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

“Acute” Post Revascularization

“Stable” Phase

Major Adverse Limb Events

4x risk of ALI Long-term vs. no Revascularization

Cumulative Incidence

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

Hess…Hiatt et al. JACC 2020
Jones…Fowkes et al. Circulation 2017
Bonaca…Sabatine et al. JACC 2017
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.

Index-graft occlusion, revascularization, major amputation, or death

HR 0.98

(95% CI 0.78 – 1.23), P=NS

DAPT with Aspirin and Clopidogrel

Increased GUSTO 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)

Belch et al. Journal of Vascular Surgery. 2010

Dutch Bypass Oral anticoagulants or Aspirin (BOA) Study Group. Lancet. 2000
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.
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

Rivaroxaban 2.5 mg twice daily

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

Placebo

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

NCT02504216

*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)
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
## Steering Committee and National Lead Investigators

<table>
<thead>
<tr>
<th>Country</th>
<th>National Lead Investigators</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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<tr>
<td>China</td>
<td>W. Fu / Z. Shi</td>
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<tr>
<td>Denmark</td>
<td>H. Sillesen</td>
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<td>M. Venermo</td>
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<td>A. Bura-Rivière</td>
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<tr>
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<td>J. Baptiste Ricco</td>
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<td>H. Lawall</td>
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<td>L. Matyas</td>
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<td>C. Rabbia</td>
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<td>D. Krievins</td>
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<td>F. Moll</td>
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<td>A. Mansilh</td>
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<td>I. Koncar</td>
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<td>D. Choi</td>
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<td>V. Riambau Alonso</td>
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<td>L. Norgren</td>
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<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>A. Hirsch (Co-Chair)*</td>
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<td>R. Powell (Co-Chair)</td>
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<td>J. Chung</td>
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<td>J. Kittelson (Biostatistician)</td>
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<td></td>
<td>J. Mills</td>
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<tr>
<td></td>
<td>J. Mustapha</td>
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<td></td>
<td>F. Saab</td>
</tr>
</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
Poland: 168
Italy: 184
Belgium: 126
Sweden: 42
Czech Republic: 243
Hungary: 261
Netherlands: 78
Latvia: 203
Slovakia: 126
Russia: 737
Japan: 459
United Kingdom: 129
Austria: 212
France: 107
Portugal: 75
Spain: 96
Belgium: 126
Italy: 184
Switzerland: 91
Argentina: 299
Austria: 212
Hungary: 261
Ukraine: 299
Poland: 168

CPC

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Disposition

6,772 Patients Enrolled

6,564 Patients Randomized

Lost to Follow up = 3 (0.09%)

Not Randomized = 208
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%)

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>
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<tr>
<td>Caucasian</td>
<td>81</td>
<td>81</td>
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<tr>
<td>Diabetes Mellitus</td>
<td>40</td>
<td>40</td>
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<td>Current Smoking</td>
<td>35</td>
<td>35</td>
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<tr>
<td>COPD</td>
<td>11</td>
<td>11</td>
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<tr>
<td>eGFR &lt; 60 ml/min/1.73m²</td>
<td>20</td>
<td>20</td>
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<tr>
<td>Coronary Artery Disease</td>
<td>32</td>
<td>31</td>
</tr>
<tr>
<td>Prior MI</td>
<td>11</td>
<td>11</td>
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<tr>
<td>Known Carotid Stenosis</td>
<td>9</td>
<td>9</td>
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<tr>
<td>Clopidogrel</td>
<td>51</td>
<td>51</td>
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<tr>
<td>Statin</td>
<td>79</td>
<td>81</td>
</tr>
<tr>
<td>ACEi or ARB</td>
<td>64</td>
<td>63</td>
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</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><strong>Prior Peripheral Artery Disease History</strong></td>
<td></td>
<td></td>
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<tr>
<td>History of Claudication</td>
<td>95</td>
<td>96</td>
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<tr>
<td>History of Revascularization</td>
<td>36</td>
<td>35</td>
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<tr>
<td>History of Amputation</td>
<td>6</td>
<td>6</td>
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<tr>
<td>Ankle Brachial Index, Median (IQR)</td>
<td>0.56 (0.42 – 0.67)</td>
<td>0.56 (0.42 – 0.67)</td>
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<tr>
<td><strong>Indication for Revascularization</strong></td>
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<tr>
<td>Critical limb ischemia</td>
<td>23</td>
<td>24</td>
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<tr>
<td>Claudication</td>
<td>77</td>
<td>76</td>
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<tr>
<td><strong>Type of Revascularization</strong></td>
<td></td>
<td></td>
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<tr>
<td>Surgical</td>
<td>35</td>
<td>35</td>
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<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
Primary Endpoint

