Efficacy and Safety of Rivaroxaban in Patients with PAD with Concomitant Diabetes After Lower Extremity Revascularization

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European Society of Cardiology Congress 2021
Latest Science in Special Populations
**Disclosures**

- VOYAGER PAD was funded through a grant from Bayer and Janssen to CPC Clinical Research
- Other research grants to CPC Clinical Research from Arca, Amgen, Astra Zeneca, Bayer, Janssen, Merck, Novo Nordisk
VOYAGER PAD Primary Results

6,564 patients with symptomatic PAD undergoing limb revascularization (all on aspirin; clopidogrel at investigator’s discretion)

Low dose rivaroxaban plus aspirin reduced the risk of major adverse cardiovascular (CV) and limb events

Primary Endpoint*
ITT - HR 0.85 (0.76 – 0.96) P=0.0085 ARR 2.6%, NNT 39

TIMI Major Bleeding On Treatment - HR 1.43 (0.97 – 2.10) P=0.0695 ARI 0.8%, NNH 125

*Composite of acute limb ischemia, major amputation of a vascular cause, myocardial infarction, ischemic stroke, cardiovascular death

Bonaca MP…Hiatt WR. NEJM 2020
Aims

• To characterize the risk profile of patients with symptomatic PAD after LER based on diabetes status at baseline

• To assess the consistency of efficacy and safety of rivaroxaban for vascular events and bleeding on the basis of diabetes at baseline

Methods

• Prespecified analysis by DM identified at baseline

• Primary efficacy endpoint composite of acute limb ischemia, major amputation of vascular etiology, MI, ischemic stroke, CV death

• Principal safety outcome TIMI major bleeding

• All efficacy and safety outcomes adjudicated by blinded CEC

• Exploratory analysis of risk for bleeding events (high vs low)

• On treatment exploratory analysis, i.e. occurrence of first outcome event within 2 days of last dose of study drug
## Baseline Characteristics (n=6564)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>DM (40%; n=2629)</th>
<th>No DM (60%; n=3933)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr), median</td>
<td>67</td>
<td>66</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Female (%)</td>
<td>27</td>
<td>25</td>
<td>0.1077</td>
</tr>
<tr>
<td>Caucasian (%)</td>
<td>76</td>
<td>84</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BMI (kg/m²), median</td>
<td>27</td>
<td>25</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Current smoking (%)</td>
<td>28</td>
<td>39</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HTN (%)</td>
<td>89</td>
<td>77</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>eGFR &lt; 60 ml/min/1.73m² (%)</td>
<td>27</td>
<td>16</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Coronary Artery Disease (%)</td>
<td>40</td>
<td>26</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Statin (%)</td>
<td>83</td>
<td>78</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ACEi or ARB (%)</td>
<td>73</td>
<td>57</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Clopidogrel use at randomization (%)</td>
<td>56</td>
<td>47</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Ankle Brachial Index, Median (IQR)</td>
<td>0.54 (0.28 – 0.80)</td>
<td>0.53 (0.28 – 0.78)</td>
<td>0.0122</td>
</tr>
<tr>
<td>History of Amputation (%)</td>
<td>10 (80% below ankle)</td>
<td>3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Baseline CLI (%)</td>
<td>27</td>
<td>21</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Surgical revascularization: Surgical (%)</td>
<td>25</td>
<td>38</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
Three Year Outcomes in those With and Without Diabetes Randomized to Placebo

With DM: n=2629

Without DM: n=3933

Primary Outcome* KM (%) at 3 yrs

Days from Randomization

Mortality KM (%) at 3 yrs

*ALI, major amputation of a vascular cause, MI, ischemic stroke, CV death
Primary Endpoint* in Patients With and Without Diabetes Mellitus

Overall Population

Diabetes

No (n=3933)

Yes (n=2629)

HR for primary endpoint

Rivaroxaban better  Placebo better

HR 0.85  95% CI 0.76-0.96

HR 0.79  95% CI 0.67-0.93

HR 0.94  95% CI 0.79-1.11

p-interaction 0.16

*ALI, major amputation of a vascular cause, MI, ischemic stroke, CV death
Secondary Endpoints in Patients with DM
(n=2629)

