Is there enough evidence for DAPT after endovascular intervention for PAOD?

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University Hospital Bern
Disclosure

Speaker name:

.........I. Baumgartner..............................................................

I have the following potential conflicts of interest to report:

- Consulting
- Employment in industry
- Stockholder of a healthcare company
- Owner of a healthcare company
- X Other(s)

- **Member of Executive Committee**: EUCLID trial

I do not have any potential conflict of interest
CAPRIE
Efficacy of Clopidogrel vs. Aspirin for MI, Ischemic Stroke, or Vascular Death

Clopidogrel is superior to aspirin in PAD and indicated

ASA=aspirin.
Mean follow-up=1.91 years.
*ITT analysis.
PLATO
Subgroup with PAD at baseline
RCT to determine whether BRILINTA is superior to clopidogrel for prevention of vascular events and death in ACS

Positive signal for ticagrelor vs clopidogrel in PAD

Time since randomization (months)

EUCLID Study Design

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

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

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

Ticagrelor 90 mg bid
Clopidogrel 75 mg od

1:1 Double-blind Double-dummy
N=13,885

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

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

Primary Safety Endpoint: TIMI major bleeding
Primary Efficacy Endpoint (CV Death, MI, or Ischemic Stroke)

- Caution extrapolating evidence from CAD to PAD
  - individual studies in PAD patients are needed
EUCLID
Prior Lower Limb Revascularization (> 30 d)
Subgroup Analysis

Is more intensive antiplatelet therapy more effective and safe over time after revascularization
## Efficacy Outcomes

### Patients with Prior Revascularization According to Treatment Group

<table>
<thead>
<tr>
<th></th>
<th>Ticagrelor (N=3923)</th>
<th>Clopidogrel (N=3952)</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcome:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CV death, MI, or ischemic stroke, no. (%)</td>
<td>447 (11.4)</td>
<td>447 (11.3)</td>
<td>1.01 (0.88–1.15)</td>
<td>0.898</td>
</tr>
<tr>
<td>CV death, no. (%)</td>
<td>190 (4.8)</td>
<td>182 (4.6)</td>
<td>1.05 (0.86–1.29)</td>
<td>0.634</td>
</tr>
<tr>
<td>MI, no. (%)</td>
<td>237 (6.0)</td>
<td>229 (5.8)</td>
<td>1.05 (0.87–1.25)</td>
<td>0.629</td>
</tr>
<tr>
<td>Ischemic stroke, no. (%)</td>
<td>76 (1.9)</td>
<td>100 (2.5)</td>
<td>0.76 (0.57–1.03)</td>
<td>0.078</td>
</tr>
<tr>
<td><strong>Key secondary efficacy outcome:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CV death, MI, ischemic stroke plus ALI requiring hospitalization, no. (%)</td>
<td>522 (13.3)</td>
<td>529 (13.4)</td>
<td>1.00 (0.88–1.12)</td>
<td>0.947</td>
</tr>
</tbody>
</table>

ALI indicates acute limb ischemia; CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MI, myocardial infarction. Median f-u approximately 30 months
# Efficacy Outcomes

Patients with Prior Revascularization According to Treatment Group

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<tr>
<td><strong>Composite of CV death, MI, all-cause stroke (ischemic or hemorrhagic), no. (%)</strong></td>
<td>456 (11.6)</td>
<td>461 (11.7)</td>
<td>1.00 (0.88–1.14)</td>
<td>0.970</td>
</tr>
<tr>
<td><strong>Hospitalization for ALI, no. (%)</strong></td>
<td>99 (2.5)</td>
<td>97 (2.5)</td>
<td>1.03 (0.78–1.36)</td>
<td>0.835</td>
</tr>
<tr>
<td><strong>Lower extremity revascularization, no. (%)</strong></td>
<td>654 (16.7)</td>
<td>680 (17.2)</td>
<td>0.97 (0.87–1.07)</td>
<td>0.519</td>
</tr>
<tr>
<td><strong>Composite of all revascularizations (coronary and peripheral [limb, mesenteric, renal, carotid, or other]), no. (%)</strong></td>
<td>906 (23.1)</td>
<td>914 (23.1)</td>
<td>1.00 (0.91–1.09)</td>
<td>0.929</td>
</tr>
</tbody>
</table>

ALI indicates acute limb ischemia; CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MI, myocardial infarction. Median f-u approximately 30 months
CHARISMA
Effect of clopidogrel/ASA vs ASA on MI, stroke or CV death

First occurrence of MI (fatal / non-fatal), stroke (fatal / non-fatal) or CV death

