October 31, 2019

Conundrums and Opportunities with Anticoagulation in CAD, PAD, and VTE

1

Program Overview

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2

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Conundrums and Opportunities with Antithrombotic and Antiplatelet Therapies in Reducing CAD and PAD Residual Risk

Putting Data into Perspective

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Faculty Disclosures

- Executive steering committee member: ISCHEMIA Trial, funded by NHLBI; TRAVERSE Trial, funded by Abbvie, Inc.
- Research Funding: VA Cooperative Studies Program; Amarin; Amgen
- Data monitoring committee: VA Cooperative Studies Program; National Coordinator, STRENGTH trial, with honoraria from the Cleveland Clinic Clinical Coordinating Center.
- Consultant Fees/Speaker's Honoraria: Abbvie; Amarin; Arbor Pharmaceuticals; AstraZeneca; Bristol-Myers Squibb; Janssen Pharmaceuticals; Pfizer.

Heart Disease Remains the #1 Cause of Death in the U.S. Stroke Is #5.

- This year, **~720,000 Americans will have a new coronary event** (defined as first hospitalized MI or CHD death), and ~335,000 will have a recurrent event
- The estimated annual incidence of **MI is 605,000 new attacks and 200,000 recurrent attacks**
  - Average age at 1st MI is 65.6 years for males and 72.0 years for females
  - ~25% are silent

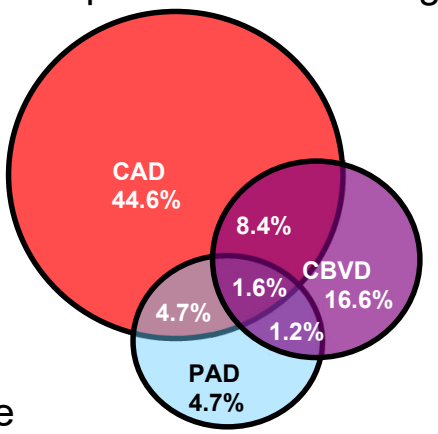
Population Group	Prevalence, CHD, 2011-2014 Age ≥20 y	Prevalence, MI, 2011-2014 Age ≥20 y	New and Recurrent MI and Fatal CHD, Age ≥35 y	New and Recurrent MI, Age ≥35 y	Mortality,* CHD, 2015 All Ages	Mortality,* MI, 2015 All Ages	Hospital Discharges CHD, 2014 All Ages
Both sexes	16,500,000 (6.3%)	7,900,000 (3.0%)	1,055,000	805,000	366,801	114,023	1,021,000
Males	9,100,000 (7.4%)	4,700,000 (3.8%)	610,000	470,000	209,298 (57.1%)†	65,211 (57.2%)†	649,000
Females	7,400,000 (5.3%)	3,200,000 (2.3%)	445,000	335,000	157,503 (42.9%)†	48,812 (42.8%)†	372,000

*Mortality for Hispanic, non-Hispanic (NH) American Indian or Alaska Native, and NH Asian and Pacific Islander people should be interpreted with caution because of inconsistencies in reporting Hispanic origin or race on the death certificate compared with censuses, surveys, and birth certificates. Studies have shown underreporting on death certificates of American Indian or Alaska Native, Asian and Pacific Islander, and Hispanic decedents, as well as undercounts of these groups in censuses. †These percentages represent the portion of total CHD and MI mortality that is for males vs females.

CHD=coronary heart disease; MI=myocardial infarction. American Heart Association (AHA) Statistical Update. Benjamin EJ et al. *Circulation*. 2018;137:e67-e492.

Prevalence of Atherothrombosis at Baseline

- Atherothrombotic status of international outpatient REACH Registry patients at baseline:
  - 18.2% Risk factors only (n=12,389)
  - 59.3% CAD (n=40,258)
  - 27.8% CVD (n=18,843)
  - 12.2% PAD (n=8,273)
  - (single bed disease and overlap in patients with polyvascular disease shown at right)

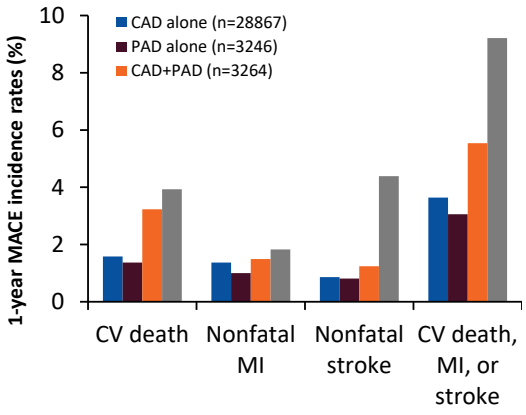


- Cardiovascular risk-factor profiles were consistent across patient types and across all participating regions.

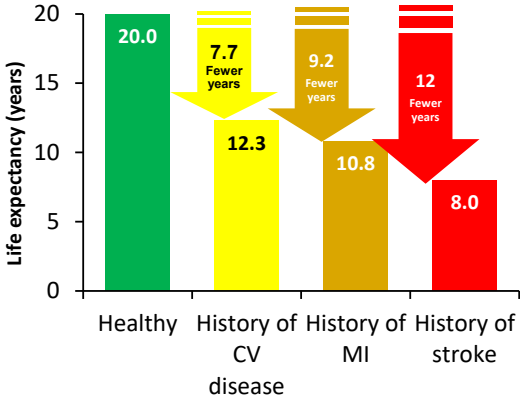
CVD=cerebrovascular disease; REACH=Reduction of Atherothrombosis for Continued Health.
Bhatt DL et al. *JAMA.* 2006;295:180-9.

Consequences of Polyvascular Thrombosis Are Life-threatening

Every year, patients with CAD and PAD are at risk for MACE[1]

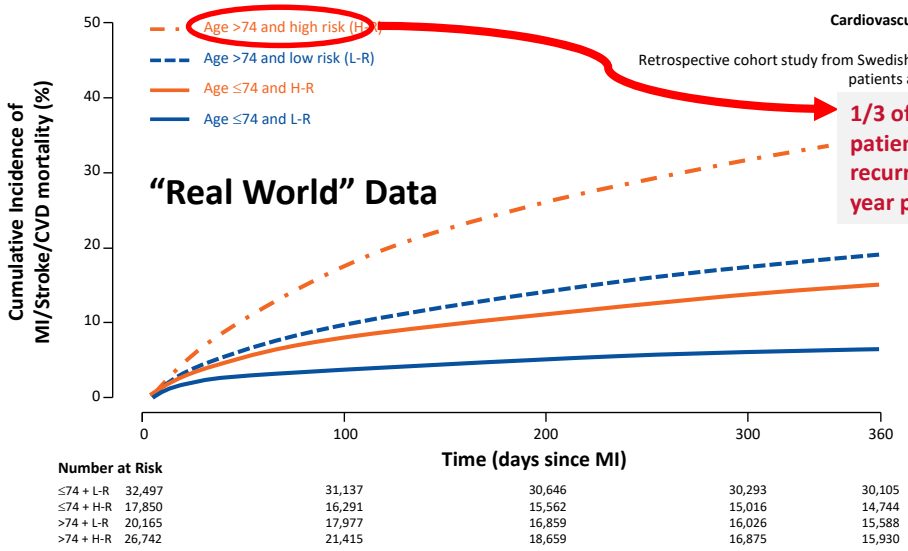


This disease negatively impacts the life expectancy of an average 60-year-old*[2]



*Based on state-specific life expectancy of male patients.
1. Steg PG et al. *JAMA.* 2007;297:1197-206. 2. Peeters A et al. *Eur Heart J.* 2002;23:458-66.

High Risk of MI, Ischemic Stroke, or CV Death during the 1st Year Following MI



Cardiovascular risk in post-MI patients: Nationwide real-world data

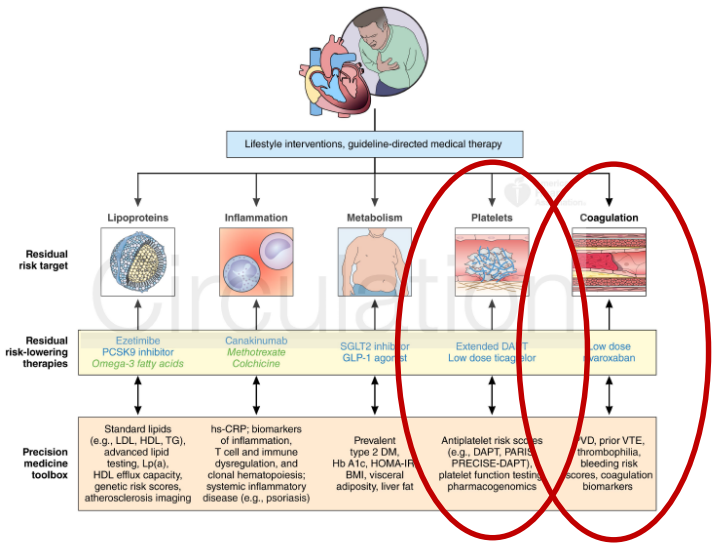
Retrospective cohort study from Swedish national registries: 108,315 patients admitted with MI 2006-2011

1/3 of elderly high-risk patients will have a recurrent event in the 1st year post-ACS

ACS=acute coronary syndrome; CV=cardiovascular. Jernberg T et al. *Eur Heart J*. 2015;36:1163-70.

9

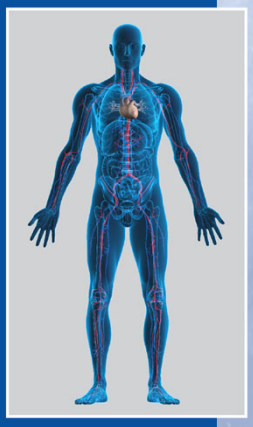
Medicine is Moving Toward a Personalized, Precision Approach to CVD Management



Patel KV, Pandey A, De Lemos JA. *Circulation*. 2018;137:2551-3.

10

Challenges of Antiplatelet Use to Prevent Thrombosis in Post-discharge ACS and Stable CAD



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11

A Clinical Conundrum: Longer-term DAPT for 2º Prevention Reduces Primary Events, But Causes Major Bleeding

CV Death, MI, or Stroke

Study	Extended DAPT Events	Extended DAPT Total	Aspirin Alone Events	Aspirin Alone Total	Risk Ratio (95% CI)
CHARISMA	125	1903	162	1943	0.77 (0.61-0.98)
PRODIGY	63	732	69	733	0.91 (0.65-1.28)
ARCTIC-Int'n	3	156	4	167	0.79 (0.18-3.51)
DAPT	59	1805	108	1771	0.52 (0.38-0.72)
DES-LATE	56	1512	66	1551	0.85 (0.60-1.21)
PEGASUS	980	14,095	578	7067	0.84 (0.76-0.94)
TOTAL	1286	20,203	987	13,232	0.78 (0.67-0.90)
	6.4%		7.5%		

P=0.001

0.2 0.5 1 2

Extended DAPT Better | Aspirin Alone Better

Major Bleeding

Study	Extended DAPT Events	Extended DAPT Total	Aspirin Alone Events	Aspirin Alone Total	Risk Ratio (95% CI)
CHARISMA	45	1903	39	1943	0.17 (0.76-1.79)
PRODIGY	9	732	6	733	0.50 (0.53-4.20)
ARCTIC-Int'n	2	156	0	167	5.35 (0.26-110.6)
DAPT	34	1805	14	1771	2.38 (1.27-4.43)
DES-LATE	39	1512	31	1551	1.27 (0.79-2.03)
PEGASUS	242	13,946	54	6996	2.50 (1.86-3.36)
TOTAL	371	20,054	144	13,161	1.73 (1.19-2.50)
	1.9%		1.1%		

P=0.004

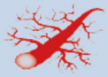
0.5 1 2 5

Extended DAPT Better | Aspirin Alone Better

CI=confidence interval; DAPT=dual antiplatelet therapy. Udell JA et al. *Eur Heart J.* 2016;37:390-9.

