VOYAGER PAD

Vascular Outcomes Study of ASA Along with Rivaroxaban in Endovascular or Surgical Limb Revascularizations for Peripheral Artery Disease


American College of Cardiology Virtual Scientific Sessions 2020
Late-Breaking Clinical Trial
March 28, 2020
Disclosures

VOYAGER PAD was funded by Bayer & Janssen

Grant support to CPC Clinical Research from:
Amgen, Aralez, AstraZeneca, Bayer, Janssen, Merck, Novo Nordisk, Pfizer, Sanofi
**Background**

**Risk in Patients Undergoing Peripheral Revascularization**

- N=393,017
- Cumulative Incidence
- Years from Index Revascularization
- “Acute” Post Revascularization
- “Stable” Phase
- 4x risk of ALI
- Long-term vs. no Revascularization
- Major Adverse Limb Events

**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
Background

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.

DAPT with Aspirin and Clopidogrel
Increased GUSTO bleeding
HR 2.84 (1.32 – 6.08)

Full Intensity Oral anticoagulation
Increased risk of Hemorrhagic Stroke
HR 3.48 (1.14 – 10.60)

Index-graft occlusion, revascularization, major amputation, or death
HR 0.98
(95% CI 0.78 – 1.23), P=NS

Graft Occlusions
HR 0.95
(95% CI 0.82 – 1.11), P=NS
Objectives

In PAD patients undergoing lower extremity revascularization for ischemic symptoms:

• Test whether rivaroxaban 2.5 mg twice daily added to low dose aspirin reduces the risk of major adverse limb and cardiovascular events compared to aspirin alone

• To evaluate the safety of rivaroxaban 2.5 mg twice daily added to low dose aspirin compared to aspirin alone
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

NCT02504216

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

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

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)
Outcomes

**Efficacy**

**Primary:** acute limb ischemia (ALI), major amputation for vascular cause (amputation), myocardial infarction (MI), ischemic stroke or CV death

**Secondary (hierarchical):**
1. ALI, amputation, MI, ischemic stroke or **coronary heart death**
2. Unplanned index limb revascularization for ischemia
3. **Vascular hospitalization** for a coronary or peripheral event of thrombotic nature
4. ALI, amputation, MI, ischemic stroke or **all-cause mortality**
5. ALI, amputation, MI, **all stroke** or CV death
6. All-cause mortality
7. Venous thromboembolism

**Safety**

**Principal:** TIMI major bleeding

**Secondary:** ISTH major bleeding, BARC 3b or above

*CPC Clinical Events Committee (CEC) adjudicated all efficacy and safety events*
Trial Organization

Executive Committee
William R. Hiatt (Chair)          Rupert M. Bauersachs (Co-Chair)
Marc P. Bonaca                   Sonia S. Anand               Manesh R. Patel
Eike Sebastian Debus            Mark R. Nehler              Fabrizio Fanelli
Lloyd P. Haskell                Scott D. Berkowitz

CPC Clinical Research
Warren H. Capell (ICAC Chair), Jennifer Armstrong (ICAC Member), Natalia Glebova, (ICAC Member), Connie N. Hess (ICAC Member), Mori Krantz (ICAC Member), Cecilia Low-Wang (ICAC Member), Lisa Cox (Executive Project Manager), Nicole Jaeger (Project Manager), Robin White (Director, Biostatistics and Programming), and Lihong Diao (Biostatistician).

Sponsors: Bayer & Janssen
Scott D. Berkowitz, Lloyd Haskell, Eva Muehlhofer, James Hung, Aneta Woroniecka-Osio MD, Uma Balasubramanian, Juliette Dehay, Alexandra Kley, Claudia Vogt, Akos Ferenc Pap

Independent Data Monitoring Committee
John Dormandy (Chair)*, Joshua Beckman (Chair), Scott Kinlay, Robert McLafferty, Robin Roberts, (Statistician), and William Robinson.

