CANADIAN SOCIETY OF INTERNAL MEDICINE

Thrombosis Canada

Thrombose Canada

Canadian Society of Internal Medicine Annual Meeting

Toronto, Ontario, November 2017

Secondary Prevention of Vascular Events
What is the optimal antithrombotic strategy?

Benjamin Bell, MD FRCPC

Lecturer, University of Toronto

Member, Thrombosis Canada

Staff Internist, North York General Hospital

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Conflict Disclosures

The speaker has received fees/honoraria from the following sources:
BMS/Pfizer, Bayer, Boehringer Ingelheim, Servier, Leo Pharma

Some of the drugs, devices, or treatment modalities mentioned in this presentation are:
ASA, clopidogrel, prasugrel, ticagrelor, rivaroxaban

Objectives

- Review risk of secondary vascular events in those with established vascular disease
- Discuss recent advances in this area
- Compare benefits and harms of long term dual antiplatelet vs aspirin/anticoagulation strategies

Background

- Atherosclerotic cardiovascular disease is common
  - 4% of worldwide population (300 million)
  - Higher in Western countries
- ASA is the standard antithrombotic agent for secondary prevention
  - but MACE (CV death, myocardial infarction, stroke) occurs at a rate of 5-10%/year in optimally managed patients
- Small studies have demonstrated inconsistent benefit for dual antiplatelet therapy
- Warfarin +/- ASA reduces MACE but is associated with excess major bleeding, including ICH

The NEW ENGLAND JOURNAL of MEDICINE

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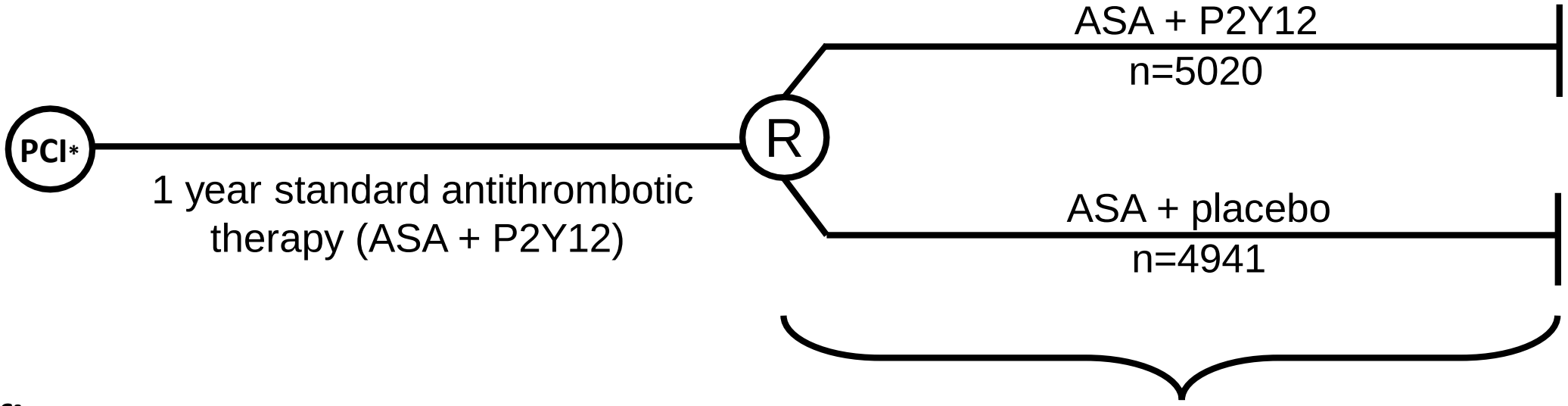
Twelve or 30 Months of Dual Antiplatelet Therapy after Drug-Eluting Stents

“DAPT Trial”

n=9961

DAPT design



Efficacy outomes

-MACE (CV death, MI, stroke)

