

# Cholesterol lowering for secondary prevention: What statin dose should we use?

Kiranbir Josan  
Finlay A McAlister

The Division of General Internal  
Medicine, University of Alberta,  
Edmonton, Canada

**Abstract:** Over the past decade, 17 large placebo-controlled trials have established that statin therapy lowers LDL cholesterol and prevents cardiovascular events and death in patients with coronary disease or at high risk for atherosclerotic events. Nine trials of higher dose vs. lower dose statins (reporting data from 29,853 patients with coronary artery disease and 486 patients with other indications for statin therapy) have established that higher dose statin therapy is more efficacious than lower dose therapy in reducing myocardial infarctions/coronary death (by 16%) and stroke (by 18%) in patients with coronary disease but only reduces all-cause mortality in patients at high risk for coronary death (such as patients immediately after acute coronary syndrome). Higher dose statins are associated with statistically significantly increased risks of myopathy and elevated transaminases compared to lower dose statins; while relative risks for these outcomes are 1.2 and 4.0, the absolute increases are small (0.5% and 1%). Secondary analyses of these trials using individual patient data and multivariate adjustment will be needed to appropriately examine the incremental benefits of different LDL targets, and trials are needed to determine whether combinations of low dose statins plus other lipid lowering agents may achieve better clinical outcomes than higher dose statin therapy alone.

**Keywords:** statins, secondary prevention, dosing, efficacy, safety

Over the past decade, an impressive number of randomized trials have confirmed that treatment with statins prevents cardiovascular events and improves survival in patients with a history of cardiovascular events as well as in patients who have not yet had an event but are at increased risk due to elevated cholesterol levels, diabetes mellitus, or hypertension (Law et al 2003; Cholesterol Treatment Trialists 2005). As a result of this randomized trial evidence, the indications for statin drugs have expanded rapidly and current guidelines recommend statin use in patients with, or at high risk for, atherosclerosis (Grundy et al 2004; Joint British Societies 2005; Khan et al 2006). Although meta-regression analyses of these randomized trials have confirmed that statins appear to exert their beneficial effects primarily via reduction of LDL cholesterol levels (Robinson et al 2005), the target LDL for patients with coronary artery disease (CAD) has remained a point of debate as this evidence base has accumulated.

Although large observational studies consistently demonstrate a strong log-linear relationship between blood cholesterol levels and coronary mortality (Verschuren et al 1995; Padwal et al 2001), these studies have not identified a threshold level for LDL cholesterol which separates those who will suffer a coronary event from those who will not (Chen et al 1991; O'Keefe 2004). While the cardiovascular relative risk reductions achieved with statin therapy appear to be similar regardless of baseline cholesterol levels in the large placebo-controlled randomized trials published thus

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Correspondence: Finlay McAlister  
2E3.24 WMC, University of Alberta  
Hospital, 8440 112 Street, Edmonton,  
Alberta T6G 2R7, Canada  
Tel +1 780 407 1657  
Fax +1 780 407 2680  
Email [finlay.mcalister@ualberta.ca](mailto:finlay.mcalister@ualberta.ca)

far (Table 1), all of these trials enrolled patients with LDL cholesterol levels above 3.0 mmol/L. Further, while subgroup analyses demonstrated similar benefits across baseline LDL cholesterol levels, it should be recognized that even the lowest tertile in these analyses incorporated patients with baseline LDL cholesterol levels as high as 3.5 mmol/L. Thus, the question of “how low should we go in lowering LDL cholesterol” remained unanswered even after these 17 placebo-controlled statin trials were completed.

In an attempt to address the issue of optimal LDL cholesterol target levels, recent statin trials have compared higher dose statin therapy to the lower dose statin therapy employed in the 17 placebo-controlled trials which established the efficacy of statins for preventing cardiovascular events (outlined in Table 1). It deserves emphasis that since these trials compared different fixed doses of statins with each other rather than titrating drug doses to achieve different target LDL levels, they cannot provide an unconfounded answer to the target LDL question. While this may seem like an argument over semantics, it is not. As pointed out by others, “compared with empirically treating patients...with statin doses similar to those used in clinical trials, titrating lipid therapy to recommended LDL cholesterol goals entails considerably greater clinical complexity, frequent use of multidrug therapy, and greater...costs” (Hayward et al 2006, page 521). Given the paucity of published evidence exploring the benefits of different LDL cholesterol targets in unconfounded analyses, our review will instead explore the question that can be answered from the existing trial literature – what statin dose should we use in patients with coronary heart disease? In order to answer this question, in this review we will examine the evidence from randomized trials comparing higher dose statin therapy versus lower dose statin therapy.

## The randomized trials of higher dose statins versus lower dose statins

### Trials reporting surrogate endpoints

#### The ASAP trial

The Effect of Aggressive versus conventional lipid lowering in Atherosclerosis Progression in familial hypercholesterolemia trial randomized 325 patients with familial hypercholesterolemia to atorvastatin 80 mg daily or simvastatin 40 mg daily (Smilde et al 2001). The primary endpoint was change in atheroma volume as assessed by quantitative B-mode ultrasound of carotid intima media thickness (IMT). LDL cholesterol lowering was significantly greater ( $p = 0.0001$ ) with atorvastatin

(from 8.00 mmol/L to 3.88 mmol/L) than simvastatin (from 8.33 mmol/L to 4.81 mmol/L). After 2 years, IMT decreased in the patients randomized to atorvastatin therapy ( $-0.031$  mm, 95% CI  $-0.007$  to  $-0.055$ ) but increased in the simvastatin-treated patients ( $+0.036$  mm, 95% CI  $+0.014$  to  $+0.058$ ) – this between-group difference was highly statistically significant ( $p = 0.0001$ ). Both treatment regimens were equally well tolerated.