*Deceased
<table>
<thead>
<tr>
<th>Country</th>
<th>Lead Investigator(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Argentina</td>
<td>R. Diaz</td>
</tr>
<tr>
<td>Austria</td>
<td>M. Brodmann</td>
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<tr>
<td>Belgium</td>
<td>F. Vermassen</td>
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<tr>
<td>Brazil</td>
<td>D. Brasil</td>
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<tr>
<td>Bulgaria</td>
<td>V. Chervenkoff</td>
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<tr>
<td>Canada</td>
<td>D. Szalay</td>
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<tr>
<td>Czech Republic</td>
<td>K. Roztocil</td>
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<td>China</td>
<td>W. Fu / Z. Shi</td>
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<td>H. Sillesen</td>
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<td>A. Bura-Rivière</td>
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<tr>
<td>Germany</td>
<td>D. Scheinert (Co-Chair)</td>
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<td>L. Matyas</td>
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<td>C. Rabbia</td>
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<td>M. Antonella Ruffino</td>
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<tr>
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<td>D. Choi</td>
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<td>Spain</td>
<td>V. Riambau Alonso</td>
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<td>L. Norgren</td>
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<td>Switzerland</td>
<td>I. Baumgartner</td>
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<td>S. Shen Wang</td>
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<td>P. Mutirangura</td>
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<td>I. Gudz</td>
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<td>United Kingdom</td>
<td>G. Hamilton</td>
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<tr>
<td>United States</td>
<td>A. Hirsch (Co-Chair)*</td>
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<td></td>
<td>R. Powell (Co-Chair)</td>
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<td></td>
<td>J. Chung</td>
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<td></td>
<td>J. Kittelson (Biostatistician)</td>
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<td></td>
<td>J. Mills</td>
</tr>
<tr>
<td></td>
<td>J. Mustapha</td>
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<tr>
<td></td>
<td>F. Saab</td>
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</tbody>
</table>

*Deceased
Global Enrollment

6,564 patients randomized at 534 sites in 34 countries between 7/2015 – 1/2018

Brazil: 185
Canada: 170
China: 211
United States: 524
Russia: 188
Germany: 594
United Kingdom: 129
France: 107
Portugal: 75
Spain: 96
Switzerland: 91
Argentina: 299

Belgium: 126
Netherlands: 78
Poland: 168
Sweden: 42
Finland: 17
Czech Republic: 243
Estonia: 9
Latvia: 203
Slovakia: 126
Lithuania: 84

Hungary: 261
Ukraine: 299
Bulgaria: 737
Romania: 214
South Korea: 148
Japan: 459
Taiwan: 76
Thailand: 67

Czech Republic: 126
Austria: 212
Italy: 184
Sweden: 42
Denmark: 78

Argentina: 299

Serbia: 68
Sweden: 42
Poland: 168
Germany: 594
United States: 524
Russia: 188
China: 211
Brazil: 185
Canada: 170

CPC

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Disposition

6,772 Patients Enrolled

Not Randomized = 208
Inclusion/Exclusion 167
Subject decision 29
Adverse event 2
Physician decision 1
Other 9

6,564 Patients Randomized

Inclusion/Exclusion 167
Subject decision 29
Adverse event 2
Physician decision 1
Other 9

Rivaroxaban
N=3286

Premature Drug Discontinuation = 1080 (33.2%)
14.2% Annualized

Withdrawal of Consent = 32 (0.97%)
0.42% Annualized
Vital status unknown = 8 (0.24%)

Lost to Follow up = 3 (0.09%)

Vital Status Known = 3275 (99.7%)

Analyzed
ITT = 3286 (100%)
Safety = 3256 (99.1%)

Placebo
N=3278

Premature Drug Discontinuation = 1011 (31.1%)
13.2% Annualized

Withdrawal of Consent = 37 (1.13%)
0.48% Annualized
Vital status unknown = 12 (0.37%)

Lost to Follow up = 3 (0.09%)

Vital Status Known = 3263 (99.5%)

Analyzed
ITT = 3278 (100%)
Safety = 3248 (99.1%)

