Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events

Study Type: POEM
Purpose: Does the combination of clopidogrel and aspirin protect against cardiovascular events versus aspirin alone in a broad population of patients at risk?
Trial Design: Randomized, double-blinded, placebo-controlled, multicenter (32 countries, 768 sites), intention-to-treat - clopidogrel 75 mg daily plus low-dose aspirin (75 mg to 162 mg daily) versus placebo plus low-dose aspirin.
Patients: n = 15,603, mean age = 64, ~30% female, 80% white, ~77% had documented vascular disease, ~20% with multiple risk factors, 20% smokers, 74% HTN, 75% with high cholesterol, 6% HF, 34% prior MI, 4% a. fib, 24% with a prior stroke, 12% TIA, 42% DM, 23% PAD, 13% nephropathy
Other medications: patients were allowed other meds - 50% on BB, 77% on statin, 42% on diabetic meds
Inclusion: Patients 45 years of age or older with one of the following: multiple atherothrombotic risk, documented coronary disease, symptomatic PAD. Major (type 1 or type 2 DM, diabetic nephropathy, etc) and minor (HTN, hypercholesterolemia, smoking, male sex) risk was assessed
Exclusion: taking long term oral antiplatelet, NSAIDs, excluded if they needed clopidogrel due to a recent acute coronary syndrome, clopidogrel after revascularization
Outcome Events: Primary - composite of first occurrence of MI, stroke, death from cardiovascular causes. Secondary - composite of first occurrence of MI, stroke, death from cardiovascular causes OR hospitalization from unstable angina, TIA, revascularization procedure. Each of these were considered separately. Safety was assessed. The primary endpoint was performed in prospectively defined subgroups - those symptomatic (established cardiovascular disease) versus those asymptomatic (enrolled based on risk).

1. Are the results valid?
   * Randomized? yes
   * Placebo controlled? yes
   * Were the groups similar? yes
   * Where patients accounted for? yes

2. What were the results?

<table>
<thead>
<tr>
<th>Outcome clusters</th>
<th>Clopidogrel + aspirin</th>
<th>Aspirin + placebo</th>
<th>P</th>
<th>ARR</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary composite</td>
<td>6.8%</td>
<td>7.3%</td>
<td>NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All death</td>
<td>4.8%</td>
<td>4.8%</td>
<td>NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death from CV causes</td>
<td>3.1%</td>
<td>2.9%</td>
<td>NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>nonfatal MI</td>
<td>1.9%</td>
<td>2.0%</td>
<td>NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>nonfatal ischemic stroke</td>
<td>1.7%</td>
<td>2.1%</td>
<td>NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>all nonfatal stroke</td>
<td>1.9%</td>
<td>2.4%</td>
<td>.05</td>
<td>0.5%</td>
<td>200</td>
</tr>
<tr>
<td>Secondary composite</td>
<td>16.7%</td>
<td>17.9%</td>
<td>.04</td>
<td>1.2%</td>
<td>83</td>
</tr>
<tr>
<td>Hospitalization, TIA, revascularization</td>
<td>11.1%</td>
<td>12.3%</td>
<td>.02</td>
<td>1.2%</td>
<td>83</td>
</tr>
</tbody>
</table>

Subgroups
Symptomatic (n=12,153)
   * Primary composite 6.9% 7.9% .046 1.0% 100 (no bonferroni correction)
   * All death NS
   * Death from CV causes NS

Asymptomatic (n=3284)
   * Primary composite 6.6% 5.5% NS
   * All death 5.4% 3.8% .04 1.6% 63
   * Death from CV causes 3.9% 2.2% .01 1.7% 59

Safety
   * Moderate bleeding 2.1% 1.3% <.001 0.8% 125
No difference in severe, fatal bleeding, or intracranial bleeding

3. Will the results help me?
   * 20.4% discontinued clopidogrel group vs 18.2 % in placebo group (p = <.001, NND = 45)

Conclusion: There was no benefit associated with the addition of clopidogrel to aspirin to prevent atherothrombotic disease in patients at high risk. The best affect was achieved in those with symptomatic disease (NNT=100), but the p-value was marginally significant in light of multiple comparisons (no bonferroni correction). There was increase risk of death in those at high risk (asymptomatic), an unexpected finding. Dual antiplatelet therapy should be avoided in patients without established vascular disease.