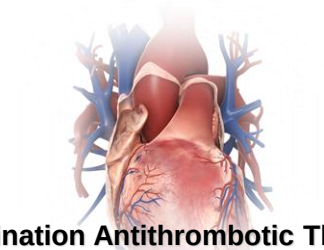


Combination Antithrombotic Therapy in CV Patients: Who, What, When and Why?

Kori Leblanc BScPhm, ACPR, PharmD

Overview

- **Update on the current literature for the use of combination antithrombotic therapy (ATT) in patients with cardiac and vascular disease**
  - Provide the rationale for the use of combination ATT
  - Framework for assessment of ATT prescriptions and practical tips for pharmacists

"Combination Antithrombotic Therapy"

≥ 1 ANTIPLATELET

- **ASA**
- **Clopidogrel**
- **Prasugrel**
- **Ticagrelor**

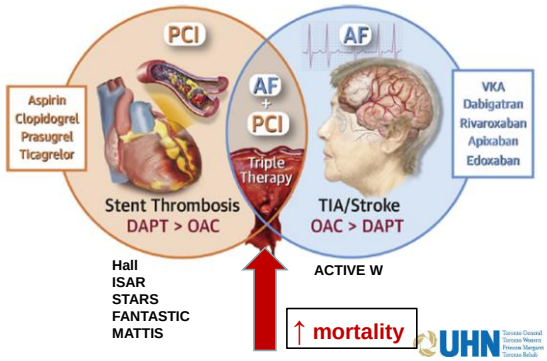
1 ANTICOAGULANT

- **Warfarin**
- **Apixaban**
- **Dabigatran**
- **Edoxaban**
- **Rivaroxaban**

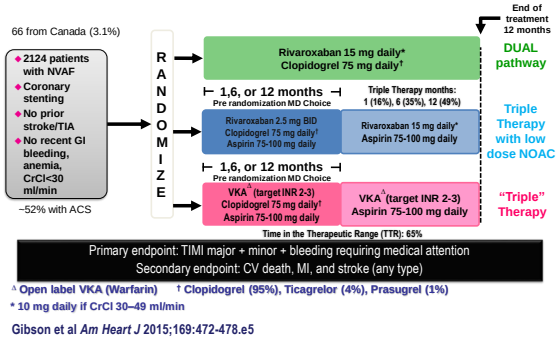
Who?

- **People who have an indication for both:**
  - AFIB patients who have had a recent ACS/PCI
  - AFIB patients who have CAD?
- **New Paradigm of vascular risk reduction**
  - CAD
  - PAD

Why do they need both?



Patients With Atrial Fibrillation Undergoing Coronary Stent Placement

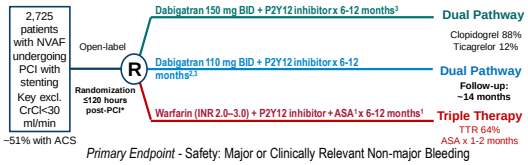


Gibson et al *Am Heart J* 2015;169:472-478.e5

Learnings:

- **Primary endpoint was bleeding NOT efficacy**
- **DUAL pathway strategy decreases bleeding: 16.8% vs 26.7%**
- **Lower dose OAC decreases bleeding: 18% vs 26.7%**
  - BUT…low dose OAC for stroke prevention?
- **Cost of thrombotic events? 6.5% vs 5.6% vs 6% (underpowered – 17% power to detect a 20% difference!)**

Evaluation of Dual Therapy With Dabigatran vs. Triple Therapy With Warfarin in AF Patients That Undergo a PCI With Stenting



Primary Endpoint - Safety: Major or Clinically Relevant Non-major Bleeding

In the initial protocol, a sample size of 8,520 patients had been planned to allow for a co-primary end-point comparison of thromboembolic event rates