Median Follow-up
28 Months

Complete primary efficacy and principal safety outcome ascertainment in 98.8% of potential patient-years of follow up
### Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristics at Randomization</th>
<th>Rivaroxaban 2.5 mg twice daily + aspirin</th>
<th>Placebo + aspirin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=3286 %</td>
<td>N=3278 %</td>
</tr>
<tr>
<td>Age, Yrs Median</td>
<td>67%</td>
<td>67%</td>
</tr>
<tr>
<td>Female</td>
<td>26%</td>
<td>26%</td>
</tr>
<tr>
<td>Caucasian</td>
<td>81%</td>
<td>81%</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>40%</td>
<td>40%</td>
</tr>
<tr>
<td>Current Smoking</td>
<td>35%</td>
<td>35%</td>
</tr>
<tr>
<td>COPD</td>
<td>11%</td>
<td>11%</td>
</tr>
<tr>
<td>eGFR &lt; 60 ml/min/1.73m²</td>
<td>20%</td>
<td>20%</td>
</tr>
<tr>
<td>Coronary Artery Disease</td>
<td>32%</td>
<td>31%</td>
</tr>
<tr>
<td>Prior MI</td>
<td>11%</td>
<td>11%</td>
</tr>
<tr>
<td>Known Carotid Stenosis</td>
<td>9%</td>
<td>9%</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>51%</td>
<td>51%</td>
</tr>
<tr>
<td>Statin</td>
<td>79%</td>
<td>81%</td>
</tr>
<tr>
<td>ACEi or ARB</td>
<td>64%</td>
<td>63%</td>
</tr>
</tbody>
</table>

\( P > 0.05 \) for all comparisons
# PAD & Procedural Characteristics

<table>
<thead>
<tr>
<th>Characteristics at Randomization</th>
<th>Rivaroxaban 2.5 mg twice daily + aspirin N=3286</th>
<th>Placebo + aspirin N=3278</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Prior Peripheral Artery Disease History</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of Claudication</td>
<td>95</td>
<td>96</td>
</tr>
<tr>
<td>History of Revascularization</td>
<td>36</td>
<td>35</td>
</tr>
<tr>
<td>History of Amputation</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Ankle Brachial Index, Median (IQR)</td>
<td>0.56 (0.42 – 0.67)</td>
<td>0.56 (0.42 – 0.67)</td>
</tr>
<tr>
<td><em>Indication for Revascularization</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Critical limb ischemia</td>
<td>23</td>
<td>24</td>
</tr>
<tr>
<td>Claudication</td>
<td>77</td>
<td>76</td>
</tr>
<tr>
<td><em>Type of Revascularization</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgical</td>
<td>35</td>
<td>35</td>
</tr>
<tr>
<td>Endovascular or Hybrid</td>
<td>66</td>
<td>65</td>
</tr>
<tr>
<td>Days from Procedure to Randomization, Median (IQR)</td>
<td>5 (2 – 7)</td>
<td>5 (2 – 7)</td>
</tr>
</tbody>
</table>

*P* > 0.05 for all comparisons
Primary Endpoint

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

Cumulative Incidence (KM%)

Placebo
Rivaroxaban

HR 0.85
95% CI 0.76 – 0.96
P=0.0085

19.9%
17.3%
Primary Endpoint

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

Cumulative Incidence (KM%)

Placebo
Rivaroxaban

HR 0.85
95% CI 0.76 – 0.96
P=0.0085

6 Months
ARR 1.5%
NNT 65

1 Year
ARR 2.0%
NNT 50

3 Year
ARR 2.6%
NNT 39

19.9%
17.3%

ARR – absolute risk reduction, NNT number needed to treat
## Primary Endpoint & Components

<table>
<thead>
<tr>
<th></th>
<th>KM% 3 Years (n)</th>
<th>KM% 3 Years (n)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rivaroxaban N=3286</td>
<td>Placebo N=3278</td>
<td></td>
</tr>
<tr>
<td><strong>Primary Efficacy Outcome</strong></td>
<td>17.3</td>
<td>19.9</td>
<td>0.85</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.76 – 0.96)</td>
</tr>
<tr>
<td><strong>Acute Limb Ischemia</strong></td>
<td>5.24</td>
<td>7.74</td>
<td>0.67</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.55 – 0.82)</td>
</tr>
<tr>
<td><strong>Major Vascular Amputation</strong></td>
<td>3.42</td>
<td>3.87</td>
<td>0.89</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.68 – 1.16)</td>
</tr>
<tr>
<td><strong>Ischemic Stroke</strong></td>
<td>2.70</td>
<td>3.01</td>
<td>0.87</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.63 – 1.19)</td>
</tr>
<tr>
<td><strong>Myocardial Infarction</strong></td>
<td>4.55</td>
<td>5.22</td>
<td>0.88</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.70 – 1.12)</td>
</tr>
<tr>
<td><strong>CV Death</strong></td>
<td>7.05</td>
<td>6.43</td>
<td>1.14</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.93 – 1.40)</td>
</tr>
</tbody>
</table>
Secondary Outcomes*