-Stent thrombosis

Safety outome

-Moderate & severe GUSTO bleeding

Most patients on clopidogrel

Table 3. Bleeding End Point during Month 12 to Month 30.*

Bleeding Complications	Continued Thienopyridine (N=4710)	Placebo (N=4649)	Difference	Two-Sided P Value for Difference
	no. of patients (%)		*percentage points (95% CI)*	
GUSTO severe or moderate†	119 (2.5)	73 (1.6)	1.0 (0.4 to 1.5)	0.001
Severe	38 (0.8)	26 (0.6)	0.2 (–0.1 to 0.6)	0.15
Moderate	81 (1.7)	48 (1.0)	0.7 (0.2 to 1.2)	0.004
BARC type 2, 3, or 5	263 (5.6)	137 (2.9)	2.6 (1.8 to 3.5)	<0.001
Type 2	145 (3.1)	72 (1.5)	1.5 (0.9 to 2.1)	<0.001
Type 3	122 (2.6)	68 (1.5)	1.1 (0.6 to 1.7)	<0.001
Type 5	7 (0.1)	4 (0.1)	0.1 (–0.1 to 0.2)	0.38

Mod-severe bleed
ARI: 0.9%
NNH: 111

Fatal bleeding
Same

Table 2. Stent Thrombosis and Major Adverse Cardiovascular and Cerebrovascular Events.*

Outcome	Continued Thienopyridine (N = 5020)	Placebo (N = 4941)	Hazard Ratio, Thienopyridine vs. Placebo (95% CI)†	P Value†
	no. of patients (%)			
Stent thrombosis‡	19 (0.4)	65 (1.4)	0.29 (0.17–0.48)	<0.001
Definite	15 (0.3)	58 (1.2)	0.26 (0.14–0.45)	<0.001
Probable	5 (0.1)	7 (0.1)	0.71 (0.22–2.23)	0.55
Major adverse cardiovascular and cerebrovascular events§	211 (4.3)	285 (5.9)	0.71 (0.59–0.85)	<0.001
Death	98 (2.0)	74 (1.5)	1.36 (1.00–1.85)	0.05
Cardiac	45 (0.9)	47 (1.0)	1.00 (0.66–1.52)	0.98
Vascular	5 (0.1)	5 (0.1)	0.98 (0.28–3.39)	0.98
Noncardiovascular	48 (1.0)	22 (0.5)	2.23 (1.32–3.78)	0.002
Myocardial infarction	99 (2.1)	198 (4.1)	0.47 (0.37–0.61)	<0.001
Stroke	37 (0.8)	43 (0.9)	0.80 (0.51–1.25)	0.32
Ischemic	24 (0.5)	34 (0.7)	0.68 (0.40–1.17)	0.16
Hemorrhagic	13 (0.3)	9 (0.2)	1.20 (0.50–2.91)	0.68
Type uncertain	0	1 (<0.1)	—	0.32

