VOYAGER PAD
Efficacy and Safety of Rivaroxaban in Patients with Symptomatic PAD undergoing Revascularization with and without Clopidogrel


American College of Cardiology Virtual Scientific Sessions 2020
Late-Breaking Clinical Trial
29 March 2020

*Drs. Hiatt and Bonaca Contributed Equally to this Presentation
William R Hiatt Disclosures

Research grants to CPC Clinical Research, an Academic Research Organization and Affiliate of the University of Colorado Anschutz Campus

- Bayer
- Janssen
- Amgen
Background

**GUSTO Bleeding**
- HR 2.84 (1.32 – 6.08)

**Increased risk of Hemorrhagic Stroke**
- HR 3.48 (1.14 – 10.60)

**Graft occlusion, revasc, major amputation, or death**
- HR 0.98 (95% CI 0.78 – 1.23), P=NS

**Chest Grade Ia**

**Zilver PTX**

**IN.PACT SFA**

**DAPT Recommendations after PAD Intervention**
- **ACC-AHA:** IIb C-LD
- **ESC:** IIa C
- **Chest Grade Ia**
- **Zilver PTX**
- **IN.PACT SFA**

DAPT may be reasonable to reduce the risk of limb-related events after LER
DAPT is recommended for 1 month after intervention
SAPT (single antiplatelet therapy). Recommend against DAPT
DAPT for 2 months
DAPT for 1 month (without stent) or 3 months (with stent)

Trial Design

6,564 Patients with Symptomatic Lower Extremity PAD* Undergoing Peripheral Revascularization

**Primary Efficacy Endpoint:** Acute limb ischemia, major amputation of vascular etiology, myocardial infarction, ischemic stroke or cardiovascular death

**Principal Safety Outcome:** TIMI Major Bleeding

Follow up Q6 Months, Event Driven, Median f/u 28 Months

ASA 100 daily for all Patients
Clopidogrel at Investigator’s Discretion

Randomized 1:1 Double Blind

Rivaroxaban 2.5 mg twice daily

Placebo

Stratified by Revascularization Approach (Surgical or Endovascular) and Use of Clopidogrel

*N: Ankle Brachial Index < 0.90 and Imaging Evidence of Occlusive Disease

Capell WH, Bonaca MP, Nehler MR…Hiatt WR. AHJ 2018
Inclusion & Exclusion

**Inclusion**

- Age ≥ 50
- Documented PAD including:
  - *Ischemic symptoms* (functional limitation, rest pain or ischemic ulceration) AND
  - *Imaging evidence* of occlusion AND
  - *Abnormal ABI*
- Successful lower extremity revascularization for ischemia

**Exclusion**

- Revascularization for asymptomatic disease
- Recent revascularization (within 10 days) or ALI (2 weeks) or ACS (30 days)
- Current major tissue loss
- Need for antiplatelet or anticoagulant other than aspirin and/or clopidogrel
- Need for long-term DAPT (intended > 6 months)
- High risk for bleeding (significant bleeding in last 6 months, prior stroke or other high-risk condition)
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=0.0085

Months from Randomization

Cumulative Incidence (KM%)
Objectives

In symptomatic PAD patients undergoing lower extremity revascularization randomized to rivaroxaban 2.5 mg twice daily with aspirin versus aspirin alone, to evaluate whether:

• Determine if efficacy and safety of rivaroxaban were consistent regardless of background clopidogrel use

• To explore temporal patterns of bleeding in relationship to exposure and duration of clopidogrel
# PAD & Procedural Characteristics