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

Cumulative Incidence (KM%)

- **Placebo**
  - 6 Months: ARR 1.5% NNT 65
  - 1 Year: ARR 2.0% NNT 50
  - 3 Year: ARR 2.6% NNT 39

- **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

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>
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</thead>
<tbody>
<tr>
<td></td>
<td>Rivaroxaban N=3286</td>
<td>Placebo N=3278</td>
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<tr>
<td><strong>Primary Efficacy Outcome</strong></td>
<td>17.3</td>
<td>19.9</td>
<td>0.85 (0.76 – 0.96)</td>
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<tr>
<td><strong>Acute Limb Ischemia</strong></td>
<td>5.24</td>
<td>7.74</td>
<td>0.67 (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 (0.68 – 1.16)</td>
</tr>
<tr>
<td><strong>Ischemic Stroke</strong></td>
<td>2.70</td>
<td>3.01</td>
<td>0.87 (0.63 – 1.19)</td>
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<td><strong>Myocardial Infarction</strong></td>
<td>4.55</td>
<td>5.22</td>
<td>0.88 (0.70 – 1.12)</td>
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<td><strong>CV Death</strong></td>
<td>7.05</td>
<td>6.43</td>
<td>1.14 (0.93 – 1.40)</td>
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</tbody>
</table>
Secondary Outcomes*

- MI, Ischemic Stroke, CHD, ALI, Amp
- Unplanned Limb Revascularization 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

- 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

*Presented in order of hierarchy from left to right

Placebo
Rivaroxaban

0%
5%
10%
15%
20%
25%

MI, Ischemic Stroke, CHD, ALI, Amp

14.7%
18.2%
433
528
Secondary Outcomes*

*Presented in order of hierarchy from left to right

![Graph showing cumulative incidence (KM%) at 3 years for different outcomes and treatments](image)

- **Placebo**
  - MI, Ischemic Stroke, CHD, ALI, Amp
  - HR 0.80 (0.71 – 0.91)
  - P=0.0008
  - ARR 3.52

- **Rivaroxaban**
  - MI, Ischemic Stroke, CHD, ALI, Amp
  - HR 0.88 (0.79 – 0.99)
  - P=0.028
  - ARR 2.48

- **Placebo**
  - Unplanned Limb Revascularization for Ischemia
  - HR 0.72 (0.62 – 0.85)
  - P=0.0001
  - ARR 2.59

- **Rivaroxaban**
  - Unplanned Limb Revascularization for Ischemia
  - HR 0.89 (0.79 – 0.99)
  - P=0.0289
  - ARR 2.63

- **Placebo**
  - Mortality
  - HR 0.86 (0.76 – 0.96)
  - P=0.0103
  - ARR 2.63

- **Rivaroxaban**
  - Mortality
  - HR 1.08 (0.92 – 1.27)
  - P=0.3360
  - ARR 2.59

- **Placebo**
  - VTE Nominal, due to position in hierarchy
  - HR 0.61 (0.37 – 1.00)
  - P=0.0469
  - ARR 2.63

* Cumulative Incidence (KM%) at 3 years

0% 5% 10% 15% 20% 25%

MI, Ischemic Stroke, CHD, ALI, Amp
Unplanned Limb Revascularization 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 Nominal, due to position in hierarchy