MACE
ARR: 1.6%
NNT: 63

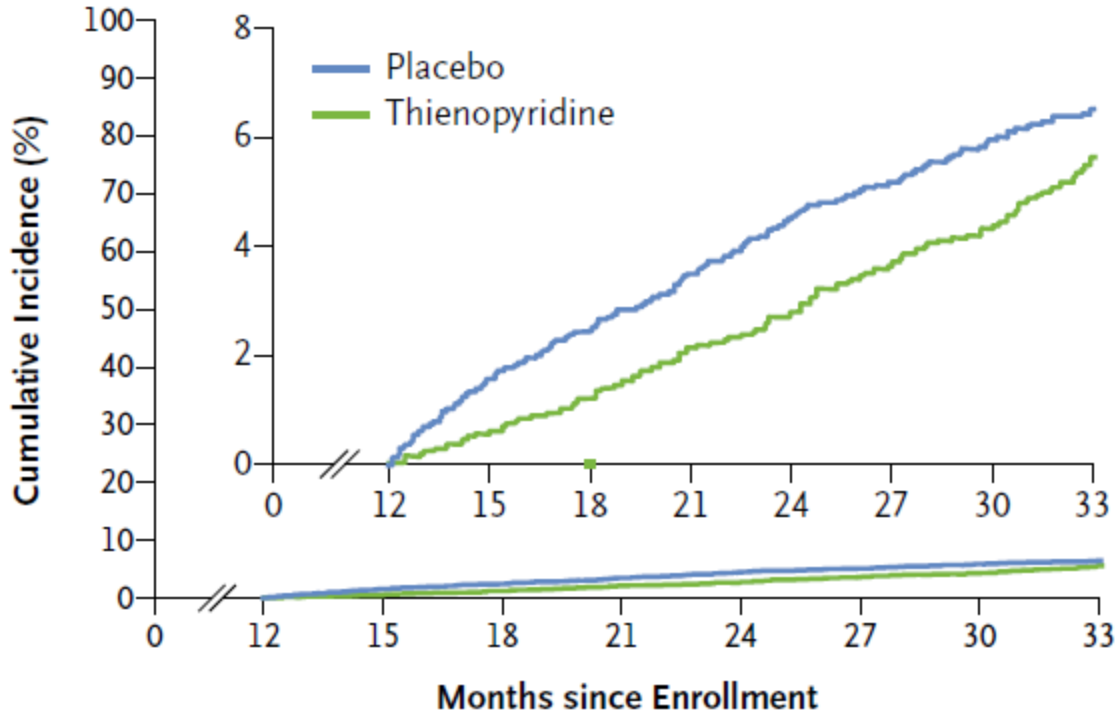
ACS
ARR: 2%
NNT: 50

Death
ARI: 0.5%
NNH: 200

Major Adverse Cardiovascular and Cerebrovascular Events

12–30 mo Thienopyridine vs. placebo, 4.3% vs. 5.9%; hazard ratio, 0.71; P<0.001

12–33 mo Thienopyridine vs. placebo, 5.6% vs. 6.5%; hazard ratio, 0.82; P=0.02



No. at Risk

Thienopyridine	5020	4917	4840	4778	4702	4611	4554	3029
Placebo	4941	4799	4715	4635	4542	4476	4412	2997

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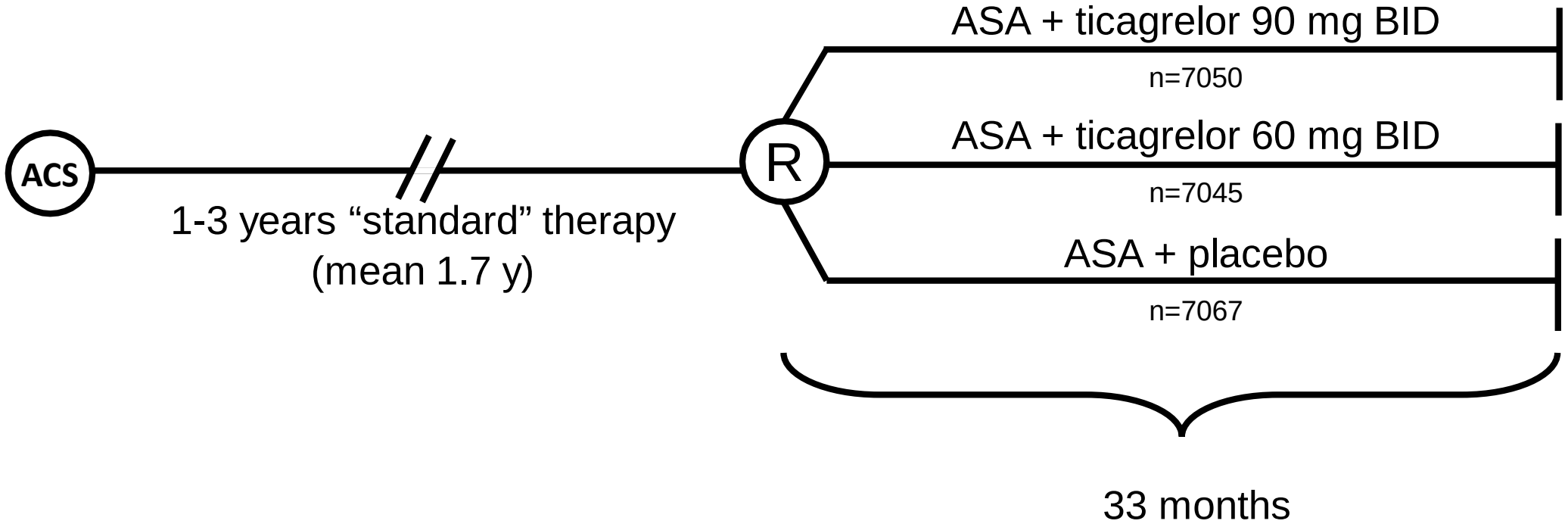
Long-Term Use of Ticagrelor in Patients with Prior Myocardial Infarction