12

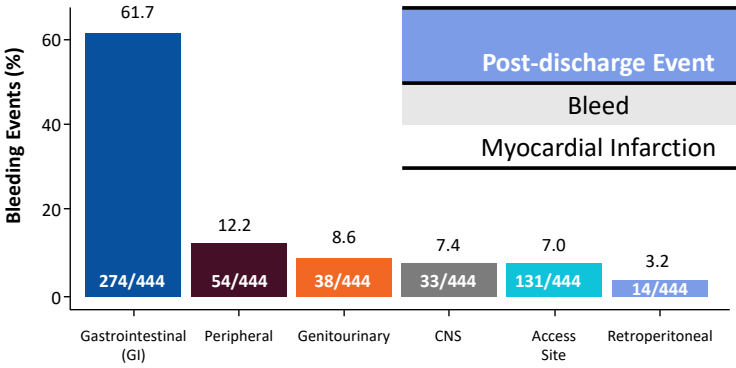
Individualizing Duration of DAPT

	≤12 months DAPT	≥12 months DAPT
Patient-related factors 	Patients with stable CAD Patients with a history of bleeding Patients with high risk of bleeding	Patients with ACS Patients with diabetes mellitus Patients with renal dysfunction Patients with CHF Patients with previous stent thrombosis Patients with PAD
Anatomy-related factors 	Short lesion Single-vessel disease	Long lesion Small vessel Bifurcation lesion Complex anatomy Left-main coronary artery
Stent-related factors 	Second-generation DES	First-generation DES Long stent Multiple stents

CHF=congestive heart failure. Eisen A, Bhatt DL. *Nat Rev Cardiol*. 2015;12:445-6.

13

Post-discharge Bleeding with DAPT Is Mostly GI, But Can Lead to Increased Mortality



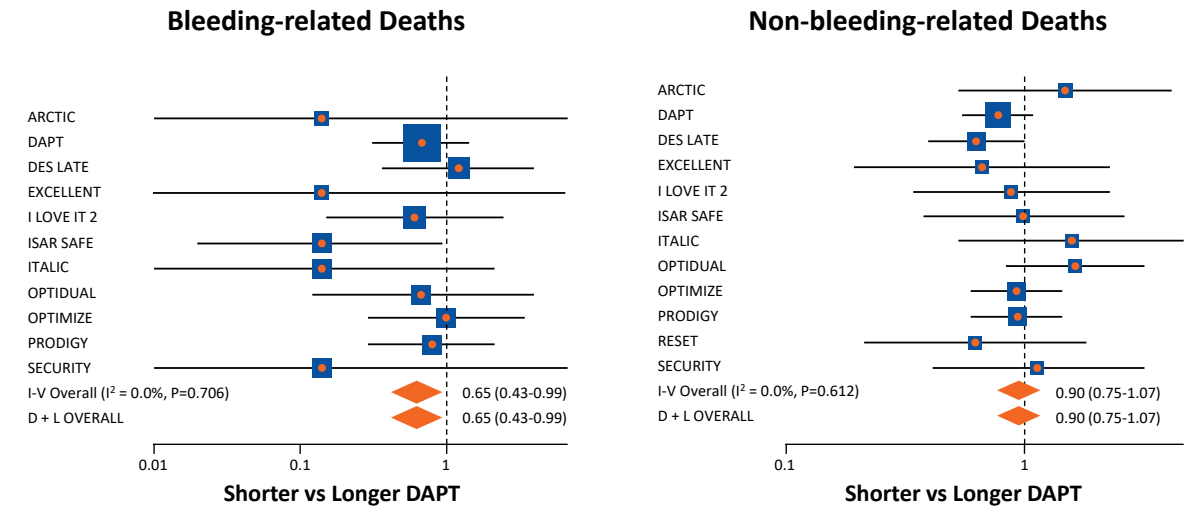
Post-discharge Event	Adjusted HR (95% CI) for 2-year mortality
Bleed	5.0 (3.3-7.7)
Myocardial Infarction	1.9 (1.2-3.1)

ADAPT-DES study was used to determine the incidence and predictors of clinically relevant bleeding events occurring within 2 years after hospital discharge. PDB occurred in 535 of 8577 hospital survivors (6.2%) at a median time of 300 days (interquartile range: 130–509 days) post-discharge.

ADAPT-DES=Assessment of Dual Antiplatelet Therapy with Drug-eluting Stents; CNS=central nervous system; HR=hazard ratio; PDB=post-discharge bleeding. Généreux P et al. *J Am Coll Cardiol*. 2015;66:1036-45.

14

Short DAPT Was Associated with Significantly Lower Rates of Bleeding-related Deaths Compared with Prolonged DAPT

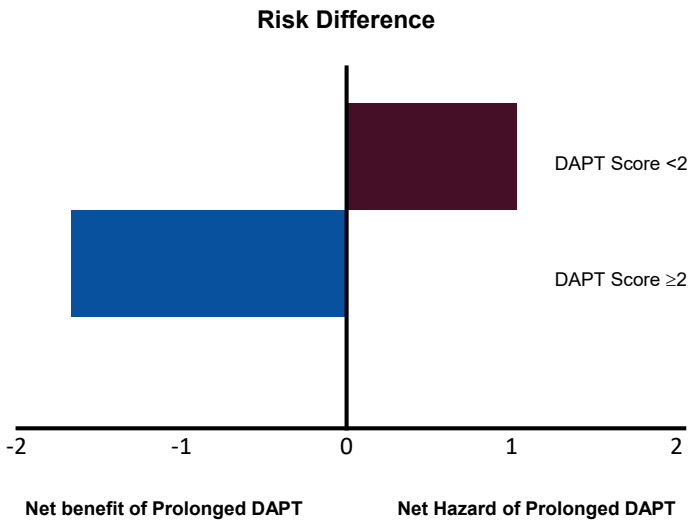


Palmerini T. et al. *J Am Coll Cardiol*. 2017;69:2011-22.

15

Continued Thienopyridine vs Placebo (High vs. Low DAPT Score), 12–30 Months: Risk vs. Benefit

Variable	Points
Patient Characteristic	
Age	
≥75	–2
65 to <75	–1
<65	0
Diabetes mellitus	1
Current cigarette smoker	1
Prior PCI or prior MI	1
CHF or LVEF <30%	2
Index Procedure Characteristic	
MI at presentation	1
Vein graft PCI	2
Stent diameter <3 mm	1



Yeh RW et al. *JAMA*. 2016;315:1735-49.

16

Antiplatelet and Anticoagulation in Post-ACS and Stable CAD Patients

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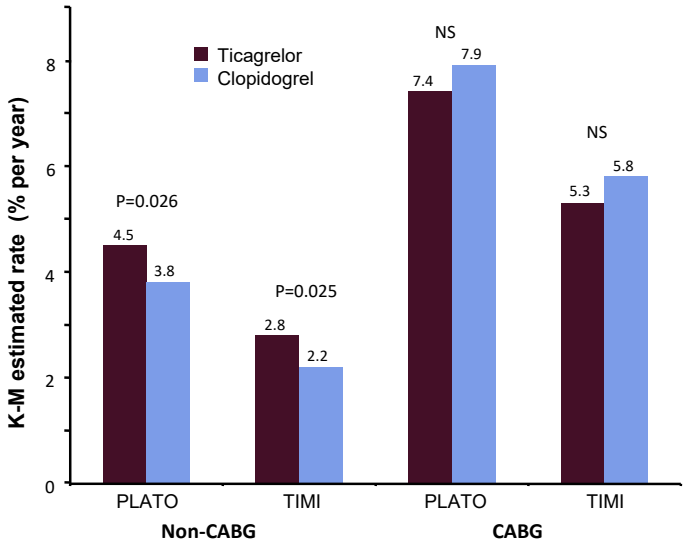
17

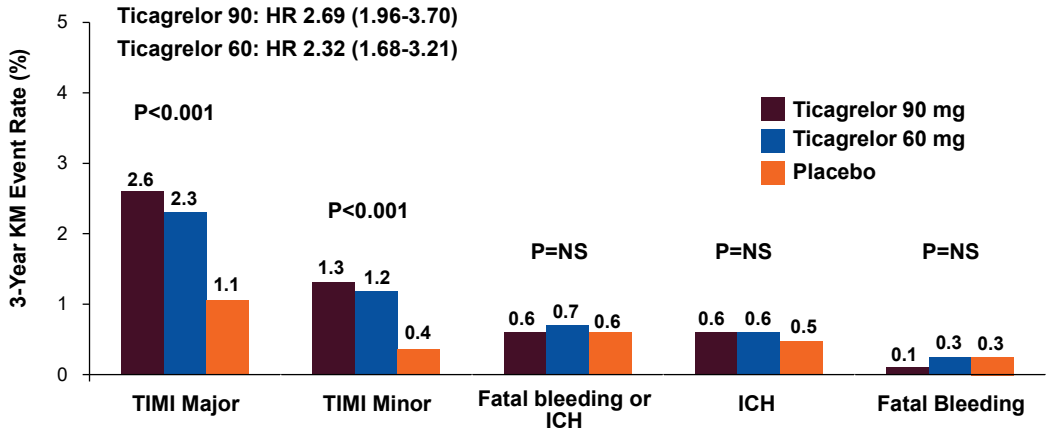
Non-CABG PLATO and TIMI Major Bleeding Rates with Clopidogrel Are Significantly Lower Compared with Ticagrelor



CABG=coronary artery bypass graft; TIMI=Thrombolysis In Myocardial Infarction.
Wallentin L et al. *N Eng J Med*. 2009;361:1045-57.

18

PEGASUS-TIMI 54: Ticagrelor TIMI Bleeding Rates



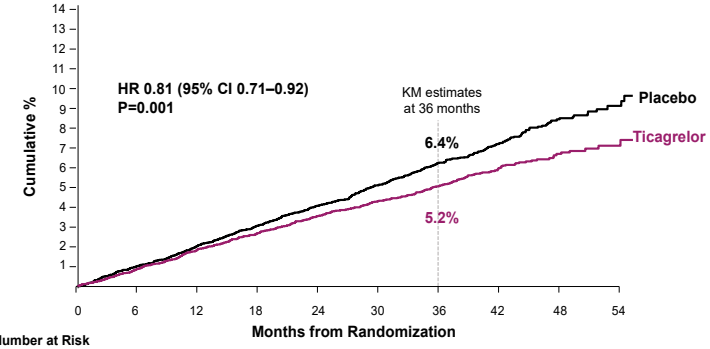
ICH=intracranial hemorrhage. Bonaca MP et al. *N Engl J Med*. 2015;372:1791-800.

