Q&A: Update on Statins

Questions coming up in light of new trials and media headlines

1. Are statins overused or underused?
   - There is evidence for underuse of statins in those at highest cardiovascular (CV) risk (e.g. Post-MI patients).  
   - There are varying opinions on their use in lower risk populations. Specifically some groups and recent reports in the media have suggested that statins may be overused in certain patients.  
   - Trials provide some insight into the number of patients that derive benefit from statin therapy given varying degrees of CV risk. Whereas better than 1 out of 10 very high risk patients may have outcome benefits over 5 years, this decreases to 1 out of 60 in high-risk primary prevention in ASCOT. In ASCOT the typical patient had hypertension plus 3.7 additional risk factors.

2. Statins are generally well tolerated. Potential serious adverse effects include liver enzyme elevation (<2%), myopathy (<1%) and rhabdomyolysis (<0.2%). Risk of adverse effects may be related to statin dose and preexisting individual risk factors. Trials often exclude patients with renal dysfunction, drug interactions and those not tolerating statin during pre-trial run-in period (HPS, 36% of enrollees eliminated during 4 week run-in phase).

3. There is controversy regarding statins in women without heart disease due to the lack of trials specific to this area and the lack of benefit in female subgroups in primary prevention trials (e.g. ASCOT). In HPS, which included women and without CHD combined, subgroup analysis showed that women did benefit from statin therapy.

4. For individuals without coronary heart disease (CHD) or CHD equivalents, the decision of whether to initiate lifelong statin therapy should be based on a careful weighing of the potential for benefit against the potential risks and costs of therapy. Table 1 (opposite page) provides the 5 year likelihood of a cardiovascular event in various population groups.

2. Should high-dose statins be used in high risk - acute coronary syndrome (ACS) - patients?
   - **Maybe Yes:** The recent PROVE-IT trial found that atorvastatin 80mg od was more effective than pravastatin 40mg in reducing major CV/stroke events in ACS patients. The aggressive dose appeared well tolerated except for an increase in ALT elevation with atorvastatin 80mg (3.3% NNH=46). The results from MIRACL also found potential outcome benefits and ALT elevation with high-dose atorvastatin.

   - **...Or Maybe Not:** In the A-Z trial (under powered since planned for 970 events yet only 652 events experienced), early-aggressive dosing of simvastatin did not result in significant benefit compared to delayed-less-aggressive simvastatin treatment (simvastatin 40mg od x 1 month, then 80mg od versus placebo x 4 months, then 20mg od). Myopathy was higher with the aggressive dose (0.4% NNH=250).

   - Why the difference? Was it the statin, the dose, the delay, the absolute reduction in LDL or the differences in the clinical trials? This is open to speculation. Some point out that statins may differ (e.g. effect on CRP).

3. What’s the objective take on the CRESTOR (rosuvastatin) controversies?
   - Rosuvastatin CRESTOR has received some bad press in both professional and lay publications.
   - It is currently the most potent statin in lowering LDL (rosuvastatin 5-10mg = atorvastatin 10-20mg). It appears to have positive effects on HDL and minimal potential for drug interactions.

   - Concerns regarding rosuvastatin include the current lack of any outcome trials, reports of rhabdomyolysis and renal effects. In Canada, there have been 14 reported cases of rhabdomyolysis. Of the first eight reported rhabdomyolysis cases in June/04, two cases occurred at the 10 mg daily starting dose BUT five cases were at 40 mg. All eight had pre-existing risk factors. For those valuing drugs and dosages with a proven outcome and safety record, simvastatin 40mg, atorvastatin 20mg (≤80mg in ACS?), or pravastatin 40mg would be suitable initial statins of choice in most patients (See Table 1). Selection of specific agent and dose may be individualized depending on comorbidity, drug interactions, cost and initial LDL. [Risk Factors for rhabdomyolysis include: ↓ renal function, drug interactions e.g. fibrates, niacin, cyclosporin, high statin doses, patients with diabetes, Asians, elderly and hypothyroidism]

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Table 1: NNTs for Statins in Various Risk Groups – Major Trial Data (Standardized for 5 years) *

