Consistent Benefit of Rivaroxaban Early and Late after Lower Extremity Revascularization

Marc P. Bonaca MD MPH, Eike Sebastian Debus MD, PhD, Manesh R. Patel, MD, Mark R. Nehler, MD, Sonia S. Anand, MD, Connie N. Hess, MD, MHS, Judith Hsia MD, Michael Szarek, Jerrod Nelms, Eva Muehlhofer, MD, Lloyd P. Haskell, MD, MBA, Scott D. Berkowitz, MD, Rupert M. Bauersachs, MD

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VOYAGER PAD Primary Results

6,564 Patients with Symptomatic Lower Extremity PAD* (CLI or Claudication)
Undergoing Peripheral Revascularization
Started ≤ 10 days – actual 5 (2-7)

*PAD defined as:
- Ischemic symptoms (functional limitation, rest pain or ischemic ulceration) AND
- Imaging evidence of occlusion AND
- Abnormal ABI/TBI

All to receive standard of care including:
- Low dose aspirin
- Clopidogrel per investigator

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

Unplanned Index Limb Revascularization
HR 0.88 (0.79 – 0.99)
P=0.028
ARR 2.5%, NNT 40

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

Km(%) at 3 years
Questions in Implementation

- How early to start?
- Transition after DAPT at 30 or 90 days?
- How long to continue?
- Is the benefit consistent early and late after LER?

**Objective**

- To evaluate whether the benefit and risk of rivaroxaban is consistent early and late after lower extremity revascularization
Methods

• Prespecified analysis (Landmark) including primary & secondary outcomes overall and within the clopidogrel subgroup

• Outcomes adjudicated by a blinded CEC

• Primary analysis at 90 days (acute post revascularization period) and majority of clopidogrel use was completed by 90 days

• Efficacy – Intention to Treat
  • Primary composite of acute limb ischemia, major amputation of a vascular etiology, MI, ischemic stroke or CV death
  • Major adverse limb events – acute limb ischemia or major amputation of a vascular etiology
  • Acute limb ischemia

• Safety – On Treatment
  • Principal safety: TIMI major bleeding – safety scope/population

• Prespecified net clinical outcome – acute limb ischemia, major amputation of a vascular etiology, MI, ischemic stroke, CV death, or TIMI major bleeding in safety scope/population
Primary Endpoint

First 90 Days

- **Placebo**: 3.8%
- **Rivaroxaban**: 3.0%

HR 0.78 (0.60 – 1.02)

Days from Randomization

From day 91 through 3 Years

- **Placebo**: 16.1%
- **Rivaroxaban**: 14.3%

HR 0.87 (0.76 – 1.00)

Days from Randomization

P vs. constant HR 0.47
Primary Endpoint & TIMI major Bleeding

First 90 Days

- **Placebo**
  - KM (%): 3.8%
  - HR: 0.78
  - (0.60 – 1.02)

- **Rivaroxaban**
  - KM (%): 3.0%
  - ARR: 0.8%

From day 91 through 3 Years

- **Placebo**
  - KM (%): 16.1%
  - HR: 0.87
  - (0.76 – 1.00)

- **Rivaroxaban**
  - KM (%): 14.3%
  - ARR: 1.8%

**Placebo**

- KM (%): 0.29%
  - HR: 2.01
  - (0.90 – 4.47)

- KM (%): 1.58%
  - HR: 1.28
  - (0.82 – 1.99)

**Rivaroxaban**

- KM (%): 0.58%
  - HR: 1.28
  - (0.82 – 1.99)

- KM (%): 2.07%
  - HR: 1.28
  - (0.82 – 1.99)

**P vs. constant HR 0.47**

**ARR 0.8%**

**ARI 0.3%**

**ARR 1.8%**

**ARI 0.5%**
Net Clinical Benefit*

First 90 Days

<table>
<thead>
<tr>
<th>Days from Randomization</th>
<th>Placebo</th>
<th>Rivaroxaban</th>
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<tbody>
<tr>
<td>0</td>
<td>0.74</td>
<td>0.56 – 0.97</td>
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<tr>
<td>90</td>
<td>3.9%</td>
<td>2.9%</td>
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From day 91 through 3 Years

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<tr>
<th>Days from Randomization</th>
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<tr>
<td>90</td>
<td>0.82</td>
<td>0.70 – 0.96</td>
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<td>274</td>
<td>14.5%</td>
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</table>

*MI, ischemic stroke, ALI, major vascular amputation, CV death, TIMI major bleeding
MALE – Acute Limb Ischemia or Major Vascular Ampulation