19

THEMIS Trial: Ticagrelor + LD ASA vs. Placebo + LD ASA in Stable CAD n=19,920; mean follow-up: 39 months

Primary Composite Endpoint

Cardiovascular death/MI/stroke – on treatment*



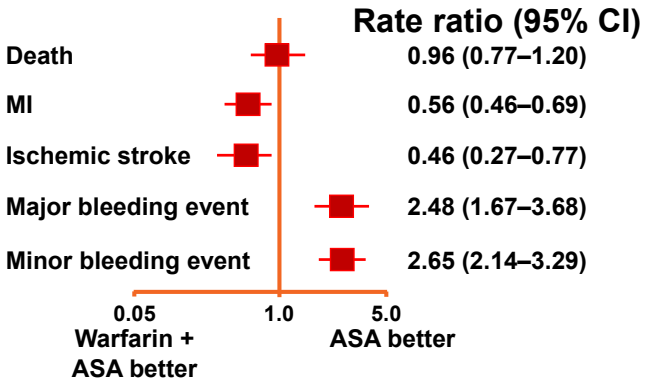
*Prespecified analysis with patients censored 3 days after the last dose; CI=confidence interval; HR=hazard ratio; KM=Kaplan-Meier; MI=myocardial infarction; N=number of patients

Steg PG, Bhatt DL, et al. *N Engl J Med*. 2019;381:1309-1320.

20

Warfarin + ASA for Secondary Prevention Showed Less MI and Stroke After ACS—But More Bleeding

Meta-analysis of 10 trials involving a total of 5,938 patients (11,334 patient-years)

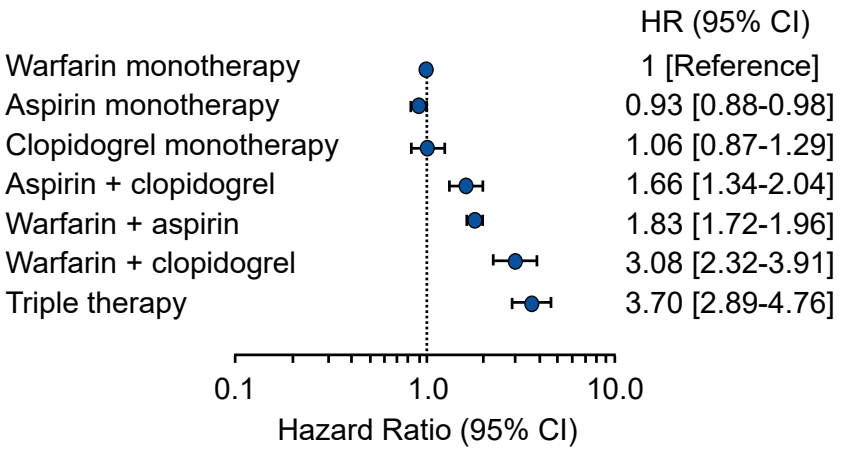


Rothberg MB et al. *Ann Intern Med.* 2005;143:241-50.

21

Bleeding Associated with Warfarin, Aspirin, Clopidogrel in Patients with AF

N=82,854



AF=atrial fibrillation. Hansen ML et al. *Arch Intern Med.* 2010;170:1433-41.

22

ATLAS ACS 2–TIMI 51: Recent ACS (STEMI, NSTEMI, UA)

Stabilized 1–7 Days Post-Index Event*

N=15,526
Standard medical therapy, including low-dose aspirin (75 to 100 mg/day)

Stratified by thienopyridine use at MD discretion, according to national or local guidelines

Placebo	Rivaroxaban	Rivaroxaban
n=5176	2.5 mg BID n=5174	5.0 mg BID n=5176

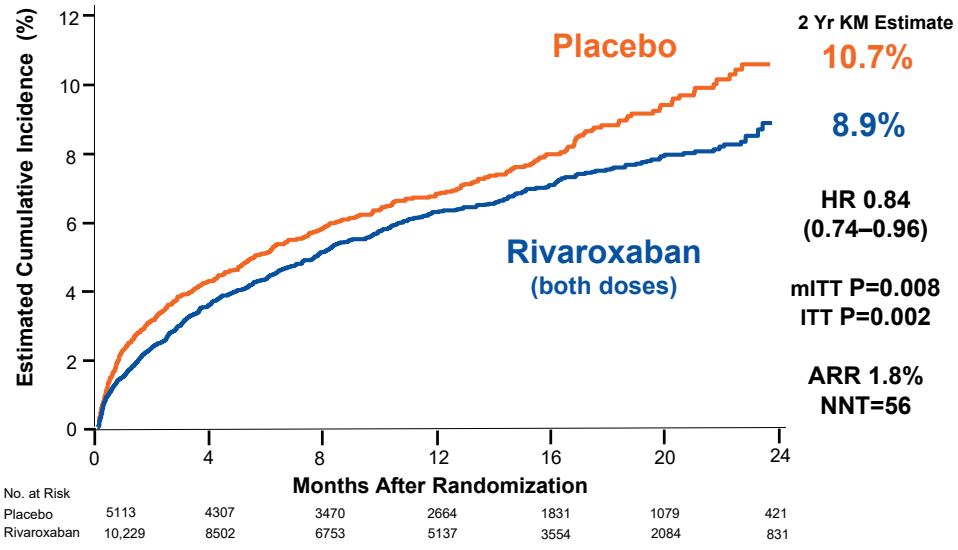
Primary Endpoints:
Efficacy: CV Death, MI, Stroke (Ischemic, Hemorrhagic, or Uncertain Origin)
Safety: TIMI major bleeding not associated with CABG

Event-driven trial with 1002 primary efficacy events

*Exclusions: Increased bleeding risk, warfarin use, ICH, prior stroke if on ASA + thienopyridine. NSTEMI=non-ST-segment elevation MI; STEMI=ST-segment elevation MI; UA=unstable angina. Mega JL et al. *N Engl J Med.* 2012;366:9-19.

23

Primary Efficacy Endpoint: CV Death / MI / Stroke



2 Yr KM Estimate
10.7%
8.9%

HR 0.84
(0.74–0.96)

mITT P=0.008
ITT P=0.002

ARR 1.8%
NNT=56

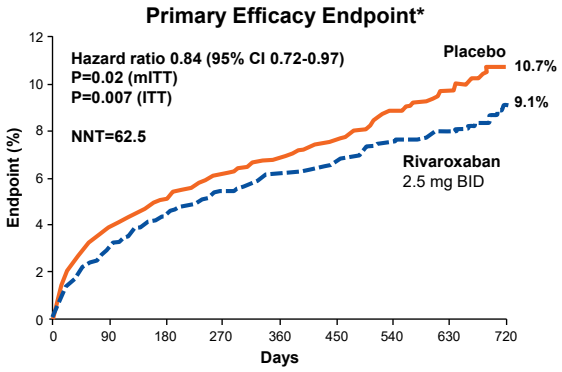
ARR=absolute risk reduction; ITT=intention-to-treat; mITT= modified ITT; NNT=number needed to treat.
Mega JL et al. *N Engl J Med.* 2012;366:9-19.

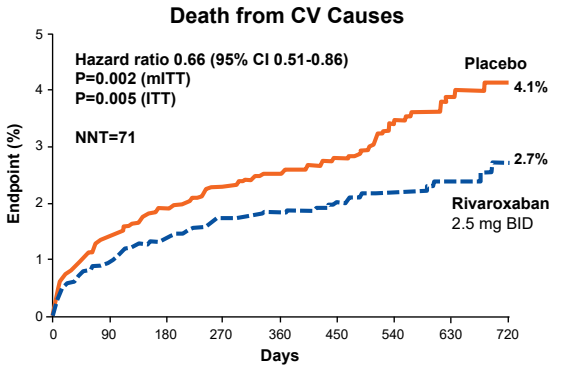
Gibson CM, AHA 2011.

24

Efficacy Endpoints: Very Low-Dose Riva (2.5 mg) BID

Patients Treated with ASA + Thienopyridine





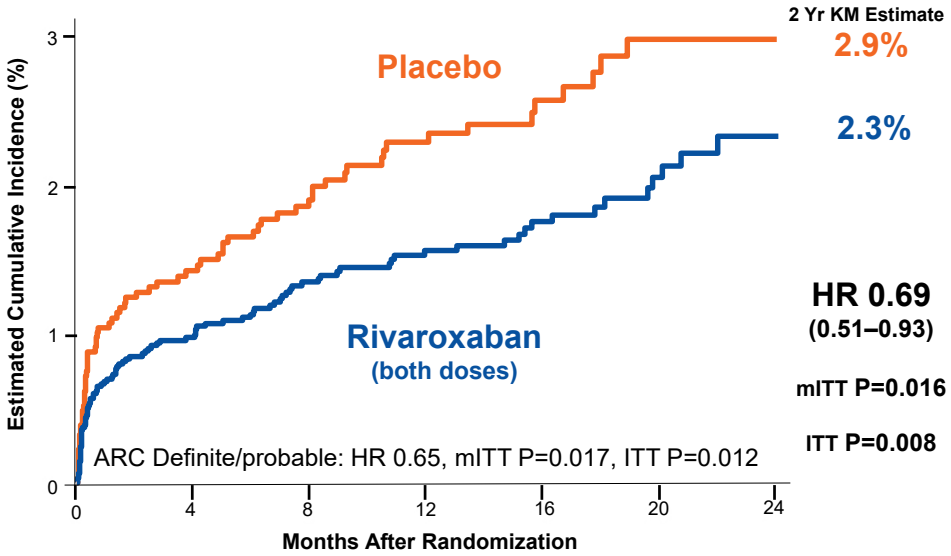
	Rivaroxaban 2.5 mg BID (N=5114)	Placebo (N=5113)	HR (95% CI)	P Value (mITT)	P Value (ITT)	NNT
Death from any cause	2.9%	4.5%	0.68 (0.53-0.87)	0.002	0.004	63

*CV death, MI, or stroke. Mega JL et al. *N Engl J Med.* 2012;366:9-19.

25

Stent Thrombosis

ARC Definite / Probable / Possible



ARC=Academic Research Consortium. Gibson CM et al. *J Am Coll Cardiol*. 2013;62:286-90.

