Preventing Adverse Cardiovascular and Limb Events in High-Risk Cardiometabolic Patients with Peripheral Artery Disease: Recent Trials and Advances

A compilation of key content from the Primetime Symposium at the 2020 15th Annual CMHC Live Online

Deepak L. Bhatt, MD, MPH
Executive Director of Interventional Cardiovascular Programs, Brigham and Women’s Hospital Heart and Vascular Center
Professor of Medicine, Harvard Medical School

Marc P. Bonaca, MD, MPH
Professor of Medicine
Director of Vascular Research
University of Colorado School of Medicine

Manesh R. Patel, MD
Richard S. Stack Professor
Chief, Division of Cardiology
Co-Director, Duke Heart Center
Impact of Prior Ischemic Events, Stable Atherosclerosis, Polyvascular Disease and Diabetes on CV Events at 4 years

All event rates adjusted for age and sex.

Diabetes Increases Risk in Patients with Prior Ischemic Events; Diabetes and Polyvascular Disease: Insights from LEADER

Dual Pathway Inhibition: Antiplatelet plus Anticoagulant

**COMPASS**

**TRIAL DESIGN**

& Primary Outcome

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Stable CAD or PAD
27,395 participants randomized

![Diagram depicting COMPASS trial design and primary outcome](image)

- Rivaroxaban 2.5 mg bid + Aspirin 100
- Rivaroxaban 5 mg bid
- Aspirin 100 mg od

Run-in* (aspirin plus rivaroxaban)

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*excluding patients enrolled 4-14 days post CABG; Bosch JJ, et al. *Can J Cardiol* 2017; 33:1027-1035.

The Role of Combination Antiplatelet and Anticoagulation Therapy in Diabetes and Cardiovascular Disease: COMPASS Diabetes

Deepak L. Bhatt MD, MPH, John W. Eikelboom MBBS, Stuart J. Connolly MD, Ph. Gabriel Steg MD, Sonia S. Anand MD, Subodh Verma MD, PhD, Kelley R. H. Branch MD, Jeffrey Probstfield MD, Jackie Bosch PhD, Olga Shestakovska MSc, Michael Szarek, Ph.D., Aldo Pietro Maggioni MD, Petr Widimský MD, Alvaro Avezum MD, Rafael Diaz MD, Basil S. Lewis MD, Scott D. Berkowitz MD, Keith A. A. Fox MBChB, Lars Ryden MD, Salim Yusuf DPhil, for the COMPASS Steering Committee and Investigators

Circulation
https://www.ahajournals.org/doi/10.1161/CIRCULATIONAHA.120.046448

Effects in patients with diabetes at baseline (N=6,922) versus without diabetes (N=11,356)

Patients randomized to *rivaroxaban plus aspirin* (N=9,126) versus *placebo plus aspirin* (N=9,126)

- 1° efficacy: CV death, MI, stroke
- 2° efficacy:
  - All-cause mortality
  - CV death, MI, stroke, MALE, including amputation
- 1° safety: modified ISTH criteria - major bleeding
- Prespecified net clinical benefit: CV death, MI, stroke, fatal bleeding, symptomatic bleeding into a critical organ
**Outcomes**

CV Death, Myocardial Infarction, or Stroke

Diabetes (N=6,922)
- Aspirin Alone
- Rivaroxaban plus Aspirin
No Diabetes (N=11,356)
- Aspirin Alone
- Rivaroxaban plus Aspirin

P value for Interaction = 0.82

Diabetes (N=6,922)
- Aspirin Alone
- Rivaroxaban plus Aspirin
No Diabetes (N=11,356)
- Aspirin Alone
- Rivaroxaban plus Aspirin