#### The ARBITER trial

The Arterial Biology for the Investigation of the Treatment Effects of Reducing cholesterol trial randomized 161 patients meeting National Cholesterol Education Program II criteria for lipid-lowering therapy (46% of whom had known cardiovascular disease) to atorvastatin 80 mg daily or pravastatin 40 mg daily (Taylor et al 2002). The primary endpoint was change in carotid IMT. LDL cholesterol lowering was significantly greater ( $p < 0.001$ ) with atorvastatin (from 3.80 mmol/L to 1.95 mmol/L) than pravastatin (from 3.98 mmol/L to 2.82 mmol/L) at 12 months. After 12 months, IMT decreased in the patients randomized to atorvastatin therapy ( $-0.034$  mm  $\pm 0.021$  mm) but did not appreciably change in the simvastatin-treated patients ( $+0.025$  mm  $\pm 0.017$  mm) – this between-group difference was statistically significant ( $p = 0.03$ ). No patient in either treatment arm suffered a drug-related side effect.

## Trials reporting clinical endpoints

### The Post-CABG trial

The Post Coronary Artery Bypass Graft Trial randomized 1351 patients who had undergone bypass surgery in the preceding decade, still had at least one patent vein graft on angiography, and who had an LDL cholesterol level between 3.34 mmol/L and 4.49 mmol/L to aggressive or moderate intensity treatment to lower LDL cholesterol levels (with lovastatin and, if needed, cholestyramine) and, using a two-by-two factorial design, to treatment with warfarin or placebo (The Post Coronary Artery Bypass Graft Trial Investigators 1997). The primary endpoint was the per-patient percentage of initially patent major grafts that had substantial progression of atherosclerosis (a decrease of 0.6 mm or more in lumen diameter) at the site of greatest change at follow-up. During follow-up, patients assigned to the aggressive lipid treatment group were taking a mean of 76 mg lovastatin daily (30% were also taking 8 g of cholestyramine daily) and patients assigned to the moderate lipid treatment group were taking a mean of 4

**Table 1** Placebo-controlled statin trials which randomized greater than 250 participants

Trial	Study design	Treatment dose	Key eligibility criteria	Control group LDL at baseline/ at follow-up	Treatment group LDL at baseline/at follow-up	LDL subgroup analysis
4S	Secondary prevention, multicenter, median f/u 5.4 years	Simvastatin 20–40 mg	35–70 yrs, prior angina or AMI, fasting total chol 5.5–8.0 mmol/L	4.87/4.92	4.87/3.17	None
WOSCOPS	Primary prevention, one center, mean f/u 4.9 years	Pravastatin 40 mg	45–64 yrs, no prior AMI, fasting LDL chol 4.0–6.0 mmol/L	4.97/not reported	4.97/3.68	Baseline LDL < 4.9 vs > 4.9
CARE	Secondary prevention, multicenter	Pravastatin 40 mg	21–75 yrs, prior AMI, fasting LDL chol 3.0–4.5 mmol/L	3.6/	3.6/2.5	Baseline LDL < 3.2 vs 3.2–3.9 vs 3.91–4.5
AFCAPS/ TexCAPS	Primary prevention, multicenter, mean f/u 5.2 years	Lovastatin 20–40 mg	45–73 yrs (males) or 55–73 (females), no prior AMI, fasting LDL chol 3.4–4.9 mmol/L	3.89/4.04 (at 1 year)	3.89/2.96	None
LIPID	Secondary prevention, multicenter, mean f/u 6.1 years	Pravastatin 40 mg	31–75 yrs, prior AMI or unstable angina, fasting total chol 4–7 mmol/L	3.9/not reported	3.9/reduced by 25% more than placebo group	Baseline LDL < 3.5 vs 3.5–4.5 vs > 4.5
GISSI prevention	Secondary prevention, multicenter, mean f/u 23 months	Pravastatin 20 mg	Recent MI (<6 months), total cholesterol > 5.18 mmol/L	3.9/3.8	3.9/3.3	Baseline LDL < 3.4 vs > 3.4
HPS	Primary and secondary prevention, multicenter, mean f/u 5 years	Simvastatin 40 mg	40–80 yrs, with coronary disease, other occlusive arterial disease, or diabetes, with non-fasting tot chol of $\geq 3.5$	3.4/not reported	3.4/(1.0 mmol/L less than placebo)	Baseline LDL < 3.0 vs 3.1–3.4 vs $\geq 3.5$
MIRACL	Secondary prevention, multicenter, 16 weeks f/u	Atorvastatin 80 mg	> 18 yrs, unstable angina or non-Q-wave AMI	3.2/3.5 (at 16 weeks)	3.2/1.9 (at 16 weeks)	Baseline LDL < 3.1 vs > 3.1
Serruys study (LIPS)	Secondary prevention, multicenter, median f/u 3.9 years	Fluvastatin 80 mg	18–80 yrs, pts with stable or unstable angina or silent ischemia who underwent PCI, tot chol 3.5–7.0 mmol/L	3.4/3.8 (at 6 weeks)	3.4/2.5 (at 6 weeks)	Baseline LDL < 3.4 vs > 3.4
PROSPER	Primary and secondary prevention, multicenter, mean f/u 3.2 years	Pravastatin 40 mg	70–82 yrs, with history of or risk factors for vascular disease	3.8/	3.8/2.8	Baseline LDL < 3.41 vs 3.41–4.11 vs > 4.11
ASCOTT-LLA	Primary prevention, multicenter, median f/u	Atorvastatin 10 mg	40–79 yrs, hypertensive pts with at least 3 additional CHD risk factors,	3.44/3.45 (at 6 months; 1,2,3 yr	3.44/2.21	None