26

Anticoagulation in Stable CAD and PAD Patients

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27

COMPASS

Population Health Research Institute
HEALTH THROUGH KNOWLEDGE

August 27, 2017

Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease

John Eikelboom, on behalf of the
COMPASS Steering Committee and Investigators

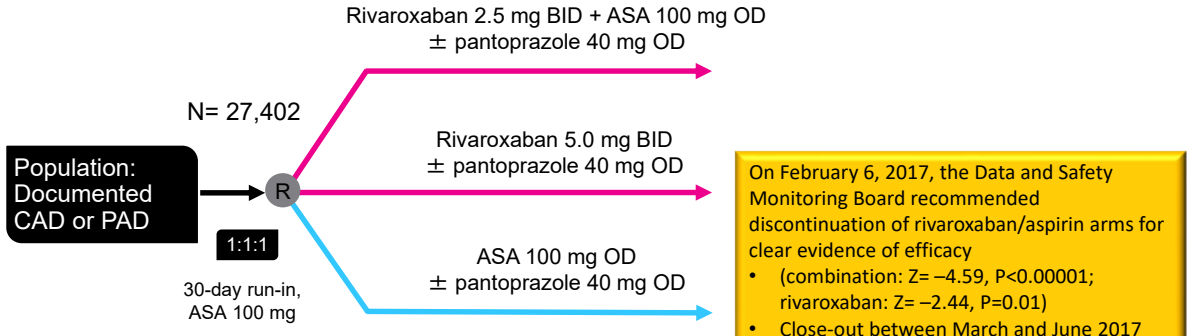
28

Background

- Aspirin is the only approved treatment for CAD secondary prevention in stable CAD (ACC/AHA and ESC)
- The CHARISMA Trial showed no overall treatment difference in clopidogrel + ASA vs. ASA alone in non-ACS patients, though in a prespecified subset with established CVD there was a significant CVD/MI/stroke reduction of C+A vs. A (P=0.04)
- Warfarin with or without aspirin is more effective than aspirin but increases bleeding, including intracranial hemorrhage
- Rivaroxaban is safer than warfarin and reduces mortality in patients with recent (ATLAS TIMI-51)

COMPASS Design: Rivaroxaban, ASA, or Both in CAD or PAD

Objective: To Assess the Efficacy and Safety of rivaroxaban, low-dose rivaroxaban plus ASA, or ASA alone for reducing risk of MI, stroke or CV death, in CAD or PAD



On February 6, 2017, the Data and Safety Monitoring Board recommended discontinuation of rivaroxaban/aspirin arms for clear evidence of efficacy

- (combination: Z= –4.59, P<0.00001; rivaroxaban: Z= –2.44, P=0.01)
- Close-out between March and June 2017
- Mean follow-up 23 months
- Follow-up 99.8% complete

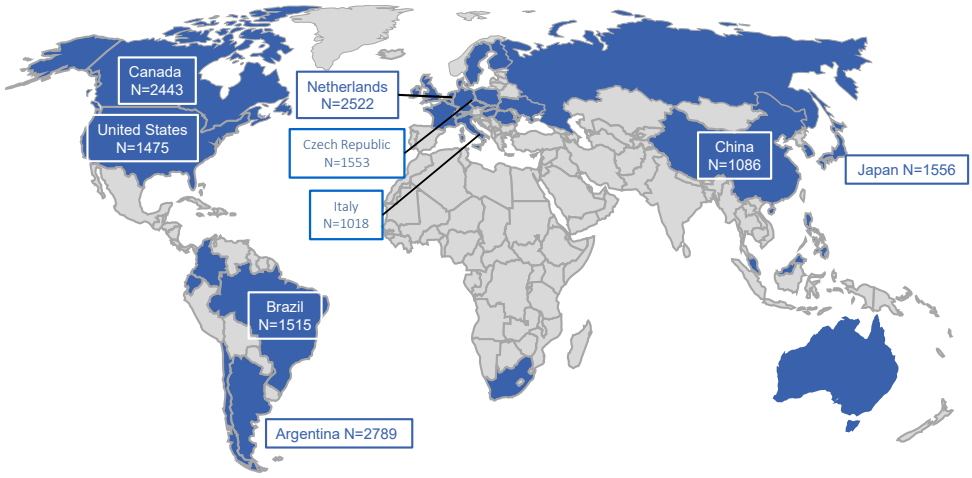
www.clinicaltrials.gov/show/NCT01776424

Outcomes

- Primary
  - CV death, stroke or myocardial infarction
- Secondary
  - CHD death, ischemic stroke, myocardial infarction, or acute limb ischemia
  - Mortality
- Safety and net benefit
  - ISTH major bleeding (modified)
  - Primary plus fatal or critical organ bleeding

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

602 sites, 33 countries



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

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%

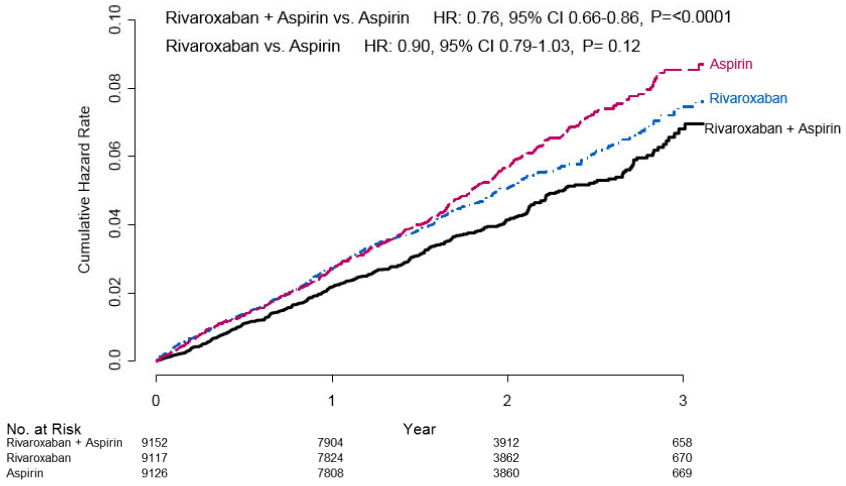
Eikelboom JW et al. *N Eng J Med*. 2017;377:1319-30.

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

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

Primary: CV Death, Stroke, MI



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

35

Primary Endpoint Components

Outcome	R + A N=9,152	A N=9,126	Rivaroxaban + 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)	<0.0001
MI	178 (1.9%)	205 (2.2%)	0.86 (0.70-1.05)	0.14

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

36

COMPASS: Major Bleeding

	R + A	R	A	Rivaroxaban + Aspirin vs Aspirin	
Outcome	**N (%)**	**N (%)**	**N (%)**	**HR (95% CI)**	**P**
Major bleeding	288 (3.1%)	255 (2.8%)	170 (1.9%)	1.70 (1.40-2.05)	<0.001
Fatal bleeding	15 (0.2%)	14 (0.2%)	10 (0.1%)	1.49 (0.67-3.33)	0.32
Non-fatal ICH*	21 (0.2%)	32 (0.4%)	19 (0.2%)	1.10 (0.59-2.04)	0.77
Non-fatal other critical organ†	42 (0.5%)	45 (0.5%)	29 (0.3%)	1.43 (0.89-2.29)	0.14

*Symptomatic. †If a participant had more than one event of major bleeding, only the most serious bleeding event was counted in these analyses.
Eikelboom JW et al. *N Eng J Med*. 2017;377:1319-30.

37

Net Clinical Benefit

Outcome	**R + A** N=9,152	**A** N=9,126	**Rivaroxaban + Aspirin vs. Aspirin**	
	N (%)	**N (%)**	**HR (95% CI)**	**P**
Net clinical benefit (Primary + Severe bleeding [fatal + critical organ] events)	431 (4.7%)	534 (5.9%)	0.80 (0.70-0.91)	0.0005

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

38

COMPASS in Perspective: Relative Risk of Antithrombotics for Secondary Prevention

	CAPRIE Clopidogrel	CHARISMA Clopidogrel + Aspirin	PEGASUS Ticagrelor 90 + Aspirin	PEGASUS Ticagrelor 60 + Aspirin	COMPASS Rivaroxaban + Aspirin
MACE	↓7%	↓7%	↓15%	↓16%	↓**24%**
Death	↓2%	↓1%	0%	↓11%	↓**18%**
Stroke	-	↓21%*	↓18%	↓25%	↓**42%**
MI	-	↓6%*	↓19%	↓16%	↓**14%**
Major Bleeds	↓27%	↑25% and ↑62%†	↑169%	↑132%	↑**70%**
ICH	↓29%	4%	↑44%	↑33%	↑**10%**

*Non-fatal. †Severe and moderate GUSTO, respectively. CAPRIE Steering Committee. *Lancet*. 1996;348:1329-39. CHARISMA Investigators. *N Engl J Med*. 2006;354:1706-17. PEGASUS-TIMI 54 Steering Committee and Investigators. *N Engl J Med*. 2015;372:1791-800. COMPASS Investigators. *N Engl J Med*. 2017;377:1319-30.

39

COMPASS in Perspective with Other Secondary Prevention Therapies: Relative Risk Reduction of CV Events

	Lipid lowering (1mmol/L)	BP Lowering (10mm Hg)	ACE (HOPE)	COMPASS Rivaroxaban+ Aspirin
MACE	↓21%	↓20%	↓22%	↓**24%**
Death	↓9%	↓13%	↓16%	↓**18%**
Stroke	↓15%	↓27%	↓32%	↓**42%**
MI	↓24%	↓17%	↓20%	↓**14%**
MALE	-	-	↓11%	↓**46%**

HOPE Investigators. *N Engl J Med*. 2000;342:145-53. Ettehad D et al. *Lancet*. 2016;387:957-67.
CTT Collaboration. *Lancet*. 2015;385:1397-405. Collins R et al. *Lancet*. 2016;388:2532-61.

40

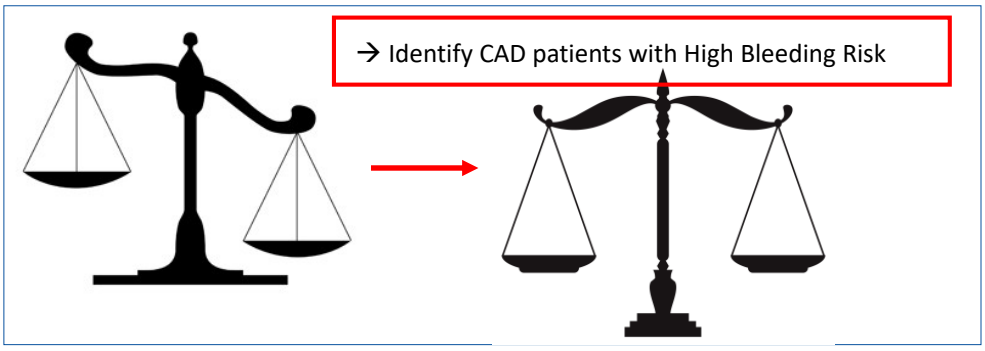
Summary of COMPASS Findings in Stable CAD

- In patients with stable CAD, rivaroxaban 2.5 mg BID plus aspirin 100 mg OD compared to aspirin alone:
  - Reduces CV death, all-cause mortality, stroke, and MI
  - Increases major bleeding without a significant increase in fatal, intracranial, or critical organ bleeding
  - Provides a net clinical benefit
- There was no significant benefit of rivaroxaban alone vs ASA monotherapy
- Compared with other secondary prevention therapies, the magnitude of treatment benefit with this "COMPASS dose" regimen affords significant event reduction, including a reduction in all-cause mortality

41

Therapeutic Conundrum: Balancing Risk vs. Benefit of Antithrombotic Rx in Appropriate CAD Patient Subsets

