An Overview of IDEAL – A Comparison of Intensive Statin vs Low-Moderate Statin Therapy in stable CAD patients with a Previous MI (e.g. High-Risk Patients)

**IDEAL Trial Overview**

- a multi-center prospective randomized open-label, blinded end-point trial to determine lipid lowering effects of high dose atorvastatin vs low-moderate dose simvastatin on major coronary events defined as ‘coronary death/ non fatal acute MI/cardiac arrest with resuscitation’ in previous MI patients (intention to treat analysis; all patients enrolled were included in final analysis)
- two treatment arms: 
  - atorvastatin 80mg daily (↓ 40% if side effects) (n=4439) 89% adherence to therapy
  - simvastatin 20-40mg daily (↑ to 40mg if total cholesterol ≥5 mmol/l at 24wks) (n=4449) 95% adherence to therapy
- 8,888 patients were followed for 4.8 years (4-5.9yrs) with the following characteristics:
  - males ~81% & females with previous MI (MIs: were ~21months before, with only 11% of MIs in the last 2 months)
  - age: mean ~62 years (<80yr) Baseline LDL levels: 3.14 mmol/l BMI: 27.3 kg/m² BP: 137/80 mm Hg
  - smokers 20%, former smokers 58%, hypertension 33% & history of diabetes 12%

**Table 1: IDEAL Results**

<table>
<thead>
<tr>
<th>Endpoints</th>
<th>Atorvastatin% (n=4439)</th>
<th>Simvastatin% (n=4449)</th>
<th>ARR %</th>
<th>RRR %</th>
<th>NNT/4.8 yrs</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><em><em>Coronary death/non fatal acute MI</em>/or cardiac arrest with resuscitation</em>*</td>
<td>9.3</td>
<td>10.4</td>
<td>1.1</td>
<td>11</td>
<td>NS</td>
<td>0.07</td>
</tr>
<tr>
<td><strong>Nonfatal MI</strong></td>
<td>6</td>
<td>7.2</td>
<td>1.2</td>
<td>17</td>
<td>84</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>Major cardiovascular events (1° &amp; stroke)</strong></td>
<td>12</td>
<td>13.7</td>
<td>1.7</td>
<td>13</td>
<td>59</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>Any CHD event</strong></td>
<td>20.2</td>
<td>23.8</td>
<td>3.6</td>
<td>16</td>
<td>28</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Any cardiovascular event</strong></td>
<td>26.5</td>
<td>30.8</td>
<td>4.3</td>
<td>16</td>
<td>23</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Cardiovascular mortality</strong></td>
<td>3.4</td>
<td>3.9</td>
<td>0.5</td>
<td>13</td>
<td>NS</td>
<td>0.2</td>
</tr>
<tr>
<td><strong>Noncardiovascular mortality</strong></td>
<td>5</td>
<td>4.9</td>
<td>0.1</td>
<td>3</td>
<td>NS</td>
<td>0.78</td>
</tr>
</tbody>
</table>

Of Note:
- concomitant meds: ASA(79%), β-blocker(75%), ACE-I(30%), CCB(19%), warfarin(13%), ARB(10%)
- LDL mean levels during treatment: atorvastatin arm: 2.1 mmol/l; simvastatin arm: 2.7 mmol/l (~75% of pts had previously been on statins ~51% of simvastatin pts were already statin users); LDL ↓33% in the simvastatin naïve arm & ↓49% in the atorvastatin naïve arm at 12 wks
- both total cholesterol by 0.74mmol/l & triglycerides by 0.67mmol/l more in the atorvastatin than the simvastatin group at year 1
- HDL by 0.03mmol/l/more in the simvastatin group at year 1 (thus small HDL differences not likely clinically important)

**SAFETY**

- Myopathy: Rate: 1 in 500; 11 simv pts & 6 atorv pts. Rhabdomyolysis: Rate: 1 in 1800; 5 cases by investigators only 2 for atorv
- ALT/AST elevations >3 x ULN occurred in 1% of patients in the atorvastatin arm and 0.1% in the simvastatin arm; NHN=112
  - atorvastatin 80mg vs 10mg in the TNT trial n=10,001 4.9yr; 1.2% vs 0.2% of pts had liver ALT levels >3 x ULN; NHN=100
  - permanently discontinued study med: atorvastatin 14% & simvastatin 7% (most switched to a different statin)
- adverse events worse with atorvastatin: D/Cmed 26.4% vs 16.1%; eg. myalgia 2.2 vs 1.1%, diarrhea 0.5 vs 0.2%, abdominal pain 0.4 vs 0.2% & nausea 5.5 vs 0.1%
- noncardiovascular deaths higher in TNT trial 2.2 % atorv 80 vs 2.5 % simv 20

What we knew and what these results add to that knowledge:

- Many large RCTs, including IDEAL have shown statins reduce the risk of death or CV events in high-risk patients. Current guidelines recommend reducing LDL to <2.5mmol/l in patients with CAD or diabetes previous studies using moderate statin doses have shown this is beneficial. TNT & IDEAL showed a ↓ in CV events but some ↑ in SE with high dose statins and resulting LDLs of ~2 mmol/l
- IDEAL: more aggressive lipid therapy (atorvastatin 80mg/d vs simvastatin 20-40mg/d) appears to provide greater benefit against major CV events & stroke compared to previous MI patients. Some adverse event rates causing discontinuation are increased with the atorvastatin 80mg which may warrant caution and or monitoring. Magnitude of benefit was “one less major CV event & stroke for every 28 previous MI pts treated over 5 years”; specifically less nonfatal acute MI 5 vs 7.2% NNT=84, but NO reduction in CV mortality, all-cause mortality or the 1° outcome (major coronary events)
- Heads-Up: 1) previous statin exposure (75%) may pre-select for patients likely to tolerate either arm
  2) most simvastatin patients at 20mg/d dose whereas most simvastatin evidence lies with a 40mg dose
  3) benefit relies on select secondary endpoints of trial since primary was not significant.
  4) may not be able to extrapolate benefit of routine high-dose atorvastatin to lower risk patients

Questions Remaining:
- What about lower risk patients requiring high dosages to reach targets? What is the benefit mechanism (ie: is it due to ↓ LDL only, CRP levels, anti-inflammation)? What is the long-term benefit/risk profile of higher aggressive dose statin therapy? Was it the dose of statin or the statin they dosed?
Upcoming Trials:

**SEARCH**
(The Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine tests)\(^9\): comparing simvastatin 20mg and 80mg in CHD patients

**SPARCL**
(Stroke Prevention by Aggressive Reduction in Cholesterol Levels)\(^9,10\): evaluating the effects of atorvastatin 80mg/day in 4,732 patients with previous stroke or TIA, but no hx of CHD

**ASPEN**
(Atorvastatin Study for the Prevention of CHD Endpoints in NIDDM)\(^11\)

References:


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