Rivaroxaban Reduces Major Cardiovascular And Limb Events In Patients With The High-risk Triad Of Chronic Kidney Disease, Peripheral Artery Disease And Recent Lower Extremity Revascularization: Insights From VOYAGER PAD


CPC Clinical Research, University of Colorado; McMaster University, Duke University; Universitatsklinikum Hamburg Eppendorf Universitäres Herzzentrum, Klinikum Darmstadt, Bayer, Janssen
Disclosures

VOYAGER was funded by Bayer and Janssen

CPC Clinical Research receives research grants from Alnylam, Amgen, Arca, AstraZeneca, Bayer, CellResearch, Eidos, Janssen, NovoNordisk, Osiris, Terumo
Background

Despite high risk, prior to VOYAGER PAD no anti-thrombotic strategy had demonstrated efficacy for reducing major adverse limb and CV 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

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

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)

Trial design

6564 Patients with Symptomatic Lower Extremity PAD* Undergoing Peripheral Revascularization

- ASA 100 daily for all Patients
- Clopidogrel at investigator’s discretion (up to 6 months)

Randomized 1:1 double-blind

Rivaroxaban 2.5 mg twice daily

Stratified by revascularization approach (surgical or endovascular with and without clopidogrel)

Placebo

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

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

Principal Safety Outcome: TIMI Major Bleeding

*PAD defined as:
- Ischemic symptoms AND
- Imaging evidence of PAD AND
- Abnormal ABI/TBI

NCT02504216

Bonaca NEJM 2020;382:1994
VOYAGER PAD Primary Results

Primary efficacy endpoint:

ITT - HR 0.85 (95% CI 0.76 – 0.96)
P=0.0085
ARR 2.6%
NNT 39

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

TIMI Major Bleeding

On Treatment - HR 1.43 (95% CI 0.97 – 2.10)
P=0.0695
ARI 0.8%
NNH 125
Patients with CKD in VOYAGER PAD

eGFR exclusion criterion

Any condition requiring dialysis or renal replacement therapy, or
eGFR <15 mL/min/ 1.73m²

If eGFR <30 prior to revascularization procedure, it must remain >15
at 72h after the procedure
Rivaroxaban in patients with renal impairment

Xarelto® USPI

The relationship between systemic exposure and pharmacodynamic activity of rivaroxaban was altered in subjects with renal impairment relative to healthy control subjects [see Use in Specific Populations (8.6)].

Table 10: Percentage Increase in Rivaroxaban PK and PD Measures in Subjects with Renal Impairment Relative to Healthy Subjects from Clinical Pharmacology Studies

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<tr>
<th>Measure</th>
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<td>Exposure</td>
<td>AUC</td>
<td>44</td>
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<td>AUEC</td>
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* Separate stand-alone study.

PT = Prothrombin time; FXa = Coagulation factor Xa; AUC = Area under the plasma concentration-time curve; AUEC = Area under the effect-time curve
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<th>Parameter</th>
<th>Creatinine Clearance (mL/min)</th>
<th>50-79</th>
<th>30-49</th>
<th>15-29</th>
<th>ESRD (on dialysis)*</th>
<th>ESRD (post-dialysis)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposure</td>
<td>AUC</td>
<td></td>
<td>44</td>
<td>52</td>
<td>64</td>
<td>47</td>
<td>56</td>
</tr>
<tr>
<td>FXa Inhibition</td>
<td>AUEC</td>
<td></td>
<td>50</td>
<td>86</td>
<td>100</td>
<td>49</td>
<td>33</td>
</tr>
<tr>
<td>PT Prolongation</td>
<td>AUEC</td>
<td></td>
<td><strong>33</strong></td>
<td><strong>116</strong></td>
<td><strong>144</strong></td>
<td><strong>112</strong></td>
<td><strong>158</strong></td>
</tr>
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PT = Prothrombin time; FXa = Coagulation factor Xa; AUC = Area under the plasma concentration-time curve; AUEC = Area under the effect-time curve
Similarly, edoxaban exposure was inversely related to creatinine clearance.

ENGAGE AF-TIMI 48: 14071 patients with atrial fibrillation randomized to edoxaban or warfarin.
Patients with normal renal function had lower edoxaban levels, more thrombotic events and less bleeding compared with warfarin.
With rivaroxaban, greater efficacy and potentially more bleeding might be anticipated in patients with CKD due to higher exposure.

