Clopidogrel And Aspirin Versus Aspirin Alone After Coronary Bypass Surgery

The Clopidogrel After Surgery For Coronary Artery Disease (CASCADE) Randomized Controlled Trial

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CABG is an effective treatment of ischemic heart disease
Long-term results compromised by vein graft disease
Within 1 year - up to 15% of vein grafts occluded
By 10 years after surgery - 60% of grafts are patent
Vein graft disease composed of 3 overlapping stages
  - Early thrombosis
  - Intimal hyperplasia
  - Atherosclerosis
Intimal hyperplasia is foundation for graft atheroma
Intimal hyperplasia is inhibited by clopidogrel
  - Cell culture experiments
  - Animal models of thrombosis
CASCADE Trial
Clopidogrel After Surgery For Coronary Artery Disease

Hypothesis: Clopidogrel plus aspirin will inhibit SVG intimal hyperplasia

Multicenter, double-blind, placebo-controlled trial

Patients undergoing CABG with at least 2 SVG’s

Aspirin 162 mg daily
Clopidogrel 75 mg daily

Aspirin 162 mg daily
Placebo

Starting on day of surgery when chest tube drainage ≤ 50 cc/hr for 2 hours

1 year duration

Coronary angiogram and intravascular ultrasound at 1 year
Outcomes

Primary outcome
- Vein graft intimal area by intravascular ultrasound

Secondary outcomes
- Vein graft patency
- Major adverse cardiovascular events
- Bleeding

Sample size
- Intimal area of normal SVG at 1 year
  5.26 ± 1.38 mm²
- 20% clinically relevant reduction with clopidogrel
- α level 0.05, power 0.90, drop out up to 35%
- Total 100 patients required

*Hozumi T et al. Heart 1996;76:317-20*
126 Patients provided consent

13 Were excluded before randomization

113 Underwent randomization

56 Received aspirin plus clopidogrel
- 46 Completed study drug
  - 46 Underwent IVUS
  - 46 Included in analysis of vein intimal area
- 10 Discontinued study drug early
- 10 Did not undergo IVUS

57 Received aspirin plus placebo
- 45 Completed study drug
  - 45 Underwent IVUS
  - 45 Included in analysis of vein intimal area
- 12 Discontinued study drug early
- 12 Did not undergo IVUS
Primary Outcome
Primary Outcome

Vein graft intimal hyperplasia assessed by IVUS in 90 patients

Vein graft intimal area at 1 year

- Aspirin-clopidogrel
  4.1 ± 2.0 mm²
- Aspirin-placebo
  4.9 ± 3.3 mm²

14.8% reduction in intimal area
(95% CI -38.1%, 8.5%)
Secondary Outcomes
# 1 Year Graft Patency

<table>
<thead>
<tr>
<th></th>
<th>Aspirin-Clopidogrel (N=56)</th>
<th>Aspirin-Placebo (N=57)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall patency (%)</td>
<td>95.2%</td>
<td>95.5%</td>
<td>1.00</td>
</tr>
<tr>
<td>ITA patency (%)</td>
<td>96.6%</td>
<td>100%</td>
<td>0.50</td>
</tr>
<tr>
<td>SVG patency (%)</td>
<td>94.3%</td>
<td>93.2%</td>
<td>0.78</td>
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</table>
# Major Adverse Cardiovascular Events

<table>
<thead>
<tr>
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<th>Aspirin-Placebo (N=57)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall death (%)</td>
<td>0 (0%)</td>
<td>1 (1.8%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Cardiovascular death (%)</td>
<td>0 (0%)</td>
<td>1 (1.8%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Myocardial infarction (%)</td>
<td>4 (7.1%)</td>
<td>1 (1.8%)</td>
<td>0.21</td>
</tr>
<tr>
<td>Stroke (%)</td>
<td>0 (0%)</td>
<td>2 (3.5%)</td>
<td>0.50</td>
</tr>
<tr>
<td>Hospitalization for coronary ischemia (%)</td>
<td>1 (1.8%)</td>
<td>3 (5.3%)</td>
<td>0.62</td>
</tr>
<tr>
<td>Need for coronary intervention (%)</td>
<td>1 (1.8%)</td>
<td>2 (3.5%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Any MACE (%)</td>
<td>4 (7.1%)</td>
<td>5 (8.8%)</td>
<td>1.00</td>
</tr>
</tbody>
</table>
Bleeding

- Postoperative chest tube drainage after study drug administration
  - Aspirin-clopidogrel: 451 ± 301 mL
  - Aspirin-placebo: 324 ± 247 mL  \( P=0.02 \)

- Major bleeding
  - Aspirin-clopidogrel: 2 patients (3.6%)
  - Aspirin-placebo: 0 patients (0%)  \( P=0.24 \)

- Minor bleeding
  - Aspirin-clopidogrel: 3 patients (5.4%)
  - Aspirin-placebo: 3 patients (5.3%)  \( P=1.00 \)
Discussion

- The addition of clopidogrel to aspirin did not lead to a significant reduction in vein graft intimal hyperplasia
- Vein graft patency rates did not differ between the two groups
- The incidence of major adverse cardiovascular events were similar
- Our results do not support the use of dual antiplatelet therapy for the prevention of vein graft disease after CABG