528433 655584 356262 679614 588514 297321 4125

*Presented in order of hierarchy from left to right
## 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>
</tr>
</thead>
<tbody>
<tr>
<td>All subjects</td>
<td>15.5</td>
<td>17.8</td>
<td>0.85 (0.76, 0.96)</td>
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<tr>
<td>Age</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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<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>
<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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<td>Female</td>
<td>15.7</td>
<td>16.2</td>
<td>0.97 (0.76, 1.23)</td>
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<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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<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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<td>Asia Pacific</td>
<td>13.3</td>
<td>15.2</td>
<td>0.88 (0.63, 1.23)</td>
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<td>South America</td>
<td>20.2</td>
<td>19.9</td>
<td>1.04 (0.70, 1.56)</td>
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<td>eGFR (ml/min/1.73m²)</td>
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<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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<tr>
<td>≥ 60</td>
<td>14.4</td>
<td>16.6</td>
<td>0.85 (0.73, 0.97)</td>
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<td>Diabetes mellitus</td>
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<td>Yes</td>
<td>18.9</td>
<td>19.8</td>
<td>0.94 (0.79, 1.11)</td>
<td>0.1588</td>
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<tr>
<td>No</td>
<td>13.2</td>
<td>16.5</td>
<td>0.79 (0.67, 0.93)</td>
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<td>Coronary Artery Disease</td>
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<tr>
<td>Yes</td>
<td>17.4</td>
<td>21.7</td>
<td>0.78 (0.64, 0.95)</td>
<td>0.2872</td>
</tr>
<tr>
<td>No</td>
<td>14.6</td>
<td>16.1</td>
<td>0.89 (0.77, 1.04)</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>20.9</td>
<td>24.4</td>
<td>0.85 (0.69, 1.05)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>13.8</td>
<td>15.8</td>
<td>0.86 (0.74, 0.99)</td>
<td></td>
</tr>
<tr>
<td>Qualifying Procedure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgical</td>
<td>17.9</td>
<td>21.9</td>
<td>0.79 (0.66, 0.95)</td>
<td>0.2896</td>
</tr>
<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>
Safety

**Principal Safety Outcome**

- **TIMI major**
  - **HR 1.43**
  - **(0.97 – 2.10)**
  - **P=0.0695**

**Secondary Safety Outcomes**

- **ARI** 0.8%
- **NNH** 125
- **ARI** 1.8%
- **ARI** 0.60% / year

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

- **2.7%**
- **1.9%**

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

**Principal Safety Outcome**

- TIMI major: 62% (Placebo) vs. 44% (Rivaroxaban) with HR 1.43 (0.97 – 2.10) P=0.0695
- ICH: 0.6% (Placebo) vs. 0.9% (Rivaroxaban) with HR 0.78 (0.38 – 1.61) P=0.50
- Fatal: 2% (Placebo) vs. 0.2% (Rivaroxaban) with HR 1.02 (0.33 – 3.15) P=0.98
- ICH or Fatal: 1.7% (Placebo) vs. 1.9% (Rivaroxaban) with HR 0.91 (0.47 – 1.76) P=0.79

**Secondary Safety Outcomes**

- ARI 0.8% (Placebo) vs. 1.8% (Rivaroxaban) with ARI 0.27% / year
- NNH 125
- TIMI minor: 46% (Placebo) vs. 31% (Rivaroxaban) with HR 1.50 (0.95 – 2.37) P=0.078
- BARC 3b or Greater: 3.9% (Placebo) vs. 2.9% (Rivaroxaban) with HR 1.29 (0.95 – 1.76) P=0.098
- ISTH major: 140 (Placebo) vs. 100 (Rivaroxaban) with HR 1.42 (1.10 – 1.84) P=0.0068

