

Intensive statin therapy compared with moderate dosing for prevention of cardiovascular events: a meta-analysis of >40 000 patients

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Aims

Statin therapy is associated with important benefits for patients at risk of, and with, established cardiovascular disease. There is widespread interest in whether intensive dosing of statins yields larger treatment effects. We aimed to determine if intensive dosing is clinically important using a meta-analysis of randomized clinical trials (RCTs).

Methods

We conducted comprehensive searches of electronic databases from inception to December 2010. We included any RCT evaluating a larger dose with a clinically common dose. Two reviewers independently extracted data, in duplicate. We performed random-effects meta-analysis and a trial sequential analysis.

Results

We identified 10 RCTs enrolling a total of 41 778 participants. Trials followed patients for a mean of 2.5 years. We did not find statistically significant effects on all-cause mortality [relative risk (RR) 0.92, 95% confidence interval (CI), 0.83–1.03, $P = 0.14$, $I^2 = 38\%$] or cardiovascular disease (CVD) deaths (RR 0.89, 95% CI, 0.78–1.01, $P = 0.07$, $I^2 = 34\%$). When we pooled the composite endpoint of coronary heart disease (CHD) death plus non-fatal myocardial infarction (MI), we found a significant protective effect of intensive statin dosing (RR 0.90, 95% CI, 0.84–0.96, $P \leq 0.0001$, $I^2 = 0\%$). We also found a significant effect on non-fatal MIs (RR 0.82, 95% CI, 0.76–0.89, $P \leq 0.0001$, $I^2 = 0\%$) and a significant reduction in the composite of fatal and non-fatal strokes (excluding transient ischaemic attacks) reported in 10 RCTs (RR 0.86, 95% CI, 0.77–0.96, $P = 0.006$, $I^2 = 0\%$). A subgroup analysis of three trials examining acute coronary syndrome patients found significant effects on all-cause (RR 0.75, 95% CI, 0.61–0.91, $P = 0.005$, $I^2 = 0\%$) and CVD mortality (RR 0.74, 95% CI, 0.59–0.94, $P = 0.013$, $I^2 = 0\%$) with intensive dosing. Applying an analysis of optimal information size on the primary analysis, we found that the evidence for CHD death plus non-fatal MIs is conclusive. The evidence for CVD deaths alone is not yet conclusive.

Conclusions

Available evidence suggests that intensive statin therapy reduces the risk of non-fatal events and may have a role in reducing mortality.

Keywords

HMG-CoA reductase inhibitors • Statins • Meta-analysis • Randomized clinical trials

Introduction

HMG-CoA reductase inhibitors (statins) are currently the largest selling prescription drug worldwide and may one day be widely available over-the-counter (OTC),¹ with a 10 mg tablet of simvastatin already on sale OTC in the UK. Used predominantly for

cardiovascular disease (CVD) protection, there is widespread evidence that statins provide protection across a wide range of populations with varying risk factors.^{2–4} Given the broad populations that statins have been evaluated in, statins have typically been compared with placebo or commonly used care control groups.⁵ More recently, there has been an increased focus on the potential that

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intensive lipid lowering with higher statin doses may have important therapeutic benefits over commonly used doses.⁶ Large randomized clinical trials (RCTs) have now evaluated varying doses of intensive statins compared with moderate or lower doses.⁷

Clinicians have recognized that much of a statin's therapeutic effect is predominantly derived from its low-density lipoprotein (LDL) lowering effects.² As a result, there has been much discussion within the cardiovascular community about providing intensive, or higher, dosing of statins to achieve an increased reduction in LDL, and subsequent clinical events.^{8–10} The evidence of this is mostly indirect.¹¹ Five previous meta-analyses have been completed, the last in 2010, including up to seven trials on clinical endpoints.^{7,12–15} Further RCTs are now available for the analysis.^{16,17} We aimed to summarize the available data and determine whether intensive statin dosing offers more favourable outcomes to patients at risk of CVD events.

