Antiplatelet Therapies in the Treatment of PAD

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Disclosures

Speaker’s Bureau:
- Astra Zeneca
- Boehringer Ingelheim
- Gilead
- Janssen
- Boston Scientific
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- Medicines Co

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Goals of antiplatelet therapies in PAD

• Reduce Major Adverse Cardiac Events (MACE): Cardiac death, Myocardial infarction or Stroke

• Reduce Major Adverse Limb Events (MALE): Vascular death, Amputation, and need for repeat revascularization

• Improve on acute and subacute procedural success reduce ST, acute or subacute vessel closure and bleeding events

• Reduce hospitalizations

• Reduce overall cost of care
Factors that may influence operator’s choice/duration of an antiplatelet

- **Patient Factors**
  - Critical limb ischemia
  - Diabetes
  - Post MI patients
  - Multivascular disease

- **Angiographic factors**
  - Poor runoff
  - In-stent restenosis
  - Long lesions
  - Thrombotic lesions

- **Procedural Factors**
  - Stent versus no stent
  - Drug eluting technologies vs not

Lack of uniformity among operators on what and how long to use antiplatelets in PAD
Which antiplatelet(s)?
Choice of antiplatelets in PAD

• Mono antiplatelet therapy (MAPT): ASA, clopidogrel

• Dual antiplatelet therapy (DAPT): ASA + (clopidogrel or ticagrelor); ASA + vorapaxar;

• Triple antiplatelet therapy (TAPT): ASA + clopidogrel + vorapaxar
Choosing an antiplatelet drug in PAD

Patient Factors
Freedom from MACE/MALE
Anatomic Factors
Procedural Factors
Bleeding Risk
Antiplatelet therapy is indicated to reduce the risk of MI, stroke, and vascular death in individuals with symptomatic atherosclerotic lower extremity PAD, including those with intermittent claudication or CLI, prior lower extremity revascularization (endovascular or surgical), or prior amputation for lower extremity ischemia.

Aspirin, typically in daily doses of 75 to 325 mg, is recommended as safe and effective antiplatelet therapy to reduce the risk of MI, stroke, or vascular death in individuals with symptomatic atherosclerotic lower extremity PAD, including those with intermittent claudication or CLI, prior lower-extremity revascularization (endovascular or surgical), or prior amputation for lower-extremity ischemia.
Recommendations for Antiplatelet and Antithrombotic Drugs

Clopidogrel (75 mg per day) is recommended as a safe and effective alternative antiplatelet therapy to aspirin to reduce the risk of MI, ischemic stroke, or vascular death in individuals with symptomatic atherosclerotic lower-extremity PAD, including those with intermittent claudication or CLI, prior lower-extremity revascularization (endovascular or surgical), or prior amputation for lower-extremity ischemia.

The combination of aspirin and clopidogrel may be considered to reduce the risk of cardiovascular events in patients with symptomatic atherosclerotic lower-extremity PAD, including those with intermittent claudication or CLI, prior lower-extremity revascularization (endovascular or surgical), or prior amputation for lower-extremity ischemia and who are not at increased risk of bleeding and who are at high perceived cardiovascular risk.
Recommendations for Antiplatelet and Antithrombotic Drugs

Antiplatelet therapy can be useful to reduce the risk of MI, stroke, or vascular death in asymptomatic individuals with an ABI less than or equal to 0.90

In the absence of any other proven indication for warfarin, its addition to antiplatelet therapy to reduce the risk of adverse cardiovascular ischemic events in individuals with atherosclerotic lower extremity PAD is of no benefit and is potentially harmful due to increased risk of major bleeding.
PEGASUS—TIMI 54 Trial Design

N ~21,000

Stable patients with history of MI 1-3 years prior + ≥1 additional atherothrombosis risk factor

RANDOMIZE DOUBLE BLIND

Ticagrelor 90 mg BID

Ticagrelor 60 mg BID

Placebo

Planned treatment with ASA 75-150 mg + standard background care

Follow-up visits
Q4 mo for 1st year, then Q6 mo

Min 12 mo and median 26 mo follow-up Event-driven trial

Primary efficacy endpoint: CV death, MI, or stroke
Primary safety endpoint: TIMI major bleeding

a Age ≥65 y, diabetes, 2nd prior MI, multivessel CAD, or chronic non–end-stage renal dysfunction.
Pegasus TIMI-54. Subgroup analysis

- 1,143 patients had known PAD (out of 21,162 patients)
- In the placebo arm, those with PAD (N=404) had higher rates of MACE at 3 years compared to those without (19.3% vs 8.4%, p<0.001)

- Patients with known PAD randomized to placebo had:
  - higher rates of acute limb ischemia (1.0% vs 0.1%)
  - Higher peripheral revascularization procedures (9.15% vs 0.46%).

- Ticagrelor (doses pooled) reduced the risk of major adverse limb outcomes (HR 0.65, 95% CI 0.44-0.95, p=0.026).

