Peripheral Arterial Disease - antiplatelet therapy

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Documented Presence of PAD

Prevalence of PAD Increases With Age

Risk Factors for PAD

- Smoking
- Diabetes
- Hypertension
- Hypercholesterolemia
- Hyperhomocysteinemia
- Fibrinogen
- C-Reactive Protein
- Alcohol

Relative Risk: 0.5, 1, 2, 3, 4, 5, 6

Reduced | Increased
Risk Factors for PAD

- Smoking
- Diabetes
- Hypertension
- Hypercholesterolemia
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- Fibrinogen
- C-Reactive Protein
- Alcohol

Relative Risk:
- .5
- 1
- 2
- 3
- 4
- 5
- 6

Reduced vs. Increased
occlusions of pelvic arteries

occlusion a.fibularis a.tib.post.
Patients with one manifestation often have coexistent disease in other vascular beds.

Diagnostic Algorithm for PAD

History, Physical examination Suggestive of PAD?

- **Yes**
  - Ankle-Brachial Index
    - **< 0.9**
    - **≥ 0.9**
      - **≥ 1.30**
        - Still suspicious?
          - PAD
          - Vascular Lab Referral
            - Segmental pressures
            - Graded treadmill test
          - Anatomic Assessment: DUS, MRA, CTA
        - **< 0.9**
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- **NO**
  - Search for alternate diagnosis
The 5-year all-cause mortality rates are as high as 30% in patients with PAD,

PAD pts are 6 times more likely to die from CV disease within 10 yrs than pts without PAD
Management of PAD

Prevention of MI, stroke & death

Improvement of function and QoL

Protection of feet – limb salvage
Treatment of All PAD Pts

Exercise programme

Risk factor normalization:
- Immediate smoking cessation
- Treatment of hypertension
- Treatment of dyslipidemia to target levels
- Treatment of diabetes mellitus to HbA$_{1c}$ < 7% (4.5%)

Pharmacological treatment:
- Antiplatelet therapy
- ACE inhibition / Sartans
- cilostazol
- naftidrofuryl

Revascularization
Antiplatelet therapy
thrombin rec. PAR-1
thrombin rec. PAR-4
serotonin rec. rec. for PAF
txA₂
ADP
vWF
rec. Ib-IX-V
thrombin rec. PAR-1
thrombin rec. PAR-4
serotonin rec. rec. for PAF
txA₂
ADP
cAMP
COX
IIb/IIIa
GP IIb/IIIa rec.
ADP
rec. P2Y₁₂
IIb/IIIa
fibrinogen
vWF
rec. Ib-IX-V
fibrinogen
IIb/IIIa
thromboxan recept.

GP IIb/IIIa rec.
klopidogrel
prasugrel
ticagrelor

GP IIb/IIIa
ASA

ADP

ADP P2Y_12

TXA_2

thrombin

COX-1

cAMP

activation

vorapaxar

atopaxar
# Efficacy of Antiplatelet therapy, ACE-I, Statins in PAD

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Event Rate (% per year)</th>
<th>No. of patients in subgroup</th>
</tr>
</thead>
<tbody>
<tr>
<td>APTC*</td>
<td>Placebo</td>
<td>6.0%</td>
<td>(&gt;9000)</td>
</tr>
<tr>
<td>CAPRIE*</td>
<td>Aspirin</td>
<td>4.9%</td>
<td>(&gt;6000)</td>
</tr>
<tr>
<td></td>
<td>Clopidogrel</td>
<td>3.7%</td>
<td></td>
</tr>
<tr>
<td>HOPE*</td>
<td>Placebo</td>
<td>4.4%</td>
<td>(4051)</td>
</tr>
<tr>
<td></td>
<td>Ramipril</td>
<td>3.4%</td>
<td></td>
</tr>
<tr>
<td>HPS*</td>
<td>Placebo</td>
<td>4.9%</td>
<td>(2701)</td>
</tr>
<tr>
<td></td>
<td>Simvastatin</td>
<td>6.1%</td>
<td></td>
</tr>
</tbody>
</table>