P value for Interaction = 0.77

**All-Cause Death**

### SAFETY OUTCOMES

#### Benefits in Diabetes +/- Prior Ischemic Events or Revascularization: CV Death/MI/Stroke

<table>
<thead>
<tr>
<th>SAFETY OUTCOMES</th>
<th>Rivaroxaban plus Aspirin</th>
<th>Aspirin Alone</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Major bleeding</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No diabetes at baseline</td>
<td>178/5704 (3.1)</td>
<td>4.4</td>
</tr>
<tr>
<td>Diabetes at baseline</td>
<td>110/3448 (3.2)</td>
<td>4.5</td>
</tr>
<tr>
<td><strong>Intracranial bleeding</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No diabetes at baseline</td>
<td>17/5704 (0.3)</td>
<td>0.4</td>
</tr>
<tr>
<td>Diabetes at baseline</td>
<td>11/3448 (0.3)</td>
<td>0.4</td>
</tr>
<tr>
<td><strong>Fatal bleeding</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No diabetes at baseline</td>
<td>10/5704 (0.2)</td>
<td>0.4</td>
</tr>
<tr>
<td>Diabetes at baseline</td>
<td>5/3448 (0.1)</td>
<td>0.2</td>
</tr>
</tbody>
</table>

CONCLUSIONS

Low-dose rivaroxaban + aspirin reduced major CV events in stable atherosclerosis, irrespective of the presence or absence of diabetes, though absolute risk reductions were numerically larger with diabetes, including for all-cause mortality.

As in the overall trial, there was a significant increase in major bleeding, but not in fatal or intracranial bleeding.

The net clinical benefit when examining irreversible outcomes appeared numerically greater in those with diabetes.

Use of dual pathway inhibition with low-dose rivaroxaban + aspirin is particularly attractive in high-risk patients, such as those with diabetes.

COMPASS Evaluated DPI with Vascular Dose Rivaroxaban + Aspirin in Patients with CAD or PAD

Benefits of COMPASS Regimen According to Number of Enrichment Criteria in REACH

Practical Algorithm for DAPT or DPI

Potential Candidates for DPI

Recent Clinical Trials in PAD

Marc P. Bonaca, MD MPH
Professor of Medicine
Director of Vascular Research
University of Colorado School of Medicine
Burden of Risk in PAD is Driven by Limb Events

Events in PAD Patients at 4 Years
- REACH Registry

Events in PAD Patients at 3 Years
- TRA2P-TIMI 50

- >200 million with PAD globally
- Incidence is increasing with key risk factors of age, obesity and diabetes
- Key morbidity is limb symptoms (claudication → critical limb ischemia)
- Most common outcome is the need for a limb revascularization procedure
- Limb tissue loss events (e.g. amputation and ALI) are as common as MI and stroke

Limb Outcomes by Type with Ticagrelor versus Placebo (THEMIS TRIAL)

- **Limb Ischemic Event**
  - Ticagrelor: 1.59%
  - Placebo: 1.30%
  - HR 0.77 (0.61 – 0.96) P=0.022

- **Peripheral Revascularization**
  - Ticagrelor: 1.51%
  - Placebo: 1.23%
  - HR 0.79 (0.62 – 0.99)

- **Acute Limb Ischemia**
  - Ticagrelor: 0.16%
  - Placebo: 0.04%
  - HR 0.24 (0.08 – 0.70)

- **Major Amputation**
  - Ticagrelor: 0.12%
  - Placebo: 0.10%
  - HR 0.63 (0.28 – 1.38)

N=19,220

Bonaca MP et al. ESC LB5 2020
COMPASS Trial

Reductions in CV Death Mortality

HR for Major Bleeding
1.70 (1.40 – 2.05), p<0.001

>90% with CAD, large subgroup with Concomitant PAD, consistent benefits for both

Prior Limb Revascularization Associated with Greater Limb Risk – COMPASS Trial

Incidence of MALE (%)

- Prior Revascularization or Amputation: 3.80%, N=86
- Claudication but no History of Revascularization or Amputation: 1.37%, N=37
- Asymptomatic low ABI (≤0.90): 0.50%, N=5

N=2264 (36% of Population)
N=2705 (42% of Population)
N=1422 (22% of Population)

MALE = major adverse limb events
Prior Limb Revascularization Associated with Greater Limb Risk

