Peripheral Arterial Disease: Clinical Management Update

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Intermittent Claudication

Prognosis

Population >55 yr

Intermittent Claudication

Peripheral Vascular Outcomes
- Worsening Claudication 18%
- Lower Extremity Bypass Surgery 7%
- Major Amputation 4%

Other Cardiovascular Morbidity/Total Mortality

- Nonfatal Cardiovascular Event (MI/Stroke, 5-year Rate) 20%
- 5-yr Mortality 30%
- Cardiovascular Cause 75%

Total Mortality by ABI at Baseline


Utilization of Therapies in Patients with PAD

Goals of Therapy in PAD Patients

- Improve symptoms and quality of life
- Decrease cardiovascular events and death

No disclosures related to presentation
Treatment of PAD: Decrease Cardiovascular Events and Mortality

Risk factor modification
- Smoking cessation
  - Goal: complete cessation
- Lipid management
  - High Intensity Statin
- Blood pressure control
  - Goal <130/85 mm Hg
  - ACE inhibitors
- Glucose control
  - Goal: HbA1c <7%

Antiplatelet therapies
- Aspirin or Clopidogrel
  - Goal: reduction in risk of MI, stroke, and vascular death

Impact of Smoking Cessation on Natural History of PAD

Role of Statins in PAD
Reduction of Vascular Events in Heart Protection Study

<table>
<thead>
<tr>
<th>Existing Disease</th>
<th>Statin Favorable</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous MI</td>
<td>Statin</td>
<td>Placebo</td>
</tr>
<tr>
<td>Other CHD</td>
<td>Statin</td>
<td>Placebo</td>
</tr>
<tr>
<td>No prior CHD or CVD</td>
<td>Statin</td>
<td>Placebo</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>Statin</td>
<td>Placebo</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Statin</td>
<td>Placebo</td>
</tr>
<tr>
<td>All patients</td>
<td>Statin</td>
<td>Placebo</td>
</tr>
</tbody>
</table>

2013 ACC/AHA Cholesterol Guidelines

<table>
<thead>
<tr>
<th>LDL-C (mg/dL)</th>
<th>Percentage Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;130</td>
<td>-22%</td>
</tr>
<tr>
<td>100–130</td>
<td>-30%</td>
</tr>
<tr>
<td>&lt;100</td>
<td>-22%</td>
</tr>
</tbody>
</table>

Heart Protection Study: Reduction in Major Vascular Events According to Baseline LDL-C (mg/dL)

Statins: Proven Clinical Results in the Periphery
- Reduced cardiac complications and mortality after AAA repair and other vascular surgeries
- Improved infrainguinal bypass graft patency
- Reduced CEA and CAS restenosis
- Effective primary & secondary stroke prevention
- Reduced progression of Alzheimer’s disease
- Improved wound healing rates
Effect of Atorvastatin of Walking


Maximum Walking Time
Pain Free Walking Time

Effect of ACE Inhibition on Cardiovascular Events in PAD


Management of Intermittent Claudication

- Exercise Therapy
- Drugs
  - Cilostazol
- Revascularization

Effect of Exercise on Pain-free Walking Time in PAD

Circulation 2012; 126:130-139
JAMA 2013; 310(1):57-65
Potential Mechanisms of Benefit of Exercise in PAD

- Increased capillary density
- Improved endothelial function
- Reduced inflammation
- Improved vascular remodeling
- Decreased oxidative stress
- Improved myocardial function
- Improved functional capacity and exercise tolerance
- Improved cardiovascular conditioning

Improvement in Maximal Walking Distance with Cilostazol

<table>
<thead>
<tr>
<th>% Change from Baseline</th>
<th>Cilostazol 100 mg bid</th>
<th>Pentoxifylline 400 mg tid</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>4</td>
<td>8</td>
<td>12</td>
</tr>
<tr>
<td>20</td>
<td>40</td>
<td>60</td>
<td>80</td>
</tr>
<tr>
<td>40</td>
<td>60</td>
<td>80</td>
<td>100</td>
</tr>
</tbody>
</table>

P < 0.05 at all time points


Antiplatelet Drug Therapy for PAD

- Prevent platelet activation and thrombotic events secondary to intervention
- Prevent and/or manage acute peripheral ischemic events
  - acute limb ischemia, blue toe syndrome, renal failure, TIA/stroke
- Reduce incidence of restenosis
- Impact cardiovascular and cerebrovascular morbidity and mortality
  - MI, TIA/stroke, SURVIVAL!

