From Registries to Clinical Trials: Impact on Guidelines for PAD

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Conflicts of interest

AstraZeneca, B. Braun, Biotronik, Boehringer Ingelheim, Bayer, BMS, Correvio, Daiichi Sankyo, Eli Lilly, Medtronic, Medicines Company, MSD, Novartis, Pfizer, Sanofi
Influence of PAD on 1-year mortality after ACS

<table>
<thead>
<tr>
<th>Known PAD</th>
<th>Odds ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subclinical PAD</td>
<td>4.38</td>
<td>1.96–9.82</td>
</tr>
<tr>
<td>ABI &lt; 0.9</td>
<td>2.35</td>
<td>1.05–5.23</td>
</tr>
</tbody>
</table>
Patients with PAD are likely to have polyvascular disease

- Polyvascular disease at baseline in the REACH registry
  - CAD: 24.8% (22.1% two locations; 2.7% three locations)
  - CVD: 40.3% (34.5% two locations; 5.8% three locations)
  - PAD: 61.5% (48.4% two locations; 13.1% three locations)

Bhatt DL et al, JAMA 2006;295:180–189
3-year event-rate in the REACH registry: Influence of polyvascular disease


Three-year event rate (%)

- Vascular death
  - Single vascular bed: 4.7%
  - Polyvascular disease: 8.8%
  - *p* < 0.0001

- MI/stroke/vascular death
  - Single vascular bed: 10.5%
  - Polyvascular disease: 17.5%
  - *p* < 0.0001

- MI/stroke/vascular death/rehospitalization
  - Single vascular bed: 25.5%
  - Polyvascular disease: 40.5%
  - *p* < 0.0001
Patients with PAD are in “double jeopardy” – limb vs CV outcomes in patients with symptomatic PAD

Events in patients with PAD at 4 years:
REACH registry¹

<table>
<thead>
<tr>
<th>Event</th>
<th>Event rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI/stroke/CV death</td>
<td>20</td>
</tr>
<tr>
<td>Any peripheral revasc.</td>
<td>20</td>
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</tbody>
</table>

Events in patients with PAD at 3 years:
TRA 2°F-TIMI 50 trial²

<table>
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<tr>
<th>Event</th>
<th>Event rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI/stroke/CV death</td>
<td>11</td>
</tr>
<tr>
<td>Any peripheral revasc.</td>
<td>20</td>
</tr>
</tbody>
</table>

ESC guidelines for PAD

| Antiplatelet therapy is recommended in patients with symptomatic PAD. | I | $C^d$ | 37 |

Clopidogrel versus aspirin in CAPRIE

Clopidogrel versus aspirin in CAPRIE in the PAD population

CV death, MI or stroke

- Aspirin: 4.86% (patient years = 5797)
- Clopidogrel: 3.71% (patient years = 5795)

$p = 0.0028$

Aspirin versus aspirin + clopidogrel in CHARISMA in patients with PAD

VKA + aspirin versus aspirin in PAD

Impact of vorapaxar on MACE and PAD in TRA2°P-TIMI 50

TRA2 P-TIMI 50: KM rates for (A) hospitalization for ALI or (B) peripheral revascularization according to treatment allocation in the PAD cohort

A
Hospitalization for Acute Limb Ischemia

- Placebo
- Vorapaxar

2.3% vs 3.9%
HR 0.58 (0.39 – 0.86)
P=0.006

B
Peripheral Revascularization

- Placebo
- Vorapaxar

18.4% vs 22.2%
HR 0.84 (0.73 – 0.97)
P=0.017

EUCLID Design

Patient Follow up

Assessed for eligibility
(n=16,237)
- Failed inclusion criteria for symptomatic lower extremity PAD (n=489)
- 2C19 homozygous (n=616)
- Other reasons (n=1335)

Randomized (n=13,885)

Ticagrelor (n=6930)
- Never received a dose (n=20)
  - Withdrew consent (n=123 [1.8%])
  - Discontinued study drug (n=2083 [30.1%])
  - Unknown vital status
    - Due to withdrawn consent (n=6)
    - Lost to follow-up (n=1)
  - Proportion of potential patient years with follow-up (98.1%)*

Clopidogrel (n=6955)
- Never received a dose (n=23)
  - Withdrew consent (n=113 [1.6%])
  - Discontinued study drug (n=1803 [26.0%])
  - Unknown vital status
    - Due to withdrawn consent (n=3)
    - Lost to follow-up (n=4)
  - Proportion of potential patient years with follow-up (98.5%)*

*Time from randomization until first primary event, censoring or death, divided by total time until first primary event, death or primary analysis censoring date.

