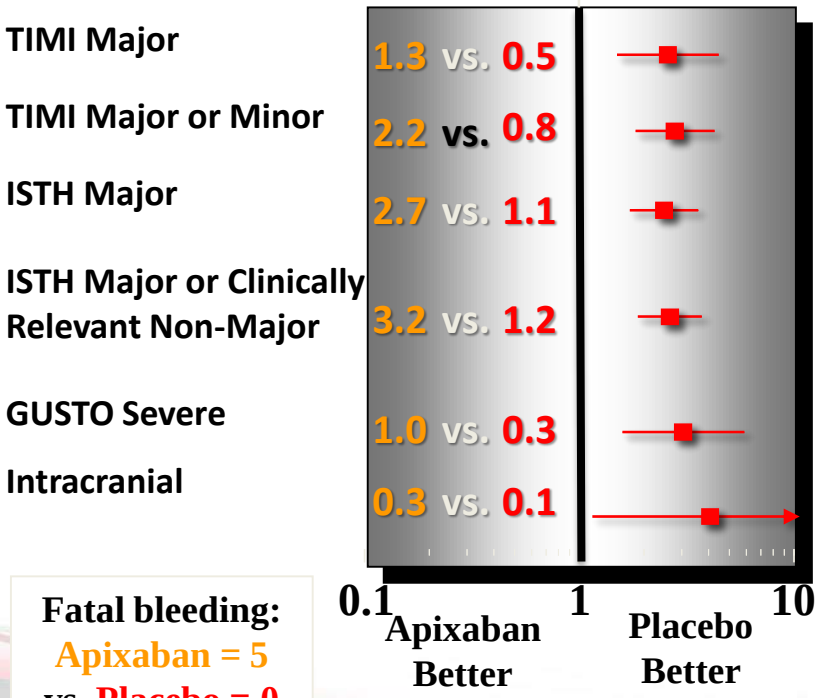
Two pathways connecting tissue injury, coagulation, and platelet response.



Atrial Fibrillation Dose Apixaban in ACS

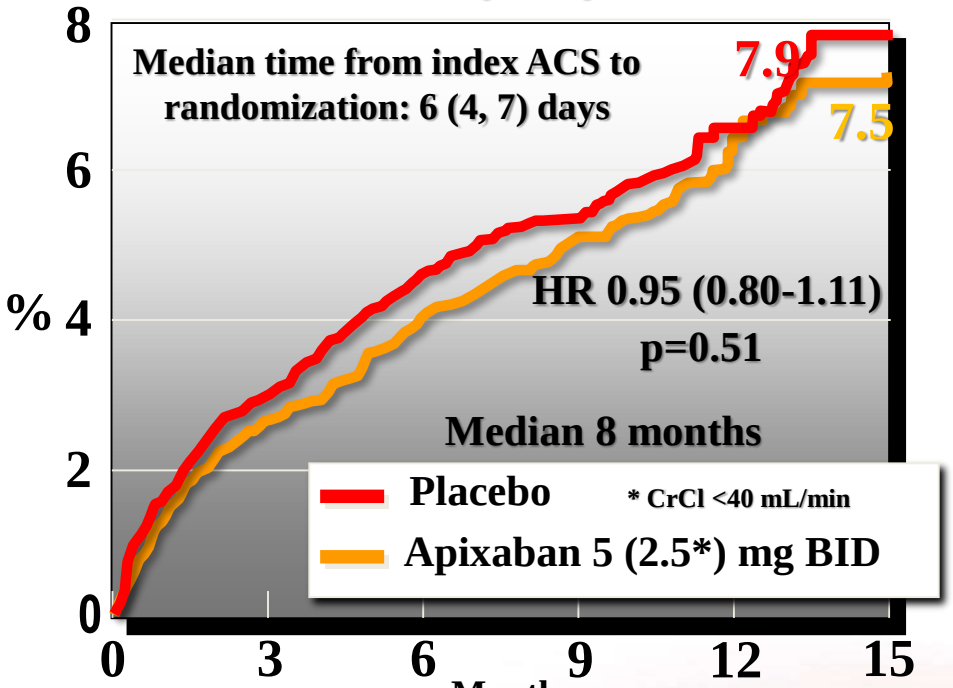
Patients (n=7392) with recent STEMI or NSTEACS (80% on dual antiplatelet therapy) and ≥2 additional risk factors (Age ≥65 yrs, DM, prior MI ≤5 yrs, CVD, PVD, HF or LVEF <40%, CrCl <60 mL/min, no revascularization for index event) → **DMC recommended trial stop due to excess of clinically important bleeding without counterbalancing reduction in ischemic events**