*Presented in order of hierarchy from left to right

MI, Ischemic Stroke, CHD, ALI, Amp
Unplanned Limb Revacularization for Ischemia Vascular Hosp. for a Coronary or Peripheral Thrombotic Event
MI, Ischemic Stroke, ALI, Amp, All Cause Mortality
MI, All Stroke, CV Death, ALI, Amp Mortality VTE

Cumulative Incidence (KM%) at 3 years

Placebo
Rivaroxaban

HR 0.80
(0.71 – 0.91)
P=0.0008
ARR 3.52

HR 0.88
(0.79 – 0.99)
P=0.028
ARR 2.48

HR 0.72
(0.62 – 0.85)
P=0.0001
ARR 3.38

HR 0.89
(0.79 – 0.99)
P=0.0289
ARR 2.59

HR 0.86
(0.76 – 0.96)
P=0.0103
ARR 2.63

HR 1.08
(0.92 – 1.27)
P=0.3360

HR 0.61
(0.37 – 1.00)
P=0.0469

Nominal, due to position in hierarchy

Placebo
Rivaroxaban

433 528
14.7% 18.2%

*Presented in order of hierarchy from left to right
Secondary Outcomes*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Placebo</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR</td>
<td>0.80</td>
<td>0.88</td>
</tr>
<tr>
<td>CI</td>
<td>(0.71 – 0.91)</td>
<td>(0.79 – 0.99)</td>
</tr>
<tr>
<td>P</td>
<td>0.0008</td>
<td>0.028</td>
</tr>
<tr>
<td>ARR</td>
<td>3.52</td>
<td>2.48</td>
</tr>
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</table>

*Presented in order of hierarchy from left to right

Cumulative Incidence (KM%) at 3 years

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI, Ischemic Stroke, CHD, ALI, Amp</td>
<td>14.7%</td>
<td>18.2%</td>
</tr>
<tr>
<td>Unplanned Limb Revascularization for Ischemia</td>
<td>20.0%</td>
<td>22.5%</td>
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<tr>
<td>Vascular Hosp. for a Coronary or Peripheral Thrombotic Event</td>
<td>8.7%</td>
<td>12.1%</td>
</tr>
<tr>
<td>MI, Ischemic Stroke, ALI, Amp, All Cause Mortality</td>
<td>20.6%</td>
<td>23.2%</td>
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<tr>
<td>MI, All Stroke, CV Death, ALI, Amp</td>
<td>17.5%</td>
<td>20.1%</td>
</tr>
<tr>
<td>Mortality</td>
<td>11.1%</td>
<td>10.9%</td>
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</table>

