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).[1]
- 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.[2,3,4] 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 4S-DM [14], this decreases to 1 out of 60 in high-risk primary prevention ASCOT [5]. In ASCOT the typical patient had hypertension plus 3.7 additional risk factors.
- **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).
- 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 [6] which included women with and without CHD combined, subgroup analysis showed that women did benefit from statin therapy.
- 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 outcome benefit 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.[7] 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.[8]
- **…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 x1month, then 80mg od versus placebo x4 months, then 20mg od).[9] 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 A-Z ~0.4mmol/l vs PROVE-IT ~0.9 mmol/l 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?

- Rosuvstatin *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).[10] 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. [11,12,13] In Canada, there have been **14** reported cases of rhabdomyolysis.[14] (US FDA: 65 by public citizen→26 FDA confirmed cases through Aug 2004) 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 ≥10mg (≤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, cyclosprorine, high statin doses, patients with diabetes, Asians, elderly and hypothyroidism}

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[1] Health Quality Council (SK). Drug Management of AMI in Saskatchewan. Sep 2004. Report accessible at www.hqc.sk.ca
[2] Center for Science in the Public Interest. http://www.cspinet.org/new/200409231.html
[3] Therapeutic Initiative. Do Statins have a Role in Primary Prevention? http://www.ti.ubc.ca/pages/letter48.htm
[4] Topol E. Top US cardiologist sees need for statin targeting. Accessed 20Oct04 at: http://yahoo.reuters.com/financeQuoteCompanyNewsArticle.jhtml?duid=mtfh61939_2004-10-19_22-46-33_n19498018_newsml
[5] Peter S Sever, et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial--Lipid Lowering Arm (**ASCOT-LLA**): a multicentre randomised controlled trial Lancet 2003; **361:** 1149-58.
[6] .MRC/BHF **HPS** study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet 2002 Jul 6;360(9326):7-22.
[7] Cannon CP, Braunwald E, McCabe et al.; Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 Investigators. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. (**PROVE-IT**) N Engl J Med. 2004 Apr 8;350(15):1495-504. Epub 2004 Mar 08.
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[10] NCEP Expert Panel. Executive summary-3rd national cholesterol education program on detection, evaluation and treatment of high blood cholesterol in adults (**A**dult **T**reatment **P**anel **III**). JAMA **2001**;285:2486-97. Grundy SM, Cleeman JI, Merz CN, et al.; National Heart, Lung, and Blood Institute; **American** College of Cardiology Foundation; American Heart Association. Implications of recent clinical trials for the National Cholesterol Education Program **Adult Treatment Panel III guidelines**. Circulation. **2004** Jul 13;110(2):227-39. http://www.acc.org/clinical/adoptions/ncep_report.pdf
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Table 1: NNTs for Statins in Various Risk Groups – Major Trial Data (Standardized for 5 years) [15] *

Typical Patient in Trial	Trial Drug & Dose	Number of patients treated for 5 years for 1 less cardiovascular event (generally CHD death or non-fatal MI +/- revascularization)		Comments
		CV Event	all-death	5yr Mortality Rate % in Placebo→Treated Group
DM or IFG (BG≥6), **CVD**, male 58yo, LDL ~ 4.9, (**2°** prevention)	**4S**-subgroup [16]; n=678 [5.4yr] Simvastatin 20-40mg od	10	18	◆highest risk: DM with CVD benefit the most
History of MI, angina, male, 58yo, LDL= 4.9 (**2°** prevention)	**4S** [17]; n=4,444 [5.4yr] Simvastatin 20-40mg od	13	33	◆Recent 10 year follow up data shows beneficial outcomes preserved [18] **10.6→7.6**
Acute Coronary Syndrome, male, age 58yo, LDL=2.7 (**2°** prevention)	**PROVE-IT** [7]; n=4,162 [2yr] Atorvastatin **80mg** od **vs** Pravastatin 40mg od	15 ◆Kaplan-Meier curves separate after 6 months (**NNT 38 / 2yrs**).	NS	◆ALT >3x ULN: 3.3 vs 1.1% [NHH=46] ◆statin started within 10 days; evaluated over 2 years
DM, CHD or other CVD, BMI 28.6$_{ave}$, BP 148/82$_{ave}$ (**2°** prevention)	**HPS** -subgroup [19]; n=3,051 [4.8yr] Simvastatin 40mg od	17	na	◆90% type 2 DM, average >9yrs since diagnosis (10% type 1, ave >28yrs since diagnosis)
High risk with or without history of CHD; LDL=3.9 (1° & **2°** prevention)	**HPS** [5]; n=20,536 [5yr] Simvastatin 40mg od	19	57	◆benefit regardless of initial LDL, in **females** [n=5,082], and in older population (up to age 80) **14.6→12.9**
DM, high risk, but no CHD BMI 28.6$_{ave}$, BP 148/82$_{ave}$ (1° prevention)	**HPS** -subgroup [19]; n=2,912 [4.8yr] Simvastatin 40mg od	23	na	◆90% type 2 DM, average >9yrs since diagnosis (10% type 1 DM, ave >28yrs since diagnosis)
Type 2 **DM**, no CHD, male, 62yo, LDL 3.0, hypertension (1° prevention)	**CARDS** [20]; n=2,838 [4yr] Atorvastatin 10mg od	25 Acute Coronary Events Only: **NNT = 43** / 5yrs)	NS	◆benefit even when LDL already ≤3mmol/L; **trial halted early** ◆high risk diabetes group (+1 additional risk factors) **7.3→5.4**
Male, ~55yo, 44% smoker, LDL=5 (1° prevention)	**WOSCOPS** [21] n=6,595 [4.9yr] Pravastatin 40mg od	41	(109? p=0.051) NS	◆trial included high risk patients (15% hypertension, 5% angina) **4.2→3.3**
Male, 63yo, no CHD, hypertension+3 additional risk factors, LDL=3.4 (1° prevention)	**ASCOT** [4]; n=10,305 [3.3yr] Atorvastatin 10mg od	60 ◆Kaplan-Meier curves separate at ~6 months & **trial halted** at **3.3 years** given apparent benefit (**NNT 91/3.3yrs**).	NS	◆average: 3.7 risk factors in addition to hypertension (eg. age, male, microalbuminuria, smoker, family history, diabetes [25%]) **6.2→5.5**
Female – hypertension +3 risk factors), no CHD, LDL=3.4 (1° prevention)	**ASCOT** [4] -subgroup n=1,942 [3.3yr] Atorvastatin 10mg od	**???** ◆even with hypertension and 3+ risk factors, these women appear relatively low risk	na	◆no benefit apparent in the **female** subgroup ◆MI or Fatal CHD: 1.9% atorvastatin vs 1.8% placebo.
Male or **Female** with high cholesterol, & 0-1 risk factors	Not studied	**???**	na	◆NNTs, if significant would be very high, so trials not likely to ever be done

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**=impair 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 trial; 5 year NNTs are extrapolated from major trials, a few of which had quite different durations of 2yrs [PROVE-IT], 3.3yrs [ASCOT]; trial design excludes unusual 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 **$525**; **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])

[15] RxFiles – All-Cause Mortality Outcomes from Major Lipid Trials. http://www.rxfiles.ca/acrobat/CHT-lipid%20agents-major%20trials.pdf

[16] Haffner SM, Alexander CM, Cook TJ, et al. Reduced coronary events in simvastatin-treated patients with coronary heart disease and diabetes or impaired fasting glucose levels: subgroup analyses in the Scandinavian Simvastatin Survival Study (4S). Arch Intern Med. 1999 Dec 13-27;159(22):2661-7.

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