(Continued)

**Table 1** (Continued)

Trial	Study design	Treatment dose	Key eligibility criteria	Control group LDL at baseline/at follow-up	Treatment group LDL at baseline/at follow-up	LDL subgroup analysis
	3.3 years		non-fasting total chol <6.5 mmol/L	data avail)		
ALLHAT-LLT	Primary and secondary prevention, multicenter; mean f/u 4.8 years	Pravastatin 40 mg	>55yrs with stage 1 or 2 hypertension & one additional CHD risk, fasting LDL 3.1–4.9 mmol/L for no known CHD vs.. 2.6–3.3 mmol/L for known CHD	3.8/3.3 ( at 4 years; data for yr 2 & 6 also avail)	3.8/2.7	Baseline LDL < 3.37 vs. > 3.37
ALERT	Primary and secondary prevention, multicenter; mean f/u 5.1 years	Fluvastatin 40 mg	30–75 yrs, prev renal or combined renal and pancreas transplants, tot chol 4.0–9.0 mmol/L in pts with no CHD vs. 4.0–7.0 mmol/L for known CHD	4.1/	4.1/2.8 (at end of study)	None
CARDS	Primary prevention, multicenter; median f/u 3.9 years	Atorvastatin 10 mg	40–75 yrs, with type 2 diabetes and at least one of: retinopathy, albuminuria, current smoking, or hypertension; LDL ≤ 4.14 mmol/L	3.02/3.07 (at 6 months; values at 1,2, and 4 years also avail)	3.04/1.75	-Baseline LDL < 3.1, 39/696 atorvastatin vs. 61/718 placebo, HR 0.63 -Baseline LDL ≥ 3.1, 44/721 atorvastatin vs. 66/695 placebo, HR 0.62
SPARCL	Secondary prevention, multicenter; median f/u 4.9 years	Atorvastatin 80 mg	> 18 yrs, prior ischemic or hemorrhagic stroke or TIA, LDL chol 2.6–4.9 mmol/L	3.46/3.32	3.44/1.89	None
FLORIDA	Secondary prevention, multicenter; median f/u 1 year	Fluvastatin 80 mg	> 18 yrs, AMI, total chol ≤ 6.5 mmol/L	3.6/3.9	3.5/2.7	None
AVERT	Secondary prevention, multicenter; f/u 18 months	Atorvastatin 80 mg vs. PCI	Stable CAD, stenosis of ≥50% in at least one coronary artery, LDL ≥3.0 mmol/L, triglycerides ≤ 5.6 mmol/L	3.8/3.1	3.7/2.0	None

mg of lovastatin daily (and only 5% were also taking 8 g of cholestyramine daily). LDL cholesterol was reduced to 2.4 mmol/L in the aggressive treatment group and 3.5 mmol/L in the moderate treatment arm. After a mean follow-up of 4.3 years, the number of grafts demonstrating substantial progression of disease was statistically significantly reduced

in the aggressive-treatment group (27% vs. 39%,  $p < 0.001$ ). No significant differences in angiographic outcomes were observed between the warfarin and placebo groups and there was no interaction between warfarin and aggressive lipid lowering. Clinical events and adverse effects were uncommon and did not differ significantly between groups.

### The REVERSAL trial

The REVERSAL of atherosclerosis with Aggressive Lipid lowering Trial randomized 654 patients with angiographically proven CAD to atorvastatin 80 mg daily or pravastatin 40 mg daily (Nissen et al 2004). The primary endpoint was change in atheroma volume assessed by intravascular ultrasound. LDL cholesterol lowering was significantly greater ( $p < 0.001$ ) with atorvastatin (from 3.86 mmol/L to 2.03 mmol/L) than pravastatin (from 3.86 mmol/L to 2.84 mmol/L) at the end of the 18 month follow-up in this trial. After 18 months, atheroma volume progressed in the pravastatin arm (+2.7%, 95% CI 0.24% to 4.67%) but was stable in the patients randomized to atorvastatin therapy (−0.4%, 95% CI −2.35% to +1.49%) – this between-group difference was statistically significant ( $p = 0.02$ ). The beneficial effects of atorvastatin on atheroma progression were seen in all 23 subgroups examined. Both treatment regimens were equally well tolerated, although there were too few cardiovascular events (15) or drug-related discontinuations/adverse effects (43) for useful comparisons between treatment arms.

### The PROVE IT- TIMI 22 trial

The Pravastatin or Atorvastatin Evaluation and Infection Therapy – Thrombolysis in Myocardial Infarction 22 Trial randomized 4,162 patients with acute coronary syndrome to either atorvastatin 80 mg daily or pravastatin 40 mg daily (Cannon et al 2004). The primary endpoint was a composite of death from any cause, myocardial infarction, unstable angina requiring hospitalization, revascularization (performed at least 30 days after randomization), or stroke. LDL cholesterol lowering was significantly greater ( $p < 0.001$ ) with atorvastatin (from 2.74 mmol/L to 1.60 mmol/L) than pravastatin (from 2.74 mmol/L to 2.46 mmol/L) at the end of the trial (24 months). At the end of 24 months, the rates of the primary endpoint were 22.4% in the atorvastatin group and 26.3% in the pravastatin group – this between-group difference was statistically significant ( $p = 0.005$ ). The beneficial effects of atorvastatin on the primary endpoint were consistent across all 17 subgroups examined, with the benefits appearing to be greater in those patients with baseline LDL cholesterol levels of at least 3.2 mmol/L ( $p = 0.02$  for interaction). The intensive treatment arm had a statistically significant increase in rates of alanine aminotransferase elevations when compared to the moderate lipid lowering treatment arm ( $p < 0.001$ ), but there were no significant differences between groups in myopathy or drug discontinuation rates.