HR 0.80 (0.71 – 0.91) P=0.0008 ARR 3.52
HR 0.88 (0.79 – 0.99) P=0.028 ARR 2.48
HR 0.72 (0.62 – 0.85) P=0.0001 ARR 3.38
HR 0.89 (0.79 – 0.99) P=0.0289 ARR 2.59
HR 0.86 (0.76 – 0.96) P=0.0103 ARR 2.63
HR 1.08 (0.92 – 1.27) P=0.3360 ARR 2.59
HR 0.61 (0.37 – 1.00) P=0.0469 ARR 2.63
# Primary Efficacy Outcome in Selected Subgroups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Rivaroxaban 2.5 mg bid plus ASA daily n/N (%)</th>
<th>Placebo bid plus ASA daily n/N (%)</th>
<th>HR (95% CI)</th>
<th>P-interaction</th>
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<tbody>
<tr>
<td><strong>All subjects</strong></td>
<td></td>
<td></td>
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<tr>
<td>Age</td>
<td></td>
<td></td>
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<tr>
<td>&lt; 75</td>
<td>15.0</td>
<td>17.0</td>
<td>0.86 (0.75, 0.98)</td>
<td>0.8314</td>
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<tr>
<td>≥ 75</td>
<td>17.4</td>
<td>21.0</td>
<td>0.82 (0.64, 1.05)</td>
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<tr>
<td>Sex</td>
<td></td>
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</tr>
<tr>
<td>Male</td>
<td>15.4</td>
<td>18.4</td>
<td>0.82 (0.71, 0.94)</td>
<td>0.2385</td>
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<tr>
<td>Female</td>
<td>15.7</td>
<td>16.2</td>
<td>0.97 (0.76, 1.23)</td>
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</tr>
<tr>
<td>Region</td>
<td></td>
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<tr>
<td>North America</td>
<td>18.4</td>
<td>19.3</td>
<td>0.95 (0.67, 1.33)</td>
<td>0.2286</td>
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<tr>
<td>Western Europe</td>
<td>12.9</td>
<td>18.4</td>
<td>0.67 (0.53, 0.84)</td>
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<tr>
<td>Eastern Europe</td>
<td>16.4</td>
<td>17.6</td>
<td>0.92 (0.76, 1.11)</td>
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<tr>
<td>Asia Pacific</td>
<td>13.3</td>
<td>15.2</td>
<td>0.88 (0.63, 1.23)</td>
<td></td>
</tr>
<tr>
<td>South America</td>
<td>20.2</td>
<td>19.9</td>
<td>1.04 (0.70, 1.56)</td>
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<tr>
<td>eGFR (ml/min/1.73m²)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 60</td>
<td>19.7</td>
<td>21.9</td>
<td>0.90 (0.71, 1.15)</td>
<td>0.6177</td>
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<td>≥ 60</td>
<td>14.4</td>
<td>16.6</td>
<td>0.85 (0.73, 0.97)</td>
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<tr>
<td>Diabetes mellitus</td>
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<td>Yes</td>
<td>18.9</td>
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<tr>
<td>No</td>
<td>13.2</td>
<td>16.5</td>
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<tr>
<td>Coronary Artery Disease</td>
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<td>Yes</td>
<td>17.4</td>
<td>21.7</td>
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<td>Critical Limb Ischemia</td>
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<tr>
<td>Yes</td>
<td>20.9</td>
<td>24.4</td>
<td>0.85 (0.69, 1.05)</td>
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<tr>
<td>No</td>
<td>13.8</td>
<td>15.8</td>
<td>0.86 (0.74, 0.99)</td>
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<td>Qualifying Procedure</td>
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<tr>
<td>Surgical</td>
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<td>21.9</td>
<td>0.79 (0.66, 0.95)</td>
<td>0.2896</td>
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<tr>
<td>Endovascular</td>
<td>14.2</td>
<td>15.7</td>
<td>0.90 (0.77, 1.05)</td>
<td></td>
</tr>
</tbody>
</table>
**Principal Safety Outcomes**

- **TIMI major**
  - Placebo: 0.8% (ARI 0.27% / year, NNH 118)
  - Rivaroxaban: 1.8% (ARI 0.60% / year, NNH 125)
- **TIMI minor**
  - Placebo: 0.0% (ARI 0.0% / year, NNH 0)
  - Rivaroxaban: 0.6% (ARI 0.2% / year, NNH 167)
- **BARC 3b or Greater**
  - Placebo: 0.0% (ARI 0.0% / year, NNH 0)
  - Rivaroxaban: 0.6% (ARI 0.2% / year, NNH 167)

**Secondary Safety Outcomes**

- **TIMI major**
  - Placebo: 1.9% (HR 1.43, 0.97 – 2.10, P=0.0695)
  - Rivaroxaban: 0.9% (HR 0.78, 0.38 – 1.61, P=0.50)
- **TIMI minor**
  - Placebo: 1.0% (HR 1.02, 0.33 – 3.15, P=0.98)
  - Rivaroxaban: 1.2% (HR 0.91, 0.47 – 1.76, P=0.79)
- **BARC 3b or Greater**
  - Placebo: 1.2% (HR 1.50, 0.95 – 2.37, P=0.078)
  - Rivaroxaban: 1.4% (HR 1.42, 1.10 – 1.84, P=0.0068)
- **BARC 2 or Greater**
  - Placebo: 1.0% (HR 1.29, 0.95 – 1.76, P=0.098)

**Notes**

- **ARI** – absolute risk increase
- **NNH** – number needed to harm
Safety

**Principal Safety Outcome**

- **TIMI major ICH Fatal ICH or Fatal BARC 3b or Greater**  
  - **HR 1.43 (0.97 – 2.10) P=0.0695**
  - **HR 0.78 (0.38 – 1.61) P=0.50**
  - **HR 1.02 (0.33 – 3.15) P=0.98**
  - **HR 0.91 (0.47 – 1.76) P=0.79**

**Secondary Safety Outcomes**

- **TIMI minor**  
  - **HR 1.50 (0.95 – 2.37) P=0.078**
  - **HR 1.29 (0.95 – 1.76) P=0.098**
  - **HR 1.42 (1.10 – 1.84) P=0.0068**