Bleeding



Fatal bleeding:
Apixaban = 5
vs. Placebo = 0

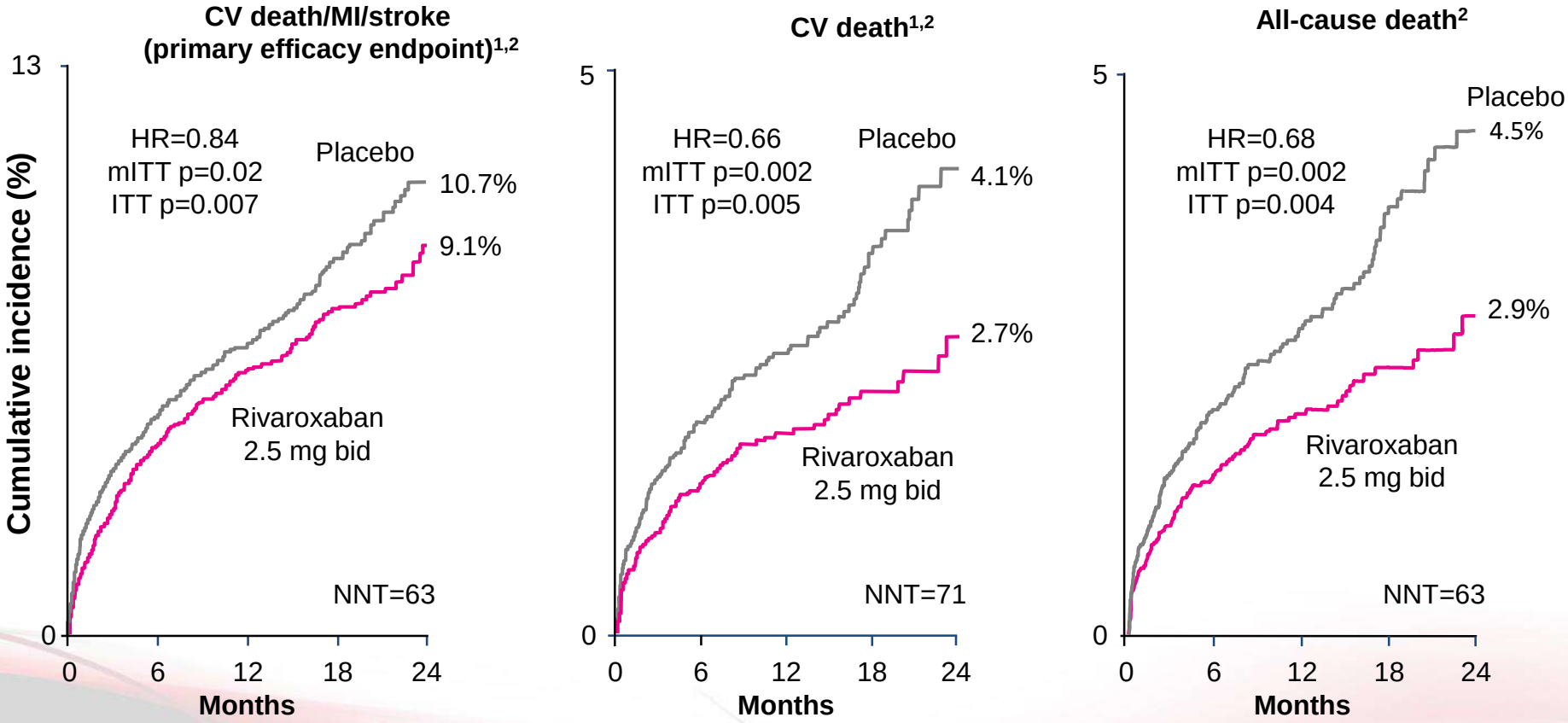
CV Death/MI/Stroke



Apix:	279	2025	1277	561	154
3705	9	2030	1248	571	164
Plac:	275				
3687	1				

ATLAS ACS 2-TIMI 51: Efficacy endpoints rivaroxaban 2.5 mg bid

The primary efficacy endpoint reduction was driven by reduced mortality



Both strata. CV=Cardiovascular; HR=Hazard ratio; ITT=Intention to treat; MI=Myocardial infarction; mITT=Modified intention to treat; NNT=Number needed to treat.

1. Mega JL, et al. *N Engl J Med*. 2012;366:9–19; 2. Gibson CM et al. LBCT.01. Presented at American Heart Association (AHA) Scientific Sessions 2011; 12-16 November, Orlando, Florida, USA.

Inclusion and Exclusion Criteria Ensured That Patients Had Chronic CAD/PAD and Moderate Cardiovascular Risk

Key inclusion criteria CAD

- CAD (prior MI, multivessel coronary disease or multivessel revascularization)
- Plus ≥1 of:
  - Age ≥65 years
  - Age <65 years plus atherosclerosis in ≥2 vascular beds or ≥2 additional risk factors
    - Current smoker
    - Diabetes mellitus
    - Renal dysfunction (eGFR<60 ml/min)
    - Heart failure
    - Non-lacunar ischaemic stroke ≥1 month ago

Key inclusions criteria PAD

- History of:
  - PAD of the lower extremities (previous peripheral bypass surgery or angioplasty, limb or foot amputation, intermittent claudication with objective evidence of peripheral artery disease),
  - Carotid arteries (previous carotid artery revascularisation or asymptomatic carotid artery stenosis of at least 50%), or
  - Coronary artery disease with an ankle–brachial index of less than 0·90.

Exclusion criteria: Stroke within the past month or any haemorrhagic or lacunar stroke; Severe HF with known ejection fraction <30% or NYHA class III or IV symptoms; **Need for dual antiplatelet therapy, other non-aspirin antiplatelet therapy or oral anticoagulant therapy;** eGFR <15 ml/min

[#]Including but not limited to; [#]Any other exclusion criteria in conjunction with the local Product Information and any other contraindication listed in the local labelling for rivaroxaban or the comparator have to be considered

Bosch J *et al*, *Can J Cardiol* 2017;33:1027–1035