Methods

Eligibility criteria

We included any RCT of atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin for CVD therapeutic effects, as determined by the Canadian Compendium of Pharmaceuticals and Specialties (2009).¹⁸ Studies had to compare a statin of moderate dose with the same or another statin of higher dose and be of >6 months duration. We did not include cerivastatin as it has been withdrawn from the market due to serious adverse events. Studies had to compare a statin to another statin and report on any of the following clinically important cardiovascular outcomes: All-cause mortality; CVD mortality; coronary heart disease (CHD) death plus non-fatal myocardial infarction (MI); fatal MI; non-fatal MI; strokes; and non-CVD deaths. We excluded studies reporting only on surrogate outcomes (e.g. LDL and HDL levels) and follow-up studies where randomization had been subverted.¹⁹ We additionally excluded dose-ranging studies that were not head-to-head clinical evaluations.

Search strategy

In consultation with a medical librarian, we established a sensitive search strategy (available from the authors upon request). Our search strategy has been used in numerous published statin evaluations^{3–5,20,21} and uses the MeSH term 'Hydroxymethylglutaryl-CoA Reductase Inhibitors' and truncated 'random*'. We searched independently, in duplicate, the following 10 databases (from inception to 1 December 2010): MEDLINE, EMBASE, Cochrane CENTRAL, AMED, CINAHL, TOXNET, Development and Reproductive Toxicology, Hazardous Substances Databank, Psych-info and Web of Science, databases that included the full text of journals (*OVID*, *ScienceDirect*, and *Ingenta*, including articles in full text from ~1700 journals since 1993). In addition, we searched the bibliographies of published systematic reviews^{2,5,21–27} and health technology assessments.^{28–30} Finally, we searched our own comprehensive rolling database of statin trials, updated monthly. We also contacted the authors of 5 RCTs for study clarifications,^{6,16,31–33} and the authors of two individual patient data meta-analysis of statins, which 5 head-to-head trials and 21 inert controlled trials.^{2,7,27} Searches were not limited by language, sex, or age.

Study selection

Two investigators (P.W., E.M.) working independently, in duplicate, scanned all abstracts and obtained the full text reports of records,

that indicated or suggested that the study was a RCT evaluating statin therapy on the outcomes of interest. After obtaining full reports of the candidate trials (either in full peer-reviewed publication or press article) the same reviewers independently assessed eligibility from full text papers.

Data collection

The same two reviewers conducted data extraction independently using a standardized pre-piloted form. The reviewers collected information about the statin and type of interventions tested, the population studied (age, sex, underlying conditions), the treatment effect on specified outcomes, absolute and proportion change in LDL, HDL, and total cholesterol and the length of follow-up. Study evaluation included general methodological quality features, including sequence-generation, blinding, use of intent-to-treat analysis, % follow-up and allocation concealment.³⁴ We extracted data on the incidence of the following clinical outcomes: all-cause mortality; CVD mortality; CHD death plus non-fatal MI (includes any MI); fatal MI; non-fatal MI; fatal and non-fatal strokes; and non-CVD deaths. We also abstracted data on adverse events including increases in aspartate (AST) and alanine (ALT) aminotransferase, creatine kinase (CK) levels beyond normal, and rhabdomyolysis (CK level > 10 000 U/L). We entered the data into an electronic database such that duplicate entries existed for each study; when the two entries did not match, we resolved differences through discussion and consensus.

