An Overview of PROVE IT-TIMI 22 – A Comparison of Intensive Statin Therapy and Moderate Statin Therapy in Acute Coronary Syndrome Patients.

PROVE IT-TIMI 22 Trial Overview

- a multi-center randomized treatment-controlled trial to determine lipid lowering effects of high dose atorvastatin vs. moderate dose pravastatin on ‘all-cause mortality/MI/unstable angina/vascularization/stroke’ in patients recently hospitalized with an acute coronary syndrome (ACS).
- two treatment arms: • atorvastatin 80mg daily plus standard treatment for ACS (n=2099)
  • pravastatin 40mg daily plus standard treatment for ACS (n=2063)
- 4,162 patients were followed for 24 months (18-36 months) with the following characteristics:
  - males and females recently hospitalized for an ACS (MI or high risk unstable angina within last 10 days)
  - age: ~58 years
  - sex: ~78% male
  - baseline LDL levels: 2.74 mmol/l
  - Peripheral Arterial Disease: 5% ator vs 6.6% prav

Table 1: PROVE IT-TIMI 22 results

<table>
<thead>
<tr>
<th>Endpoints</th>
<th>atorvastatin % (n=2099)</th>
<th>Pravastatin% (n=2063)</th>
<th>ARR %</th>
<th>RRR %</th>
<th>NNT</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. All cause mortality/MI/unstable angina*/revascularization**/stroke</td>
<td>22.4</td>
<td>26.3</td>
<td>3.9</td>
<td>15</td>
<td>26</td>
<td>0.005</td>
</tr>
<tr>
<td>2. CHD death, nonfatal MI or revascularization</td>
<td>19.7</td>
<td>22.3</td>
<td>2.6</td>
<td>14</td>
<td>38</td>
<td>0.029</td>
</tr>
<tr>
<td>3. All-cause mortality</td>
<td>2.2</td>
<td>3.2</td>
<td>1.0</td>
<td>28</td>
<td>NS</td>
<td>0.07</td>
</tr>
<tr>
<td>4. Death/nonfatal MI</td>
<td>8.3</td>
<td>10.0</td>
<td>1.7</td>
<td>18</td>
<td>NS</td>
<td>0.06</td>
</tr>
<tr>
<td>5. Unstable angina</td>
<td>3.8</td>
<td>5.1</td>
<td>1.3</td>
<td>29</td>
<td>77</td>
<td>0.02</td>
</tr>
<tr>
<td>6. Revascularization</td>
<td>18.8</td>
<td>16.3</td>
<td>2.5</td>
<td>14</td>
<td>40</td>
<td>0.04</td>
</tr>
</tbody>
</table>

* requiring hospitalization ** either percutaneous coronary intervention or coronary artery bypass grafting

Of Note:

- study based on intention to treatment
- concomitant meds: ASA(93%), warfarin(8%), clopidogrel or ticlodipine (72% initially, 20% @ 1 yr), β-blocker(85%), ACE-I(69%), ARB(14%)
- short trial (~2 years); lack data on long term benefits; lack data on adverse reactions
- LDL at follow up: pravastatin arm: 2.46 mmol/l (2.04-2.92 mmol/l); atorvastatin arm: 1.60 mmol/l (1.29-2.04 mmol/l)
- 75% of patients had not previously been on statin therapy: LDL ↓ 22% in the pravastatin arm & ↓ 51% in the atorvastatin arm at 30 days (p<0.001)
- 25% were on previous statin therapy; LDL was essentially unchanged in the pravastatin arm & an additional 32% in the atorvastatin arm (p=0.001)
- (Statistical benefit only seen in the subgroup with LDL >3.2 mmol/l.)
- C-reactive protein levels were ↓ 83% 12.3→1.3 mg/l in the pravastatin arm & ↓ 89% 12.3→1.3 mg/l in the atorvastatin arm
- SAFETY: Creatine kinase ↑ in 2.7% of pravastin pts & 3.3% of atorvastatin pts. NO cases of rhabdomyolysis in either arm
- elevations in ALT levels >3 x ULN occurred in 1.1% of patients in the pravastatin arm and 3.3% in the atorvastatin arm (p=0.001; NNH=46)
- atorvastatin 80mg was one treatment arm in the AVERT2,3 trial - 2% of those pts had ALT levels >3 x ULN
- atorvastatin 80mg was one treatment arm in the MIRACL2,4 trial - 2.5% had ALT levels >3 x ULN, and 3 hepatitis cases occurred
- REVERSAL (The Reversal of Atherosclerosis with Aggressive Lipid Lowering) trial: compared atorvastatin 80mg/day and pravastatin 40mg/day in 654 stable coronary dx pts to measure the rate of dx progression over 18 months using intravascular ultrasound (limitation=small # of pts in the trial). The 1° end point (% change in atheroma vol) showed significantly lower progression rate in the atorvastatin arm. C-reactive protein ↓ 5.2% 3→2.9 mg/l in the pravastatin arm & ↓ 36.4% 2.8→1.3 mg/l in the atorvastatin arm. (p=0.001)

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

- There are many large randomized controlled trials that have shown statins reduce the risk of death or CV events in high risk patients. Current guidelines recommend reducing LDL levels to <2.5 mmol/l in patients with CAD or diabetes; previous studies using moderate statin doses have shown this is beneficial.1
- PROVE IT has demonstrated that an early, more aggressive lipid lowering regimen (atorvastatin 80mg/day) provides greater benefit against ‘death or CV events’ in ACS patients. An aggressive lipid lowering regimen resulting in LDL levels lower than currently recommended targets may provide greater benefit for these high risk patients.2,6 Adverse event rates increase at higher doses, therefore caution is warranted, especially when considering aggressive lipid lowering in patients at lower risk.
- Magnitude of benefit was “one less ‘death or CV event’ for every 26 ACS patients treated over 2 years”; additional reductions seen in other endpoints such as unstable angina and revascularization.

Questions Remaining:

- Would benefits be seen in lower risk patients? What is the mechanism of the benefit (ie: is it due to ↓ CRP levels/anti-inflammation)1? 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? What would have happened if they compared atorvastatin 10mg with atorvastatin 80mg?

(See next page for list of upcoming trials.)
Upcoming Trials:

**TNT** (Treating to New Targets)\(^7,8\): comparing atorvastatin 10mg and 80mg in ~10,000 CHD pts for 5 years. They are investigating the benefits of aggressive lipid lowering therapy. 1° endpoint=time to occurrence of a major CV event. Results expected in 2005.

**IDEAL** (Increment Decrease in Endpoints through Aggressive Lipid Lowering)\(^8\): comparing atorvastatin 80mg/day vs simvastatin 20-40mg/day in patients with an acute MI or a hx of MI. They are investigating the benefits of aggressive lipid lowering therapy. Results expected in 2005.

**SEARCH** (The study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine tests)\(^8\): comparing simvastatin 20mg and 80mg in CHD patients. Results expected in 2004/2005.

**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. Results expected in October 2004.

**ASPEN** (Atorvastatin Study for the Prevention of CHD Endpoints in NIDDM)\(^11\) and **CARDS** (Collaborative AtoRvastatin Diabetes Study)\(^11\): evaluating if aggressive lipid lowering (using atorvastatin vs placebo) can lead to 1° prevention of CV events in >4000 type II diabetes pts with no previous MI over 4 years. Also investigating the benefits of ↓ LDL below the current recommended guidelines.

References:

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