### Phase Z of the A to Z trial

Phase Z of the A to Z Trial randomized 4,497 patients with acute coronary syndrome (ACS) to receive 40 mg of simvastatin daily for 1 month followed by 80 mg daily thereafter or placebo for 4 months followed by 20 mg of simvastatin daily (de Lemos et al 2004). The primary endpoint was a composite of cardiovascular death, nonfatal myocardial infarction, readmission for ACS, or stroke. LDL cholesterol lowering was significantly greater ( $p < 0.001$ ) with the higher dose simvastatin group (from 2.90 mmol/L to 1.71 mmol/L) than the lower dose simvastatin group (from 2.87 mmol/L to 2.10 mmol/L) at the end of the trial (24 months). After 24 months, the primary endpoint occurred in 14.4% of the higher dose simvastatin group and 16.7% in the lower dose group – this between-group difference was not statistically significant ( $p = 0.14$ ). There were no significant treatment interactions in any of the 21 subgroups examined. The higher dose treatment arm demonstrated statistically significant increases in liver enzyme elevations and myopathy when compared to the lower dose treatment arm.

### The Vascular Basis for the Treatment of Myocardial Ischemia Study

The Vascular Basis for the Treatment of Myocardial Ischemia Study randomized 300 patients with stable CAD and a positive exercise stress test to one of 3 groups: atorvastatin 80 mg daily, atorvastatin 80 mg daily plus vitamins C and E, or the control group of low dose (median 5 mg) lovastatin (Stone et al 2005). The primary endpoint was number of ischemic episodes on ambulatory ECG monitoring. LDL cholesterol lowering was significantly greater ( $p < 0.0001$ ) in both of the atorvastatin groups (from 3.9 mmol/L to 2.2 mmol/L) than in the lovastatin (from 3.9 mmol/L to 3.2 mmol/L) at the end of the trial (12 months). After 12 months, patients in all 3 treatment arms experienced significant declines in the frequency and duration of myocardial ischemia episodes – between 31% and 61%, but with no statistically significant difference between groups ( $p = 0.15$ ). There were too few clinical events (12 deaths, MI, unstable angina, or stroke) to draw conclusions between treatment arms and no adverse events were reported.

### The TNT trial

The Treating to New Targets Trial randomized 10,001 patients with stable CAD to either atorvastatin 80 mg daily or atorvastatin 10 mg daily after completion of an open-label run-in period (LaRosa et al 2005). The primary endpoint was the occurrence of a first major cardiovascular event,

defined as death from coronary heart disease, nonfatal non-procedure-related myocardial infarction, resuscitation after cardiac arrest, or fatal/nonfatal stroke. LDL cholesterol lowering was significantly greater ( $p < 0.001$ ) with high dose atorvastatin (from 2.6 mmol/L to 2.0 mmol/L) than low dose atorvastatin (remained unchanged from post run-in period value of 2.6 mmol/L) at the end of the trial (4.9 years). After 4.9 years, 8.7% of patients in the higher dose group had a primary event vs 10.9% in the lower dose group – this between-group difference was statistically significant ( $p < 0.001$ ). When compared to patients receiving 10 mg of atorvastatin, those receiving 80 mg of atorvastatin demonstrated statistically significant increases in liver enzyme elevations as well as increased rates of drug discontinuation due to adverse events ( $p < 0.001$  for both).

### The IDEAL trial

The Incremental Decrease in End points through Aggressive Lipid lowering Trial randomized 8,888 with stable CAD to atorvastatin 80 mg daily or simvastatin 20 mg daily (Pedersen et al 2005). The primary endpoint was time to first occurrence of a major coronary event, defined as coronary death, hospitalization for nonfatal acute myocardial infarction, or cardiac arrest with resuscitation. LDL cholesterol lowering was significantly greater ( $p < 0.001$ ) with atorvastatin (from 3.15 mmol/L to 2.07 mmol/L) than simvastatin (from 3.14 mmol/L to 2.58 mmol/L). After 4.8 years, 9.3% of the atorvastatin group had suffered a primary outcome vs 10.4% of the simvastatin group – this between-group difference was not statistically significant ( $p = 0.07$ ). Patients in the high dose treatment arm had a statistically significant increases in liver enzyme elevations and adverse events leading to drug discontinuation when compared to those in the lower dose treatment arm (both  $p < 0.001$ ).

## Summary of the higher dose vs lower dose statin trials

These 9 trials report data from 29,853 patients with coronary artery disease and 486 patients with other indications for statin therapy randomized to higher dose vs. lower dose statin therapy. Study participants in the 7 trials of secondary prevention were demographically similar, although baseline LDL cholesterol levels ranged between 2.74 mmol/L in PROVE IT to 3.98 mmol/L in Post-CABG (Table 2). These trials were methodologically robust (all scored greater than 3 on the 5-point Jadad scale for randomized trials) but some potential threats to the generalizability of study results are worth pointing out. For example, the TNT trial excluded

almost half of those initially screened and included a run-in phase before randomization (both design features can bias the results towards an underestimation of adverse effects and an overestimation of benefits since patients who are identified to be at increased risk for adverse effects due to comorbidities at screening, or indeed suffer adverse effects during the run-in phase, are excluded). Further, the proportion of patients using statins prior to randomization varied widely amongst the trials, with only A-to-Z excluding anyone previously using statins (inclusion of patients previously exposed to a medication can also bias results towards an underestimation of adverse effects and an overestimation of benefits).

