Optimal Use of ACE Inhibitors, Cilostazol and Statins in Patients Undergoing Open and Endovascular Procedures

Anthony J. Comerota, MD, FACS, FACC
Executive Director Research
ProMedica Health System
Jobst Vascular Institute
Toledo, Ohio

Disclosures
- None -

Statins

- Perhaps the most studied class of pharmacologic agents
- Reduced stroke, graft failure, neointimal fibroplasia, VTE and death

Statins

- All patients operated for atherosclerotic disease should be on maximal dose
  - Statin: Atorvastatin 80mg
    Rosuvastatin 40mg

- Consider statin re-load
  - Preop: Additional maximal dose

Statins and Vascular Disease

Observations
- Statins reduce cholesterol/LDL-C
- Cholesterol reduction associated with fewer CV events and improved survival

However...
- Statins show benefit out of proportion to reduction of cholesterol, and...
- Statins show early benefit, especially procedure related...
  therefore mechanisms other than cholesterol reduction are operative (pleiotrophic effects)
Summary
- High-intensity statins
  - All patients ≤ 75 years with ASCVD
  - All with LDL-C ≥ 190 mg/dl
  - Diabetics with LDL-C > 70 mg/dl or
    10 years risk of ASCVD ≥ 7.5%
  - 40–75 years with ASCVD risk ≥ 7.5%
- Do not “treat to target” use standard dose
- Monitoring of hepatic function unnecessary

Role of Angiotensin System in Atherosclerosis

Background
- Angiotensin II favors development of atherosclerosis
  *Am J Physiol Heart Circ Physiol 2013; 305:H1309-H1320*
- Human macrophages express all components of the RAS and release of ANG II
  *J Hypertension 1999; 17:537*
- Renin deficient mice have reduced atherosclerosis
  *Circ Res 2008; 102:1445*

Are there clinical implications of ACE inhibition?

ACE inhibitors and statins acutely improve endothelial dysfunction of human coronary arteries

**Background**
- Atherosclerosis severely compromises endothelium-dependent relaxation of human coronary resistance arteries
- ACE inhibitors and statins reverse impaired endothelium-dependent relaxation by increasing availability of NO

**NEJM 2000; 342(3):145**

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**NUMBER 3**

**EFFECTS OF AN ANGIOTENSIN-CONVERTING-ENZYME INHIBITOR, RAMIPRIL, ON CARDIOVASCULAR EVENTS IN HIGH-RISK PATIENTS**

**The Heart Outcomes Prevention Evaluation Study Investigators**

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**EFFECTS OF AN ANGIOTENSIN-CONVERTING-ENZYME INHIBITOR, RAMIPRIL, ON CARDIOVASCULAR EVENTS IN HIGH-RISK PATIENTS**

**The Heart Outcomes Prevention Evaluation Study Investigators**
**Study Design**
- 9,297 high-risk patients, ≥55 years
- PAD or diabetes + other CV risk factor
- No known cardiac dysfunction or CHF
- Randomized: Ramipril 10mg Daily vs. Placebo × 5 years
- Primary outcome: Composite of... MI... stroke... CV death

**Results**
- **PAD Subgroup Analysis**

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of Patients</th>
<th>Incidence (%) of Composite Outcome in Placebo Group</th>
<th>Relative Risk in Ramipril Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAD</td>
<td>4051</td>
<td>22.0</td>
<td></td>
</tr>
<tr>
<td>NoPAD</td>
<td>5246</td>
<td>14.3</td>
<td></td>
</tr>
</tbody>
</table>

**Conclusions**
- Ramipril significantly reduces rates of death, MI, stroke in:
  1. Broad range of high risk patients
  2. PAD patients:... who are not known to have a low LVEF or CHF

**ACC/AHA Guidelines**

**Class Ila**
- ACE-1 reasonable for symptomatic patients with lower extremity PAD to reduce risks of CV events

**Class I Ib**
- ACE-1 may be considered for asymptomatic lower extremity PAD to reduce risks of CV events

**Pharmacologic Effects of Cilostazol**
- Inhibits phosphodiesterase-3
- Increases intercellular cAMP
- Inhibits phosphodiesterase-3
- Increases intercellular cAMP
- Antithrombotic activity
- Produces vasodilation
- Increases HDL-C
- Increases blood flow
  - Mildly increases heart rate
  - Decreases triglycerides
  - In vitro inhibition of vascular smooth muscle cells

**Cilostazol**
Change in Meters Walked

- 6 Pooled US Randomized Trials –

Beebe HG, et al
Arch Inten Med 1999;159:2041-50

Cilostazol, Pentoxifylline and Placebo

Maximal Walking Distance

Pain-Free Walking Distance

Dose Response Treadmill Results

Randomized Trial

ACC/AHA PAD Management Guidelines

Intermittent Claudication

Cilostazol 100 mg BID
- Effective
- Increases walking distance
- Avoid in patients with heart failure

Intermittent Claudication

ACC/AHA PAD Management Guidelines

Cilostazol Reduces Target Lesion Revascularization After Percutaneous Transluminal Angioplasty in the Femoropopliteal Artery

- Retrospective review
- 141 consecutive patients
- Femoral-popliteal PTA
- Primary outcome: Target lesion revas.
- Analysis: Cilostazol vs. no cilostazol
- Observational study

Cilostazol Reduces Target Lesion Revascularization After Percutaneous Transluminal Angioplasty in the Femoropopliteal Artery

Target Lesion Revascularization

p<0.01
• 80 patients randomized
  ASA
  ASA + Clopidogrel

• Primary endpoint: Freedom from TVR
• Secondary endpoints: Rate of restenosis
  Major adverse CV events

Cilostazol reduces restenosis after carotid artery stenting

• Review of 113 consecutive CAS procedures
• All patients received dual platelet inhibition with:
  ASA
  Ticlopidine
  Clopidogrel
  Cilostazol
  ...2 day Rx and 2 – 3 month post Rx
• Repeat carotid duplex at 6 month intervals

Cilostazol in Patients with PAD

Conclusions
1. Well studied
2. Improves walking distance in patients with intermittent claudication
3. Reduced recurrent stenosis following:
   – Coronary angioplasty
   – Peripheral angioplasty

JACC 2009; 53:48
Soga Y et al
Cilostazol