<table>
<thead>
<tr>
<th>Typical Patient in Trial</th>
<th>Trial Drug &amp; Dose</th>
<th>Number of patients treated for 5 years for 1 less cardiovascular event (generally CHD death or non-fatal MI +/- revascularization)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CV Event</td>
<td>all-death</td>
<td></td>
</tr>
<tr>
<td>DM or IFG (BG≥6), CVD, male 58yo, LDL ~ 4.9, (2° prevention)</td>
<td><strong>4S</strong>: subgroup 16, n=678 3.3yr Simvastatin 20-40mg od</td>
<td>10</td>
<td>18</td>
</tr>
<tr>
<td>History of MI, angina, male, 58yo, LDL= 4.9 (2° prevention)</td>
<td><strong>4S</strong>: n=4,444 3.3yr Simvastatin 20-40mg od</td>
<td>13</td>
<td>33</td>
</tr>
<tr>
<td>Acute Coronary Syndrome, male, age 58yo, LDL=2.7 (2° prevention)</td>
<td><strong>PROVE-IT</strong>: n=4,162 2.7 yr Atorvastatin 80mg od vs Pravastatin 40mg od</td>
<td>15</td>
<td>NS</td>
</tr>
<tr>
<td>DM, CHD or other CVD, BMI 28.6ave, BP 148/82_ave (2° prevention)</td>
<td><strong>HPS</strong>: subgroup 19; n=3,051 4.3yr Simvastatin 40mg od</td>
<td>17</td>
<td>na</td>
</tr>
<tr>
<td>High risk with or without history of CHD; LDL=3.9 (1° &amp; 2° prevention)</td>
<td><strong>HPS</strong>: n=20,536 5yr Simvastatin 40mg od</td>
<td>19</td>
<td>57</td>
</tr>
<tr>
<td>DM, high risk, but no CHD, BMI 28.6_ave, BP 148/82_ave (1° prevention)</td>
<td><strong>HPS</strong>: subgroup 19; n=2,912 3.3yr Simvastatin 40mg od</td>
<td>23</td>
<td>na</td>
</tr>
<tr>
<td>Type 2 DM, no CHD, male, 62yo, LDL 3.0, hypertension (1° prevention)</td>
<td><strong>CARDS</strong>: n=2,838 4yr Atorvastatin 10mg od</td>
<td>25</td>
<td>NS</td>
</tr>
<tr>
<td>Male, ~55yo, 44% smoker, LDL=5 (1° prevention)</td>
<td><strong>WOSCOPS</strong>: n=6,595 4.3yr Pravastatin 40mg od</td>
<td>41</td>
<td>109 10%=0.035 NS NS</td>
</tr>
<tr>
<td>Male, 63yo, no CHD, hypertension+3 additional risk factors, LDL=3.4 (1° prevention)</td>
<td><strong>ASCOT</strong>: n=10,305 3.3yr Atorvastatin 10mg od</td>
<td>60</td>
<td>NS</td>
</tr>
<tr>
<td>Female – hypertension+3 risk factors), no CHD, LDL=3.4 (1° prevention)</td>
<td><strong>ASCOT</strong>: subgroup n=1,942 3.3yr Atorvastatin 10mg od</td>
<td>??</td>
<td>na</td>
</tr>
<tr>
<td>Male or Female with high cholesterol, &amp; 0-1 risk factors</td>
<td>Not studied</td>
<td>???</td>
<td>na</td>
</tr>
</tbody>
</table>

1°=Primary prevention 2°=Secondary prevention ALT=alanine aminotransferase BG=blood glucose CRP=C-reactive protein CHD=coronary heart disease CVD=cardiovascular disease DM=diabetes mellitus IFG=impaired fasting glucose LDL=low density lipoprotein na=not available NNT(H)=number needed to treat (harm) NS=non-significant ULN=upper limit of normal yr=year

*The above table is devised to demonstrate general differences in the potential for benefit as demonstrated in outcome trials. The quantitative values indicated are subject to various assumptions and should be interpreted with this in mind. (Note: typical patient may not reflect range of patient risk in usual patients and generally required patients to survive a 4 week “run-in” period before inclusion in the trial.

**Cost** per year in Sask:  **Atorvastatin 10mg od $800, 80mg od $1,050; Pravastatin 40mg od $90, Simvastatin 20-40mg od $550** 5yr drug cost per CHD event prevented: 2° prevention: 4S $35,000 1° prevention: ASCOT $240,000 5yr drug cost per life saved: 2° prevention: 4S $90,000 1° prevention: ASCOT NS ($530,000 assumes benefit based on NS trend).