## Pooled results from the seven higher dose vs lower dose statin trials in patients with coronary disease

### Changes in LDL cholesterol and reductions in primary endpoints (Figure 1)

Patients treated with higher dose statins in all trials achieved lower LDL cholesterol levels than those treated with lower dose statins (Figure 1) and higher dose statins were associated with relative reductions in each study's primary endpoint compared to lower intensity statin treatment (from 11% in IDEAL to 20% in TNT). The differences in achieved LDL levels between the higher and lower dose statin arms ranged from a low of 0.39 mmol/L in the A-to-Z Trial to 1.0 mmol/L in the Vascular Basis Trial.

### All-cause mortality (Figure 2)

Higher dose statin therapy was associated with non-significant trends towards lower all-cause mortality rates in 4 of the 7 secondary prevention trials (with OR ranging from 0.71 (95% CI 0.49–1.02) in PROVE-IT TIMI 22 to 0.98 (95% CI 0.84–1.14) in IDEAL) – pooling the data across all 7 trials using a random effects model revealed a 25% reduction in mortality in patients after acute coronary syndromes (OR 0.75; 95% CI 0.61–0.93) with higher dose statin therapy, but no apparent impact on mortality in patients with chronic CAD (OR 0.99; 95% CI 0.89–1.10) (Josan et al 2007).

### Myocardial infarction or coronary death (Figure 2)

Higher dose statins were associated with a significant reduction in this composite endpoint in the TNT trial (OR 0.79, 95% CI 0.68–0.91) and non-significant trends towards lower event rates in 5 of the other 6 trials (with OR ranging from 0.57 (95% CI 0.16–1.95) in REVERSAL to 0.88

**Table 2** Randomized trials comparing higher dose statin therapy with lower dose statin therapy in patients with coronary artery disease

Trial	Sample size	Comparators	Key eligibility criteria	Key demographics (mean age, % men, mean LDL at baseline)	LDL at follow-up (more intensive therapy arm)	LDL at follow-up (less intensive therapy arm)	Duration of follow-up
Post-CABG	1351	Lovastatin 80 mg vs lovastatin 5 mg	Post CABG 1–11 years before	62 years 92% 3.98 mmol/L	2.4 mmol/L	3.5 mmol/L	4.3 years
REVERSAL	654	Pravastatin 40 mg vs atorvastatin 80 mg	Stable CAD	56 years 72% 3.9 mmol/L	2.04 mmol/L	2.85 mmol/L	18 months
Vascular basis	300	Lovastatin 5 mg vs atorvastatin 80 mg vs atorvastatin 80 mg + antioxidant	Stable CAD	not reported 86% 3.9 mmol/L	2.2 mmol/L	3.2 mmol/L	12 months
PROVE IT-TIMI 22	4,162	Pravastatin 40 mg vs atorvastatin 80 mg	Post ACS	58 years 78% 2.74 mmol/L	1.60 mmol/L	2.46 mmol/L	24 months
A to Z	4,497	Placebo × 4 months then simvastatin 20 mg vs simvastatin 40 mg × 1 month then 80 mg	Post ACS	61 years 76% 2.89 mmol/L	1.71 mmol/L	2.10 mmol/L	24 months
TNT	10,001	Atorvastatin 10 mg vs 80 mg	Stable CAD	61 years 81% 2.6 mmol/L (after run-in)	2.0 mmol/L	2.6 mmol/L	4.9 years
IDEAL	8,888	Simvastatin 20 mg vs atorvastatin 80 mg	Stable CAD	62 years 81% 3.2 mmol/L	2.1 mmol/L	2.7 mmol/L	4.8 years

(95% CI 0.71–1.01) in IDEAL). Pooling the data across all 7 trials using a random effects model confirmed that higher dose statins provided further reductions (over lower dose statin therapy) in myocardial infarction or coronary death in patients after acute coronary syndromes (OR 0.84; 95% CI 0.72–0.97) and in patients with chronic CAD (OR 0.84; 95% CI 0.76–0.92) (Josan et al 2007).

### Stroke (Figure 2)

Higher dose statins significantly reduced stroke in the TNT trial (OR 0.75, 95% CI 0.59–0.96) and was associated with trends to benefit in 3 of the other 6 trials. Pooling the data across all 7 trials using a random effects model confirmed that, compared to lower dose statin therapy, higher dose statins further reduced stroke in patients with chronic CAD (OR 0.82; 95% CI 0.70–0.96); although a similar trend was

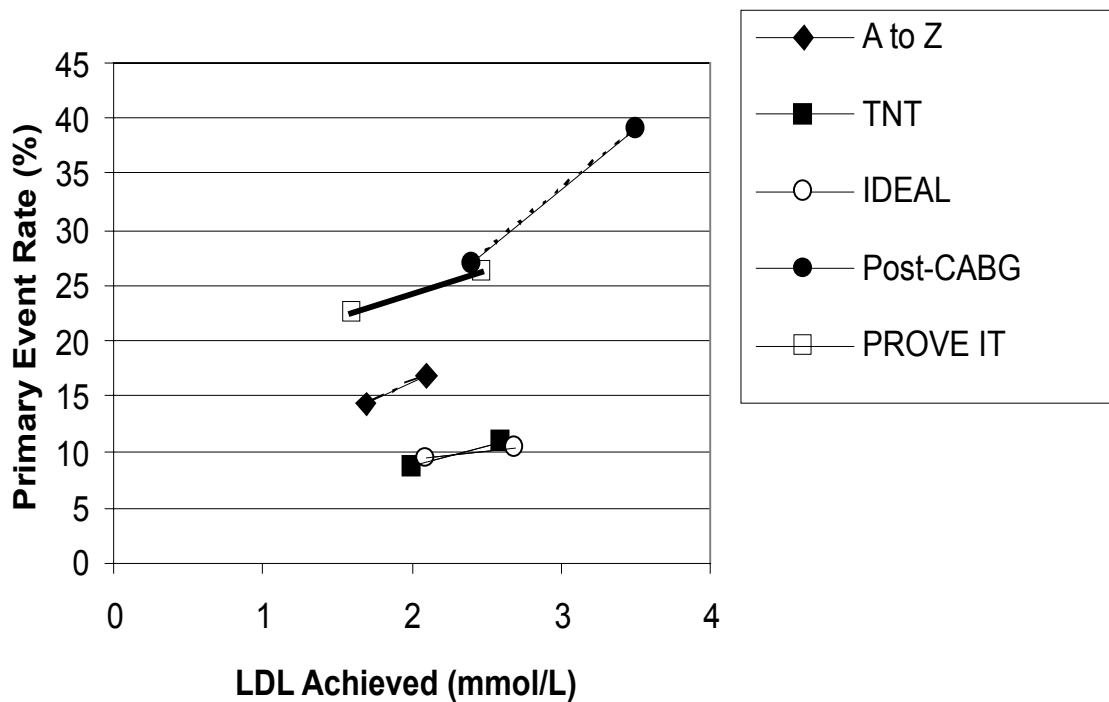
observed in patients after acute coronary syndromes (OR 0.91; 95% CI 0.61–1.35) there were too few events in this smaller subgroup of patients for the data to be definitive (Josan et al 2007).