**Cumulative Incidence (KM%) at 3 years**

- **ARI 0.8%**  
  - **NNH 125**
- **ARI 0.27% / year**

**ARI 1.8%**  
- **ARI 0.60% / year**

**ARI** – absolute risk increase, **NNH** number needed to harm
Principal Safety Outcome in Selected Subgroups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Rivaroxaban 2.5 mg bid plus ASA daily n/N (%)</th>
<th>Placebo bid plus ASA daily n/N (%)</th>
<th>HR (95% CI)</th>
<th>P-Interaction</th>
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</thead>
<tbody>
<tr>
<td>All subjects</td>
<td>1.9</td>
<td>1.4</td>
<td>1.43 (0.97, 2.10)</td>
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</tr>
<tr>
<td>Age</td>
<td></td>
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</tr>
<tr>
<td>&lt; 75</td>
<td>1.8</td>
<td>1.1</td>
<td>1.60 (1.01, 2.55)</td>
<td>0.3807</td>
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<tr>
<td>≥ 75</td>
<td>2.4</td>
<td>2.3</td>
<td>1.11 (0.55, 2.26)</td>
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</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Male</td>
<td>1.9</td>
<td>1.5</td>
<td>1.35 (0.87, 2.10)</td>
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<tr>
<td>Female</td>
<td>1.8</td>
<td>1.1</td>
<td>1.79 (0.78, 4.09)</td>
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<tr>
<td>Region</td>
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<tr>
<td>North America</td>
<td>2.4</td>
<td>0.9</td>
<td>2.65 (0.70, 9.99)</td>
<td>0.9858</td>
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<tr>
<td>Western Europe</td>
<td>2.1</td>
<td>1.7</td>
<td>1.26 (0.64, 2.48)</td>
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<tr>
<td>Eastern Europe</td>
<td>0.9</td>
<td>0.9</td>
<td>1.10 (0.49, 2.50)</td>
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<tr>
<td>Asia Pacific</td>
<td>4.0</td>
<td>2.9</td>
<td>1.41 (0.71, 2.81)</td>
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<tr>
<td>South America</td>
<td>1.7</td>
<td>0.4</td>
<td>3.95 (0.44, 35.38)</td>
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<tr>
<td>eGFR (ml/min/1.73m²)</td>
<td></td>
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<td></td>
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<tr>
<td>&lt; 60</td>
<td>3.2</td>
<td>1.8</td>
<td>1.86 (0.92, 3.79)</td>
<td>0.3726</td>
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<tr>
<td>≥ 60</td>
<td>1.5</td>
<td>1.2</td>
<td>1.27 (0.79, 2.05)</td>
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<tr>
<td>Diabetes mellitus</td>
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<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2.4</td>
<td>1.0</td>
<td>2.45 (1.28, 4.69)</td>
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<tr>
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<td>1.6</td>
<td>1.6</td>
<td>1.01 (0.61, 1.66)</td>
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<tr>
<td>Coronary artery disease</td>
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<td></td>
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<tr>
<td>Yes</td>
<td>2.4</td>
<td>1.1</td>
<td>2.24 (1.10, 4.56)</td>
<td>0.1245</td>
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<tr>
<td>No</td>
<td>1.7</td>
<td>1.5</td>
<td>1.15 (0.72, 1.84)</td>
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</tr>
<tr>
<td>Critical Limb Ischemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2.0</td>
<td>1.6</td>
<td>1.37 (0.64, 2.94)</td>
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</tr>
<tr>
<td>No</td>
<td>1.9</td>
<td>1.3</td>
<td>1.47 (0.94, 2.30)</td>
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<tr>
<td>Qualifying procedure</td>
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<tr>
<td>Surgical</td>
<td>1.2</td>
<td>1.1</td>
<td>1.02 (0.47, 2.19)</td>
<td>0.3155</td>
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<tr>
<td>Endovascular</td>
<td>2.3</td>
<td>1.5</td>
<td>1.60 (1.02, 2.51)</td>
<td></td>
</tr>
</tbody>
</table>

23
First Events Prevented / Caused for 10,000 Patients Treated* for 1 Year

Primary Efficacy Outcome
- Acute Limb Ischemia: 
  -20 (53 – 12)
- Major Amputation of Vascular Etiology: 
  -20 (53 – 12)
- Myocardial Infarction: 
  -42 (84 – 1)
- Ischemic Stroke: 
  -19 (50 – 13)
- Cardiovascular Death: 
  -10 (48 – 28)

