**Evidence review for statins:**

We know that Atorvastatin 80mg is significantly more effective than most other statins at lowering cholesterol (lowers LDL cholesterol by 55%) and we also know from large reviews of statin trials that, on average, each “1 point” (mmol/litre) in reduction of bad cholesterol reduces heart attacks by 20% and reduces the risk of death by 12%. On average, atrovastatin 80mg tended to reduce LDL cholesterol by a further 0.5 points compared to other statins in the trials, but it all depends on what statin (if any) we are comparing to, of course.

The “CTT review” of trails looked at 14 randomised trials of statin therapy, and involved over 90,000 patients, about half a million “patient-years” of treatment, 8000 deaths, 14,000 major vascular events, and 5000 cancers among 90,056 participants[2]. The mean duration of treatment in these trials was about 5 years. Overall, there was a 12% reduction in all-cause mortality per 1 mmol/l LDL cholesterol reduction, mainly due to a reduction of about one fifth in heart-attack deaths per 1 mmol/l lower LDL cholesterol (https://www.ctsu.ox.ac.uk/research/meta-trials/ctt/ctt-website)

A CVD risk reduction benefit was observed in 2 randomized controlled trials (RCTs) of atorvastatin 80 mg compared to either atorvastatin 10 mg or simvastatin 20-40 mg in individuals with chronic coronary heart disease (TNT and IDEAL). In these trials, there was no lower limit to LDL for eligibility, supporting treatment with a statin regardless of the LDL level.

An additional reduction in CVD events from a high intensity statin was shown specifically in individuals with acute coronary syndromes in the PROVE-IT trial where those assigned to atorvastatin 80 mg/day a greater reduction in CVD events than those assigned to pravastatin 40 mg daily after 2 years of treatment.

IDEAL trial did not show increased mortality benefit compared to simvastatin, but there was clear CV event reduction.

1. TNT study showed atorva 80 reduced risk of non-fatal MI and stroke, NNT 48 over 5 years.
2. TIMI22 trial showed atorva 80, compared to prava 40, reduced 30 day and 6 month CV event rates significantly (about 23% RRR).

Specific info on intensive statins:

**CTT “second wave”:**

**Comparisons of more versus less intensive regimens**: The first cycle indicated that there was an approximately linear relationship between the absolute reductions in LDL cholesterol and the proportional reductions in major vascular events. However, a direct test of the hypothesis that further reductions in LDL-cholesterol

would provide additional reduction in risk requires randomised trials of a more intensive versus less intensive LDL-lowering regimen. To date, five large trials have examined this hypothesis: two have been conducted among patients with a recent acute coronary syndrome (PROVE-IT [Pravastatin or Atorvastatin Evaluation and Infection Therapy][5] and A to Z[6]) and three among patients with a prior MI (TNT [Treating to New Targets][7], IDEAL [Incremental Decrease in Endpoints Through Aggressive Lipid Lowering][8] and SEARCH [Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine][9]) (figure).

**Extended comparisons of statin versus control**: The first cycle included 14 trials comparing a statin versus a control regimen. In this updated analysis the additional trials are: ALLIANCE (Aggressive Lipid-Lowering Initiation Abates New Cardiac Events)[10]; 4D (Die Deutsche Diabetes Dialyze)[11]; ASPEN (Atorvastatin Study for Prevention of coronary heart disease Endpoints in non-insulin dependent diabetes mellitus)[12]; MEGA (Management of Elevated cholesterol in the primary prevention group of Adult Japanese)[13]; JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin)[14]; GISSI-HF (Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza cardiaca)[15] and AURORA (A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events)[16] (figure).

## Results

The second cycle of analyses included 26 randomised trials of statin therapy: 5 trials were of more vs. less statin therapy (39,612 patients, median follow up 5.1 years) and 21 trials were of statin vs. control (129,526 patients, median follow up 4.8 years). Taken together, these trials involved 15,969 deaths, 24,323 major vascular events, and 10,124 cancers among 169,138 participants[4]. The average difference in LDL cholesterol at 1 year among the statin vs. control trials was 1.07 mmol/L, whilst in the trials of more versus less intensive statin therapy the weighted mean further reduction in LDL cholesterol at 1 year was 0·51 mmol/L. Analyses were done both before and after weighting for the absolute difference in LDL cholesterol in each trial after 1 year of treatment.