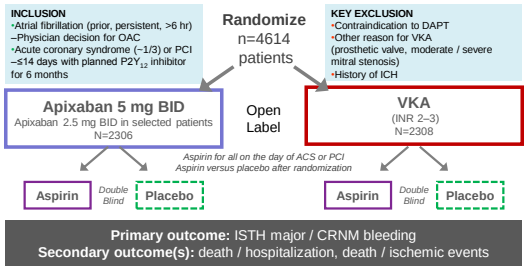
*≤72 hrs preferred; study drug administered 6 hrs after sheath removal
[1]ASA should be discontinued at 1 month (BMS) or 3 months (DES ~83%)
[2]P2Y12 inhibitor can be discontinued or switched to ASA≤100 mg/day from month 12
[3]Pts ≥80 yrs outside of U.S. randomized to dabigatran 110 mg BID or warfarin

Cannon et al *Clin Cardiol* 2016;39:555-64 and *N Engl J Med* 2017;377:1513-24

Learnings

- **First trial with full "AFIB" dose of DOAC**
- **Dual Pathway less bleeding:**
  - **15.4%** vs **26.9%**
  - **20.2%** vs **25.7%**
- **Thromboembolic events higher with dabigatran 110mg strategy:**
  - **11%** vs **8.5%, p: 0.07**
  - **Driven by MI**
- **BUT is DOAC preferred?**

AUGUSTUS



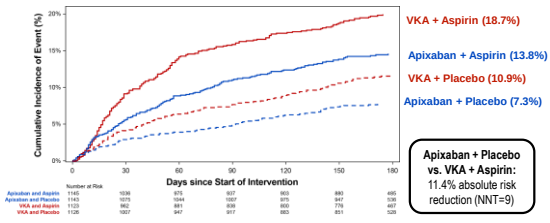
Lopes et al *Am Heart J* 2018;200:17-23

Learnings

- **DOAC is safer than warfarin:**
  - 10.5% vs 14.7%, p<0.001
- **DUAL pathway safer than TRIPLE:**
  - 9.0% vs 16.1%, p<0.001

Major / CRNM Bleeding

Augustus



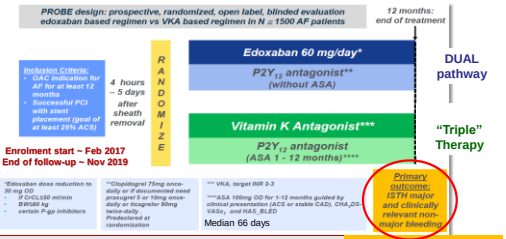
Lopes et al *N Engl J Med* 2019;DOI:10.1056/NEJMoa1817083

Learnings

- **DOAC is safer than warfarin:**
  - **10.5%** vs 14.7%, p<0.001
- **DUAL pathway safer than TRIPLE:**
  - **9.0%** vs **16.1%**, p<0.001
- **Numerically more ischemic events without ASA**
  - **6.5%** vs **7.3%,** p NS
  - DUAL pathway patients got ~6 days of ASA
- **Stopping ASA did not increase death or CV hospitalization**
- **Ischemic risk is highest in the early days**
  - Early withdrawl of ASA not tested in Augustus

EdoxabaN Treatment versUS VKA in paTients with AF undergoing PCI

ENTRUST AF-PCI



Key Secondary Objectives:

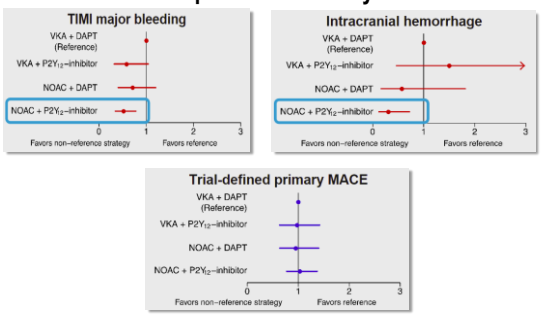
1. **Efficacy – CV death, stroke, systemic embolism (SE), spontaneous MI, definite stent thrombosis**
2. **Net Clinical Benefit – Efficacy and ISTH Major Bleeding**
3. **Thromboembolic Event – Cardiac or thromboembolic death, ischemic stroke, SE, spontaneous MI and stent thrombosis**