### Non-cardiovascular mortality (Figure 2)

There was no appreciable difference between higher or lower dose statin therapy in any of the trials or either in patients with chronic CAD (OR 1.07, 95% CI 0.79–1.46) or in patients after acute coronary syndromes (OR 0.78, 95% CI 0.49–1.24) when the data were pooled across trials.

### Adverse events

Discontinuation of study drug due to adverse events was higher in the higher dose statin arms of these trials (pooled estimate 7.7% versus 5.1% for the lower dose statin arms,



**Figure 1** Association between achieved LDL cholesterol levels and primary outcome in both arms of the higher dose versus lower dose statin trials. The results for the less intensive arm of each trial are expressed on the right of each trial's line; the results for the more intensive arm of each trial are expressed on the left of each trial's line.

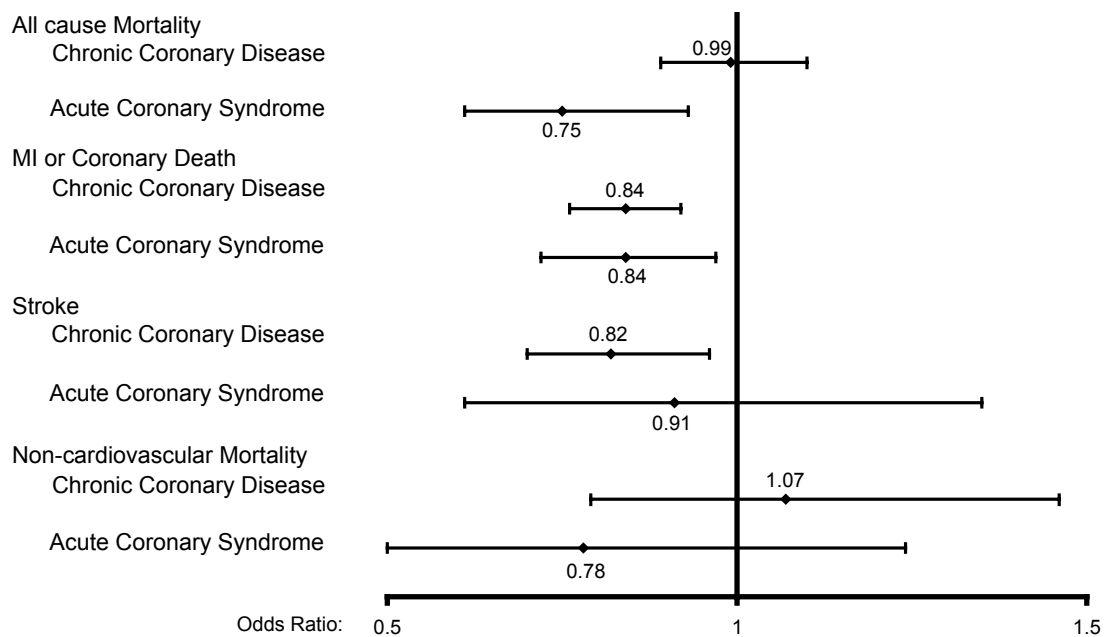
$p < 0.0001$ ) (Josan et al 2007). In contrast, the discontinuation rate attributed to study drug in the placebo-controlled trials in Table 1 was 7.7% in 25,723 placebo-treated patients and 7.8% in 25,742 statin-treated patients ( $p = 0.98$ ). The frequency of elevated transaminases (AST or ALT greater than 3 times the upper limit of normal) was significantly greater with higher dose statin therapy vs. lower dose therapy (1.4% vs. 0.4%,  $p < 0.0001$ ) (Josan et al 2007). In contrast, the frequency of elevated transaminases in the Table 1 statin placebo-controlled trials was 1.2% in 33,465 placebo-treated patients and 1.6% in 33,494 statin-treated patients ( $p = 0.0001$ ). Myopathic adverse events were inconsistently reported in these trials and in the placebo-controlled statin trials. While the A-to-Z trial reported a small but statistically significant increase in cases of rhabdomyolysis among the patients receiving higher dose statin therapy (0.4% vs 0.04%,  $p = 0.02$ ), neither the IDEAL (0.05% vs 0.07%,  $p = 0.99$ ) nor TNT (0.04% vs 0.06%,  $p = 0.99$ ) trials found any significant difference in rhabdomyolysis risk. The pooled frequency of statin-associated myopathy (as per the American College of Cardiology/American Heart Association definition, myopathy covers any muscle complaints, with or without elevated CK levels) (Pasternak et al 2002) was 3.3% in patients randomized to higher dose statins and 2.8% in patients randomized to lower dose statins ( $p = 0.008$ ); in comparison, the rates were 0.9% in 34,830 placebo-treated

patients and 0.9% in 34,848 statin-treated patients in the Table 1 trials ( $p = 0.89$ ).