Principality Safety Outcome
- Intracranial Hemorrhage: 
  -6 (22 – 11)
- Fatal Bleeding: 
  0 (10 – 11)

*: Efficacy and safety on-treatment

Favors Rivaroxaban 2.5 mg twice daily plus aspirin
Favors aspirin monotherapy
Summary & Conclusion

• In symptomatic PAD after revascularization, ~1 in 5 have acute limb ischemia, major amputation of vascular etiology, MI, ischemic stroke or cardiovascular death at 3 years

• In this population and setting, rivaroxaban 2.5 mg twice daily with aspirin compared to aspirin alone:

  ✓ **Significantly reduces this risk** with…
  • **Benefits apparent early and continued over time**
  • **Consistent benefit across major subgroups**
  • **Broad benefits including reductions in unplanned index limb revascularization**

  ✓ **Increases bleeding**: in VOYAGER PAD, there was a numerical increase in TIMI major bleeding and significantly increased ISTH major bleeding but no excess in intracranial or fatal bleeding

  ✓ **Prevents ~6 times as many ischemic events relative to bleeds caused in PAD patients after revascularization**
Rivaroxaban in Peripheral Artery Disease after Revascularization


Slides for Download at:
https://cpcclinicalresearch.org/  @cpcresearch
Backup Slides
Designed as a PAD Intervention Study:

- **Population:** symptomatic lower extremity PAD undergoing intervention, without further enrichment for risk
  - 4-fold risk of ALI long-term vs no revascularization
  - ALI outcomes after hospitalization 15% disabled or dead

- **Setting:** post-intervention (particularly high risk for limb and bleeding complications)

- **Treatment:** rivaroxaban on top of standard of care, including clopidogrel

- **Primary efficacy outcome:** severe limb & cardiovascular events

- Enriched for polyvascular disease (e.g. CAD in ~66%)
- Broad definition of PAD (including asymptomatic low ABI)
- Stable setting
- MACE primary outcome
- Clopidogrel not allowed

---

### In PAD Subgroup

**Primary Endpoint MACE**

- HR 0.72
- (0.57-0.90)

**Safety**

- ISTH major bleeding
- HR 1.61
- (1.12 – 2.31)

---

Anand SA et al. Lancet 2017
Perspective

A regimen of rivaroxaban 2.5 mg twice daily added to aspirin reduces the risk of major adverse limb and cardiovascular outcomes from acute intervention to long-term secondary prevention.

N=393,017

“Acute” Post Revascularization

“Stable” Phase

Major Adverse Limb Events

MACE

Years from Index Revascularization

Cumulative Incidence
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)

- 181
(-269 to -94)

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

+ 29
(-2 to +60)

*Efficacy and safety on-treatment
Risk & Benefit Over Time

Primary endpoint composite of acute limb ischemia, major amputation of vascular cause, MI, ischemic stroke or CV death

TIMI major bleeding
Efficacy – Intention To Treat versus & Treatment

**Intention To Treat**

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALI</td>
<td>3.0%</td>
<td>2.0%</td>
</tr>
<tr>
<td>Amp</td>
<td>2.5%</td>
<td>2.2%</td>
</tr>
<tr>
<td>Ischemic Stroke</td>
<td>1.9%</td>
<td>1.7%</td>
</tr>
<tr>
<td>MI</td>
<td>1.0%</td>
<td>1.9%</td>
</tr>
<tr>
<td>CV Death</td>
<td>0.9%</td>
<td>1.7%</td>
</tr>
</tbody>
</table>

**On Treatment***

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALI</td>
<td>3.1%</td>
<td>1.9%</td>
</tr>
<tr>
<td>Amp</td>
<td>2.0%</td>
<td>1.0%</td>
</tr>
<tr>
<td>Ischemic Stroke</td>
<td>1.9%</td>
<td>1.0%</td>
</tr>
<tr>
<td>MI</td>
<td>1.7%</td>
<td>0.9%</td>
</tr>
<tr>
<td>CV Death</td>
<td>1.3%</td>
<td>1.3%</td>
</tr>
</tbody>
</table>

---

*includes events from randomization until 2 days following permanent drug discontinuation