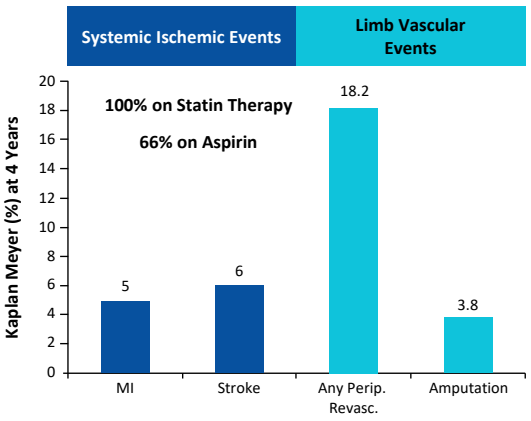
Remaining task: To determine which patients with CAD could benefit the most with additional anticoagulation treatment without increased risk of bleeding



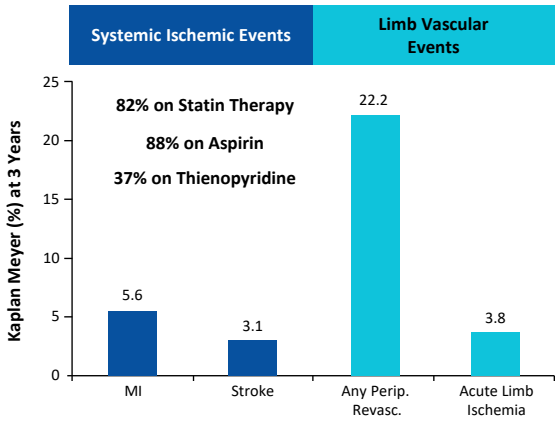
42

Major Events Are Common in Patients with PAD

Events in Symptomatic* PAD Patients at 4 Years in the REACH Registry



Events in Symptomatic* PAD Patients Randomized to Placebo at 3 Years in TRA^{2}P-TIMI 50

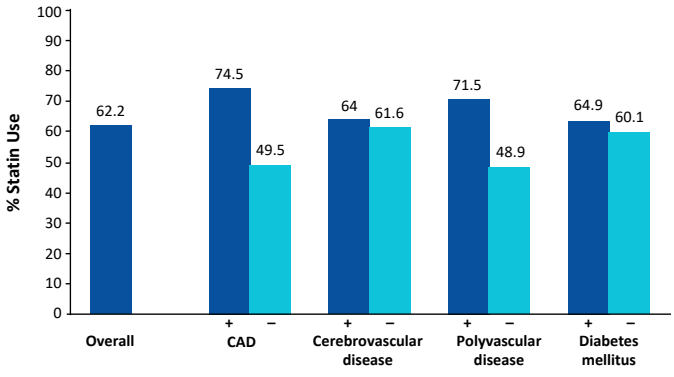


*Intermittent claudication with an ABI <0.90 and a history of intermittent claudication along with prior peripheral revascularization or amputation.
Bonaca MP, Creager MA. *Circ Res.* 2015;116:1579-98.

CAD/PAD Unmet Needs Remain Even with Current Treatments

Despite medical therapy, including lipid-lowering agents and antiplatelet drugs, patients with CAD or PAD remain at risk of vascular events leading to disability, death and limb amputation[1,2]

- Major amputation is the 6th most expensive surgical procedure in U.S.[3]
- 48.3% of Medicare patients die within the first year after major lower-extremity amputation[4]



Kumbhani DJ et al. *Eur Heart J.* 2014;35:2864-72.

REACH Registry of 5861 patients with established PAD. Statins are guideline-recommended in all patients with PAD.

1. Steg PG et al. *Eur Heart J.* 2012;33:2831-40. 2. Hirsch AT et al. *Circulation.* 2006;113:e463-654.
3. Elixhauser A, Andrews RM. *Arch Surg.* 2010;145:1201-8. 4. Jones WS et al. *Am Heart J.* 2013;165:809-15.

COMPASS PAD Rationale

- PAD patients have widespread atherosclerosis and increased risk of CV & limb adverse outcomes
- Vascular events are high despite effective interventions
- Few therapies have clearly reduced both Major Adverse CV Events (MACE) and Major Adverse Limb Events (MALE)

COMPASS Primary Objective

To determine in PAD whether:

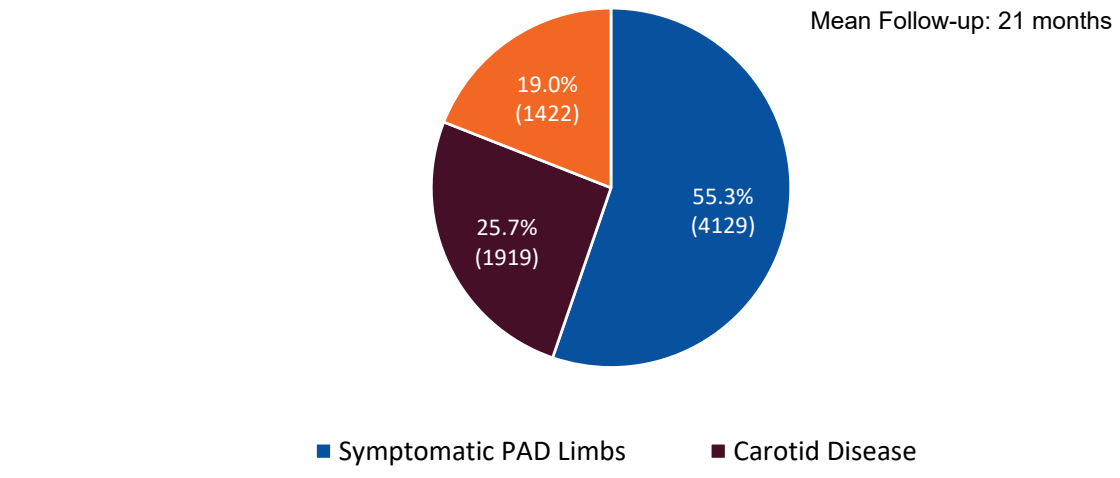
- Rivaroxaban 2.5 mg BID + aspirin 100 mg QD, or
- Rivaroxaban 5 mg BID

Reduce the risk of MACE and MALE as compared with aspirin 100 mg QD

Eligibility: PAD

- Peripheral artery revascularization
- Limb or foot amputation for arterial vascular disease
- Intermittent claudication plus:
  - Low ABI (<0.90), or
  - Significant peripheral artery stenosis (≥50%)
- Previous carotid revascularization, asymptomatic carotid artery stenosis ≥50%
- CAD + low ABI (<0.90)

PAD Patients in COMPASS (N=7,470)



Anand SS et al. *Lancet*. 2017;pii:S0140-6736(17)32409-1.

Key Efficacy Outcomes

- Primary Cardiovascular Outcome (MACE):
  - CV Death, Stroke, or MI
- Major Adverse Limb Events (MALE):
  - Severe limb ischemia leading to an intervention (angioplasty, bypass surgery, amputation, thrombolysis)
  - Major Amputation above forefoot due to vascular cause

Primary Safety Outcome

- Major Bleeding: Modified ISTH
- Net Clinical Benefit: MACE, MALE, major amputation, fatal bleeding, or symptomatic bleeding into a critical organ

Primary Outcomes & Components: PAD Patients

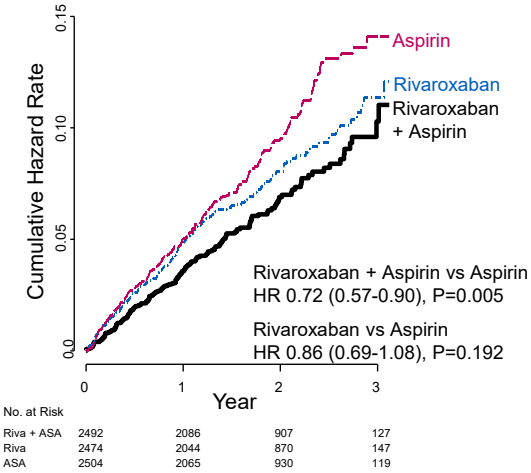
Outcome	R + A N=2,492	R N=2,474	A N=2,504	Riva + aspirin vs. aspirin		Riva vs. aspirin	
	N (%)	N (%)	N (%)	HR (95% CI)	P	HR (95% CI)	P
MACE	126 (5.1)	149 (6.0)	174 (6.9)	0.72 (0.57-0.90)	0.005	0.86 (0.69-1.08)	0.19
MI	51 (2.0)	56 (2.3)	67 (2.7)	0.76 (0.53-1.09)	-	0.84 (0.59-1.20)	-
Stroke	25 (1.0)	43 (1.7)	47 (1.9)	0.54 (0.33-0.87)	-	0.93 (0.61-1.40)	-
CV Death	64 (2.6)	66 (2.7)	78 (3.1)	0.82 (0.59-1.14)	-	0.86 (0.62-1.19)	-

August 11, 2017

51

COMPASS and PAD: MACE and Limb Outcomes

Primary Outcome: CV death, MI, or stroke



Major adverse limb event (MALE) and Major Amputation

	R + A N=2492	A N=2504	Rivaroxaban + Aspirin vs Aspirin	
	N (%)	N (%)	HR (95% CI)	P
MALE	30 (1.2)	56 (2.2)	0.54 (0.35-0.84)	0.005
Major amp.	5 (0.2)	17 (0.7)	0.30 (0.11-0.80)	0.01

Anand SS et al. *Lancet*. 2017;pii:S0140-6736(17)32409-1.

52

COMPASS in PAD: Major Bleeding

	R + A N=2492	R N=2474	A N=2504	Riva + Aspirin vs Aspirin		Riva vs Aspirin	
Outcome	**N (%)**	**N (%)**	**N (%)**	**HR (95% CI)**	**P**	**HR (95% CI)**	**P**
Major Bleeding	77 (3.1)	79 (3.2)	48 (1.9)	1.61 (1.12-2.31)	0.009	1.68 (1.17-2.40)	0.004
Fatal	4 (0.2)	5 (0.2)	3 (0.1)	-	-	-	-
Non-Fatal ICH	4 (0.2)	3 (0.1)	8 (0.3)	-	-	-	-
Non-fatal other critical site (symptomatic)	13 (0.5)	18 (0.7)	8 (0.3)	1.55 (0.64-3.74)	0.33	2.15 (0.94-4.96)	0.06

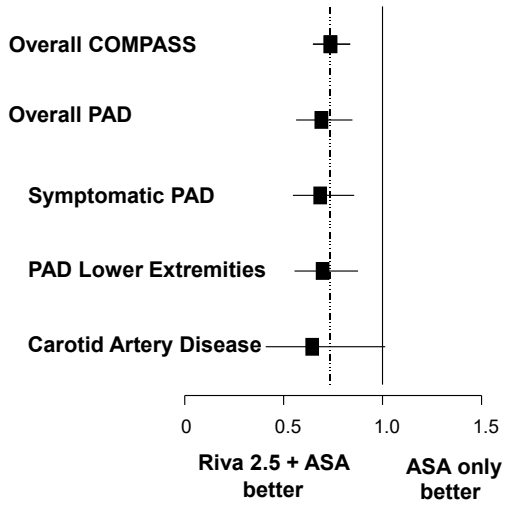
Anand SS et al. *Lancet*. 2017;pii:S0140-6736(17)32409-1.