Non inferiority Design

Learnings

- **Edoxaban DUAL pathway was non-inferior to warfarin TRIPLE therapy, but NOT superior**
  - Primary endpoint **17%** vs **20%, p=0.001**
- **No difference in "efficacy" (CV death, stroke, MI, embolism, stent thrombosis at 12 months: 7% vs 6%)**
  - BUT – very early increase in ischemic events without ASA
- **Reinforcement for DUAL pathway with some ASA early on**

Patients with AF undergoing PCI: Updated Meta-analysis



Updated from Lopes et al *JAMA Cardiol* 2019;Published Online: June 19, 2019 (doi:10.1001/jamacardio.2019.1880)

Balancing Risk…

Factors that Increase Risk of Bleeding

- **Patient Factors**
  - Age (> 65 years)
  - Low body weight (< 60 kg)
  - Hypertension
  - History of bleeding (esp. within 1y)
  - Prior Stroke or intracranial bleed
  - Combined OAC and antiplatelet use
  - Concomitant NSAID or prednisone use
  - Excess alcohol consumption
  - Abnormal liver function
  - CKD (eGFR < 60 mL/min)
  - Anemia (hemoglobin <110 g/L)
  - Labile INR (TTR <60%)

Factors that Increase Risk of Ischemic Coronary Events

- **Patient Factors**
  - Diabetes mellitus treated with OHG or insulin
  - Current smoker
  - CKD (eGFR < 60 mL/min)
  - Prior ACS
  - Prior stent thrombosis
- **Clinical Presentation**
  - ACS (STEMI, NSTEMI, UA)
- **Angiographic factors**
  - Multi-vessel disease
  - Multiple (≥ 3) stents implanted
  - Stenting of a bifurcation lesion
  - Total stent length > 60 mm
  - Left main or proximal LAD stenting
  - Chronic occlusion intervention
  - Bioabsorbable vascular scaffold

Risk Assessment

- **At a minimum ensure that the Rx:**
  - Covers stroke risk
    - Ideally DOAC at SPAF dose
    - IF not SPAF dose, ensure clear plan to change to SPAF dose
  - If TRIPLE THERAPY strategy
    - Ensure stop date for ASA is clear
    - If no stop date, action required
    - If no contraindications, use DOAC over warfarin
    - Assess based on objective bleeding risk factors
    - Consider PPI for GI protection

What about AFIB and "STABLE" CAD

Do they have an indication for both?

AF Patients with Coronary or Peripheral Arterial Disease and an Indication for OAC (Age ≥ 65 years or $CHADS_2$ ≥ 1)

Stable CAD/PAD

OAC[4]

RECOMMENDATION

9. For patients with AF aged ≥ 65 years or with a $CHADS_2$ score ≥ 1 and coronary or arterial vascular disease (peripheral vascular disease or aortic plaque), we recommend long-term therapy with an OAC alone (Strong Recommendation, High-Quality Evidence).

Values and preferences. For patients with AF and stable coronary or arterial vascular disease, the CCS AF Guidelines Committee believed that routine use of combination therapy (an OAC with a single antiplatelet agent) was not justified because of the increased risk of bleeding without a significant reduction in ischemic coronary and cerebrovascular thrombotic events.

Practical tip. For patients with high-risk clinical or angiographic features for ischemic coronary outcomes (Fig. 2) who are at low risk of bleeding, some clinicians prefer a combination of an OAC and single antiplatelet therapy (either aspirin or clopidogrel) in preference to OAC therapy alone.[52]

Atrial Fibrillation and Ischemic events with Rivaroxaban in patiEnts with stable CAD — AFIRE

A multicenter, prospective, randomized, open-label, parallel-group trial

2200 patients with AF ($CHADS_2$≥1) and stable CAD

Key inclusion criteria
- Underwent PCI or CABG more than 1 year earlier
- Angiographically confirmed CAD (with stenosis of ≥50%) not requiring revascularization

Key exclusion criteria
- A history of stent thrombosis
- Coexisting active tumor
- Poorly controlled hypertension