Data analysis

In order to assess inter-rater reliability on inclusion of articles, we calculated the *Phi* (ϕ) statistic, which provides a measure of inter-observer agreement independent of chance.³⁵ We calculated the relative risk (RR) and appropriate 95% confidence intervals (CIs) of outcomes according to the number of events reported in the original studies or sub-studies on an intent-to-treat basis. We pooled studies as an analysis of all-statin combined using the DerSimonian–Laird random effects method,³⁶ which recognizes and anchors studies as a sample of all potential studies, and incorporates an additional between-study component to the estimate of variability.³⁷ We also conducted an optimal information size analysis to determine the strength of information for our meta-analysis on the primary outcome of CVD death and CHD plus non-fatal MI to determine the conservative number of patients required to provide an authoritative answer of therapeutic efficacy.³⁸ Some argue that the reliability of the evidence in a meta-analysis should only be established in rigorous decision-making frameworks similar to those of Data Safety Monitoring Boards for single RCTs. The concatenation of meta-analysis, and formal monitoring boundaries (or stopping rules), such as the Lan–DeMets alpha-spending monitoring boundary is analogous to group sequential analysis in single RCTs.^{39,40} For the outcome of CV death, we conducted a random effects cumulative meta-analysis assessing the effect of high- vs. low-dose statin therapy on cardiovascular mortality risk. The Lan–DeMets sequential monitoring boundary assumes a 5.5% control event rate, 20% RR reduction, 80% power, and a two-sided $\alpha = 0.01$. For the outcome of CHD plus non-fatal MI, the Lan–DeMets sequential monitoring boundary assumes a 7.0% control event rate, a 20% RR reduction, 80% power, and a two-sided $\alpha = 0.01$. We conducted a subgroup analysis examining acute coronary syndrome patients as this population has higher event rates and also pleiotropic effects of statins may be more relevant than in stable patients.⁴¹ We calculated numbers needed to treat for the outcome of CHD death plus non-fatal MI across secondary prevention populations and CVD death for acute coronary syndrome patients using

an approach recommended by Aaron and Fergusson that considers events over person-time.⁴² E.J.M. and O.B. conducted all analyses.

Results

Figure 1 displays the flow diagram of study inclusion. We excluded two studies that we inferred as non-intensive vs. moderate dosing.^{43,44} Two studies were published during peer review and included.^{16,31} Additional data on one these, the SEARCH trial, were available in unpublished format.⁴⁵ In total, we identified 10 RCTs enrolling a total of 20 919 patients into intensive statin dosages and 20 859 in moderate and lower dosages. The interrater reliability for study inclusion was very good ($\phi = >0.9$).

Table 1 displays the study characteristics and interventions. Three trials included exclusively acute coronary syndrome patients,^{6,16,46} one atherosclerosis³³ and the remainder were secondary prevention patients.^{17,31,32,47–49} Women represented ~24% of trial participants. The average age of included participants was 55.5 years (SD 23), mean ages ranging from 56 to 74 years. Trials followed patients for a mean 2.5 years (SD 2.13), ranging from 0.5 to 6.7 years. The mean pre-trial LDL cholesterol was 122 mg/dL and ranged from 97⁴⁸ to 150 mg/dL.

The reporting and quality of specific methodological trial components were variable. Seven trials reported adequate methods of randomization sequence generation.^{6,16,31,33,46–49} All studies reported on who was blinded in the trial.^{6,16,17,31–33,46–49} Seven reported allocation of study participants as concealed.^{6,16,17,31,33,46,47} Adequate follow-up was reported in all trials^{6,16,17,31–33,46–49} and eight trials specifically reported using an intention-to-treat analysis.^{6,16,31,33,46–49}

Mortality

We included data from all 10 trials on incidence of all-cause mortality.^{6,16,17,31–33,46–49} Our pooled analysis found a non-significant trend towards decreased mortality (1791 vs. 1853 deaths, RR 0.92, 95% CI, 0.83–1.03, $P = 0.14$, $I^2 = 38\%$, see Figure 2). The majority of deaths that occurred were CV deaths. We pooled data from seven RCTs reporting CV deaths and found a non-significant effect (1012 vs. 1086 deaths, RR 0.89, 95% CI, 0.78–1.01, $P = 0.07$, $I^2 = 34\%$, see Figure 3) on CVD mortality.^{6,16,31,46–49} Fatal MIs were poorly reported and available from only two trials (164 vs. 299, RR 0.75, 95% CI, 0.41–1.35, $P = 0.34$).^{31,49} Similarly, non-CVD deaths were reported in only four RCTs (565 vs. 581, RR 0.97, 95% CI, 0.87–1.09, $P = 0.65$, $I^2 = 0\%$, see Supplementary material online, Figure S1).^{31,46,47,49} Only one study reported on fatal strokes (57 vs. 67, RR 0.85, 95% CI, 0.59–1.20).³¹