## Discussion

The expected relative risk reductions associated with lower dose statin regimens over placebo are 23% for myocardial infarction, 17% for stroke, and 13% for all-cause mortality (Cholesterol Treatment Trialists 2005). Compared to lower dose statin therapy, higher dose statin therapy reduces myocardial infarctions by a further 16% and strokes by 18% in patients with CAD – both of these values are relative risk reductions and the absolute benefits depend on the baseline risk of the patients in which these drugs are used. Although there is no appreciable effect on survival in patients with chronic CAD, in those patients at higher risk for death due to recent acute coronary syndromes higher dose statin therapy does confer an additional 25% relative reduction in all-cause mortality over and above the reductions expected with low dose statin therapy. Higher dose statin regimens are also associated with statistically significantly increased risks of myopathy, elevated transaminases, and drug discontinuation compared to lower dose statins. However, although relative risks for these outcomes range from 1.2 to 4.0, the absolute increases are small (particularly when balanced against the absolute reductions of 1.6% in myocardial infarction and 0.5% in stroke seen in the trials reviewed above).





**Figure 2** Event rates with higher dose vs. lower dose statin therapy.

However, there are two caveats to our findings. First, although the current literature supports the use of higher dose statin regimens in patients with established CAD, it provides limited insight into whether high or low dose statins should be employed in patients without CAD but with elevated cholesterols and/or multiple atherosclerotic risk factors. Although the ASAP and ARBITER Trials have shown that higher dose statin therapy does reduce the surrogate outcome of progression in carotid intima media thickness in patients with familial hypercholesterolemia (Smilde et al 2001) or a wide variety of conditions which placed them at risk for atherosclerosis (Taylor et al 2002), the number of clinically apparent events (ie, MI, stroke, or death) was far too few in these trials to make definitive conclusions at this time. We do not believe that the secondary prevention trials that we reviewed can be generalized to patients without coronary disease and this is an area that should be a research priority (particularly given a recent secondary analysis of TNT suggesting that patients with metabolic syndrome may derive even greater benefits from higher dose statin therapy than other patients (Deedwania et al 2006).

Second, although our analysis provides information on the benefits and safety of higher dose versus lower dose statin therapy, none of these trials provide data which can directly answer the question of optimal LDL targets as none provide a breakdown of event rates by LDL achieved. Although patients randomized to lower dose statins in the dose comparison trials we reviewed had higher event rates,

it is possible that only a subset of the patients in the randomized arms contributed to the difference. That is, the worse outcomes in the lower dose statin group may be the result of events occurring in those patients with persisting LDL elevations rather than a result of the mean LDL achieved not being low enough (Mann 2006). As previously mentioned, multidrug therapy is frequently required to achieve lower LDL targets thus resulting in increased risk of adverse effects and/or patient non-adherence to prescribed therapy. Although short-term trials with LDL cholesterol endpoints have demonstrated that non-statin agents can further lower LDL cholesterol when added to statin therapy (Brown et al 2001; Stein et al 2004; Bissonette et al 2006), there is currently a paucity of long-term trials proving that these agents provide further reductions in clinical outcomes (such as myocardial infarction, stroke, or death) above those achieved with statin therapy alone.

Without individual patient data we cannot calculate risk reductions per mmol/L reduction in LDL cholesterol but extrapolating from the expected benefits based on the Cholesterol Treatment Trialists' Collaboration suggests that the benefits seen in these trials are generally consistent with what would have been expected given the mean LDL reduction observed in these trials (0.61 mmol/L) and their relatively long duration. This latter point is relevant since the placebo-controlled statin trials demonstrated that the benefits of statins are approximately half as large in the first year of use as in subsequent years (Cholesterol Treatment

Trialists' Collaboration 2005). Although the general consistency of the clinical event reductions for the observed LDL reductions lends support to those asserting that the lower the LDL the better (O'Keefe et al 2004), it does not provide any information about whether there is a lower threshold below which further reduction in LDL cholesterol is not helpful (or is even harmful). Indeed, it could be argued that although the data from the 7 intensive therapy trials is generally consistent with that from the placebo-controlled trials, the clinical event reduction seen in these trials is slightly lower than would be expected for trials of such long duration. Thus, although it is commonly asserted that for every 1% reduction in LDL levels, the relative risk for major coronary events is reduced by approximately 1% (Grundy 2004), all 4 of the intensive therapy trials that reported data on major coronary events failed to show such a relationship. For example, although LDL levels were reduced by 35% in PROVE IT, this was associated with only a 16% relative risk reduction in major coronary events and although LDL levels were reduced by 22% in IDEAL the major coronary event rate was only reduced by 11%. While the current literature is inadequate to assess whether there may be an LDL threshold below which further reductions in LDL do not improve clinical outcomes, such a study could be done with the trial data at hand if a cohort analysis to explore the association between LDL levels and clinical outcomes was conducted with multivariate adjustment for prescribed therapies (statins and concomitant anti-atherosclerotic therapies), adherence, and changes in other risk factors as well as baseline imbalances in prognostic risk factors (Hayward et al 2006).