First 90 Days

- Placebo: 2.5%
  - HR 0.55 (0.38 - 0.79)
- Rivaroxaban: 1.4%

From day 91 through 3 Years

- Placebo: 7.3%
  - HR 0.81 (0.66 - 0.99)
- Rivaroxaban: 6.0%

P vs. constant HR 0.06
Acute Limb Ischemia

**First 90 Days**

- **Placebo**: HR 0.48 (0.31 – 0.73)
- **Rivaroxaban**: HR 2.1%

**P vs. constant HR 0.059**

**From day 91 through 3 Years**

- **Placebo**: HR 0.75 (0.60 – 0.95)
- **Rivaroxaban**: HR 4.3%, 5.7%

HR 0.48, 0.75 (0.31 – 0.73, 0.60 – 0.95)
Benefit – Risk Consistent Regardless of DAPT

**With Clopidogrel**
- N=3313
- Primary Efficacy Endpoint: 16.0% ARR 2.3%
- Principal Safety Outcome: 2.7% ARI 0.4%

**Without Clopidogrel**
- N=3234
- Primary Efficacy Endpoint: 18.7% ARR 2.8%
- Principal Safety Outcome: 2.6% ARI 1.1%

Hiatt WR et al. Circulation 2020
Is DAPT Alone Enough for Early Limb Events?

With Clopidogrel
N=3313

DAPT Only
18.3%
16.0%

DAPT + Rivaroxaban
ARR 2.3%
ARI 0.4%
6:1 Benefit
Risk Ratio for Adding Rivaroxaban on top of DAPT

Bleeding Risk based on Duration of DAPT

Rivaroxaban Better Placebo Better

0.50 1.0 1.50
1.37
1.30
3.20
P-interaction 0.069

Hiatt WR et al. Circulation 2020
MALE and ALI in those Receiving DAPT – First 90 Days

**Acute Limb Ischemia**
- First 90 Days

DAPT 1.7%

**Acute Limb Ischemia or Major Amputation of a Vascular Etiology**
- First 90 Days

DAPT 2.0%
MALE and ALI in those Receiving DAPT – First 90 Days

**Acute Limb Ischemia at 90 Days**

- Rivaroxaban + DAPT: 0.7%
- DAPT: 1.7%

**HR 0.45**

**(0.25 – 0.83)**

**Acute Limb Ischemia or Major Amputation of a Vascular Etiology**

**First 90 Days**

- Rivaroxaban + DAPT: 0.9%
- DAPT: 2.0%

**HR 0.43**

**(0.22 – 0.84)**
Primary Outcome* and Acute Limb Ischemia Early and Late

**Primary Outcome** Overall

- **≤30 Days**
  - On top of DAPT: 0.87 (0.56 – 1.33)
  - On top of Aspirin Alone: 0.85 (0.75 – 0.96)

- **>30 Days**
  - P vs. constant HR 0.94

- **≤90 Days**
  - On top of DAPT: 0.78 (0.60 – 1.02)
  - On top of Aspirin Alone: 0.87 (0.76 – 1.00)

- **>90 Days**
  - P vs. constant HR 0.47

**Acute Limb Ischemia Overall**

- **≤30 Days**
  - On top of DAPT: 0.45 (0.24 – 0.85)
  - P-interaction 0.93

- **>30 Days**
  - P vs. constant HR 0.18

- **≤90 Days**
  - On top of DAPT: 0.48 (0.31 – 0.73)
  - P vs. constant HR 0.059

- **>90 Days**
  - P vs. constant HR 0.71 (0.57 – 0.88)

**Rivaroxaban Better**

**Placebo Better**

*acute limb ischemia, major amputation of a vascular etiology, myocardial infarction, ischemic stroke, or CV death*
Summary

After LER, rivaroxaban 2.5 mg twice daily added to antiplatelet therapy

- Reduces MACE and MALE and increases bleeding but with an overall favorable benefit-risk profile
- This favorable benefit-risk profile is present both early and late after LER
- Rates of acute limb ischemia and major amputation of vascular etiology are high early LER despite DAPT (2%)
- Rivaroxaban reduced this risk when started within 10 days of LER (~50% within 5 days in trial) after LER by ~50%
Conclusions

• VOYAGER PAD and other contemporary datasets (e.g. BEST CLI) demonstrate high rates of morbid limb complications after lower extremity revascularization for symptomatic PAD

• Rates of acute limb ischemia and amputation are high after LER despite the use of DAPT

• Rivaroxaban 2.5 mg twice daily reduces irreversible harm events of the heart limb and brain:
  • Early after LER
  • When added to aspirin alone or to DAPT
  • In chronic PAD (including mortality & amputation benefit – COMPASS)

• In eligible patients, rivaroxaban 2.5 mg twice daily should be started early after LER and continued long-term regardless of DAPT