Non-fatal myocardial infarction

We found a significant reduction in non-fatal MIs (935 vs. 1132, RR 0.82, 95% CI, 0.76–0.90, $P \leq 0.0001$, $I^2 = 0\%$) reported in five RCTs.^{16,31,47–49}

Composite endpoints

When we pooled the composite endpoint of CHD death plus non-fatal MI from nine trials,^{6,16,17,31–33,46,47,49} we found a significant protective effect of intensive statin dosages (1490 vs. 1660

deaths or MIs, RR 0.90, 95% CI, 0.84–0.96, $P \leq 0.0001$, $I^2 = 0\%$, see Figure 4). We did not find a linear relationship between LDL lowering effects and log RR for this outcome in a meta-regression analysis (β coefficient 0.26, 95% CI, -0.15 , 0.68, $P = 0.21$). We also found a significant reduction in the composite of fatal and non-fatal strokes (excluding TIAs) reported in the 10 RCTs (576 vs. 669, RR 0.86, 95% CI, 0.77–0.96, $P = 0.006$, $I^2 = 0\%$, see Supplementary material online, Figure S2).^{6,16,17,31–33,46–49} Applying a weighted event rate number needed to treat (NNT), we estimate that patients receiving intensive statin dosing for secondary prevention have an NNT of 250 (95% CI, 162–735) to prevent a CHD or non-fatal MI per year.

Acute coronary syndrome

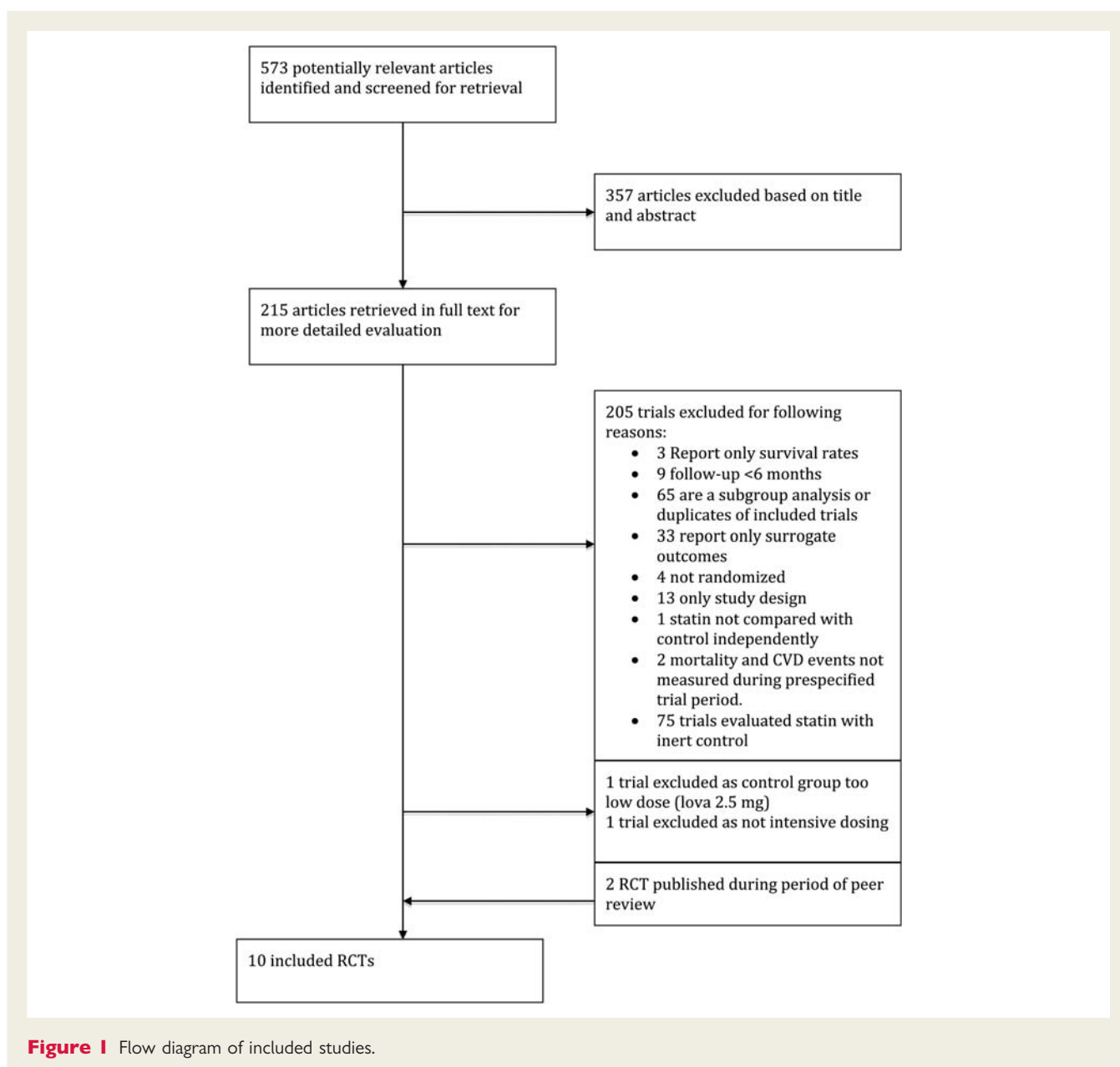
We conducted a subgroup analysis examining three trials that included patients with acute coronary syndrome.^{6,16,46} When examining all-cause mortality, we found a reduction in RR 0.75 (95% CI, 0.61–0.91, $P = 0.005$, $I^2 = 0\%$).^{6,16,46} This was consistent when examining CV deaths (RR 0.74, 95% CI, 0.59–0.94, $P = 0.013$, $I^2 = 0\%$, see Supplementary material online, Figure S3).^{6,16,46} This was not the case when examining CHD death plus non-fatal MI (RR 0.85, 95% CI, 0.71–1.03, $P = 0.10$, $I^2 = 32\%$).^{6,16,46} Nor did we demonstrate a significant effect of this subgroup for non-CVD deaths (RR 0.98, 95% CI, 0.54–1.08, $P = 0.96$)⁴⁶ or non-fatal MI (RR 0.55, 95% CI, 0.28–1.07, $P = 0.08$).¹⁶ In no case, did we demonstrate an effect that was significantly different than the overall pooled primary analyses. Applying a weighted event rate NNT for CVD death, we estimate that 119 (95% CI, 63–1364) patients should be treated to prevent one event per year.