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Adjusted HR for ALI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior Peripheral Revascularization</td>
<td>HR 3.60 (2.10 – 6.18) P&lt;0.001</td>
</tr>
<tr>
<td>ABI ≤ 0.5</td>
<td>HR 2.86 (1.81 – 4.51)</td>
</tr>
<tr>
<td>ABI ≥ 1.3</td>
<td>HR 2.71 (1.09 – 6.72)</td>
</tr>
<tr>
<td>Current Smoking</td>
<td>HR 2.17 (1.01 – 4.67) P=0.046</td>
</tr>
</tbody>
</table>

Bonaca et al. Circulation 2016

<table>
<thead>
<tr>
<th>Study</th>
<th>Adjusted HR for ALI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEGASUS-TIMI 54 PAD</td>
<td>Adjusted HR for ALI 3.76 (2.26 – 6.25)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>EUCLID</td>
<td>Adjusted HR for ALI 4.23 (2.86 – 6.25)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Bonaca et al. JACC 2016
Jones et al. Circulation 2016
PAD Patients Vulnerable After Revascularization

Risk in Patients Undergoing Peripheral Revascularization

- **“Acute” Post Revascularization**
- **“Stable” Phase**

N=393,017

Major amputation/limb revascularization

4x risk of ALI long term vs no revascularization

Outcomes in Patients with Acute Limb Ischemia

- Median hospitalization 8 days (IQR 5–15)
- ~4% die at presentation
- ~1/5 → major amputation
- ~1/3 → prolonged ICU stay
- ~3/4 → major surgery

Outcomes after hospitalization are poor, with ~15% disabled or dead
Despite the high risk, currently there is no proven antithrombotic strategy that has demonstrated efficacy for reducing major adverse limb and cardiovascular events after peripheral intervention for ischemia.

**Index-Graft Occlusion, Revascularization, Replacement, Major Amputation, or Death**

- HR 0.98
- (95% CI 0.78–1.23), P=NS

**DAPT with aspirin and clopidogrel**

- Increased GUSTO moderate-severe bleeding
- HR 2.84 (1.32–6.08)

**Graft Occlusions**

- HR 0.95
- (95% CI 0.82–1.11), P=NS

**Full intensity oral anticoagulation**

- Increased risk of hemorrhagic stroke
- HR 3.48 (1.14–10.60)

**VOYAGER PAD**

**NCT02504216**

*6,564 patients with symptomatic lower extremity PAD* under going peripheral revascularization

ASA 100 daily for all patients
Clopidogrel at Investigator’s discretion

Randomized 1:1 double blind

**Rivaroxaban 2.5 mg twice daily**

Stratified by revascularization approach (surgical or endovascular) and use of clopidogrel

**Placebo**

Follow-up at 1, 3 and 6 months then Q6 Months, Event driven, median follow-up 28 months

Primary efficacy endpoint: Acute limb ischemia, major amputation of vascular etiology, myocardial infarction, ischemic stroke, or cardiovascular death

Principal safety outcome: TIMI major bleeding

*Ankle–brachial index ≤ 0.85 and imaging evidence of occlusive disease*
Primary Endpoint

Acute Limb Ischemia, Major Amputation for Vascular Cause,
Myocardial Infarction, Ischemic Stroke, CV Death

**Cumulative Incidence (KM%)**

- **Placebo**
- **Rivaroxaban**

**6 Months**
- ARR 1.5%
- NNT 65

**1 Year**
- ARR 2.0%
- NNT 50

**3 Year**
- ARR 2.6%
- NNT 39

**HR 0.85**
- 95% CI 0.76–0.96
- P=0.009

ARR, absolute risk reduction;
NNT, number needed to treat

## Primary Endpoint & Components

<table>
<thead>
<tr>
<th>Event</th>
<th>KM% 3 Years (n)</th>
<th>KM% 3 Years (n)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary efficacy outcome</strong></td>
<td>17.3</td>
<td>19.9</td>
<td>0.85 (0.76–0.96)</td>
</tr>
<tr>
<td>Acute limb ischemia</td>
<td>5.2</td>
<td>7.8</td>
<td>0.67 (0.55–0.82)</td>
</tr>
<tr>
<td>Major vascular amputation</td>
<td>3.4</td>
<td>3.9</td>
<td>0.89 (0.68–1.16)</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>2.7</td>
<td>3.0</td>
<td>0.87 (0.63–1.19)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>4.6</td>
<td>5.2</td>
<td>0.88 (0.70–1.12)</td>
</tr>
<tr>
<td>CV death</td>
<td>7.1</td>
<td>6.4</td>
<td>1.14 (0.93–1.40)</td>
</tr>
</tbody>
</table>
Effect of Rivaroxaban on Acute Limb Ischemia