Net Clinical Benefit in PAD

Outcome	**R + A N=2,492**	**R N=2,474**	**A N=2,504**	**Riva + aspirin vs. aspirin**		**Riva vs. aspirin**	
	N (%)	**N (%)**	**N (%)**	**HR (95% CI)**	**P**	**HR (95% CI)**	**P**
Net Clinical Benefit	169 (6.8)	207 (8.4)	234 (9.3)	0.72 (0.59-0.87)	0.0008	0.89 (0.74-1.07)	0.23

August 14, 2017

MACE, MALE, or Major Amputation



Anand SS et al. *Lancet*. 2017;pii:S0140-6736(17)32409-1.

55

Conclusions

Rivaroxaban 2.5 mg BID plus aspirin is:

- The first adjunctive treatment that lowers CV events in stable CAD patients and is superior to ASA alone
- Significantly superior to aspirin alone in reducing MACE or MALE or major amputation (31% RRR)
- Associated with an increased rate of major bleeding (principally GI), but no significant increase in fatal, ICH, or critical organ bleeding

56

Table. Current Roles for Various Forms of Antithrombotic Therapy and Potential Roles for the COMPASS Regimen in the Future

	Antiplatelet Therapy	Anticoagulant Therapy	COMPASS Regimen
ACS first 12 mo	DAPT for at least a year if no bleeding issues; lower mortality with ticagrelor instead of clopidogrel	None other than specific concomitant conditions such as LV thrombus or atrial fibrillation	ATLAS ACS 2–TIMI 51 showed benefit, including lower mortality, largely on a background of ASA plus clopidogrel, with increased bleeding
ACS after 12 mo	CHARISMA and PEGASUS–TIMI 54 support longer durations of DAPT in patients at low risk of bleeding, although no reduced mortality	None other than specific concomitant conditions such as LV thrombus or atrial fibrillation	ATLAS ACS 2-TIMI 51 had maximum follow up of ≈2.5 y, with continued divergence of the mortality curves; COMPASS trial confirms in patients not receiving DAPT
Stable CAD, without prior ACS	ASA	None	COMPASS showed benefit, including lower mortality
Stable PAD	ASA; clopidogrel	None	COMPASS showed benefit, including a lower rate of amputations and major adverse limb events
Cerebrovascular disease	ASA; ASA/dipyridamole; clopidogrel; limited role for ASA plus clopidogrel for 3 mo after minor stroke or when there is another indication for DAPT such as ACS or PCI	None	Some patients included in COMPASS, but patients with ischemic stroke in past month or any previous hemorrhagic or lacunar stroke were excluded; further study warranted
Elective PCI	DAPT for at least 6 mo, although trials of shorter duration ongoing	None	None
Primary prevention	ASA, although trials are ongoing to delineate whether there is a benefit in the current era	None	None

ACS indicates acute coronary syndrome; ASA, aspirin; CAD, coronary artery disease; DAPT, dual antiplatelet therapy; LV, left ventricular; PAD, peripheral artery disease; and PCI, percutaneous coronary intervention.

57

Managed Care Pharmacists' Role in Chronic Management of Polyvascular Disease

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medtelligence℠

58

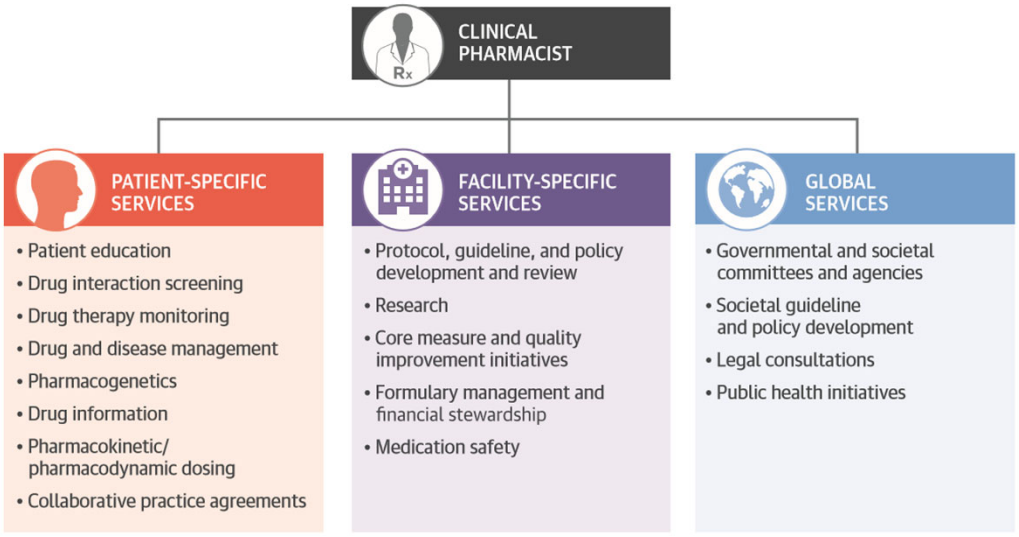
Objectives

- Describe the role of the managed care pharmacist in patients with polyvascular disease
- Discuss the economics of anticoagulation in polyvascular disease
- Recognize and choose a checklist to improve the appropriate use and monitoring of NOAC therapy
- Identify gaps in NOAC use in patients with polyvascular disease

Goals of Managed Care

- Prevent disease
- Focus on wellness and improved quality of life for patients
- Improve outcomes
- Improve quality and accessibility of health care and drug therapy
- Control and contain costs

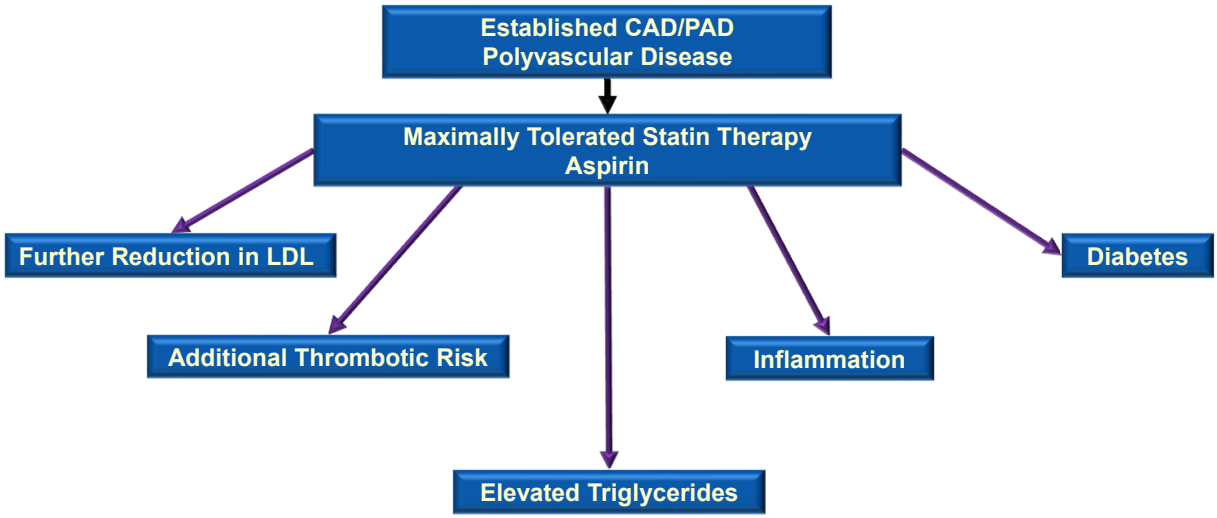
Role of Pharmacist in CV Care



Dunn SP, et al. *J Am Coll Cardiol.* 2015;66:2129-2139.

61

Therapeutic Approaches to CV Risk Reduction



62

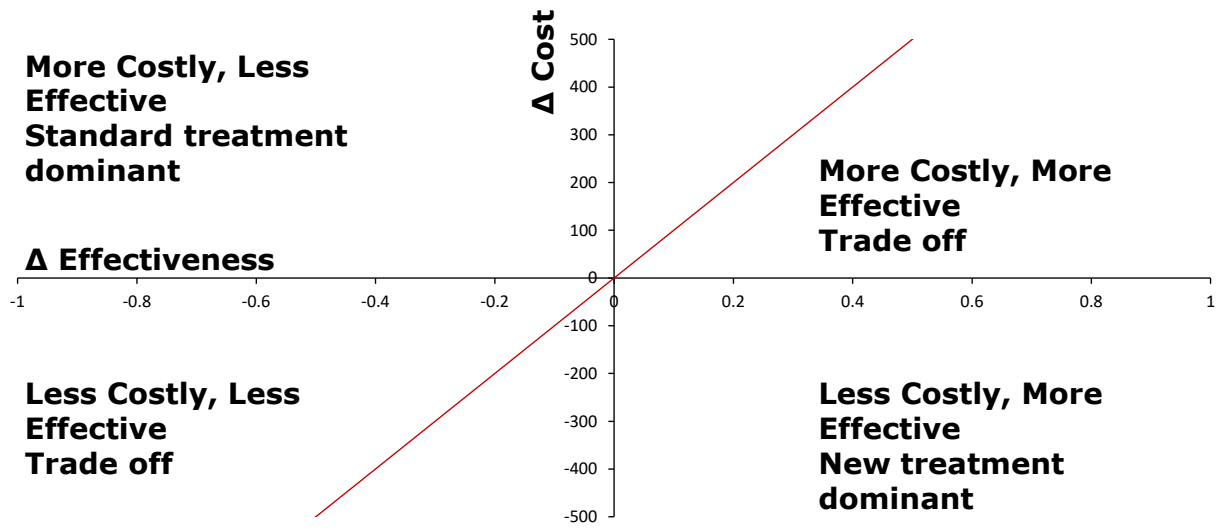
Types of Economic Evaluation

- Cost of illness evaluation
- Cost minimization analysis
- Cost benefit analysis
- Cost effectiveness analysis
- Cost utility analysis

Cost Effectiveness Analysis

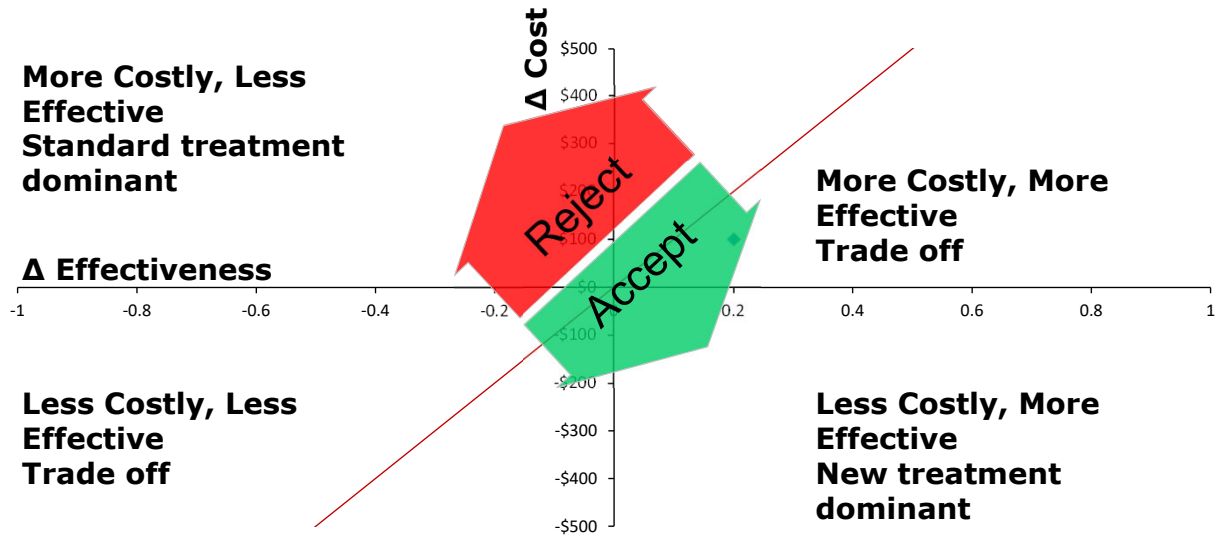
- Description: Compares costs of two or more alternatives versus outcomes measured in natural units
- Measurement Unit: Monetary for cost, outcome in physical measures i.e., event avoided
- Incremental cost to achieve a one unit increase in outcome
  - ICER = ΔCost/ΔEffect = $(C_{Tx1} - C_{Tx2})/(E_{Tx1} - E_{Tx2})$
- Application: Compare treatment alternatives for a given condition that differ in outcomes and costs
- Example: ASA + rivaroxaban vs ASA alone and effect on CV risk reduction ($/event avoided) in stable CAD/PAD

