Coumadin, Plavix, Aspirin, or...Does Anything Improve Patency After Revascularization

Chris Owens, MD

Disclosures
- No disclosures
- No conflicts of interest

Objectives
- Overview of MOA of anti-platelets
- Introduce a novel MOA of aspirin
- Discuss and contrast Dutch BOA and VA CSP #362
- Discuss CASPAR data
Platelet score card

- 2-4 micrometers
- 100,000,000,000 platelets/day
- Lifespan 7-10 days
- Platelet derived products
  - PDGF
  - TGF-B
  - FGF
  - IGF-1
  - PDEGF
  - VEGF

Scanning electron micrograph of an injured vein 24 after arterial blood flow

Risk factors, medical therapies and perioperative events in limb salvage surgery. Observations from the PREVENT III multicenter trial

Michael A. Caputo, MD1,2,3, David F. Bresnitz, MD4, Alexander W. Chreu, MD1, Gregory L. Mancini, MD1, Howard Razzouk, PhD1, and Lynne Bria, RN, BSN, MBA, RN, CEN, CRNI, Ford, Shore, OCN, and staff atARC, University of California, San Francisco, Calif.

(AMS 1992;14:225-31.)

Classical MOA for ASPIRIN

Protective effects against platelet aggregation are due to inhibition of Thromboxane $A_2$ — formally called rabbit aorta contracting substance.

- Salicylate containing plants
  - Willow bark
  - Myrtle
  - Popular tree
  - Meadow sweet
  - Wintergreen

Salicylate’s bitter taste prompted Felix Hoffman of Bayer to acetylate salicylate in 1897 leading to the birth of aspirin.

Aspirin triggers antiinflammatory 15-epi-lipoxin $A_4$ and inhibits thromboxane in a randomized human trial

PNAS 2004, vol 101, 42, 15178-15183
Relative deficiency in 15 epi-LXA4 or aspirin triggered lipoxin (ATL) in patients with PAD

To be presented at the ATVB annual meeting, Washington, DC. Next week

Sequential changes in coagulation and platelet function following femorotibial bypass

- Increased platelet reactivity seen is with patients with severe PAD
- There is an increase in platelet reactivity in the immediate post op
- Because of the increased reactivity careful monitoring of platelet function is necessary to identify those patients in which antiplatelet therapy may be beneficial

Anticoagulants, antiplatelets and bypass grafts

- The early years:
  - 1970 and 1980's animal studies shows aspirin and dipyridamole decrease intimal hyperplasia
  - Clinical studies did not confirm these results
- Interest was still high because
  - Overwhelming laboratory data
  - Relative hypercoaguable state post-vascular surgery

The aspirin papers: Anitplatelet Trialist Collaboration

- BMJ 1994, 50 pages covering over 142 trials, and 73,000 patients
- First, reviewed efficacy of preventing death, MI, and stroke
- Second, reviewed efficacy of aspirin enhancing patency in grafts
- Third, reviewed the effect of aspirin on venous thromboembolism
Collaborative overview of randomised trials of antiplatelet therapy - II: Maintenance of vascular graft or arterial patency by antiplatelet therapy.

Antiplatelet Trialists' Collaboration

- 39 trials of antiplatelet therapy v. controls were identified
- Systematic monitoring of occlusion was only noted in 14 trials
  - Antiplatelet therapy was associated with a 43% reduction in vascular occlusion in these 14 trials
  - Intermittent claudication (% odds reduction) 64%
  - Peripheral grafts 38%
  - Peripheral angioplasty 47%

"...As well as preventing about one quarter of clinical vascular events in patients undergoing such vascular procedures, antiplatelet therapy also reduced the odds of vascular graft or arterial occlusion by about 40% while treatment continued"
A 1991 survey showed that 75% of Dutch vascular surgeons prescribed anticoagulants following bypass surgery in contrast to a worldwide survey showing that 60% of all vascular surgeons prescribed antiplatelet agents (aspirin).

What do the Dutch know that we don’t?