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

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>
</tr>
</thead>
<tbody>
<tr>
<td>All subjects</td>
<td>1.9</td>
<td>1.4</td>
<td>1.43 (0.97, 2.10)</td>
<td></td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</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>
</tr>
<tr>
<td>≥ 75</td>
<td>2.4</td>
<td>2.3</td>
<td>1.11 (0.55, 2.26)</td>
<td></td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1.9</td>
<td>1.5</td>
<td>1.35 (0.87, 2.10)</td>
<td>0.5974</td>
</tr>
<tr>
<td>Female</td>
<td>1.8</td>
<td>1.1</td>
<td>1.79 (0.78, 4.09)</td>
<td></td>
</tr>
<tr>
<td><strong>Region</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<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>
</tr>
<tr>
<td>Western Europe</td>
<td>2.1</td>
<td>1.7</td>
<td>1.26 (0.64, 2.48)</td>
<td></td>
</tr>
<tr>
<td>Eastern Europe</td>
<td>0.9</td>
<td>0.9</td>
<td>1.10 (0.49, 2.50)</td>
<td></td>
</tr>
<tr>
<td>Asia Pacific</td>
<td>4.0</td>
<td>2.9</td>
<td>1.41 (0.71, 2.81)</td>
<td></td>
</tr>
<tr>
<td>South America</td>
<td>1.7</td>
<td>0.4</td>
<td>3.95 (0.44, 35.38)</td>
<td></td>
</tr>
<tr>
<td><strong>eGFR (ml/min/1.73m²)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<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>
</tr>
<tr>
<td>≥ 60</td>
<td>1.5</td>
<td>1.2</td>
<td>1.27 (0.79, 2.05)</td>
<td></td>
</tr>
<tr>
<td><strong>Diabetes mellitus</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2.4</td>
<td>1.0</td>
<td>2.45 (1.28, 4.69)</td>
<td>0.0334</td>
</tr>
<tr>
<td>No</td>
<td>1.6</td>
<td>1.6</td>
<td>1.01 (0.61, 1.66)</td>
<td></td>
</tr>
<tr>
<td><strong>Coronary artery disease</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2.4</td>
<td>1.1</td>
<td>2.24 (1.10, 4.56)</td>
<td>0.1245</td>
</tr>
<tr>
<td>No</td>
<td>1.7</td>
<td>1.5</td>
<td>1.15 (0.72, 1.84)</td>
<td></td>
</tr>
<tr>
<td><strong>Critical Limb Ischemia</strong></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>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1.9</td>
<td>1.3</td>
<td>1.47 (0.94, 2.30)</td>
<td></td>
</tr>
<tr>
<td><strong>Qualifying procedure</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgical</td>
<td>1.2</td>
<td>1.1</td>
<td>1.02 (0.47, 2.19)</td>
<td>0.3155</td>
</tr>
<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>
First Events Prevented / Caused for 10,000 Patients Treated* for 1 Year

**Primary Efficacy Outcome**
- Acute Limb Ischemia: (-181) (-269 – -94)
- Major Amputation of Vascular Etiology: (-110) (-165 – -56)
- Myocardial Infarction: (-42) (-84 – -1)
- Ischemic Stroke: (-19) (-53 – 12)
- Cardiovascular Death: (-10) (-50 – 13)

**Principal 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

Marc P. Bonaca, M.D., M.P.H., Rupert M. Bauersachs, M.D.,
Sonia S. Anand, M.D., Eike S. Debus, M.D., Ph.D., Mark R. Nehler, M.D.,
Manesh R. Patel, M.D., Fabrizio Fanelli, M.D., Warren H. Capell, M.D.,
Lihong Diao, , Nicole Jaeger, , Connie N. Hess, M.D., M.H.S., Akos F. Pap, ,
John M. Kittelson, Ph.D., Ivan Gudz, M.D., Ph.D., Lajos Mátyás, M.D.,
Dainis K Krievins, M.D., Rafael Diaz, M.D., Marianne Brodmann, M.D.,
Eva Muehlhofer, M.D., Lloyd P. Haskell, M.D., Scott D. Berkowitz, M.D., and
William R. Hiatt, M.D.