“PEGASUS Trial”

n=21,162

PEGASUS design



Efficacy outome

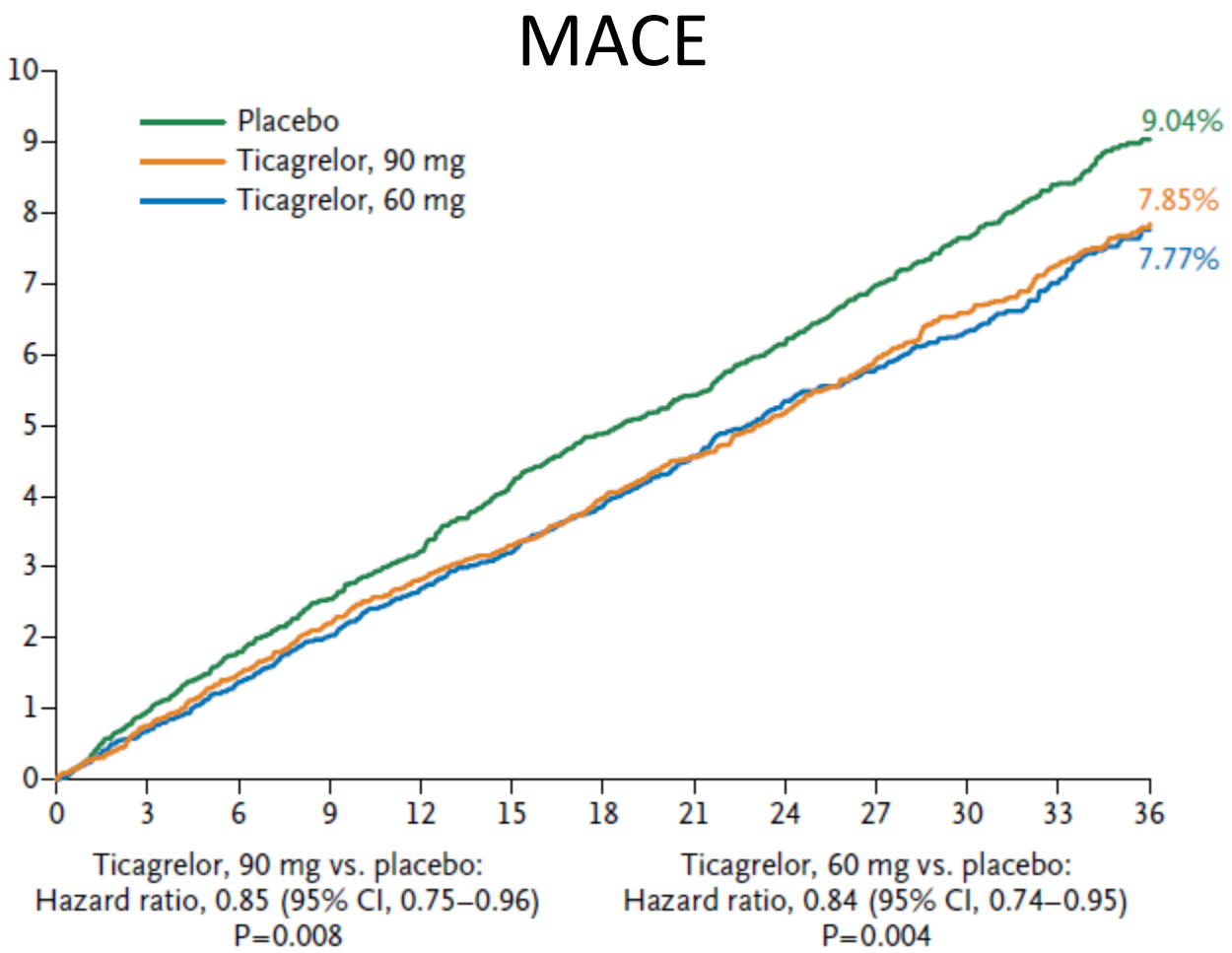
-MACE (CV death, MI, stroke)