<table>
<thead>
<tr>
<th>PAD Indication and History</th>
<th>Yes Clopidogrel</th>
<th>No Clopidogrel</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indication: Claudication</td>
<td>80 (%)</td>
<td>73 (%)</td>
<td>0.7826</td>
</tr>
<tr>
<td>Indication: Critical limb threatening ischemia</td>
<td>20 (%)</td>
<td>27 (%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Prior limb revascularization</td>
<td>40 (%)</td>
<td>31 (%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Prior major amputation</td>
<td>1.2 (%)</td>
<td>0.8 (%)</td>
<td>0.1287</td>
</tr>
<tr>
<td>ABI at Screening (Median – IQR)</td>
<td>0.58 (0.46-0.70)</td>
<td>0.52 (0.40-0.64)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Type of Revascularization</td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Surgical</td>
<td>9 (%)</td>
<td>58 (%)</td>
<td></td>
</tr>
<tr>
<td>Endovascular</td>
<td>91 (%)</td>
<td>42 (%)</td>
<td></td>
</tr>
</tbody>
</table>
## Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic at Randomization</th>
<th>Yes Clopidogrel N=3313</th>
<th>No Clopidogrel N=3234</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (Median-IQR)</td>
<td>67 (61-73)</td>
<td>67 (61-73)</td>
<td>0.3519</td>
</tr>
<tr>
<td>Female n</td>
<td>28</td>
<td>24</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>White Caucasian</td>
<td>80</td>
<td>82</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>82</td>
<td>80</td>
<td>0.0265</td>
</tr>
<tr>
<td>Diabetes Mellitus (type 2)</td>
<td>43</td>
<td>34</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>65</td>
<td>55</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Current smoking</td>
<td>34</td>
<td>35</td>
<td>0.1013</td>
</tr>
<tr>
<td>COPD</td>
<td>10</td>
<td>12</td>
<td>0.0477</td>
</tr>
<tr>
<td>eGFR &lt; 60 ml/min/1.73m²</td>
<td>22</td>
<td>19</td>
<td>0.0028</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>34</td>
<td>29</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Prior CABG</td>
<td>9</td>
<td>7</td>
<td>0.0399</td>
</tr>
<tr>
<td>Prior coronary intervention</td>
<td>16</td>
<td>10</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Carotid stenosis ≥ 50%</td>
<td>9</td>
<td>7</td>
<td>0.0035</td>
</tr>
</tbody>
</table>
## Clopidogrel Use

<table>
<thead>
<tr>
<th></th>
<th>Rivaroxaban 2.5 mg twice daily + aspirin</th>
<th>Placebo + aspirin</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=3286 %</td>
<td>N=3278 %</td>
<td></td>
</tr>
<tr>
<td><strong>Clopidogrel use at randomization</strong></td>
<td>50.5</td>
<td>50.5</td>
<td>0.7926</td>
</tr>
<tr>
<td><strong>Median duration days (IQR)</strong></td>
<td>29.0 (25.0-49.5)</td>
<td>29.0 (26.0-50.0)</td>
<td>0.0700</td>
</tr>
<tr>
<td>≤ 30 days</td>
<td>59.6</td>
<td>56.5</td>
<td></td>
</tr>
<tr>
<td>31- 90 days</td>
<td>29.0</td>
<td>31.7</td>
<td></td>
</tr>
<tr>
<td>91-180 days</td>
<td>6.3</td>
<td>6.3</td>
<td></td>
</tr>
<tr>
<td><strong>Median duration days (IQR) for drug-coated products</strong></td>
<td>31.0 (27.0-59.0)</td>
<td>32.0 (27.5-59.0)</td>
<td>0.9311</td>
</tr>
</tbody>
</table>

*38% of endovascular procedures with clopidogrel were for drug coated products
Primary Endpoint

Acute limb ischemia, major amputation for vascular cause, myocardial infarction, ischemic stroke, CV death

**With Clopidogrel**

- N=3313
- 16.0%
- ARR 2.3%
- Rivaroxaban plus aspirin versus aspirin alone
  - HR = 0.85 (95% CI 0.71 – 1.01)

**Without Clopidogrel**

- N=3234
- 18.7%
- ARR 2.8%
- Rivaroxaban plus aspirin versus aspirin alone
  - HR = 0.86 (95% CI 0.73 – 1.01)

*P-interaction 0.9163*
Primary Endpoint at 180 Days
Acute limb ischemia, major amputation for vascular cause, myocardial infarction, ischemic stroke, CV death

With Clopidogrel
N=3313

Placebo
Rivaroxaban

Without Clopidogrel
N=3234

Days from Randomization
Cumulative Incidence (KM%)

Days from Randomization
Cumulative Incidence (KM%)

ARR 1.5%
5.6%
4.1%
5.7%
7.0%
Benefit of Rivaroxaban for the Primary Outcome and Components with and without Background Clopidogrel

**Primary Endpoint**
- With Clopidogrel: HR (95% CI) - 0.86 (0.71-1.01)
- Without Clopidogrel: HR (95% CI) - 0.85 (0.73-1.01)

**Acute Limb Ischemia**
- With Clopidogrel: HR (95% CI) - 0.63 (0.46-0.89)
- Without Clopidogrel: HR (95% CI) - 0.70 (0.53-0.92)

**Amputation of Vascular Etiology**
- With Clopidogrel: HR (95% CI) - 0.98 (0.64-1.49)
- Without Clopidogrel: HR (95% CI) - 0.85 (0.60-1.20)

**Myocardial Infarction**
- With Clopidogrel: HR (95% CI) - 0.90 (0.65-1.24)
- Without Clopidogrel: HR (95% CI) - 0.87 (0.61-1.22)

**Ischemic Stroke**
- With Clopidogrel: HR (95% CI) - 0.78 (0.50-1.22)
- Without Clopidogrel: HR (95% CI) - 0.97 (0.61-1.54)