*PAD Subgroup only

APTC Antiplatelet Trialists' Collaboration BMJ 1994; 308:81-106
CAPRIE Steering Committee Lancet 1996; 348: 1329-1339
HPS Collaborative group Lancet; 2002; 360:7-22
Antithrombotic Trialists’ Collaboration: PAD

- 42 clinical trials
- 9,214 patients with PAD
- **23% reduction** of serious adverse vascular events ($P=0.004$)
- Benefits similar among PAD subtypes (intermittent claudication, peripheral grafting, and peripheral angioplasty)

Antithrombotic Trialists’ Collaboration
Risk of Vascular Events in High-Risk Patients

<table>
<thead>
<tr>
<th>Risk Category (number of trials)</th>
<th>Patients with Event (%)</th>
<th>Risk versus Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>intermittent claudication (N=26)</td>
<td>APT=6.4</td>
<td>control=7.9</td>
</tr>
<tr>
<td>peripheral grafting (N=12)</td>
<td>APT=5.4</td>
<td>control=6.5</td>
</tr>
<tr>
<td>peripheral angioplasty (N=4)</td>
<td>APT=2.5</td>
<td>control=3.6</td>
</tr>
<tr>
<td>All PAD trials (N=42)</td>
<td>APT=5.8</td>
<td>control=7.1</td>
</tr>
</tbody>
</table>

APT=antiplatelet therapy with aspirin, clopidogrel, dipyridam ide, or a glycoprotein IIb/IIIa antagonist

N=9706
Is really the acetylsalicylic acid so beneficial drug for the patients with PAD?
Aspirin for the Prevention of Cardiovascular Events in Patients With Peripheral Artery Disease: A Meta-analysis of Randomized Trials

Jeffrey S. Berger; Mori J. Krantz; John M. Kittelson; et al.


- 18 trials involving 5 269 pts (1966-2008)
- CV events in 8.9% taking ASA and by 11% in the control group – nonsignificant 12% RR
- Reduction of nonfatal stroke but not associated with significant reduction in all-cause or cardiovascular mortality, MI
- 3 019 taking ASA alone (7 trials) – the same results
Aspirin for the Prevention of Cardiovascular Events in Patients With Peripheral Artery Disease: A Meta-analysis of Randomized Trials

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- 18 trials involving 5269 pts (1966-2008)

Limitations:
- no evaluation of peripheral vascular events
- the analysis is underpowered to detect a difference in primary outcome of less than 25%

Aspirin is efficacious in reducing vascular events with a benefit of less than 15%

60% of the data come from: POPADAD trial, VA-Cooperative trial
The prevention of progression of arterial disease and diabetes (POPADAD) trial: factorial randomised placebo controlled trial of aspirin and antioxidants in patients with diabetes and asymptomatic peripheral arterial disease

Jill Belch, professor of vascular medicine,1 Angus MacCuish, consultant diabetologist,2 Iain Campbell, professor of diabetic medicine,3 Stuart Cobbe, Walton professor of cardiology,4 Roy Taylor, professor of medicine and metabolism,5 Robin Prescott, professor of health technology assessment,6 Robert Lee, research associate,8 Jean Bancroft, senior research nurse,1 Shirley MacEwan, honorary senior research fellow,1 James Shepherd, professor of pathological biochemistry,6 Peter Macfarlane, professor of

- ASA was not effective in the primary of CV events in pts with asymptomatic PAD
- Antioxidants showed no benefit as well

BMJ 2008, 337: 1840
The prevention of progression of arterial disease and diabetes (POPADAD) trial: factorial randomised placebo controlled trial of aspirin and antioxidants in patients with diabetes and asymptomatic peripheral arterial disease

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Did they have PAD?  (ABI < 0.99)
Asymptomatic diabetics, aged > 40
No benefit of aspirin in this population

• Antioxidants showed no benefit as well
Aspirin for Prevention of Cardiovascular Events in a General Population Screened for a Low Ankle Brachial Index
A Randomized Controlled Trial