Safety outome

-TIMI major bleeding

PEGASUS efficacy results

- MACE reduction driven by all components
- Significant reductions in ACS, stroke individual outcomes
- No significant difference in rates of death from any cause



MACE	ACS	Stroke
ARR 1.23%	ARR 0.78%	ARR 0.4%
NNT 81	NNT 128	NNT 250

Table 3. Safety End Points as 3-Year Kaplan–Meier Estimates.*

End Point	Ticagrelor, 90 mg (N = 6988)	Ticagrelor, 60 mg (N = 6958)	Placebo (N = 6996)	Ticagrelor, 90 mg vs. Placebo		Ticagrelor, 60 mg vs. Placebo	
				Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value
	number (percent)						
Bleeding							
TIMI major bleeding	127 (2.60)	115 (2.30)	54 (1.06)	2.69 (1.96–3.70)	<0.001	2.32 (1.68–3.21)	<0.001
TIMI minor bleeding	66 (1.31)	55 (1.18)	18 (0.36)	4.15 (2.47–7.00)	<0.001	3.31 (1.94–5.63)	<0.001
Bleeding requiring transfusion	122 (2.43)	105 (2.09)	37 (0.72)	3.75 (2.59–5.42)	<0.001	3.08 (2.12–4.48)	<0.001
Bleeding leading to study-drug discontinuation	453 (7.81)	354 (6.15)	86 (1.50)	5.79 (4.60–7.29)	<0.001	4.40 (3.48–5.57)	<0.001
Fatal bleeding or nonfatal intracranial hemorrhage	32 (0.63)	33 (0.71)	30 (0.60)	1.22 (0.74–2.01)	0.43	1.20 (0.73–1.97)	0.47
Intracranial hemorrhage	29 (0.56)	28 (0.61)	23 (0.47)	1.44 (0.83–2.49)	0.19	1.33 (0.77–2.31)	0.31
Hemorrhagic stroke	4 (0.07)	8 (0.19)	9 (0.19)	0.51 (0.16–1.64)	0.26	0.97 (0.37–2.51)	0.94
Fatal bleeding	6 (0.11)	11 (0.25)	12 (0.26)	0.58 (0.22–1.54)	0.27	1.00 (0.44–2.27)	1.00
Other adverse event							
Dyspnea	1205 (18.93)	987 (15.84)	383 (6.38)	3.55 (3.16–3.98)	<0.001	2.81 (2.50–3.17)	<0.001
Event leading to study-drug discontinuation	430 (6.50)	297 (4.55)	51 (0.79)	8.89 (6.65–11.88)	<0.001	6.06 (4.50–8.15)	<0.001
Serious adverse event	22 (0.41)	23 (0.45)	9 (0.15)	2.68 (1.24–5.83)	0.01	2.70 (1.25–5.84)	0.01
Renal event	166 (3.30)	173 (3.43)	161 (2.89)	1.17 (0.94–1.46)	0.15	1.17 (0.94–1.45)	0.15
Bradyarrhythmia	107 (2.04)	121 (2.32)	106 (1.98)	1.15 (0.88–1.50)	0.31	1.24 (0.96–1.61)	0.10
Gout	115 (2.28)	101 (1.97)	74 (1.51)	1.77 (1.32–2.37)	<0.001	1.48 (1.10–2.00)	0.01