*Placebo vs Rivaroxaban

**Risk Ratios**

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALI</td>
<td>0.64 (0.55 – 0.80)</td>
<td>0.80 (0.56 – 1.15)</td>
</tr>
<tr>
<td>Amp</td>
<td>0.87 (0.63 – 1.19)</td>
<td>0.80 (0.55 – 1.17)</td>
</tr>
<tr>
<td>Ischemic Stroke</td>
<td>0.87 (0.93 – 1.40)</td>
<td>0.80 (0.56 – 1.17)</td>
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<tr>
<td>MI</td>
<td>0.75 (0.56 – 1.00)</td>
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<tr>
<td>CV Death</td>
<td>0.92 (0.68 – 1.25)</td>
<td>0.92 (0.68 – 1.25)</td>
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</tbody>
</table>

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*includes events from randomization until 2 days following permanent drug discontinuation
Procedural Bleeding

Post-Procedural Bleeding Requiring Unplanned “Take Back” for Management

- Rivaroxaban plus Aspirin: 0.9%
- Aspirin Alone: 0.8%

Any Bleeding Associated with a Revascularization Procedure

- Rivaroxaban plus Aspirin: 2.3%
- Aspirin Alone: 2.2%
Medical Cost Reduction with Rivaroxaban versus Placebo Per Year

Medical costs of efficacy outcomes (primary + secondary)
Medical costs of major bleeding

Cost of rivaroxaban for 30-day supply = $470 (@25% discount = $352.5)
Most patients pay between $0 and $47 per month depending on health insurance plan
https://www.xarelto-us.com/xarelto-cost/co-pay-and-list-price

Total medical costs reduced = $21MM per 10,000 patient-years
Medical Cost Reduction with Rivaroxaban versus Placebo Per Year

Costs per 10,000 patient-years (2019 US$)

- **Rivaroxaban + aspirin**
  - Medical costs of efficacy outcomes (primary + secondary)
  - Medical costs of major bleeding
  - Total medical costs reduced = $22MM per 10,000 patient-years

- **Aspirin**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Cost per 10,000 patient-years</th>
<th>Reduction</th>
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</thead>
<tbody>
<tr>
<td>PAD, peripheral artery disease</td>
<td>$22.9MM</td>
<td>-$7.3MM</td>
</tr>
<tr>
<td>ALI, acute limb ischemia</td>
<td>$15.6MM</td>
<td></td>
</tr>
<tr>
<td>MI, myocardial infarction</td>
<td>$15.5MM</td>
<td></td>
</tr>
<tr>
<td><em>IS, ischemic stroke</em></td>
<td>$13.4MM</td>
<td>-$1.6MM</td>
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<tr>
<td><em>Vascular hospitalization</em></td>
<td>$11.8MM</td>
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<tr>
<td><em>Revascularization</em></td>
<td>$6.1MM</td>
<td>-$838K</td>
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<tr>
<td>VTE, venous thromboembolism</td>
<td>$5.3MM</td>
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<tr>
<td>Major Bleeding</td>
<td>$40.3MM</td>
<td>-$5.8MM</td>
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<tr>
<td>Vascular Hospitalization</td>
<td>$21.9MM</td>
<td>-$965K</td>
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<tr>
<td>Revascularization</td>
<td>$16.1MM</td>
<td>$579K</td>
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</table>

Cost of rivaroxaban for 30-day supply = $470 (@25% discount = $352.5)
Most patients pay between $0 and $47 per month depending on health insurance plan

https://www.xarelto-us.com/xarelto-cost/co-pay-and-list-price

PAD, peripheral artery disease; ALI, acute limb ischemia; MI, myocardial infarction; IS, ischemic stroke; Revasc, revascularization; Vas Hosp, vascular hospitalization; VTE, venous thromboembolism; WAC, wholesale acquisition cost.

* Hospitalization and emergency room related costs only
• Acute thrombotic occlusion of an artery threatening tissue loss
• “Time Is Muscle”
• Outcomes determined by time to acute reperfusion
• Reperfusion injury is a complication

1. Zeymer et al. EORP EU STEMI Registry 2019

Mortality at 1 year 8.1%\(^1\)
Recurrent MACE at 1 year 3.4%\(^1\)
HF at 1 year 7.4%\(^1\)

ALI

• Acute thrombotic occlusion of an artery threatening tissue loss
• “Time Is Muscle”
• Outcomes determined by time to acute reperfusion
• Reperfusion injury is a complication


Mortality at 1 year 12.1%\(^2\)
MACE 11.7%, Recurrent ALI 24% (1 yr) \(^2\)
Amputation at 1 year 27%\(^2\)