Polyvascular Disease with and without Diabetes and the risk of Cardiovascular and Limb Events: Observations from EUCLID

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Disclosures

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In ACS Patients:

- polyvascular disease and diabetes are each associated with the risk of MACE
- The combination of both is associated with further heightened risk
Background

- PAD and microvascular disease are each associated with the risk of amputation

- The combination of both is associated with further heightened risk

Beckman JA et al. Circulation 2019
Objectives

1. Does the observation that polyvascular disease and diabetes are each associated with MACE risk and the combination with further heightened risk extend to patients with lower extremity peripheral artery disease (PAD)?

2. Do polyvascular disease and diabetes also predict the risk of major adverse limb events, including:
   - *Acute limb ischemia*
   - *Major amputation*
Patients with symptomatic PAD

Key exclusion criteria:
- Poor metabolizer for CYP2C19
- Patients requiring dual anti-platelet therapy

Ticagrelor 90 mg bid

Double-blind Double-dummy

1:1

N=13,885

Clopidogrel 75 mg od

Duration: Event Driven Trial
Approximately 14-month recruitment and 26-month follow-up

Primary Endpoint: cardiovascular death, myocardial infarction, or ischemic stroke

Inclusion criteria:
Symptomatic PAD AND one of the following:
A. ABI ≤0.80 at Visit 1 ≤0.85 at Visit 2
OR
B. Prior lower extremity revascularization > 30 days
Methods

PAD defined as:
1. Previous revascularization of lower limbs for symptomatic disease at least 30 days before randomization OR
2. Hemodynamic evidence of PAD (ABI of < 0.80 at screening)

Polyvascular disease (PVD) defined as:
- Number of disease vascular beds (e.g. coronary or cerebrovascular) in addition to PAD (1=PAD only)

Diabetes (DM) defined as a reported history of diabetes at randomization

Endpoint Definitions
MACE = composite of CV death, MI, Ischemic Stroke
MALE = composite of ALI and Major Amputation
Methods

• KM event rates for each subgroup and endpoint

• Cox proportional hazards model used to assess relationship between PVD x DM and clinical outcomes (MACE, MALE, and each of their component pieces) with referent the absence of both PAD and DM

• Proportional hazards assumption assessed using weighted Schoenfeld residuals

• Risk for factor and outcome adjusted for baseline differences including age, weight, sex, region, ABI, GFR, statin use, ARB use, tobacco use
Results - Population

- No polyvascular disease or diabetes: 5,078 (27%)
- Diabetes but no polyvascular disease: 2,724 (20%)
- Diabetes and polyvascular disease: 2,621 (19%)
- Polyvascular disease and no diabetes: 3,460 (25%)
## Results - Population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>-PVD -DM</th>
<th>+PVD -DM</th>
<th>-PVD +DM</th>
<th>+PVD +DM</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Age (y)</td>
<td>65</td>
<td>67</td>
<td>66</td>
<td>67</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female (%)</td>
<td>29</td>
<td>24</td>
<td>32</td>
<td>26</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HTN (%)</td>
<td>65</td>
<td>85</td>
<td>81</td>
<td>90</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HLD (%)</td>
<td>65</td>
<td>85</td>
<td>72</td>
<td>88</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tobacco Use (%)</td>
<td>37</td>
<td>34</td>
<td>25</td>
<td>22</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prior amp (%)</td>
<td>1.8</td>
<td>1.4</td>
<td>4.5</td>
<td>3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Previous Periph Revasc (%)</td>
<td>58</td>
<td>60</td>
<td>48</td>
<td>59</td>
<td>NA</td>
</tr>
<tr>
<td>CAD (%)</td>
<td>-</td>
<td>63</td>
<td>-</td>
<td>71</td>
<td>NA</td>
</tr>
<tr>
<td>MI (%)</td>
<td>-</td>
<td>40</td>
<td>-</td>
<td>43</td>
<td>NA</td>
</tr>
<tr>
<td>Stroke (%)</td>
<td>-</td>
<td>18</td>
<td>-</td>
<td>21</td>
<td>NA</td>
</tr>
<tr>
<td>Cilostazol Use (%)</td>
<td>15</td>
<td>12</td>
<td>18</td>
<td>16</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Statin (%)</td>
<td>65</td>
<td>83</td>
<td>66</td>
<td>84</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Results – Risk of Major Adverse Cardiovascular Events

<table>
<thead>
<tr>
<th>Group</th>
<th>Cumulative Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>+PVD, +DM</td>
<td>19%</td>
</tr>
<tr>
<td>+PVD, -DM</td>
<td>12%</td>
</tr>
<tr>
<td>-PVD, +DM</td>
<td>12%</td>
</tr>
<tr>
<td>-PVD, -DM</td>
<td>7%</td>
</tr>
</tbody>
</table>

Months
Results – Risk of Major Adverse Cardiovascular Events

Rate of MACE per 100-patient years of follow up

- Presence or Absence of Polyvascular Disease (PVD) or Diabetes Mellitus (DM)

*Adjusted for: age, weight, sex, region, ABI, GFR, statin use, ARB use, tobacco use
Results – Risk of Major Adverse Limb Events

Presence or Absence of Polyvascular Disease (PVD) or Diabetes Mellitus (DM)

*Adjusted for: age, weight, sex, region, ABI, GFR, statin use, ARB use, tobacco use
Results – Risk of Major Adverse Limb Events

**ALI**

- **-PVD/-DM**: 0.73%
- **+PVD/-DM**: 0.68%
- **-PVD/+DM**: 0.67%
- **+PVD/+DM**: 0.60%

**Major Amputation**

- **-PVD/-DM**: 0.50%
- **+PVD/-DM**: 0.36%
- **-PVD/+DM**: 1.15%
- **+PVD/+DM**: 0.74%

*Adjusted for: age, weight, sex, region, ABI, GFR, statin use, ARB use, tobacco use
Results – Summary

**Both polyvascular disease and diabetes independently associated with MACE**

**Diabetes but not polyvascular disease independently associated with Amputation**

**Neither polyvascular disease or diabetes independently associated with Acute limb ischemia**

The predictors of MACE and limb outcomes may differ and the predictors of limb outcomes may depend on the type and underlying biology.
Summary

• The risk relationship for diabetes, polyvascular disease and the combination for MACE extends to patients with lower extremity PAD

• The relationship of these factors MALE risk is different overall and by type of event:

  – Acute limb ischemia, a thrombotic complication, is not associated with concomitant coronary or cerebrovascular disease or diabetes

  – Amputation, of multifactorial etiology including infection and microvascular disease, is driven by concomitant diabetes
Conclusion

• Risk factors for cardiovascular and limb events may differ based on the underlying etiology of the events

• Polyvascular disease and diabetes are potent and independent predictors of major adverse cardiovascular events

• Diabetes is an independent predictor of amputation

• Acute limb ischemia, a severe thrombotic event, does not appear to be driven by polyvascular disease or diabetes and additional investigation to enable risk stratification for this outcome is needed