F. Gerald R. Fowkes, FRCPE
Jacqueline F. Price, MD
Marlene C. W. Stewart, PhD
Isabella Butcher, PhD
Gillian C. Leng, MD
Alistair C. H. Pell, MD
Peter A. G. Sandercock, DM
Keith A. A. Fox, FRCP
Gordon D. O. Lowe, DSc
Gordon D. Murray, PhD

for the Aspirin for Asymptomatic Atherosclerosis Trialists

AAA trial
Aspirin for Asymptomatic Atherosclerosis

• among participants without clinical CV disease, identified with a low ABI based on screening a general population, the administration of ASA did not reduce vascular events
AAA trial
Aspirin for Asymptomatic Atherosclerosis

- among participants without clinical CV disease, identified with a low ABI based on screening a general population, the administration of ASA did not reduce vascular events

- most pts with borderline ABI
- 70% of participants women
- the rate of events lower than expected
- limited power of the study
- enteric coated acetylsalicylic acid
Prevention of serious vascular events by aspirin amongst patients with peripheral arterial disease: randomized, double-blind trial

Critical Leg Ischaemia Prevention Study (CLIPS) Group*

- Prevention of vascular events by aspirin amongst 366 pts with stage I-II (ABI < 0.85)
- Randomized, placebo-controlled
- 4 treatment groups: aspirin/vitE+C+betacarotene/both/neither
- 7/185 aspirin X 20/181 placebo suffered major CV event – reduction of 64%, 5 vs 8 cases of critical limb ischemia
Prevention of serious vascular events by aspirin amongst patients with peripheral arterial disease: randomized, double-blind trial

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- Randomized, placebo-controlled
- 4 treatment groups:
  - aspirin/vitE+C+betacarotene/both/neither
- Small study, small No of events
- Antioxidants - no effect
- 7/185 aspirin X 20/181 placebo suffered CV event – reduction
Clopidogrel is a prodrug

-> Metabolism through the cytochrome P450 enzyme system

Active metabolite binds to platelet P2Y12 receptor and irreversibly blocks platelet activation by ADP

Simon et al., NEJM 2009;360:363-375.
CAPRIE Study
Efficacy of Clopidogrel in Primary Analysis of MI, Ischemic Stroke, or Vascular Death

ITT Analysis

CAPRIE Steering Committee   Lancet 1996; 348: 1329-1339
CAPRIE Study
Outcome by Subgroup

Mean & 95% CI

Stroke
MI
PAD
All patients

Aspirin better

Clopidogrel better
CHARISMA
Primary Endpoint (MI/Stroke/CV Death) in Patients with Previous MI, IS, or PAD*

**RRR: 17.1 % [95% CI: 4.4%, 28.1%]**
**p=0.01**

**Primary outcome event rate (%)**
- Clopidogrel + ASA: 7.3%
- Placebo + ASA: 8.8%

N=9,478

*Post hoc analysis*

Bhatt DL. Presented at ACC 2006.
Summary

- PAD is a marker of atherosclerosis in the coronary and cerebral arteries
- PAD is often underestimated and underdiagnosed, and requires proper diagnosis
- Antiplatelet therapy reduces the risk of myocardial infarction, stroke and vascular death in patients with peripheral arterial disease, including patients with a history of angioplasty or bypass surgery\(^1,2\)
- Most of the evidence with antiplatelet therapy in PAD is from ASA and ADP-receptor antagonists including clopidogrel\(^1,3\)
- An ADP-receptor antagonist improves the long-term peripheral patency after revascularization procedures\(^2\)

Summary

• The effect of aspirin in patients with PAD caused risk reduction of 20%, only 12% in primary prevention trials

• The benefit of aspirin in PAD pts is clear in reduction of nonfatal stroke

• Clopidogrel provides increased benefit over aspirin for secondary prevention in atherothrombotic patients, including those with diagnosed PAD

• Dual antiplatelet therapy may be beneficial in pts with extensive atherosclerotic disease
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