Adverse events

We found no evidence of increased risk of cancers among intensively treated patients compared with moderate treatment from five trials (826 vs. 865, RR 0.95, 95% CI, 0.87–1.04, $P = 0.31$, $I^2 = 0\%$).^{31,33,46,48,49} We also did not find an increased incidence of rhabdomyolysis from six trials (16 vs. 7, RR 1.70, 95% CI, 0.56–5.19, $P = 0.34$, $I^2 = 20\%$).^{6,16,31,46–48} We did, however, find an increase in the incidence of increased AST beyond normal, reported in six trials (67 vs. 19, RR 3.15, 95% CI, 1.31–7.54, $P = 0.01$, $I^2 = 53\%$),^{33,46–49} also observed with ALT increases (430 vs. 272, RR 1.57, 1.29–1.91, $P = 0.002$, $I^2 = 93\%$).^{16,31,33,46–49} We did not find a significant increase in risk of CK beyond normal (203 vs. 100, RR 2.86, 95% CI, 2.02–4.04, $P \leq 0.001$), only reported in four trials.^{6,16,31,46} However, in one trial with high-dose simvastatin, CK increases in 10 times the upper limit of normal associated with myopathy were more common with simvastatin 80 mg than simvastatin 40 mg (nine vs. one)⁴⁶ and in one trial of atorvastatin 80 mg, CK increases in two times the normal limit associated with myopathy required discontinuation of the drug in two patients.¹⁶

Optimal information size

We calculated the *post hoc* optimal information size based on seven RCTs addressing CV death that assesses whether a sufficient number of events have accrued to provide conclusive evidence.^{6,16,31,46–49} For CV deaths the cumulative evidence is still



inconclusive regarding this outcome as a further 4000 patients at similar risk would need to be randomized. When we examined the outcome of CHD plus non-fatal MI with data from nine RCTs, we note that the evidence for CHD plus non-fatal MI reduction is conclusive at the 80% power level.