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
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.
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

Events Prevented or Caused (n)

TIMI major bleeding

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

Days from Randomization

Events Prevented or Caused (n)
Efficacy – Intention To Treat versus & Treatment

**Intention To Treat**

<table>
<thead>
<tr>
<th>ALI</th>
<th>Amp</th>
<th>Ischemic Stroke</th>
<th>MI</th>
<th>CV Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.0%</td>
<td>2.0%</td>
<td>2.0%</td>
<td>2.2%</td>
<td>2.5%</td>
</tr>
</tbody>
</table>

**On Treatment***

<table>
<thead>
<tr>
<th>ALI</th>
<th>Amp</th>
<th>Ischemic Stroke</th>
<th>MI</th>
<th>CV Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.1%</td>
<td>1.9%</td>
<td>1.9%</td>
<td>1.7%</td>
<td>1.3%</td>
</tr>
</tbody>
</table>

*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)

<table>
<thead>
<tr>
<th>Option</th>
<th>Cost per 10,000 patient-years (2019 US$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivaroxaban + aspirin</td>
<td>$10,042</td>
</tr>
<tr>
<td>Aspirin</td>
<td>$12,146</td>
</tr>
</tbody>
</table>

## Medical costs of major bleeding

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

<table>
<thead>
<tr>
<th>Option</th>
<th>Cost per 10,000 patient-years (2019 US$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivaroxaban + aspirin</td>
<td>$22.9MM</td>
</tr>
<tr>
<td>Aspirin</td>
<td>$15.6MM</td>
</tr>
<tr>
<td><strong>Total medical costs reduced</strong></td>
<td>$21MM per 10,000 patient-years</td>
</tr>
</tbody>
</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

---

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

<table>
<thead>
<tr>
<th>Option</th>
<th>Cost per 10,000 patient-years (2019 US$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAD</td>
<td>-$2,104</td>
</tr>
<tr>
<td>ALI</td>
<td>-$7.3MM</td>
</tr>
<tr>
<td>Major Amputation</td>
<td>-$1.6MM</td>
</tr>
<tr>
<td>MI</td>
<td>-$1.6MM</td>
</tr>
<tr>
<td>IS</td>
<td>-$838K</td>
</tr>
<tr>
<td>Revasc</td>
<td>-$4.5MM</td>
</tr>
<tr>
<td>Vas Hosp</td>
<td>-$5.8MM</td>
</tr>
<tr>
<td>Major Bleeding</td>
<td>+$579K</td>
</tr>
</tbody>
</table>
Medical Cost Reduction with Rivaroxaban versus Placebo Per Year

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

$22.9MM
$15.6MM
$15.5MM
$13.9MM
$13.4MM
$11.8MM
$6.1MM
$5.3MM
$40.3MM
$35.8MM
$21.9MM
$16.1MM
$2.5MM
$1.5MM
$1.4MM
$2.0MM
$6.1MM
$5.3MM
$40.3MM
$35.8MM
$21.9MM
$16.1MM
$2.5MM
$1.5MM
$1.4MM
$2.0MM
$6.1MM
$5.3MM
$40.3MM
$35.8MM
$21.9MM
$16.1MM
$2.5MM
$1.5MM
$1.4MM
$2.0MM
$6.1MM
$5.3MM
$40.3MM
$35.8MM
$21.9MM
$16.1MM
$2.5MM
$1.5MM
$1.4MM
$2.0MM

Cost per patient-year (2019 US$)

Rivaroxaban + aspirin
Aspirin

$9,991
$12,249
$12,392
$201
$143
$2,000
$4,000
$6,000
$8,000
$10,000
$12,000
$14,000

$10,192
$12,392

$22.9MM
$15.6MM
$15.5MM
$13.9MM
$13.4MM
$11.8MM
$6.1MM
$5.3MM
$40.3MM
$35.8MM
$21.9MM
$16.1MM
$2.5MM
$1.5MM
$1.4MM
$2.0MM

Total medical costs reduced = $22MM per 10,000 patient-years

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

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.
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 8.1%¹

Recurrent MACE at 1 year 3.4%¹

HF at 1 year 7.4%¹

1. Zeymer et al. EORP EU STEMI Registry 2019

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