All p-interactions for DM vs no DM > 0.05

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI, ischemic stroke, CHD, ALI, major amputation</td>
<td>20.2%</td>
<td>23.8%</td>
</tr>
<tr>
<td>Unplanned index limb revascularization</td>
<td>23.0%</td>
<td>23.8%</td>
</tr>
<tr>
<td>Hospitalization for a coronary or peripheral event</td>
<td>11.5%</td>
<td>9.2%</td>
</tr>
<tr>
<td>MI, ischemic stroke, mortality, ALI, major amputation</td>
<td>24.9%</td>
<td>26.2%</td>
</tr>
<tr>
<td>MI, all stroke, CVD, ALI, major amputation</td>
<td>21.3%</td>
<td>22.6%</td>
</tr>
<tr>
<td>Mortality</td>
<td>14.4%</td>
<td>12.9%</td>
</tr>
<tr>
<td>VTE</td>
<td>0.7%</td>
<td>2.0%</td>
</tr>
</tbody>
</table>

Cumulative Incidence (KM%) at 3 years

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo (95% CI)</th>
<th>Rivaroxaban (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI, ischemic stroke, CHD, ALI, major amputation</td>
<td>0.89 (0.74 – 1.08)</td>
<td>0.99 (0.83 – 1.17)</td>
</tr>
<tr>
<td>Unplanned index limb revascularization</td>
<td>0.84 (0.66 – 1.09)</td>
<td>0.95 (0.81 – 1.11)</td>
</tr>
<tr>
<td>Hospitalization for a coronary or peripheral event</td>
<td>0.94 (0.79 – 1.12)</td>
<td>1.17 (0.93 – 1.47)</td>
</tr>
<tr>
<td>MI, ischemic stroke, mortality, ALI, major amputation</td>
<td>0.84 (0.66 – 1.09)</td>
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<tr>
<td>Mortality</td>
<td>0.52 (0.23 – 1.17)</td>
<td>1.17 (0.93 – 1.47)</td>
</tr>
<tr>
<td>VTE</td>
<td>0.52 (0.23 – 1.17)</td>
<td>1.17 (0.93 – 1.47)</td>
</tr>
</tbody>
</table>
Safety of Rivaroxaban by DM at Randomization

**With DM**
- **N=2603**

**Without DM**
- **N=3900**

**Cumulative incidence at 3 Years (%)**

**p-interaction 0.03**
- **Placebo**
  - HR 2.45 (1.28 – 4.69) *p*=0.005
- **Rivaroxaban**
  - HR 1.01 (0.61 – 1.66) *P*=0.98

**p-interaction 0.20**
- **Placebo**
  - HR 1.67 (0.54 – 5.09) *p*=0.37
- **Rivaroxaban**
  - HR 0.65 (0.28 – 1.51) *P*=0.32

**p-interaction 0.08**
- **Placebo**
  - HR 1.79 (1.11 – 2.87) *P*=0.01
- **Rivaroxaban**
  - HR 1.01 (0.67 – 1.52) *P*=0.96

**p-interaction 0.43**
- **Placebo**
  - HR 1.59 (1.09 – 2.33) *P*=0.02
- **Rivaroxaban**
  - HR 1.30 (0.91 – 1.84) *P*=0.15

**TIMI major with DM**

- Placebo: 3.9% (31)
- Rivaroxaban: 1.2% (13)

**TIMI major without DM**

- Placebo: 1.9% (31)
- Rivaroxaban: 2.3% (31)

**ICH or Fatal with DM**

- Placebo: 1.1% (8)
- Rivaroxaban: 0.5% (5)

**ICH or Fatal without DM**

- Placebo: 0.5% (9)
- Rivaroxaban: 1.2% (14)

**BARC 3b and above with DM**

- Placebo: 5.3% (47)
- Rivaroxaban: 2.5% (27)

**BARC 3b and above without DM**

- Placebo: 2.9% (46)
- Rivaroxaban: 3.1% (46)

**ISTH major with DM**

- Placebo: 8.1% (68)
- Rivaroxaban: 4.2% (44)

**ISTH major without DM**

- Placebo: 4.6% (72)
- Rivaroxaban: 3.9% (56)
Safety of Rivaroxaban by DM at Randomization