RANDOMIZE

OAC Monotherapy
- **Rivaroxaban** 10 or 15 mg/day

Combination Therapy
- **Rivaroxaban** 10 or 15 mg/day
- **Single antiplatelet**
  Aspirin <100mg daily or P2Y12 inhibitor (ASA 70%, Clopidogrel 25%)

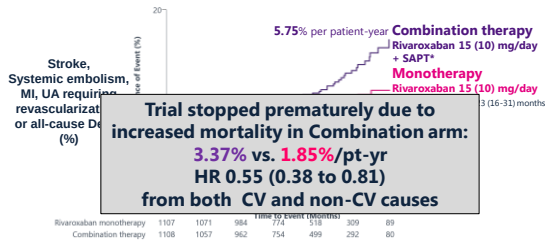
UMIN Clinical Trials Registry number, UMIN000016612.
ClinicalTrials.gov number, NCT02642419.

1) Yasuda S, et al. *Int J Cardiol.* 2018. *2)* Tanigawa T, et al. *Drug Metab Pharmacokinet.* 2013.

Atrial Fibrillation and Ischemic events with Rivaroxaban in patiEnts with stable CAD — AFIRE

First Occurrence of Primary Efficacy Events

2236 AF pts >1 year post-PCI (71%) or CABG (11%) or with angiographic CAD (≥50%) not requiring revasc.

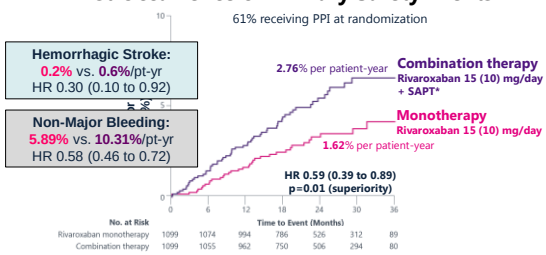


Yasuda et al *N Engl J Med* 2019; 2019;381:1103-13

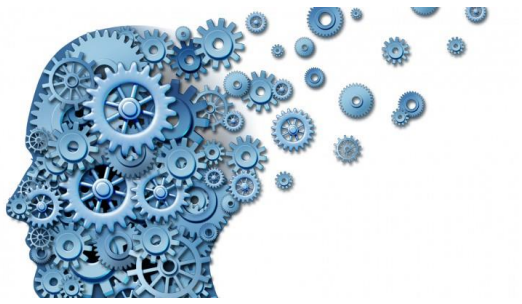
Atrial Fibrillation and Ischemic events with Rivaroxaban in patiEnts with stable CAD — AFIRE

First Occurrence of Primary Safety Events

61% receiving PPI at randomization

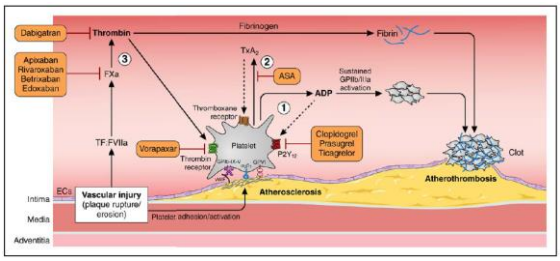


Yasuda et al *N Engl J Med* 2019; 2019;381:1103-13



Changing gears…

Paradigm Shift

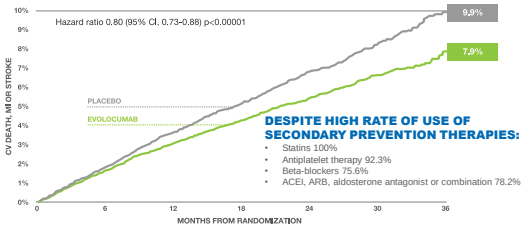


What if we try a small amount of clotting factor inhibition PLUS platelet inhibition?