TIMI major bleed
ARI: 1.24%
NNH: 81

Fatal bleeding
Same

ICH
Same

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

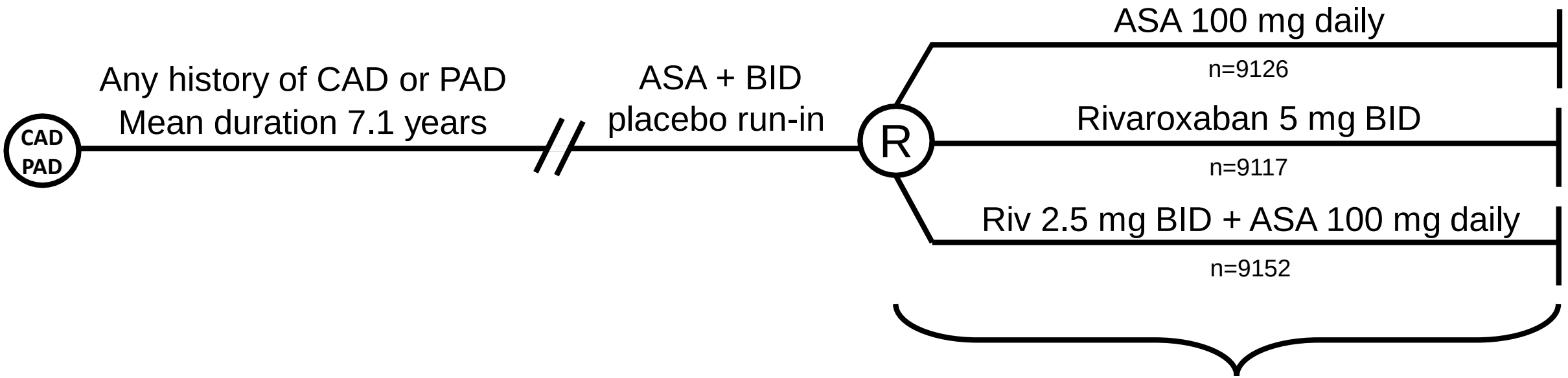
Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease

AUGUST 27, 2017

"COMPASS"

n=27,395

COMPASS design



Efficacy outome

-MACE (CV death, MI, stroke)