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

### TIMI major bleeding at 3 Years (%)

**Placebo**
- 3.9%
- 1.9%
- 1.2%
- 2.3%

**Rivaroxaban**
- 1.9%
- 2.3%

**HR for TIMI major bleeding**
- HR 2.45 (1.28 – 4.69), p=0.005
- HR 1.01 (0.61 – 1.66), P=0.98

**p-interaction 0.03**

**DM Overall**
- **Lower Bleeding Risk**
  - 73% of Population
  - HR 1.01 (0.61 – 1.66), P=0.98
- **Higher Bleeding Risk**
  - 27% of Population
  - HR 2.45 (1.28 – 4.69), p=0.005

**Higher Bleeding Risk** = age ≥ 85 years or eGFR < 60 mL/min

**Rivaroxaban Better**

**Placebo Better**

**Abbreviations**
- HR: Hazard Ratio
- DM: Diabetes Mellitus
- TIMI: Thrombolysis In Myocardial Infarction

**N=2603**

**N=3900**

0% 1% 2% 3% 4% 5% 6% 7% 8% 9% 10%

TIMI major bleeding at 3 Years (%)
Premature Treatment Discontinuation

Placebo  Rivaroxaban

<table>
<thead>
<tr>
<th></th>
<th>Diabetes N=2603</th>
<th>No Diabetes N=3901</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diabetes</strong></td>
<td>36.4%</td>
<td>35.9%</td>
</tr>
<tr>
<td><strong>No Diabetes</strong></td>
<td>31.0%</td>
<td>27.9%</td>
</tr>
</tbody>
</table>

**Study AE**

<table>
<thead>
<tr>
<th></th>
<th>Diabetes N=2603</th>
<th>No Diabetes N=3901</th>
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</thead>
<tbody>
<tr>
<td><strong>Diabetes</strong></td>
<td>3%</td>
<td>8%</td>
</tr>
<tr>
<td><strong>No Diabetes</strong></td>
<td>5%</td>
<td>4%</td>
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**Subject Decision**

<table>
<thead>
<tr>
<th></th>
<th>Diabetes N=2603</th>
<th>No Diabetes N=3901</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diabetes</strong></td>
<td>20%</td>
<td>16%</td>
</tr>
<tr>
<td><strong>No Diabetes</strong></td>
<td>3%</td>
<td>7%</td>
</tr>
</tbody>
</table>

**Protocol/Physician**

<table>
<thead>
<tr>
<th></th>
<th>Diabetes N=2603</th>
<th>No Diabetes N=3901</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diabetes</strong></td>
<td>3%</td>
<td>4%</td>
</tr>
<tr>
<td><strong>No Diabetes</strong></td>
<td>7%</td>
<td>16%</td>
</tr>
</tbody>
</table>

**Admin/Other**

<table>
<thead>
<tr>
<th></th>
<th>Diabetes N=2603</th>
<th>No Diabetes N=3901</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diabetes</strong></td>
<td>3%</td>
<td>7%</td>
</tr>
<tr>
<td><strong>No Diabetes</strong></td>
<td>16%</td>
<td>16%</td>
</tr>
</tbody>
</table>
Primary Endpoint* in Patients With and Without Diabetes Mellitus

On Treatment

Overall Population

Diabetes

No

Yes

HR for primary endpoint

Rivaroxaban better

Placebo better

HR 0.75
95% CI 0.65-0.86

HR 0.68
95% CI 0.56-0.82

HR 0.85
95% CI 0.69-1.04

*p-interaction 0.12

*ALI, major amputation of a vascular cause, MI, ischemic stroke, CV death
Summary and Conclusions

• Subjects with PAD with DM have a different baseline risk with more HTN, CAD, CLI, lower eGFR and more clopidogrel use, and are at extremely high risk of adverse events of the heart, limb, and brain after LER

• The efficacy of rivaroxaban 2.5 mg BID was consistent regardless of DM status at baseline, however a higher rate of discontinuation among these patients may have attenuated the observed benefit (ITT)

• Risk of TIMI major bleeding was greater in DM vs no DM, possibly driven by different baseline risk associated with bleeding and/or the low rate of bleeding observed in DM patients randomized to placebo (on ASA+/−clopi)

• Additional analyses are planned to understand the impact of competing risks (e.g. hospitalizations, all-cause mortality) to foster optimal patient selection for intensive prevention therapy