Discussion

Our study found that intensive dosing of statins results in important reductions in non-fatal events, including the composite of CHD death plus non-fatal MI and the composite of fatal and non-fatal strokes, in addition to non-fatal MIs alone. These benefits did not appear to result in significantly reduced mortality for secondary prevention populations, although the direction of treatment effect is almost consistently towards a benefit. We found an increase in liver enzyme increases beyond normal associated

with intensive dosing in addition to possible important increases in CK associated with rhabdomyolysis. The SEARCH trial has examined the genotypic risks that may predict statin-induced myopathy, a major step forward for patient-guided treatment.⁵⁰ Within a subgroup of acute coronary syndrome patients, intensive statin use was associated with a reduced risk of all-cause and CVD mortality. On balance, intensive dosing of statins appears to offer benefits to patients and should be considered in light of patient history and profile and possible adverse consequences.

There are strengths and limitations to consider in our analysis. We extensively searched the literature and clarified our data abstraction with study authors. We identified trials prior to their publication (published during peer review of this article).³¹ We updated the results of previous meta-analyses^{6,7,13,14} and included additional RCTs. We applied the optimal information size and found that conclusive evidence for the benefit of CHD plus non-

Table 1 Study characteristics

Study	Year	Patient status/ condition at baseline	Treatment comparisons (mg/day)	Follow up, years	Randomized individuals	Age, mean, years	Men, %	Prior CHD, %	Diabetes, %	Hyper tension, %	Current smokers, %	Baseline, mean mg/dL (change)	
												LDL	HDL
A–Z ⁴⁶	2004	Acute coronary syndrome	S40–80 vs. S0– 20	2	4497	61	76	100	24	50	41	111 (–37)	39 (–0.7)
IDEAL ⁴⁷	2005	CHD	A80 vs. S20	4.8	8888	62	81	100	12	33	21	121 (–22)	46 (–0.5)
PROVE-IT ⁶	2004	Acute coronary syndrome	A80 vs. P40	2	4162	58	78	100	18	50	37	106 (–33)	39 (0.65)
REVERSAL ³³	2004	Atherosclerotic	A80 vs. P40	1.5	654	56	72	100	19	69	26	150 (–32)	43 (0.7)
TNT ⁴⁸	2005	CHD	A80 vs. A10	4.9	10001	61	81	100	15	54	13	98 (–22)	47 (0)
Vascular basis. ³²	2005	CHD	A80 vs. L5	1	199	—	86	100	16	64	0	148 (–33)	45 (7.0)
SAGE ⁴⁹	2007	CHD	A80 vs. P40	1	893	72	69	100	23	65	6	147 (–30)	46 (11)
Yu <i>et al.</i> ¹⁷	2007	CHD	A80 vs. A10	0.5	112	66	82	100	28	51	44	116 (–39)	50 (26)
Colivicchi <i>et al.</i> ¹⁶	2010	Acute coronary syndrome	A80 vs. A20/40	1	290	74	52	100	71	89	—	126 (–64)	40 (–)
SEARCH ³¹	2008	CHD	S80 vs. S20	6.7	12064	—	83	100	—	—	—	97 (–14)	39 (–)

A–Z, Aggrastat and Zocar; IDEAL, incremental decrease in events through aggressive lipid lowering; PROVE-IT TIMI, pravastatin or atorvastatin evaluation and infection therapy–thrombolysis in myocardial infarction 22; REVERSAL, reversal of atherosclerosis with aggressive lipid lowering; SAGE, study assessing goals in the elderly; SEARCH, study of the effectiveness of additional reductions in cholesterol and homocysteine; TNT, treating to new targets; vascular basis, Vascular Basis for the Treatment of Myocardial Ischaemia Study.