Safety outome

-modified ISTH major bleed

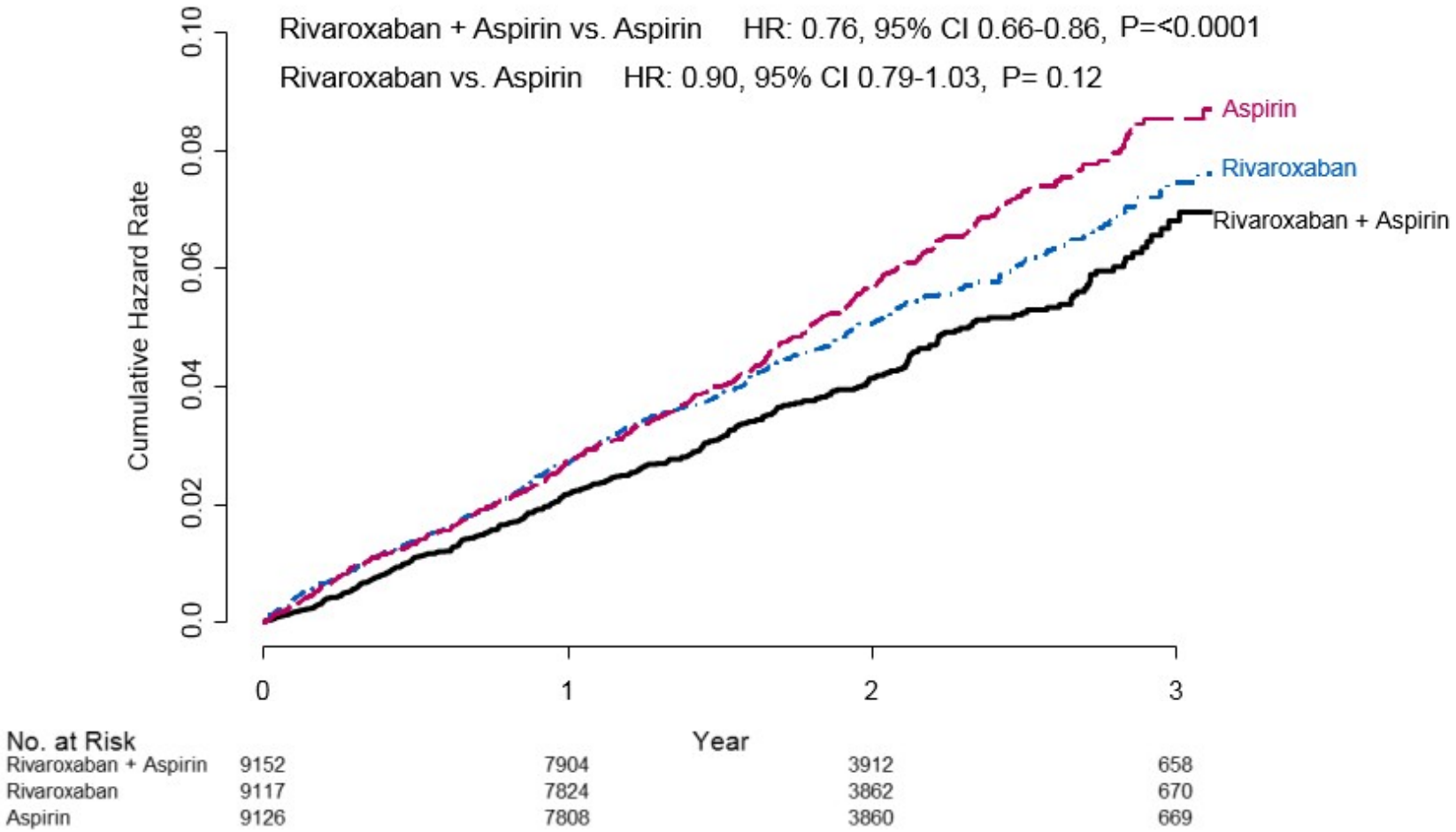
Baseline characteristics

Characteristic	Rivaroxaban + aspirin N=9,152	Rivaroxaban N=9,117	Aspirin N=9,126
Age, yr	68	68	68
Blood pressure, mmHg	136/77	136/78	136/78
Total cholesterol, mmol/L	4.2	4.2	4.2
CAD	91%	90%	90%
PAD	27%	27%	27%
Diabetes	38%	38%	38%
Lipid-lowering	90%	90%	89%
ACE-I or ARB	71%	72%	71%

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		448 (4.9%)	496 (5.4%)			0.90 (0.79-1.03)	0.12
CV death		195 (2.1%)	203 (2.2%)			0.96 (0.79–1.17)	0.69
Stroke		117 (1.3%)	142 (1.6%)			0.82 (0.65–1.05)	0.12
MI		182 (2.0%)	205 (2.2%)			0.89 (0.73–1.08)	0.24
Death from any cause		366 (4.0%)	378 (4.1%)			0.97 (0.84–1.12)	0.67

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%)		496 (5.4%)	0.76 (0.66-0.86)	<0.0001	ARR 1.3% NNT 77	
CV death	160 (1.7%)		203 (2.2%)	0.78 (0.64-0.96)	0.02	ARR 0.5% NNT 200	
Stroke	83 (0.9%)		142 (1.6%)	0.58 (0.44-0.76)	<0.0001	ARR 0.7% NNT 143	
MI	178 (1.9%)		205 (2.2%)	0.86 (0.70-1.05)	0.14		
Death from any cause	313 (3.4%)		378 (4.1%)	0.82 (0.71–0.96)	0.01	ARR 0.7% NNT 143	

Primary: CV death, stroke, MI



Major bleeding

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
ICH	28 (0.3%)	43 (0.5%)	24 (0.3%)	1.16 (0.67–2.00)	0.60	1.80 (1.09–2.96)	0.02
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

TIMI major bleeding
ARI 1.2%
NNH 83

Summary

- Adding antithrombotic medications to ASA in those with established atherosclerotic vascular disease…
  - is efficacious in preventing MACE
  - associated with excess (major) bleeding
  - has not been associated with mortality benefit
- Further study and/or subgroup analyses are needed to…
  - define subgroups who stand to benefit most
  - define the optimal strategy (ASA + P2Y12, ASA + OAC, other…)
  - determine optimal timing of initiation of multimodal antithrombotic meds
- We must optimize such patients in other/less toxic ways
  - lifestyle
  - targets (glycemic, lipid, BP)
  - appropriate meds (ACEi/ARB/BB/statin/MRA), where indicated