Compared with less intensive regimens, **more intensive regimens produced a highly significant 15% (95% CI 11–18; p<0·0001) further reduction in major vascular events (figure), consisting of separately significant reductions in coronary death or non-fatal myocardial infarction of 13% (95% CI 7–19; p<0·0001), in coronary revascularisation of 19% (95% CI 15–24; p<0·0001), and in ischaemic stroke of 16% (95% CI 5–26; p=0·005) (figure).** Overall the weighted average further reduction in major vascular events was 28% (22-34; p<0.0001) per mmol/L reduction in LDL-cholesterol (figure) with separately significant reductions in each of the major components of this composite outcome (figure).

The results of the updated meta-analysis of the 21 statin vs. control trials were similar to those observed in the first cycle: there was a highly significant 21% (95% CI 19-23;p<0.0001) reduction per mmol/L LDL cholesterol reduction. The proportional reductions per mmol/L LDL cholesterol reduction were separately significant for coronary death or non-fatal myocardial infarction (24%, 95% CI 21–27;p<0·0001), coronary revascularisation (24%, 95% CI 20–27; p<0·0001), and ischaemic stroke (20%, 95% CI 14–26; p<0·0001) (figure).

When both types of trial were combined, similar proportional reductions in major vascular events per mmol/L LDL cholesterol reduction were found in all types of patient studied (figure, figure cont.) (rate ratio [RR] 0·78, 95% CI 0·76–0·80; p<0·0001), including those with LDL cholesterol lower than 2 mmol/L on the less intensive or control regimen (figure).

Across all 26 trials, all-cause mortality was reduced by 10% per mmol/L LDL reduction (RR 0·90, 95% CI 0·87–0·93; p<0·0001), largely reflecting significant reductions in deaths due to coronary heart disease (RR 0·80, 99% CI 0·74–0·87; p<0·0001) and other cardiac causes (RR 0·89, 99% CI 0·81–0·98; p=0·002), with no significant effect on deaths due to stroke (RR 0·96, 95% CI 0·84–1·09; p=0·5) or other vascular causes (RR 0·98, 99% CI 0·81–1·18; p=0·8) (figure). No significant effects were observed on deaths due to cancer or other non-vascular causes (RR 0·97, 95% CI 0·92–1·03; p=0·3) or on cancer incidence (RR 1·00, 95% CI 0·96–1·04; p=0·9) (figure), even at low LDL cholesterol concentrations.

Excerpt from BMJ 2014 ;349:g3743:

In an analysis from PROVE IT the safety and efficacy of atorvastatin 80 mg was assessed. Subjects in the intensive therapy arm were divided into subgroups by achieved LDL-C levels at 4 months and the risk of subsequent adverse events assessed.

Among nearly 2000 subjects with 4-month LDL-C data available about 90% had a LDL-C < 2.56 mmol/l.

Muscle side effects were infrequent, with no episodes of rhabdomyolysis observed.

Similar results were observed for liver-related side effects with no relationship between achieved LDL-C and the frequency of either liver enzyme elevations or discontinuation for abnormal liver enzyme levels.

In contrast, outcome data related to on-treatment LDL-C levels in patients with CAD suggest that an alternative approach may simply be to use the most powerful evidence-based treatments available (a population-based approach) but acknowledge that there will be a wide range of LDL-C achieved in the population, but each individual's long-term risk will be related to their achieved LDL-C.

In conclusion, achieving extremely low LDL-C levels appears both safe and effective, and it does not appear to be necessary to reduce the dose of a statin, if the resultant LDL-C levels fall well below the current guideline recommendations.

**SPARCL study**

Atorvastatin 80mg daily vs placebo

Incidence of fatal or non-fatal stroke reduced atorvastatin 11.2% vs. 13.1% placebo

=ARR 2.2% (adjusted P=0.05) , NNT 45 (95%CI 24 to 500)

Reduced incidences of TIA (6.5% vs. 8.8%) and major CV events (14.1% vs. 17.2%)

(Increased risk of haemorrhagic stroke -2.3% vs. 1.4% - which is a complex subject – Stroke guidance advises avoid high dose atorvastatin in previous haemorrhagic stroke).

**More info on myalgia and CK:**

Although CK may be useful at baseline in certain high-risk individuals or in those with a history of statin myopathy, the CK should not be routinely measured. In the statin RCTs, CK elevations occurred with similar frequencies in the statin and placebo/control groups. A CK should be performed if the patient complains of severe muscle pain or weakness. Re-challenge with a statin would determine whether any muscle aches were indeed caused by any previous statin. FDA and MHRA advise against routine use of simvastatin 80mg.

**Re: LFTs and liver failure:**

On 2/28/12, the FDA determined, based on all available data, including the RCT data reviewed by the Expert Panel, that “all currently marketed statins appear to be associated with a very low risk of serious liver injury and that routine periodic monitoring of serum alanine aminotransferase (ALT) does not appear to detect or prevent serious liver injury in association with statins.”