**Cardiovascular Death**
- With Clopidogrel: HR (95% CI) - 1.27 (0.94-1.72)
- Without Clopidogrel: HR (95% CI) - 1.06 (0.80-1.39)
Benefit of Rivaroxaban for Secondary Outcome with and without Background Clopidogrel

<table>
<thead>
<tr>
<th>Outcome</th>
<th>HR (95% CI)</th>
</tr>
</thead>
</table>
| MI, ischemic stroke, CHD, ALI, or major amputation of vascular etiology | With Clopidogrel: 0.80 (0.66-0.96)  
Without Clopidogrel: 0.81 (0.68-0.96) |
| Unplanned index limb revascularization for recurrent limb ischemia      | With Clopidogrel: 0.89 (0.76-1.03)  
Without Clopidogrel: 0.88 (0.74-1.04) |
| Hospitalization for a coronary or peripheral event (either lower limb) of a thrombotic nature | With Clopidogrel: 0.70 (0.55-0.89)  
Without Clopidogrel: 0.74 (0.59-0.92) |
| MI, ischemic stroke, all-cause mortality, ALI, and major amputation of vascular etiology | With Clopidogrel: 0.86 (0.73-1.10)  
Without Clopidogrel: 0.91 (0.78-1.06) |
| MI, all-cause stroke, CV death, ALI, and major amputation of vascular etiology | With Clopidogrel: 0.85 (0.71-1.01)  
Without Clopidogrel: 0.87 (0.74-1.02) |
| All Cause Mortality                                                     | With Clopidogrel: 1.10 (0.87-1.39)  
Without Clopidogrel: 1.07 (0.86-1.32) |
| Venous thromboembolism                                                 | With Clopidogrel: 0.69 (0.32-1.48)  
Without Clopidogrel: 0.55 (0.29-1.06) |
Safety of Rivaroxaban With and Without Clopidogrel

- Placebo
- Rivaroxaban

**P-interaction** 0.6901

<table>
<thead>
<tr>
<th>Event with Clopidogrel</th>
<th>Event without Clopidogrel</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIMI major</td>
<td>HR 1.32 (0.78–2.24)</td>
</tr>
<tr>
<td>ICH or Fatal</td>
<td>HR 1.55 (0.88–2.73)</td>
</tr>
<tr>
<td>ISTH major</td>
<td>HR 1.36 (0.96–1.91)</td>
</tr>
<tr>
<td></td>
<td>HR 1.55 (0.88–2.73)</td>
</tr>
</tbody>
</table>

KM Rate at 3 Years (%)

- TIMI major with clopidogrel: 2.7% (2.3%)
- TIMI major without clopidogrel: 2.6% (1.5%)
Safety of Rivaroxaban With and Without Clopidogrel

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

### KM Rate at 3 Years (%)

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIMI major with clopidogrel</td>
<td>2.7%</td>
<td>2.3%</td>
</tr>
<tr>
<td>TIMI major without clopidogrel</td>
<td>2.6%</td>
<td>1.5%</td>
</tr>
<tr>
<td>ICH or Fatal with clopidogrel</td>
<td>0.3%</td>
<td>1.1%</td>
</tr>
<tr>
<td>ICH or Fatal without clopidogrel</td>
<td>1.2%</td>
<td>0.8%</td>
</tr>
<tr>
<td>ISTH major with clopidogrel</td>
<td>6.5%</td>
<td>4.9%</td>
</tr>
<tr>
<td>ISTH major without clopidogrel</td>
<td>5.4%</td>
<td>3.3%</td>
</tr>
</tbody>
</table>

**HR**

- TIMI major with clopidogrel: **HR 1.32** (0.78 – 2.24)
- TIMI major without clopidogrel: **HR 1.55** (0.88 – 2.73)
- ICH or Fatal with clopidogrel: **HR 0.44** (0.14 – 1.43)
- ICH or Fatal without clopidogrel: **HR 1.35** (0.59 – 3.07)
- ISTH major with clopidogrel: **HR 1.36** (0.96 – 1.91)
- ISTH major without clopidogrel: **HR 1.50** (1.02 – 2.20)

**P-interaction**

- 0.6901
- 0.1261
- 0.7002
ISTH Major Bleeding With and Without Clopidogrel

Cumulative Incidence (KM%)

Days from Randomization

With Clopidogrel

Without Clopidogrel

ARI = Absolute Risk Increase
ISTH Major Bleeding With and Without Clopidogrel in Year 1