Although the Cholesterol Treatment Trialists suggested that there was an approximately linear relationship between the LDL cholesterol achieved and the reductions in clinical outcomes, the mean pre-treatment LDL cholesterol of 3.79 mmol/L in their meta-analysis is considerably higher than that of patients in the higher vs. lower dose statin trials reviewed in this manuscript. As a result, there were undoubtedly fewer patients that had baseline LDLs lower than 2.59 mmol/L in the placebo-controlled trials. Indeed, while several of the placebo-controlled trials did examine whether patients with lower baseline LDL levels derived the same benefits from LDL reduction as those starting from higher LDL levels, the results were mixed. For example, while the CARE trial (Sacks et al 1996) demonstrated no benefit with statin therapy in patients with baseline LDL level <3.2 mmol/L (22% rate of major coronary events vs 21% in placebo-treated patients) and the LIPID trial (LIPID study group 1998) reported less

benefit with statins in patients with baseline LDL < 3.5 mmol/L (mortality relative risk reduction 16% vs 30% benefit in those patients with higher baseline LDL levels), the Heart Protection Study (MRC/BHF 2002), PROSPER (Shepherd et al 2002), CARDS (Colhoun et al 2004), and MIRACL (Schwartz et al 2001) trials all demonstrated similar benefits across subgroups regardless of baseline LDL level.

Although they are most effective at decreasing LDL levels, statins are also known to exert varying effects on triglyceride and HDL levels (Jones 2003) and statins do differ in their non-cholesterol pleiotropic effects (Davignon 2004). However, as the trials comparing more intensive vs less intensive statin therapy do not consistently report post treatment triglyceride and HDL levels or non-cholesterol risk factors (such as C-reactive protein) one cannot determine the contribution of these factors. As a result, we believe there is currently no evidence to support assertions that a higher dose of one statin is more efficacious than higher doses of any other statin (assuming equipotent dosing and equal reductions in LDL cholesterol) for clinical outcomes.

In considering the benefits of lipid lowering with higher dose statin therapy, one must also weigh the potential harms to the patient. After all, cholesterol is a cell membrane component and plays a key role in vitamin synthesis. While ecological and cohort data did raise concerns that very low cholesterol levels may be associated with increases in non-cardiovascular mortality, intracranial hemorrhage, cancer, or suicide, these concerns have been proven unfounded by the randomized trial literature (and likely reflected the fact that systemic illnesses which predisposed to those outcomes also lowered cholesterol levels). Indeed, a recent meta-analysis of 35 randomized placebo-controlled statin trials (with data on over 74,000 patients followed for a mean of 17 months) documented that there was no appreciable increase in the risk of myalgias, CK elevations, rhabdomyolysis, or drug discontinuation with non-cerivastatin statins over placebo-treated patients, and although the risk of transaminase elevations was higher with statin treatment, the absolute risk was only 4 cases per 1000 patients (Kashani 2006). In our analysis of trials comparing different doses of statins (none of which were included in the aforementioned meta-analysis), we found that although adverse event rates (particularly myopathy and hepatotoxicity) were higher with higher dose statin therapy than with lower dose therapy, the absolute rates of adverse events were low in these trials (and in the placebo-controlled statin trials). Further, post-hoc analyses suggest that adverse events are not related to achieved LDL cholesterol levels (Wiviott 2005).

However, it should be acknowledged that adverse events may be more common in clinical practice since trial participants tend to be healthier and more closely followed than usual patients. Indeed, these trials excluded over half of all patients screened because of various factors known to increase the risk of adverse events: advanced age, renal failure, hepatic failure, hypothyroidism, or concomitant use of fibrates, macrolide antibiotics, antifungal agents, HIV protease inhibitors, verapamil, or cyclosporine (Grundy 2005). Having raised this objection, however, it should be acknowledged that adverse events with statin therapy appear to be relatively similar when used in the non-trial setting as in the randomized trials, at least based on analyses of large cohort studies, administrative databases, and FDA reports published so far (Thompson et al 2003; Bays 2005; Charles 2005). However, the relatively short time frame of the randomized trials of higher dose vs. lower dose statin therapy conducted thus far should be acknowledged and emphasizes the importance of post-marketing surveillance to track complication rates over longer time periods, and in larger samples (witness the problems with cerivastatin which only became apparent when scores of thousands of patients had been prescribed the drug in North America). The ongoing SEARCH (Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine) Trial will provide much needed safety information on high dose statin therapy (simvastatin 80 mg daily vs. 20 mg daily) over a longer time-frame (12,064 study participants, with an expected average follow-up of 7 years).

In addition to the adverse events attributed to statin use, attention should be drawn to the overall discontinuation rate with higher dose vs. lower dose statin therapy which likely reflects adverse effects such as nausea, diarrhea, and abdominal pain. These symptoms are typically dismissed as nuisance effects rather than true adverse events and thus not systematically captured in randomized trial case reports. However, if such nuisance effects lead patients to discontinue potentially life saving drugs, they are clearly important contributors to patient outcomes. Thus, the argument could be made that in those intolerant to higher dose statin therapy, it may be beneficial to derive some benefit from a low dose statin than no benefit from a discontinued high dose statin.

In closing, the current literature does prove conclusively that higher dose statin therapy (for example, 80 mg of simvastatin or atorvastatin) in patients with established CAD provides incremental benefits over and above those expected with lower dose statin therapy; however, this literature is

insufficient to define optimal LDL targets in these patients. Secondary analyses of the existing randomized trial data using individual patient data and multivariate adjustment will be needed to appropriately examine the incremental benefits of different LDL targets (Hayward 2006), and future trials will have to determine whether lower dose statin therapy plus other lipid lowering agents may achieve better LDL levels and clinical outcomes than maximal dose statin therapy. Indeed, further research is needed to conclusively establish whether the benefits associated with statin treatment are determined by the LDL level achieved, the percent reduction in LDL, the absolute reduction in LDL, or the dose of the statin. Based on the current evidence base, the use of higher dose statin therapy should be restricted to patients with established CAD at this time.

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