RESIDUAL RISK REMAINS DESPITE THE USE OF SECONDARY PREVENTIVE THERAPIES

FOURIER

27 564 high-risk, stable patients with established CV disease: Prior MI (81%), prior non-hemorrhagic stroke (19%) or symptomatic PAD (13%)



DESPITE HIGH RATE OF USE OF SECONDARY PREVENTION THERAPIES:

- Statins 100%
- Antiplatelet therapy 92.3%
- Beta-blockers 75.6%
- ACEI, ARB, aldosterone antagonist or combination 78.2%

ACEI: angiotensin-converting–enzyme inhibitor; ARB: angiotensin-receptor blocker; CI: confidence interval; CV: cardiovascular; MI: myocardial infarction; PAD: peripheral artery disease.
Sabatine, M.S., et al. *N Engl J Med* 376(18) (May 4, 2017):1713-22.

COMPASS

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 OCTOBER 5, 2017 VOL. 377 NO. 14

Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease

J.W. Eikelboom, S.J. Connolly, J. Bosch, G.R. Dagenais, R.G. Hart, O. Shestakovska, R. Diaz, M. Alings, E.M. Lonn, S.S. Anand, P. Widimsky, M. Hori, A. Avezum, L.S. Piegas, K.R.H. Branch, J. Probstfield, D.L. Bhatt, J. Zhu, Y. Liang, A.P. Maggioni, P. Lopez-Jaramillo, M. O'Donnell, A.K. Kakkar, K.A.A. Fox, A.N. Parkhomenko, G. Ertl, S. Störk, M. Keltai, L. Ryden, N. Pogosova, A.L. Dans, F. Lanas, P.J. Commerford, C. Torp-Pedersen, T.J. Guzik, P.B. Verhamme, D. Vinereanu, J.-H. Kim, A.M. Tonkin, B.S. Lewis, C. Felix, K. Yusoff, P.G. Steg, K.P. Metsarinne, N. Cook Bruns, F. Misselwitz, E. Chen, D. Leong, and S. Yusuf, for the COMPASS Investigators*

Study Design

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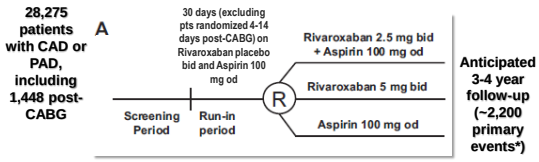


≥80% adherence (2,320 [8%] excluded)

***3.3 per 100 person-yrs Aspirin event rate → 90% power to detect 20% lower risk with 2 comparisons of rivaroxaban**

Primary Outcome: Composite of CV death, Stroke, MI

Bosch et al *Can J Cardiol* 2017;33:1027-35
Eikelboom et al *N Engl J Med* 2017;377:1319-1330

Key Inclusion and Exclusion Criteria

COMPASS

- **Coronary or peripheral artery disease (MI/angina/PCI/CABG)**
  - Patients with CAD must also have
    - Age ≥65 years, or
    - Age <65 years and documented atherosclerosis or revascularization involving ≥2 vascular beds or ≥2 additional risk factors (e.g., current smoker, diabetes, eGFR<60 ml/min, HF, non-lacunar ischemic stroke ≥1 month ago)
  - Criteria for PAD
    - Claudication, previous amputation or revascularization
    - Carotid revascularization
    - Asymptomatic carotid disease with >50% stenosis
- **Key Exclusion**
  - Need for dual antiplatelet, other non-aspirin antiplatelet, or oral anticoagulant therapy
  - Stroke ≤1 month, history of hemorrhagic or lacunar stroke
  - Severe HF (EF<30%, NYHA class ≥3)
  - eGFR <15 ml/min

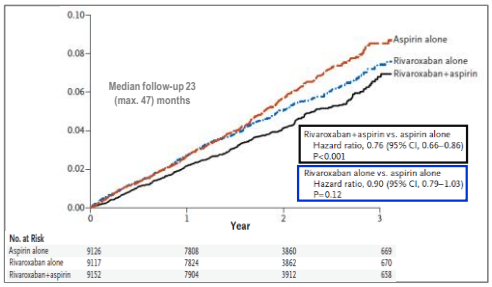
Bosch et al *Can J Cardiol* 2017;33:1027-35
Eikelboom et al *N Engl J Med* 2017;377:1319-1330