ARI = Absolute Risk Increase

Median Exposure to clopidogrel 30 days

Period with Clopidogrel + Rivaroxaban + Aspirin

ARI with Clopidogrel 1.4%
Net +0.2% after Clopidogrel window

ARI without Clopidogrel 0.7%
Net +0.3% second 6 months

1 Year

Placebo

Rivaroxaban

Days from Randomization

Cumulative Incidence (KM%)

6 Months

ARI with Clopidogrel 1.2%

ARI without Clopidogrel 0.4%

6 Month

0 90 180 270 360

0 1 2 3 4

0 1 2 3 4
ISTH Major Bleeding by Clopidogrel Duration

Period where Clopidogrel Allowed

> 30 Days Clopidogrel
N=1390

- 6 Months
ARI with Clopidogrel 2.1%
3.0%

- 3 Year ARI 2.2%
Net +0.73% per year

≤ 30 Days Clopidogrel
N=1923

- 6 Month
ARI without Clopidogrel 0.7%
0.9%

- 3 Year ARI 2.2%
Net +0.73% per year

Cumulative Incidence (KM%)

Days from Randomization

ARI = Absolute Risk Increase
Risk and Benefit of Rivaroxaban with and without Clopidogrel

**With Clopidogrel**
- N=3313
- Primary Efficacy Endpoint: 18.3%
- ARR 2.3%
- Principal Safety Outcome: 2.7%
- ARI 0.4%

**Without Clopidogrel**
- N=3234
- Primary Efficacy Endpoint: 21.5%
- ARR 2.8%
- Principal Safety Outcome: 2.6%
- ARI 1.1%
Summary

• In patients with symptomatic PAD undergoing revascularization:
  – The benefit of rivaroxaban plus aspirin versus aspirin alone is consistent regardless of background clopidogrel
    • Primary efficacy endpoint HR ~0.85 with rivaroxaban regardless of clopidogrel with NNT < 50 with or without clopidogrel
  – The safety of rivaroxaban plus aspirin versus aspirin alone is consistent regardless of background clopidogrel
    • Principal safety outcome TIMI major bleeding HR ~1.3-1.5 regardless of clopidogrel with NNH > 90 with or without clopidogrel
  – However, clopidogrel exposure was associated with higher rates of bleeding overall, particularly with longer durations (e.g. > 30 days)
Conclusions & Perspective

In patients with symptomatic PAD undergoing revascularization:

- The benefit of DAPT is uncertain, with the only RCT in surgical bypass showing no benefit and significantly increased bleeding

- Rivaroxaban added to aspirin significantly reduces limb and cardiovascular risk with consistent benefits regardless of clopidogrel

- The safety and risk/benefit of rivaroxaban plus aspirin are consistent regardless of background clopidogrel

- In patients receiving rivaroxaban, the addition of clopidogrel as a third agent, is associated with higher rates of bleeding during exposure

- More bleeding with background clopidogrel, even if not severe by adjudication, may be associated with broad consequences, including discontinuation of therapies. In the absence of clear benefit, clopidogrel exposure along with aspirin and rivaroxaban should be minimized or avoided to reduce this risk
Extra Slides
851 patients with PAD undergoing surgical bypass randomized aspirin + placebo or clopidogrel + aspirin. DAPT had no benefit on the composite of index-graft occlusion or revascularization, above-ankle amputation of the affected limb, or death, HR 0.98 (95% CI 0.78-1.23, p=NS)

GUSTO bleeding was increased on aspirin + clopidogrel - HR 2.84 (95% CI 1.32-6.08)

Study drug discontinuation (median follow up 1 year) was 21% on placebo and 25% on clopidogrel

All-cause mortality HR 1.44 (95% CI, 0.77-2.68), CV death HR 1.49 (95% CI, 0.73-3.01)

J Vasc Surg 2010;52:825-3
Hospitalization for Coronary or Peripheral Event of a Thrombotic Nature

**With Clopidogrel**
- N=3313
- Cumulative Incidence (KM%): 8.0%
- ARR 2.6%
- Rivaroxaban plus aspirin versus aspirin alone
  - HR = 0.70
  - (0.55 – 0.89)

**Without Clopidogrel**
- N=3234
- Cumulative Incidence (KM%): 13.6%
- ARR 4.2%
- Rivaroxaban plus aspirin versus aspirin alone
  - HR = 0.74
  - (0.59 – 0.92)

**P-interaction 0.757**
Unplanned Index Limb Revascularization

P-interaction 0.9035

With Clopidogrel
N=3313

Placebo
Rivaroxaban

Without Clopidogrel
N=3234

HR 0.89
(0.76 – 1.03)

HR 0.88
(0.74 – 1.04)

24.7%
22.5%
20.1%
17.6%

Cumulative Incidence (KM%)

Days from Randomization