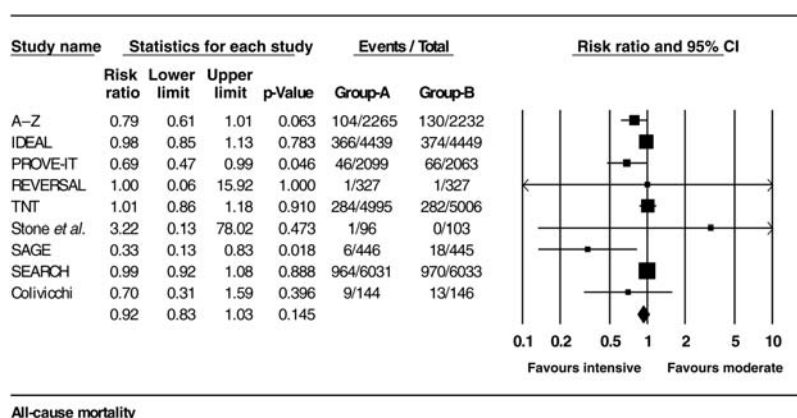


Figure 2 Forest plot of all-cause mortality.

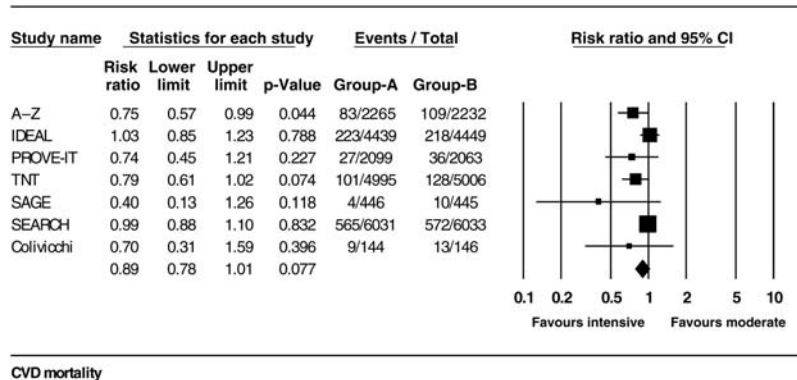


Figure 3 Forest plot of cardiovascular death mortality.

fatal MI risk reductions is robust, but that the impact of intensive dosing on any cause of mortality was less so. Limitations of our analysis include that we are employing study level data and an individual patient data may provide stronger inferences on the LDL lowering effects of intensive vs. moderate dosing. The Cholesterol Treatment Trialists Collaboration (CTTC)² have updated their analysis with the addition of the SEARCH trial and found a significant association between LDL reduction and vascular events, data unavailable through publications.⁷ A limitation associated with any meta-analysis is the conclusiveness of an analysis, based on the adequacy of events. Our analysis used event rates at the conclusion of each trial and did not adjust for time effects, as a meta-analysis using time-to-event data may permit. In our analysis, we considered statins as a class of drugs, expecting that each drug exerts a similar therapeutic effect. We previously examined this in statin vs. placebo trials.⁵¹ It is possible that there are differing effects between statins when using intensive dosing. Several of the trials did not report the component endpoints in the individual trials, leaving some of our analyses underpowered. An analysis that examined the impact of unreported outcomes on summary

estimates from Cochrane reviews found overestimation of summary estimates when outcomes were inadequately contributing to the analysis.⁵² It is likely that in some of our analyses, we are also experiencing bias, but cannot infer the direction of that bias. Our analysis of CVD mortality is inconclusive, according to the trial sequential analysis, and has comparatively wide confidence intervals for this major endpoint, and demonstrates that data on a further 4000 randomized patients would be needed to provide robust evidence. Our analysis only examined statins and therefore did not examine whether there is any benefit in using other agents (nicotinic acid, fibrates, ezetimibe) as add-on treatments to a statin to achieve additional LDL-C lowering and possible reduction in events.