Follow-Up and Adherence

COMPASS

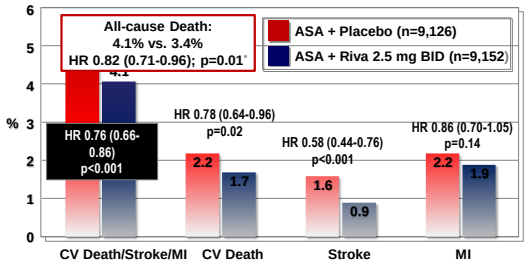
- **On February 6, 2017 the Data and Safety Monitoring Board recommended discontinuation of rivaroxaban/aspirin arms for clear evidence of efficacy**
  - Riva + Aspirin: Z= -4.59, p<0.00001
  - Rivaroxaban: Z= -2.44, p=0.01
- **Close-out March-June 2017**
- **Mean follow-up 23 months (99.8% complete)**
  - Permanent study drug discontinuation in ~17% of the rivaroxaban groups, ~16% in the aspirin alone group

CV Death/Stroke/MI



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

Primary Outcome Components



* pre-specified threshold p=0.0025

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

Subgroup Analysis for Primary Outcome

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

Cerebrovascular Disease (CVD): ~6.4% vs. 11.3% (HR 0.57)

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

PAD Patients

PAD Groups	Number of patients
All Patients	7,470 (27%)
Symptomatic PAD Limbs	4,129 (15%)
Carotid Disease	1,919 (7%)
CAD + Low ABI (<0.90) only	1,422 (5%)

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

Bosch et al *Can J Cardiol* 2017;33:1027-35
Anand et al *Lancet* 2018;391:219-29

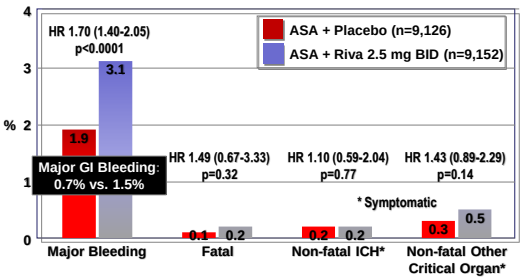
PAD Limb Outcomes

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
MALE*	30 (1.2)	35 (1.4)	56 (2.2)	0.54 (0.35-0.84)	0.005	0.63 (0.41-0.96)	0.03
Major amputation	5 (0.2)	8 (0.3)	17 (0.7)	0.30 (0.11-0.80)	0.01	0.46 (0.20-1.08)	0.07

*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

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

Major Bleeding



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

Net Clinical Benefit

Outcome	Riva + Aspirin N=9,152	Aspirin N=9,126	Rivaroxaban + Aspirin vs. Aspirin	
	N (%)	N (%)	HR (95% CI)	P
Net clinical benefit (Primary + Severe bleeding events)	431 (4.7%)	534 (5.9%)	0.80 (0.70-0.91)	0.0005

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

ESC Guidelines for "Chronic Coronary Syndromes"

Adding a second antithrombotic drug to aspirin for long-term secondary prevention should be considered in patients with a **high risk** of ischaemic events[c] and without high bleeding risk[d] (see *Table 9* for options).[289,296,297,307]	IIa
Adding a second antithrombotic drug to aspirin for long-term secondary prevention may be considered in patients with at least a **moderately increased risk** of ischaemic events[c] and without high bleeding risk[d] (see *Table 9* for options).[289,296,297,307]	IIb

Rivaroxaban 2.5mg bid for patients >1 year since MI or multivessel atherosclerotic disease

European Heart Journal (2019) 00, 1-71
doi:10.1093/eurheartj/ehz425

Implications

- **Risk is bleeding**
  - Highest CV risk, lowest Bleeding risk patients?
  - PAD patients?
- **Cost**
- **Medication dosing errors?**
  - We now have FIVE rivaroxaban dosing strategies