CAPRIE: Clopidogrel vs. Aspirin in Prevention of Ischemic Events

<table>
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<tr>
<th>Months of Follow-Up</th>
</tr>
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<tbody>
<tr>
<td>Aspirin</td>
</tr>
<tr>
<td>Clopidogrel</td>
</tr>
<tr>
<td>Overall Event Rate (%)</td>
</tr>
<tr>
<td>Aspirin</td>
</tr>
<tr>
<td>Clopidogrel</td>
</tr>
<tr>
<td>P = 0.045</td>
</tr>
</tbody>
</table>


Risk Reduction of Clopidogrel vs. Aspirin

Event Rate per Year

- Reduction in Combined Primary End Point (ischemic stroke, MI, or vascular death)

Ticagrelor

- Ticagrelor is a high-affinity ADP analogue
- Causes reversible inhibition of the P2Y12 receptor
- Directly antagonizes ADP binding to the P2Y12 receptor without the need for any metabolic activation

Ticagrelor vs. Clopidogrel in ACS Patients by PAD Status
Results from the PLATO trial (n=1,144)

Event
CV Death/MI/Stoke
Death From Any Cause
CV Death
Death From Vascular Causes or MI
Stroke
Severe Recurrent Ischemia
Recurrent Ischemia
Definite Stent Thrombosis


EUCLID Study Design

Patients with Symptomatic PAD

Ticagrelor vs. Clopidogrel in ACS Patients by PAD Status

Follow-Up Visits 2, 6, 12 Months; Every 6 months after 1st year

Duration: approximately 18 month recruitment and 12 month follow up

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

EUCLID Trial Results
AHA 11/13/16

N Engl J Med 11/13/16

EUCLID Trial Results
AHA 11/13/16

Outcome
Ticagrelor (p=0.0001)
Clopidogrel (p=0.0001)
 Hazard Ratio
95% CI
Primary outcome cardiovascular death, myocardial infarction, or ischemic stroke
752 (6.8)
749 (6.8)
3.94
(1.96 - 7.90)
0.00
Cardiovascular death
169 (1.6)
151 (1.5)
1.12
(0.79 - 1.57)
0.48
Myocardial infarction
149 (1.4)
134 (1.3)
1.12
(0.77 - 1.64)
0.48
Ischemic stroke
113 (1.1)
95 (0.9)
1.19
(0.78 - 1.81)
0.00
Key secondary efficacy outcomes: cardiovascular death, myocardial infarction, or ischemic stroke requiring hospitalisation
Other secondary outcomes
Death from any cause
636 (3.0)
581 (2.9)
0.90
(0.79 - 1.03)
0.06
Cardiovascular death, myocardial infarction, or ischemic stroke requiring hospitalisation
166 (1.5)
156 (1.5)
1.09
(0.76 - 1.56)
0.00
Hospitalisation for acute limb ischaemia
117 (0.6)
111 (0.5)
1.07
(0.81 - 1.41)
0.00
Lower limb revascularisation
846 (4.5)
802 (3.9)
1.06
(0.83 - 1.36)
0.00
Days of prongual therapy for any reason inclusive of days, including, days, revascularisation, amputation, or other forms
3525 (2.9)
3091 (2.7)
0.97
(0.89 - 1.01)
0.16

TRA 2P TIMI 50 Trial Design

Vorapaxar

Prior MI, CVA, or PAD
Placebo

Randomize 1:1 Double-Blind

Placebo

Follow up visits: Days 14, 28, 56, and 12 mo.

Principal Efficacy Analysis: CVD/MI/Stroke in the Primary Care Setting

Primary Safety Analysis: 30-Day MACE Analysis

Final Visit

Limb Vascular Events in Symptomatic PAD Patients in TRA2P-TIMI 50

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Any Perip. Ulcer</th>
<th>Acute Limb Ischemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verapar</td>
<td>18.4 (95% CI: 9.7 - 30.9)</td>
<td>23.0 (95% CI: 0.5 - 45.4)</td>
</tr>
<tr>
<td>Placebo</td>
<td>22.2 (95% CI: 13.5 - 33.4)</td>
<td>3.9 (95% CI: 0.6 - 6.5)</td>
</tr>
</tbody>
</table>

66 yo, h/o IDDM, with left 1st toe ulceration
3 months s/p left popliteal stent

Adherence to Guideline-Recommended Therapy in Patients with PAD

**Major Adverse Cardiovascular Events (MACE)**
- Statin therapy
- BP control (ACEI or ARB)
- ASA or thienopyridine

**Major Adverse Limb Events (MALE)**
- Exercise
- Cilostazol
- Statin
- Revascularization

Conclusions
- **Therapies for Reduction of MACE**
  - Lifestyle modification (no smoking cessation)
  - Statin therapy
  - BP control (ACEI or ARB)
  - ASA or thienopyridine

- **Therapies for Symptomatic Improvement**
  - Exercise
  - Cilostazol
  - Statin
  - Revascularization

- **Therapies for Reduction of MALE**
  - Statin
  - PAR-1 antagonist in selected patients