Our analysis should be interpreted in the context of previous meta-analyses. Five previous meta-analyses have aimed to determine the effectiveness of intensive vs. moderate dosing.^{7,12–15} We have added two additional studies. Regardless, our study is in keeping with previous analysis findings of no significant reduction in mortality although there seems a favourable trend for intensive dosing of statins. A recent individual patient data meta-analysis by

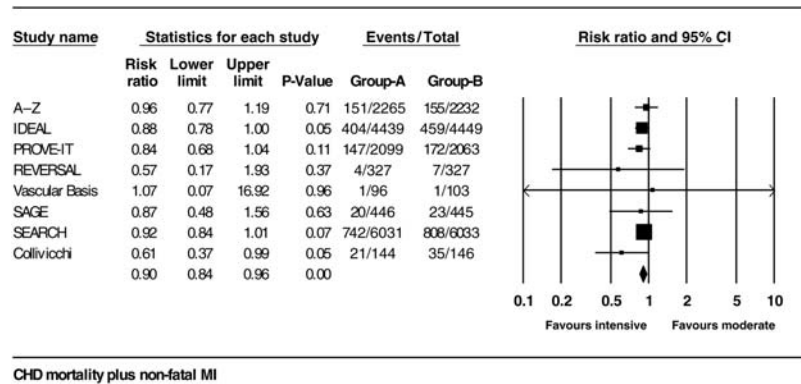


Figure 4 Forest plot of coronary heart disease death plus non-fatal MI. Yu *et al.* reported zero events in both arms and therefore did not contribute to this analysis.

Murphy *et al.* found a significant decrease in acute coronary patient mortality when combining the PROVE-IT and the A-Z trials involving patients with acute coronary syndrome (0.77, 95% CI, 0.63–0.95, $P = 0.015$).⁵³ We also conducted an analysis of exclusively acute coronary syndrome patients, involving three RCTs, and found a significant reduction both all-cause and CVD mortality.^{6,16,46} Event rates are higher in the short period after an acute coronary syndrome than more stable disease.⁵⁴ It is possible that the effect detected is because acute coronary syndrome trials have better power, due to larger event rates, than secondary prevention trials. It is also possible that pleiotropic effects of statins might be more relevant in acute coronary syndrome than in stable disease.⁵⁴

Clinicians should take note that our analysis found important reductions in non-fatal events and may not translate to reduced mortality. Along with this finding is the increased risk of adverse events associated with hepatic enzyme elevations and possible liver damage. However, a longitudinal analysis of the Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) Study evaluated long-term outcomes of those randomized to moderate dose atorvastatin vs. placebo and found more favourable liver outcomes in statin than placebo patients.⁵⁵ One of our most concerning findings was an increased risk for rhabdomyolysis associated with intensive simvastatin dosing in the A-Z trial⁴⁶ and also in the SEARCH trial.³¹ Given that this is a relatively rare event and was inadequately reported across trials, this provides an early inference to continually examine for serious myopathy associated with intensive dosing. While many physicians consider all statins to be the same, compelling evidence of differential adverse events associated with the now withdrawn statin, cerivastatin, suggest that not all statins may have the same therapeutic or adverse event profiles. Notably, the evidence for cerivastatin harms was drawn from post-marketing surveillance.⁵⁶ Physicians suspicious of myopathy should consider CK measurements, statin dosage reduction, discontinuation, and rechallenge; and treatment alternatives, such as extended-release fluvastatin, low-dose, or alternate-day rosuvastatin.⁵⁷

There is considerable interest in combining statin therapy with emerging drug developments. The problem with current combination therapies involving, for example, simvastatin and ezetimibe or statins with fibrates is that, although they are likely to improve reductions in LDL-targets, the results from only a few clinical trials have yielded consistently disappointing results in terms of major clinical endpoints. More evidence on this is expected with ongoing RCTs.⁵⁸

In conclusion, our study found no significant improvement in mortality associated with intensive statin use, but did find a reduction in non-fatal events. In a subgroup of acute coronary syndrome patients, intensive dosing reduced mortality. For patients at sufficient risk for a cardiovascular event, the decision on which agent to use and at what dose remains one to be agreed jointly between the patient and the treating physician after a discussion on relative benefits and risks.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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Conflict of interest: none declared.

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