Hess CH et al. ESC LBS 2020

Effect of Rivaroxaban on Early Acute Limb Ischemia

Hess CH et al. ESC LBS 2020
SAFETY

Placebo
Rivaroxaban

**Principal Safety Outcome**
- **TIMI major**
  - Placebo: 2.7%
  - Rivaroxaban: 1.9%
- **ICH**
  - Placebo: 0.6%
  - Rivaroxaban: 0.9%
- **Fatal**
  - Placebo: 0.2%
  - Rivaroxaban: 0.2%
- **ICH or fatal**
  - Placebo: 0.7%
  - Rivaroxaban: 1.0%

**Secondary Safety Outcomes**
- **TIMI minor**
  - Placebo: 1.9%
  - Rivaroxaban: 1.2%
- **BARC 3b or greater**
  - Placebo: 3.9%
  - Rivaroxaban: 2.9%
- **ISTH major**
  - Placebo: 5.9%
  - Rivaroxaban: 4.1%

**HR**
- **1.43** (0.97–2.10) P=0.0695
- **0.78** (0.38–1.61) P=0.50
- **1.02** (0.33–3.15) P=0.96
- **0.91** (0.47–1.76) P=0.79
- **1.50** (0.96–2.37) P=0.078
- **1.29** (0.96–1.76) P=0.096
- **1.42** (1.10–1.84) P=0.0068

**ARI**
- Placebo: 0.8%
- Rivaroxaban: 1.8%

**NNH**
- Placebo: 126
- Rivaroxaban: 126

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**Notes:**
- ARI, absolute risk increase
- NNH, number needed to harm
Risk–Benefit

First Events Prevented / Caused for 10,000 Patients Treated* for 1 Year

Primary Efficacy Outcome
Events Prevented
(95% CI)
(acute limb ischemia, major amputation for vascular cause; MI, ischemic stroke, or CV death)

Principal Safety Outcome
Events Caused
(95% CI)
(TIMI major bleeding)

+ 29
(-2 to +66)

−181
(−269 to −94)

First Events Prevented / Caused from Time from Randomization


*Efficacy and safety on treatment
Rivaroxaban 2.5 mg bid should be used with caution in ACS and CAD/PAD patients ≥75 years of age and/or with body weight <60 kg if co-administered with aspirin alone or with aspirin plus clopidogrel or ticlopidine. The benefit-risk of the treatment should be assessed individually on a regular basis.

Reduction in *Early Acute Limb Ischemia* with Rivaroxaban With and Without Clopidogrel

Risk of ISTH Bleeding with Rivaroxaban by Use and Duration of Concomitant Clopidogrel

OUTCOMES

MI and ALI with and without CAD

Limb Outcomes with Rivaroxaban with and without Prior LER

Hess CH et al. ESC LBS 2020
Bonaca MP et al. CIRSE 2020
Patients with PAD are at high risk of MACE and MALE but there is heterogeneity
- Polyvascular Disease (particularly PAD+CAD) is associated with a malignant MACE profile
- Prior peripheral revascularization is associated with high risk of limb events, particularly ALI

Novel strategies for risk reduction including dual pathway inhibition and intensive lipid lowering reduce MACE and MALE risk in chronic PAD

Patients with PAD are at their most vulnerable after revascularization with extremely high event rates in spite of maximal medical therapy

VOYAGER PAD tested a strategy of rivaroxaban plus aspirin versus aspirin alone and showed a 6:1 benefit risk ratio in a broad PAD population including
- Early benefit for acute limb ischemia
- Consistent efficacy regardless of background clopidogrel
- Greater absolute benefits in high-risk subgroups (e.g. prior LER, Polyvascular disease)
- Consistent benefits after surgical LER