BOA study
- Aspirin dose 81 mg vs. warfarin
- INR 3.0-4.5
- Primary outcome event: graft occlusion
  - Composite event of vascular death
  - Non-fatal MI
  - Non-fatal stroke
  - Amputation
- Nationwide network of anticoagulation clinics
- Risk of hemorrhagic stroke was 3.5 times higher in the Coumadin group

Efficacy of oral anticoagulants compared with aspirin after infrainguinal bypass surgery (The Dutch Bypass Oral anticoagulants or Aspirin study): a randomised trial

Benefits, morbidity, and mortality associated with long-term administration of oral anticoagulant therapy to patients with peripheral arterial bypass procedures: A prospective randomized study
Conclusions of the VA Cooperative trial #362

- The addition of warfarin may benefit patients with 6 mm fem-pop prosthetic grafts
- Warfarin did not reduce occlusions in veins or 8mm fem-fem or ax-bifem patients
- The risk of a major bleeding event was 0.41/patient yr in the WASA group (INR 1.4-2.8) v 0.015 in ASA group.
- In the BOA study the risk of a bleeding event was 0.047 patient year (twice as high as the aspirin alone group).

Differences between BOA and VA# 362

- BOA: warfarin vs. aspirin: VA# 362: warfarin and aspirin vs. aspirin
- Degree of anticoagulation was higher in BOA (3-4.5) v. (1.4-2.8)
- BOA measured levels twice per month/ VA once per month
- 40% discontinuation rate in the VA v. 14% in BOA
- Sample size: BOA n=2690 (4560 pt/ys); VA n=831(2638 pt/ys)
- Anticoagulation clinics

The effect of anticoagulation therapy and graft selection on the ischemic consequences of femoropopliteal bypass graft occlusion: Results from a multicenter randomized clinical trial

Subset of VA #362 looking at failed femoral popliteal BPG. The severity of ischemia at the time of occlusion was analyzed. The effect of anticoagulation on the severity of ischemia was also investigated.
Effect Of Adding Clopidogrel To Aspirin On The Success Of Below Knee Arterial Bypass Grafts. A Randomised Placebo Controlled Study CASPAR

- Objective: clopidogrel vs. aspirin vs. aspirin alone will lead to an increase rate of primary patency, limb salvage, and survival, in patients receiving below knee bypass grafts for PAD
- Stratified venous vs. prosthetic for pre-specified subgroup analysis
- Sponsored by Sanofi-Aventis Bristol-Myers Squibb
- Completed enrollment
- Not published
- Presented at the VEITH symposium by Iris Baumgartner of Bern University Hospital, Switzerland

| Table II: Comparison of ischemia grade after occlusion of polytetrafluoroethylene femoropopliteal bypass grafts |
|---|---|---|
| Grade I ischemia | PTFE | After three PTFE |
| Grade II ischemia | 8/38 (21.1%) | 14 (37.8%) | 20 (52.6%) |
| *p = 0.051 vs. PTFE |
| *p = 0.040 vs. After three PTFE |

1/3 of PTFE place for claudication

| Table III: Comparison of ischemia grade after occlusion of polyethylene/oxide femoropopliteal bypass grafts: effect of antiplatelet treatment |
|---|---|---|
| Grade I ischemia | clopidogrel vs. ASA |
| Grade II ischemia | 12 (72.2%) | 21 (44.7%) |
| *p = 0.002 |

Clopidogrel vs. aspirin: ASA, aspirin alone; clopidogrel: CASPAR Study Population

- N = 851 patients
- Prosthetic: 29.7% n = 253
- Venous: 70.3% n = 598

Median time from surgery to randomization [Q1–Q3]: 3 days [2–4]
Effect of Adding Clopidogrel to Aspirin on the Success of Below Knee Arterial Bypass Grafts. A Randomised Placebo Controlled Study CASPAR

<table>
<thead>
<tr>
<th>Primary endpoint</th>
<th>C n(425)</th>
<th>P n(426)</th>
<th>Hazard ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All grafts</td>
<td>149</td>
<td>151</td>
<td>0.98 (0.78; 1.23)</td>
<td>0.86</td>
</tr>
<tr>
<td>Venous</td>
<td>101</td>
<td>85</td>
<td>1.25 (0.94; 1.67)</td>
<td>0.13</td>
</tr>
<tr>
<td>Prosthetic</td>
<td>48</td>
<td>66</td>
<td>0.65 (0.45; 0.95)</td>
<td>0.025</td>
</tr>
</tbody>
</table>

Graft occlusions*

| All grafts       | 93       | 97       | 0.94 (0.71; 1.25)     | 0.64    |
| Venous           | 52       | 38       | 1.45 (0.95; 2.20)     | 0.08    |
| Prosthetic       | 41       | 59       | 0.63 (0.42; 0.95)     | 0.021   |