EUCLID Results

Primary Efficacy Endpoint (CV Death, MI, or Ischemic Stroke)

Ticagrelor 90 mg bd (751/6930) vs. Clopidogrel 75 mg od (740/6955)

Percent of patients with event

Ticagrelor vs. clopidogrel:
HR (95% CI): 1.02 (0.92, 1.13)
P value: 0.65

## EUCLID
### Secondary endpoints

#### Other Secondary Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Ticagrelor (N=6930)</th>
<th>Clopidogrel (N=6955)</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All-cause mortality, no. (%)</strong></td>
<td>628 (9.1)</td>
<td>635 (9.1)</td>
<td>0.99 (0.89–1.11)</td>
<td>0.91</td>
</tr>
<tr>
<td><strong>Composite of CV death, MI, or all-cause stroke (ischemic or hemorrhagic), no. (%)</strong></td>
<td>766 (11.1)</td>
<td>759 (10.9)</td>
<td>1.02 (0.92–1.13)</td>
<td>0.72</td>
</tr>
<tr>
<td><strong>Hospitalization for ALI, no. (%)</strong></td>
<td>117 (1.7)</td>
<td>115 (1.7)</td>
<td>1.03 (0.79–1.33)</td>
<td>0.85</td>
</tr>
<tr>
<td><strong>Lower extremity revascularization, no. (%)</strong></td>
<td>846 (12.2)</td>
<td>892 (12.8)</td>
<td>0.95 (0.87–1.05)</td>
<td>0.30</td>
</tr>
<tr>
<td><strong>Composite of all revascularizations (coronary and peripheral [limb, mesenteric, renal, carotid, or other]), no. (%)</strong></td>
<td>1211 (17.5)</td>
<td>1250 (18.0)</td>
<td>0.97 (0.90–1.05)</td>
<td>0.46</td>
</tr>
</tbody>
</table>

ALI indicates acute limb ischemia; CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MI, myocardial infarction.
Current ESC guidelines for PAD management recommend treatment of symptomatic but not asymptomatic PAD

**2017 ESC guideline recommendations for antithrombotic therapies in patients with PAD**

<table>
<thead>
<tr>
<th>Patients with...</th>
<th>Recommendation</th>
<th>Class</th>
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</thead>
<tbody>
<tr>
<td>Symptomatic PAD</td>
<td>Antiplatelet therapy is recommended</td>
<td>lc</td>
</tr>
<tr>
<td>Lower extremity PAD</td>
<td>In patients requiring antiplatelet therapy, clopidogrel may be preferred over aspirin</td>
<td>IIb</td>
</tr>
<tr>
<td></td>
<td>Long-term SAPT is recommended in all patients who have undergone revascularization</td>
<td>lc</td>
</tr>
<tr>
<td></td>
<td>DAPT (ASA plus clopidogrel) for ≥1 month should be considered after infra-inguinal stent implantation</td>
<td>Ila</td>
</tr>
<tr>
<td></td>
<td>SAPT is recommended after infrainguinal bypass surgery</td>
<td>la</td>
</tr>
<tr>
<td></td>
<td>DAPT (ASA plus clopidogrel) may be considered in the case of below-knee bypass with a prosthetic graft</td>
<td>IIb</td>
</tr>
<tr>
<td></td>
<td>Anticoagulation with VKAs may be considered after autogenous vein infrainguinal bypass</td>
<td>IIb</td>
</tr>
<tr>
<td></td>
<td>Because of the lack of proven benefit, antiplatelet therapy is not routinely indicated in patients with isolated asymptomatic LEAD</td>
<td>IIIa</td>
</tr>
</tbody>
</table>

Aboyans V et al, Eur Heart J 2017; doi:10.1093/eurheartj/ehx095
Primary outcome in REACH registry COMPASS-eligible participants vs actual COMPASS trial participants, as a function of CAD, PAD or both

There is an increasing number of patients with PAD
These patients have a high risk of cardiovascular and limb events
Current antithrombotic therapies are limited with respect to reducing cardiovascular and limb adverse events
Therefore, new approaches are needed to improve the prognosis of patients with PAD
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