Cumulative event rate* (%)

Placebo + ASA
7.3%

Clopidogrel + ASA
6.8%

RRR 7.1% (95% CI -4.5, 17.5)

P=0.22

CHARISMA
Primary efficacy results (MI/stroke/CV death) by category of inclusion

Dual anti-platelet therapy with Clopidogrel/ASA not better than Placebo/ASA

AT, atherothrombosis
*First occurrence of MI, stroke (of any cause) or CV death
Bhatt DL. Presented at ACC 2006
**ACCF/AHA Guidelines**

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<tr>
<td><strong>Symptomatic patients</strong></td>
<td></td>
</tr>
<tr>
<td><strong>IA</strong></td>
<td>Antiplatelet therapy is recommended to reduce the risk of MI, stroke and vascular death in individuals with symptomatic atherosclerotic lower extremity PAD*</td>
</tr>
<tr>
<td><strong>IB</strong></td>
<td>ASA (75–325 mg) is recommended in individuals with symptomatic atherosclerotic lower extremity PAD*</td>
</tr>
<tr>
<td><strong>IB</strong></td>
<td>Clopidogrel (75 mg QD) is recommended in individuals with symptomatic atherosclerotic lower extremity PAD*</td>
</tr>
<tr>
<td><strong>IIbB</strong></td>
<td>ASA in combination with clopidogrel may be considered in patients who are not at increased risk of bleeding and who are at high perceived CV risk</td>
</tr>
<tr>
<td><strong>Asymptomatic patients</strong></td>
<td></td>
</tr>
<tr>
<td><strong>IiaC</strong></td>
<td>Antiplatelet therapy can be useful to reduce the risk of MI, stroke or vascular death in asymptomatic individuals with an ABI ≤0.90</td>
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**ESC guidelines**

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<td><strong>Symptomatic patients</strong></td>
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<td><strong>IC</strong></td>
<td><strong>Antiplatelet therapy</strong> is recommended in patients with symptomatic PAD*</td>
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<tr>
<td><strong>Antiplatelet therapy after revascularization</strong></td>
<td></td>
</tr>
<tr>
<td><strong>IC</strong></td>
<td>Antiplatelet therapy with aspirin is recommended in all patients with angioplasty for LEAD to reduce the risk of systemic vascular events</td>
</tr>
<tr>
<td><strong>IA</strong></td>
<td><strong>Dual antiplatelet therapy</strong> with aspirin and a thienopyridine for at least one month is recommended after infrainguinal bare metal-stent implantation</td>
</tr>
<tr>
<td><strong>IIbB</strong></td>
<td>Antiplatelet treatment with aspirin or a combination of aspirin and dipyridamole is recommended after infrainguinal bypass surgery</td>
</tr>
<tr>
<td><strong>IIbB</strong></td>
<td>Dual antiplatelet therapy combining aspirin and clopidogrel may be considered in the case of below-knee bypass with a prosthetic graft</td>
</tr>
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<td><strong>Antiplatelet therapy in PAD with CAD</strong></td>
<td></td>
</tr>
<tr>
<td><strong>IiaB</strong></td>
<td>In PAD with stable CAD, clopidogrel should be considered as an alternative to aspirin for long-term antiplatelet therapy</td>
</tr>
</tbody>
</table>
OAP treatment variable & often associated with LER rather than CV risk

- Guidelines are not specific in recommendation for ASA v clopidogrel vs DAPT; do not reflect the evidence and are inconsistent between region

- Clopidogrel initiation is strongly correlated to endovascular intervention

Clopidogrel use in PAD patients undergoing LER (RW data)
Efficacy & Safety of AP for Prevention of MACE and Leg Amputations in PAD

Systematic Review and Network Meta-Analysis (49 RCT)

Surgical endovascular revascularization
- 3 RCT (of 49 RCT analysed)
- 3,527 patients
- > 8,000 person-years of follow up

short-term DAPT reduces major amputations after revascularization
Efficacy of Different Antiplatelet Agents for Prevention Leg Amputations

3 RCTs with 3,527 patients including surgical and endovascular revascularizations

number of major amputations avoided greater than number of severe bleedings
32% reduction of event rates compared to aspirin monotherapy; NNT = 94
Clopidogrel should be the indicated antiplatelet agent in PAD.

DAPT with aspirin & clopidogrel can reduce rate of major leg amputations following revascularization, but carries a slightly higher risk of severe bleeding.
Is there enough evidence for DAPT after endovascular intervention for PAOD?

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