*first episode, C=clopidogrel + aspirin, P=aspirin alone

K-M Curves of Time to Primary Outcome Event

Total Population (ITT)

<table>
<thead>
<tr>
<th>Time to event (days)</th>
<th>Proportion event free (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>50</td>
<td>90</td>
</tr>
<tr>
<td>100</td>
<td>80</td>
</tr>
<tr>
<td>150</td>
<td>70</td>
</tr>
<tr>
<td>200</td>
<td>60</td>
</tr>
<tr>
<td>250</td>
<td>50</td>
</tr>
<tr>
<td>300</td>
<td>40</td>
</tr>
<tr>
<td>350</td>
<td>30</td>
</tr>
<tr>
<td>400</td>
<td>20</td>
</tr>
<tr>
<td>450</td>
<td>10</td>
</tr>
<tr>
<td>500</td>
<td>NS</td>
</tr>
<tr>
<td>550</td>
<td>NS</td>
</tr>
</tbody>
</table>

Hazard ratio = 0.98 [95% CI 0.78–1.23], p = NS

K-M Curves of Time to Primary Outcome Event

Each Type of Graft (ITT)

<table>
<thead>
<tr>
<th>Time to event (days)</th>
<th>Proportion event free (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>50</td>
<td>90</td>
</tr>
<tr>
<td>100</td>
<td>80</td>
</tr>
<tr>
<td>150</td>
<td>70</td>
</tr>
<tr>
<td>200</td>
<td>60</td>
</tr>
<tr>
<td>250</td>
<td>50</td>
</tr>
<tr>
<td>300</td>
<td>40</td>
</tr>
<tr>
<td>350</td>
<td>30</td>
</tr>
<tr>
<td>400</td>
<td>20</td>
</tr>
<tr>
<td>450</td>
<td>10</td>
</tr>
<tr>
<td>500</td>
<td>NS</td>
</tr>
<tr>
<td>550</td>
<td>NS</td>
</tr>
</tbody>
</table>

Venous grafts Hazard ratio = 1.25 [95% CI 0.94–1.67], p = NS

Prosthetic grafts Hazard ratio = 0.65 [95% CI 0.45–0.95], p = 0.025

CASPAR bleeding risks

<table>
<thead>
<tr>
<th>Placebo</th>
<th>Clopidogrel</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=422</td>
<td>N=426</td>
<td></td>
</tr>
<tr>
<td>Total bleeding n (%)</td>
<td>30(7.1%)</td>
<td>71(16.7%)</td>
</tr>
<tr>
<td>Mild</td>
<td>21(5.0%)</td>
<td>46(10.8%)</td>
</tr>
<tr>
<td>Moderate</td>
<td>4(0.9%)</td>
<td>16(3.8%)</td>
</tr>
<tr>
<td>Severe</td>
<td>5(1.2%)</td>
<td>9(2.1%)</td>
</tr>
<tr>
<td>Fatal</td>
<td>1(0.2%)</td>
<td>2(0.5%)</td>
</tr>
</tbody>
</table>
CASPAR

- Pre-specified subgroup analysis by type of graft
- “Favor of dual treatment in prosthetic grafts was mainly driven by female patients with very distal bypass grafts”
- “NNT with dual therapy in the prosthetic group was 10 patients to save one limb.”

Summary

- Our patients remain underprescribed and undertreated with anti-platelet agents
- Aspirin inhibits platelet aggregation by inhibiting prostanoid production (TXA2)
- Aspirin exerts its anti-inflammatory and pro-resolution effects through acetylation COX 2 and modifying leukotriene metabolism at 81 mg.

Summary

- Routine infrainguinal bypass grafting, risks/benefits favors aspirin alone
  - 81 mg of aspirin is as effective as higher doses
- In prosthetic grafts the addition of low dose warfarin may decrease the severity of ischemia when the grafts occlude
  - Maybe especially useful when limited runoff or “high-risk” grafts
- The addition of warfarin will increase the incidence of hemorrhagic stroke
- The addition of clopidogrel may be useful in certain high-risk scenarios with prosthetic graft.
  - Awaiting CASPAR published results
  - The addition of plavix will increase the risk of mild to moderate bleeding

Thank you.