Cost Effectiveness Plane



65

Cost Effectiveness Plane



66

Cost Utility Analysis

- Description: Subset of cost effectiveness analysis – outcomes are measured in utility units
  - Utilities represent patient preferences and quality of life/functional status associated with disease and/or treatment
- QALY: Quality adjusted life year – factor of life expectancy and utility
  - e.g., 4 years at 25% QOL = 1 year at 100% QOL
- ICER = $(C_{Tx1} - C_{Tx2})/(QALY_{Tx1} - QALY_{Tx2})$
- Application: Same as CEA, useful when treatment extends life and/or effects quality of life
- Example: Compare survival with ASA + rivaroxaban vs ASA alone in stable CAD/PAD

ACC/AHA Cost/Value Methodology in Guidelines and Performance Measures

Table 2. Proposed Integration of Level of Value Into Clinical Guideline Recommendations*

Level of Value
High value: better outcomes at lower cost or ICER <$50,000 per QALY gained
Intermediate value: $50,000 to <$150,000 per QALY gained
Low value: ≥$150,000 per QALY gained
Uncertain value: value examined but data are insufficient to draw a conclusion because of no studies, low-quality studies, conflicting studies, or prior studies that are no longer relevant
Not assessed: value not assessed by the writing committee

Anderson JL et al. *J Am Coll Cardiol*. 2014;63:2304-22.

Number Needed to Treat

Metric	Definition	Formula	Comment
NNT-B	# patients treated to prevent one adverse outcome	1/ARR	The lower the NNT-B the better
NNT-H	# patients treated to cause on adverse outcome	1/ARI	The higher the NNT-H the better
LHH	# patients who benefit versus being harmed from treatment	NNT-B/ NNT-H	Net-clinical benefit

B=benefit; H=harm; ARR=absolute risk reduction; ARI=absolute risk increase; LHH=likelihood of being helped or harmed

Cost-Effectiveness of DOACs

- DOACs typically CE compared to traditional anticoagulant strategies
- Acquisition costs higher for DOACs
- Co-pay may still impact individual patients
- AF – lifelong therapy – Lower costs for major bleeds (ICH) for all DOACs
  - Dabi/Apix – lower risk of stroke
- DVT/PE – shorter duration of therapy
  - No significant reductions in DVT/PE
  - Less MB + CRNMB – Apix/Dabi/Edox
  - Lower initial costs – shorter hospital LOS (Apix/Riva)

Cost-Effectiveness Analysis of COMPASS Australian Perspective

Ademi Z, et al. *Int J Cardiol* 2018; 270: 54-59

Table 1
The model input parameters.

Parameters	Rivaroxaban plus Aspirin	Aspirin	Distribution	Reference
Annual Probabilities	Mean value (ranges)			
Non-fatal MI, non-fatal stroke	0.0126 (±15)	0.0169 (±15)	Uniform	COMPASS [10]
CV death	0.0092 (±15)	0.0117 (±15)	Uniform	COMPASS [10]
Non CV death	0.0088 (±15)	0.0101 (±15)	Uniform	COMPASS [10]
Death	0.0181 (±15)	0.0219 (±15)	Uniform	COMPASS [10]
Major bleeding	0.0166 (±15)	0.0098 (±15)	Uniform	COMPASS
Utilities				
No recurrent CVD	0.800 (0.789–0.811)	0.800 (0.789–0.811)	Triangle	Lewis [20]
Recurrent CVD	0. 702(0.585–0.818)	0.690 (0.567–0.815)	Triangle	Lewis [20]
Major bleeding (applied only for one month) disutility	−0.814 (−0.154–0.208)	−0.814 (−0.154–0.208)	Triangle	Sullivan et al. [40]
Annual disease costs				
No recurrent CVD	$5363 (±25)	$5363 (±25)	Uniform	AR-DRG [24]
Recurrent CVD[a]	$4946 (±25)	$4799 (±25)	Uniform	Cobiac et al. [26]
Acute disease costs				
NF MI/stroke	$11,016 (±25)	$11,223 (±25)	Uniform	AR-DRG [24]
CV death	$2666 (±25)	$2666 (±25)	Uniform	AR-DRG [24]
Non-CV death	$2666 (±25)	$2666 (±25)	Uniform	AR-DRG [24]
Major bleeding	$4364 (±25)	$4364 (±25)	Uniform	AR-DRG [24]
Annual Treatment costs	$1205	$78 (±25)	Fixed	PBS [22, 23]

71

Cost-Effectiveness Analysis of COMPASS Australian Perspective

Ademi Z, et al. *Int J Cardiol* 2018; 270: 54-59

Table 2
Base case results all costs are expressed in Australian dollars (AUD) (cohort size 1000 patient).

Parameter	Rivaroxaban plus aspirin	Aspirin	Difference
Clinical effectiveness parameters (discounted)			
Total life years	9529	9013	515,9
Total QALYs	7382	6996	386,7
Cost parameters (discounted)			
Treatment costs	$9,460,589	$699,805	$8,760,784
Disease costs	$58,170,315	$54,774,753	$3,395,562
Total costs	$67,630,903	$55,574,557	$12,156,346
Cost-effectiveness parameters			
Cost per YoLS			$ 23,560
Cost per QALY gained			$ 31,436

YoLS, years of life saved; QALY, quality adjusted life years.

72

Cost Impact – COMPASS
Lamy A, McMaster University; AHA Scientific Sessions 2017

- Translated reductions in events and procedures in COMPASS into reduced costs
- Costs – direct medical in US, France, Canada, Germany converted to USD
- Decreased stroke, MI, limb ischemia balanced against increased bleeding with combination therapy
- $4.2 million savings from fewer events and $1.9 million savings from fewer procedures over 23 months
- Total cost savings $6.1 million - $682 per patient
- Savings by patient category
  - CAD alone - $362
  - PAD alone - $1270
  - CAD and PAD - $1663
- Cost of drug therapy – unknown variable

Cost Effectiveness of Icosapent Ethyl and Rivaroxaban - Preliminary Findings

ICER INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW

Methods: Markov Model, lifetime time horizon, US based model, based on COMPASS and REDUCE-IT

Drug input costs:

Drug	WAC per Tablet/Capsule	Net Price per Tablet/Capsule	Discount from WAC	Net Price per Year
Rivaroxaban (Xarelto®, Janssen)	$7.47 per 2.5mg tablet	$3.03	59.41%	$2,215
Icosapent Ethyl (Vascepa®, Amarin Pharma)	$2.53 per 1g capsule	$1.11	56.04%	$1,625

Bottom line results:

Intervention*	Incremental Costs	Incremental LYs	Incremental QALYs	Cost per LY	Cost per QALY	Cost per MACE Avoided
Rivaroxaban vs. Medical Management	$13,000	0.41	0.37	$32,000 per LY gained	$36,000 per QALY gained	$120,000 per MACE avoided
Icosapent Ethyl vs. Medical	$9,000	0.54	0.50	$17,000 per LY	$18,000 per QALY	$53,000 per MACE

I-CHECK'D Mnemonic for DOAC Use
(DeCamillo D, Renner E – Cardiology Today)

- **I**ndication
- **C**oncomitant medications
- **H**istory
- **E**ducation
- **C**ompliance
- **K**idney function
- **D**ose

ABCDEF – A Pharmacist Checklist for DOAC Management
(Leblanc K, et al. *CPJ/RPC* March/April 2018)

- **A**dherence assessment and counseling
- **B**leeding risk assessment
- **C**reatinine clearance
- **D**rug interaction assessment and education
- **E**xamination
- **F**inal assessment and plan

	Dabigatran (Pradaxa®)	Rivaroxaban (Xarelto®)	Apixaban (Eliquis®)	Edoxaban (Savaysa®)	Betrixaban (Bevyxxa®)
Mechanism	Direct thrombin inhibitor	Factor Xa Inhibitor	Factor Xa Inhibitor	Factor Xa Inhibitor	Factor Xa Inhibitor
FDA Indications	1) AF 2) Acute DVT/PE 3) Ortho Post-THA	1) AF 2) Ortho Post-TKA/THA 3) Acute DVT/PE 4) Chronic CAD/PAD	1) AF 2) Ortho Post-TKA/THA 3) Acute DVT/PE	1) AF 2) Acute DVT/PE	1) DVT prophylaxis - acute medical illness
Bioavail-ability	3-7%	80%	66%	62%	34%
Tmax (hrs)	1.5-3	2-4	1-3	1-2	3-4
Half-life (hrs)	12-14	11-13	12	10-14	19-27
Protein binding	35%	92-95%	87%	55%	60%

77

	Dabigatran (Pradaxa®)	Rivaroxaban (Xarelto®)	Apixaban (Eliquis®)	Edoxaban (Savaysa®)	Betrixaban (Bevyxxa®)
Renal clearance	80%	36%	25%	50%	11%
CYP450 metabolism	No	Yes (3A4, 2J2)	Yes (3A4)	Yes (only 15% ~ 3A4)	60% non-CYP hydrolysis (< 1% CYP); 85% biliary
Drug interactions	PGP Inhibitors and inducers	PGP inhibitors and strong CYP3A4 inhibitors or inducers	PGP inhibitors and strong CYP3A4 inhibitors and inducers	PGP inhibitors and inducers	PGP inhibitors and inducers
Monitoring	Renal function	Renal and hepatic function	Renal and hepatic function ESRD/Dialysis (AF guidelines)	Renal and hepatic function (avoid if CrCl > 95 ml/min)	Renal and hepatic function
Miscellaneous	Swallow whole Leave in original bottle No hepatic dose adjustment	Avoid in Child-Pugh class B or C hepatic impairment Take with food (15 mg or 20 mg)	Dose adjust for Child-Pugh class A or B Avoid for Child-Pugh class C	Not recommended in Child-Pugh class B or C	Not recommended in Child-Pugh class B or C Take with food
Antidote	Praxbind®	Andexxa®	Andexxa®	No Antidote	No Antidote