PEGASUS TIMI 54 \textit{(PAD patients post MI)}

The absolute excess of TIMI major bleeding was 0.12%
PEGASUS TIMI 54 (PAD patients post MI) (90 mg vs 60 mg)

Efficacy of Ticagrelor in Patients with PAD

<table>
<thead>
<tr>
<th>Event</th>
<th>Absolute Risk Difference at 3 Years</th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVD / MI / Stroke</td>
<td>-3.0</td>
<td>0.81 (0.57 – 1.15)</td>
<td>0.24</td>
</tr>
<tr>
<td></td>
<td>-5.2</td>
<td>0.69 (0.47 – 0.99)</td>
<td>0.044</td>
</tr>
<tr>
<td>CV Death</td>
<td>-1.7</td>
<td>0.83 (0.50 – 1.38)</td>
<td>0.46</td>
</tr>
<tr>
<td></td>
<td>-5.4</td>
<td>0.47 (0.25 – 0.86)</td>
<td>0.014</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>-2.0</td>
<td>0.76 (0.45 – 1.28)</td>
<td>0.30</td>
</tr>
<tr>
<td></td>
<td>-1.0</td>
<td>0.87 (0.53 – 1.44)</td>
<td>0.59</td>
</tr>
<tr>
<td>Stroke</td>
<td>-0.9</td>
<td>0.63 (0.29 – 1.38)</td>
<td>0.25</td>
</tr>
<tr>
<td></td>
<td>-1.1</td>
<td>0.49 (0.21 – 1.14)</td>
<td>0.097</td>
</tr>
<tr>
<td>Mortality</td>
<td>-2.3</td>
<td>0.88 (0.58 – 1.32)</td>
<td>0.53</td>
</tr>
<tr>
<td></td>
<td>-5.7</td>
<td>0.52 (0.32 – 0.84)</td>
<td>0.0074</td>
</tr>
<tr>
<td>TIMI Major Bleeding</td>
<td></td>
<td>1.46 (0.39 – 5.43)</td>
<td>0.57</td>
</tr>
</tbody>
</table>

NCVH 2016
Prior MI, CVA, or PAD
N=26,449
*PAD Cohort = 3,787*

**Vorapaxar**
2.5 mg/d

**Placebo**

**RANDOMIZE 1:1 DOUBLE BLIND**

**Stratified by:**
1) Qualifying athero
2) Use of thienopyridine

**Follow up Visits**
Day 30, Mo 4, Mo 8, Mo 12
Q6 months

**Median F/U 30 Months**

**Final Visit**

**PAD Inclusion**
1) Symptoms of claudication *and* ABI < 0.85
OR
2) Prior peripheral revasc. for limb isch.

**Primary endpoint**
- CVD/MI/Stroke
- Vascular endpoint
  - Hosp. for Acute Limb Isch.
  - Peripheral revascularization
  - Urgent vascular hosp.
  - Any revascularization

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**ClinicalTrials.gov**
NCT00526474c

Vorapaxar in Stable Atherosclerosis
Overall Trial Population

CV Death, MI, or Stroke

N = 26449
Mean f/u: 2.5 years

Hazard Ratio 0.87
p < 0.001

10.5%
9.3%

Bleeding
GUSTO Mod/Sev at 3 yrs
4.2 v. 2.5%, HR 1.66, p<0.001

Morrow DA, Braunwald E, Bonaca MP, et al.
Hospitalizations for Acute Limb Ischemia

Placebo
Vorapaxar

Hazard Ratio 0.58
95% CI 0.39 to 0.86
p = 0.006

N = 3767

TRA 2°P-TIMI 50
Peripheral Revascularization

Placebo
Vorapaxar

Hazard Ratio 0.84;
95% CI 0.73 to 0.97
p = 0.017

Bonaca et al. Circulation 2013
Ticagrelor and Vorapaxar...

<table>
<thead>
<tr>
<th>PAD</th>
<th>DAPT</th>
<th>Antiplatelet therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓ MACE</td>
<td>✔</td>
<td>ASA + Vorapaxar</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ASA + Ticagrelor  (post MI with PAD)</td>
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<tr>
<td>↓ MALE</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>ASA + Ticagrelor (post MI with PAD)</td>
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Metanalysis of Antiplatelets in PAD

49 RCTs comprising 34,518 patients with 88,358 person-years of follow-up with placebo as reference treatment

**Efficacy Endpoint:**

1. MACE; including vascular deaths, non-fatal myocardial infarction and non-fatal stroke, and
2. the rate of major leg amputations.

**Safety Endpoint:**

the rate of severe bleeding events

*thromboxane synthase inhibitor and a thromboxane receptor inhibitor

ASA 81mg + Clopidogrel 75mg for clinically indicated duration (n=200)

ASA 81mg + Clopidogrel 75mg for clinically indicated duration + 12m (n=200)

12-month composite of MALE + MACE

MALE: index limb arterial occlusion, endovascular or surgical intervention, amputation; MACE: MI, ischemic stroke or death
Thank you
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