Time course of factor Xa inhibition with rivaroxaban in subjects with renal impairment.
Objectives

In PAD patients undergoing lower extremity revascularization (LER) for ischemic symptoms

1. To what extent were those with CKD at higher risk for major CV and limb events

2. Were the efficacy and safety of rivaroxaban in patients with CKD consistent with the overall cohort
Methods

- CKD defined as baseline eGFR<60 ml/min/1.73m² (MDRD equation)
- Major CV and limb events were prospectively ascertained and independently adjudicated by a blinded committee using established definitions
- Prespecified secondary analysis of VOYAGER PAD
- Effect of rivaroxaban estimated with Cox proportional hazards model stratified according to revascularization type (surgical vs endovascular) and clopidogrel use
### Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>CKD, n=1327</th>
<th>No CKD, n=4992</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, mean (SD)</td>
<td>72.4 (8.1)</td>
<td>65.7 (8.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Female, %</td>
<td>38</td>
<td>23</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Race, %</td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>White</td>
<td>73</td>
<td>82</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>22</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Black/African-American</td>
<td>3</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>91</td>
<td>79</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>53</td>
<td>37</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hyperlipidemia, %</td>
<td>65</td>
<td>59</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Current smoking, %</td>
<td>21</td>
<td>38</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>eGFR, ml/min/1.73m², mean (SD)</td>
<td>48.0 (8.7)</td>
<td>86.5 (20.9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CKD stage 3</td>
<td>1284</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CKD stage 4</td>
<td>41</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CKD stage 5</td>
<td>2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Major CV events, but not limb events, were more frequent among patients with CKD.
Primary efficacy and safety endpoints by CKD category

<table>
<thead>
<tr>
<th>Condition</th>
<th>Rivaroxaban HR (95% CI)</th>
<th>Placebo HR (95% CI)</th>
<th>p for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>0.85 (0.76, 0.96)</td>
<td>0.90 (0.71, 1.15)</td>
<td>0.62</td>
</tr>
<tr>
<td>CKD</td>
<td>0.85 (0.73, 0.97)</td>
<td>1.86 (0.92, 3.79)</td>
<td>0.37</td>
</tr>
<tr>
<td>No CKD</td>
<td>1.27 (0.79, 2.05)</td>
<td>0.90 (0.71, 1.15)</td>
<td></td>
</tr>
</tbody>
</table>

p=0.009

Cumulative incidence at 2.5y, %

- Major CV and limb events
  - Rivaroxaban: Overall = 17, CKD = 15, No CKD = 14
  - Placebo: Overall = 16, CKD = 14, No CKD = 13

- TIMI major bleeding
  - Rivaroxaban: CKD = 2, No CKD = 1
  - Placebo: CKD = 1, No CKD = 1
### Major CV and limb events by CKD category

<table>
<thead>
<tr>
<th></th>
<th>Rivaroxaban</th>
<th>Placebo</th>
</tr>
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<tbody>
<tr>
<td>HR 95% CI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>0.85</td>
<td>1.07</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.76, 0.96</td>
<td>0.82, 1.40</td>
</tr>
<tr>
<td>p = 0.009</td>
<td></td>
<td>p for interaction 0.52</td>
</tr>
<tr>
<td>MI/stroke/CV death</td>
<td>0.77</td>
<td>0.55</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.63, 0.94</td>
<td>0.36, 0.86</td>
</tr>
<tr>
<td>p for interaction</td>
<td>0.18</td>
<td></td>
</tr>
</tbody>
</table>

Cumulative incidence at 2.5y, %

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

#### MI/stroke/CV death
- Overall: 16%
- CKD: 14%
- No CKD: 8%

#### Acute limb ischemia/major amputation
- CKD: 8%
- No CKD: 6%
Summary

• Patients with PAD, recent lower extremity revascularization and CKD (mostly stage 3) had a higher rate of major CV events than patients without CKD

• Rivaroxaban reduced the composite primary endpoint of major CV and limb events with no heterogeneity by CKD category

• Rivaroxaban reduced major limb events (acute limb ischemia and major amputation) among patients with or without CKD

• TIMI major bleeding showed no heterogeneity by CKD category
Conclusion

In PAD patients undergoing lower extremity revascularization (LER) for ischemic symptoms

• Patients with CKD were at higher risk for major CV events (MI/stroke/CV death), but were not at higher risk for limb events (acute limb ischemia/major amputation)

• Efficacy and safety of rivaroxaban in patients with CKD were consistent with the overall cohort