78

Dabigatran Dosing

Indication	Dosage	
Reduction in Risk of Stroke and Systemic Embolism in Non-valvular AF	CrCl >30 mL/min:	150 mg twice daily
	CrCl 15 to 30 mL/min:	75 mg twice daily
	CrCl <15 mL/min or on dialysis:	Dosing recommendations cannot be provided
	CrCl 30 to 50 mL/min with concomitant use of P-gp inhibitors:	Reduce dose to 75 mg twice daily if given with P-gp inhibitors dronedarone or systemic ketoconazole.
	CrCl <30 mL/min with concomitant use of P-gp inhibitors:	Avoid co-administration
Treatment of DVT and PE **Reduction in the Risk of Recurrence of DVT and PE**	CrCl >30 mL/min:	150 mg twice daily
	CrCl ≤30 mL/min or on dialysis:	Dosing recommendations cannot be provided
	CrCl <50 mL/min with concomitant use of P-gp inhibitors:	Avoid co-administration
Prophylaxis of DVT and PE Following Hip Replacement Surgery	CrCl >30 mL/min:	110 mg for first day, then 220 mg once daily
	CrCl ≤30 mL/min or on dialysis:	Dosing recommendations cannot be provided
	CrCl <50 mL/min with concomitant use of P-gp inhibitors:	Avoid co-administration

79

Rivaroxaban Dosing

---------- **DOSAGE AND ADMINISTRATION** ----------

- Nonvalvular Atrial Fibrillation:
  - For patients with CrCl >50 mL/min: 20 mg orally, once daily **with the evening meal** (2.1)
  - o For patients with CrCl ≤50 mL/min: 15 mg orally, once daily **with the evening meal** (2.1)
- Treatment of DVT and/or PE: 15 mg orally twice daily with food for the first 21 days followed by 20 mg orally once daily with food for the remaining treatment (2.1)
- Reduction in the Risk of Recurrence of DVT and/or PE in patients at continued risk for DVT and/or PE: 10 mg once daily with or without food, after at least 6 months of standard anticoagulant treatment (2.1)
- Prophylaxis of DVT Following Hip or Knee Replacement Surgery: 10 mg orally once daily with or without food (2.1)
- Prophylaxis of VTE in Acutely Ill Medical Patients at Risk for Thromboembolic Complications Not at High Risk of Bleeding: 10 mg once daily, with or without food, in hospital and after hospital discharge for a total recommended duration of 31 to 39 days (2.1)
- Reduction of Risk of Major Cardiovascular Events (CV Death, MI, and Stroke) in chronic CAD or PAD: 2.5 mg orally twice daily, with or without food, in combination with aspirin (75-100 mg) once daily (2.1)

80

tctMD/the heart beat

https://www.tctmd.com/news/fda-gives-rivaroxaban-another-vte-related-indication

NEWS

FDA Gives Rivaroxaban Another VTE-Related Indication

The new indication covers VTE prophylaxis in acutely ill patients at risk for thromboembolic events without a high bleeding risk.

By Todd Neale | October 14, 2019

Rivaroxaban (Xarelto; Bayer/Janssen) has gained an additional indication, this time for venous thromboembolism (VTE) prophylaxis in acutely ill hospitalized patients at increased risk for thromboembolic complications but not at high risk of bleeding, Janssen announced Monday.

With the expanded indication, granted by the US Food and Drug Administration late last week, rivaroxaban, at a dose of 10 mg once daily, can be started during the hospital stay and continued for 31 to 39 days.

In this setting, rivaroxaban should not be used in patients with a creatinine clearance below 30 mL/min or in those at high bleeding risk. "Xarelto is not for use for primary VTE prophylaxis in these hospitalized, acutely ill medical patients at high risk of bleeding," the label states.

81

Apixaban Dosing

Reduction of Risk of Stroke and Systemic Embolism in Patients with Nonvalvular Atrial Fibrillation

The recommended dose of ELIQUIS for most patients is 5 mg taken orally twice daily.

The recommended dose of ELIQUIS is 2.5 mg twice daily in patients with at least two of the following characteristics:

- age greater than or equal to 80 years
- body weight less than or equal to 60 kg
- serum creatinine greater than or equal to 1.5 mg/dL

Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery

The recommended dose of ELIQUIS is 2.5 mg taken orally twice daily. The initial dose should be taken 12 to 24 hours after surgery.

- In patients undergoing hip replacement surgery, the recommended duration of treatment is 35 days.
- In patients undergoing knee replacement surgery, the recommended duration of treatment is 12 days.

Treatment of DVT and PE

The recommended dose of ELIQUIS is 10 mg taken orally twice daily for the first 7 days of therapy. After 7 days, the recommended dose is 5 mg taken orally twice daily.

Reduction in the Risk of Recurrence of DVT and PE

The recommended dose of ELIQUIS is 2.5 mg taken orally twice daily after at least 6 months of treatment for DVT or PE *[see Clinical Studies (14.3)]*.

82

Edoxaban Dosing

- Treatment of NVAF:
  Assess CrCL before initiating therapy (2.1)
  The recommended dose is 60 mg once daily in patients with CrCL >50 to ≤ 95 mL/min. Do not use SAVAYSA in patients with CrCL > 95 mL/min (2.1)
  Reduce dose to 30 mg once daily in patients with creatinine clearance 15 to 50 mL/min (2.1)
- Treatment of DVT and PE:
  The recommended dose is 60 mg once daily (2.2)
  The recommended dose is 30 mg once daily for patients with CrCL 15 to 50 mL/min or body weight less than or equal to 60 kg or who use certain P-gp inhibitors (2.2)

SAVAYSA is indicated for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) following 5 to 10 days of initial therapy with a parenteral anticoagulant (1.2)

83

DOAC Drug Interactions

- **CYP3A4 and/or P-gp Inducers decrease serum DOAC levels→increase thrombotic risk**
- **CYP3A4 and/or P-gp Inhibitors increase serum DOAC levels→increase bleed risk**
- **Consider the additive bleeding risk of drugs or natural supplements that have their own anticoagulant or antiplatelet effects.**

Practical management of DOAC drug-drug interactions

	Apixaban	Dabigatran	Edoxaban	Rivaroxaban
Combined P-gp and strong CYP3A4 inducers	avoid*	avoid*	avoid*	avoid*
P-gp inhibitors		avoid, if possible[2]	avoid, if possible[2]	
Combined P-gp and strong CYP3A4 inhibitors	avoid, or use reduced dose based on package insert if possible[2]			avoid, if possible[2]

84

FDA Prescribing Information – DOAC Drug Interactions

	Apixaban	Dabigatran	Edoxaban	Rivaroxaban
PGP Inducers	Not mentioned	Generally avoid (i.e., rifampin)	Avoid (i.e., rifampin)	Not mentioned
PGP Inducers and Strong CYP 3A4 Inducers	Avoid	Not mentioned	Not mentioned	Avoid
PGP Inhibitors	Not mentioned	AF – CrCl 30-50 ml/min dose reduction to 75 mg BID AF – avoid if CrCl < 30 ml/min DVT/PE – avoid if CrCl < 50 ml/min	Dose reduction to 30 mg/d with use of verapamil, quinidine, azithromycin, clarithromycin, erythromycin, itraconazole, ketoconazole	Not mentioned
PGP Inhibitors and strong CYP 3A4 inhibitors	50% dose reduction from 5 or 10 mg BID; Avoid if 2.5 mg BID	Not mentioned	Not mentioned	Avoid (e.g., azole antifungals, ritonavir)
PGP Inhibitors and moderate CYP 3A4 inhibitors	Not mentioned	Not mentioned	Not mentioned	Avoid in CrCl < 80 unless benefit justifies risk (e.g., diltiazem, verapamil, dronedarone, erythromycin)

85

Role of Clotting Assays For New Anticoagulants Measuring vs Monitoring

- Not intended for routine dosing adjustments
- Might be useful to:
  - Assess compliance
  - Evaluate drug interactions
  - Assess overdose
  - Evaluate use in hepatic and/or renal impairment
  - Evaluate use in under/overweight patients

86

Role of Clotting Assays For New Anticoagulants Measuring vs Monitoring

- Dabigatran (direct thrombin inhibitors)
  - ECT or TT best
  - PTT is effected (most widely available)
  - PT/INR lacks sensitivity to be useful
- Rivaroxaban, apixaban, edoxaban (direct Xa inhibitors)
  - Anti-Xa is probably the best test
  - PT is effected (most widely available)
  - Less variability in PT compared to INR
  - PTT lacks sensitivity to be useful

87

Peri-operative Management Considerations with Dabigatran

CrCl	Half life (hrs)	Timing of discontinuation after last dose of dabigatran before surgery	
		Low risk of bleeding	High risk of bleeding (major surgery, spinal puncture or placement of spinal/epidural cath, in whom complete hemostasis may be required)
> 80	~13-14	24 hrs	2-3 days
80-51	~15-17	24 hrs	2-4 days
50-31	~18-20	At least 48 hrs	4 days
≤ 30	~27 (22-35)	2-5 days	> 5 days

88

Peri-operative Management Considerations with Factor X Inhibitors

Timing of discontinuation after last dose of Factor X inhibitors before surgery	
Lower risk of bleeding (minor procedures, arterial puncture, sites where bleeding can be controlled)	**High risk of bleeding** (major surgery, spinal puncture or placement of spinal/epidural cath, in whom complete hemostasis may be required)
24 hrs	**48 hrs**

Antidote for Dabigatran

- **Idarucizumab (Praxbind®)– evaluated in the RE-VERSE AD**
  - Murine monoclonal antibody
  - Humanized Fab fragment directly binds to dabigatran at 350 X greater affinity than for thrombin
  - Binding is largely irreversible until delivered to kidney
  - 5 g infused or given as two x 2.5 g consecutive boluses
  - Study included a bleeding (n = 51) and procedure arm (n = 39)
  - Time to cessation of bleeding ~11 hours (difficult to determine)
  - 88% to 98% had lab evidence of normal hemostasis after 1st dose
  - 18 deaths and one thrombotic event in 90 patients
  - Perception of a safety net
  - Cost 5 g = $3710

Antidote for Xa Inhibitors

- **Plasma derived recombinant factor Xa (Andexxa®)**
  - **Binds to Xa inhibitors rendering them inactive (inhibits an inhibitor)**
  - **Dose**
    - **Low dose 400 mg (30 mg/min) then 4 mg/min x 2 hrs ($27,500)**
    - **High dose 800 mg (30 mg/min) then 8 mg/min x 2 hrs ($49,500)**

FXa Inhibitor	FXa Inhibitor Last Dose	Timing of FXa Inhibitor Last Dose Before ANDEXXA Initiation	
		< 8 Hours or Unknown	≥ 8 Hours
Rivaroxaban	≤ 10 mg	Low Dose	Low Dose
	> 10 mg / Unknown	High Dose	
Apixaban	≤ 5 mg	Low Dose	
	> 5 mg / Unknown	High Dose	

91

Gaps in Use of DOACs

- Elderly
- Underweight/Obesity
- ESRD/Dialysis
- Drug Interactions
- Hepatic Dysfunction
- Cancer VTE Prophylaxis

92

Future DOAC Use

- Expanded indications
- Patient selection
- Monitoring
- Education

93

Panel Discussion and Q&A

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94