RESEARCH

The efficacy and safety of intensive statin therapy: a meta-analysis of randomized trials

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ABSTRACT

Background: Recent lipid guidelines recommend aggressive low-density lipoprotein (LDL) cholesterol lowering in patients with coronary artery disease. To clarify the evidence for this recommendation, we conducted a meta-analysis of randomized controlled trials that compared different intensities of statin therapy.

Methods: We searched electronic databases (MEDLINE, EMBASE, Cochrane Central Registery of Controlled Trials, Web of Science) for randomized controlled trials published up to July 19, 2007, that compared statin regimens of different intensities in adults with coronary artery disease and that reported cardiovascular events or mortality. Data were pooled using random-effects models to calculate odds ratios (OR).

Results: A total of 7 trials (29 395 patients) were included. Compared with less intensive statin regimens, more intensive regimens further reduced LDL levels (0.72 mmol/L reduction, 95% confidence interval [CI] 0.60–0.84 mmol/L), and reduced the risk of myocardial infarction (OR 0.83, 95% CI 0.77–0.91) and stroke (OR 0.82, 95% CI 0.71–0.95). Although there was no effect on mortality among patients with chronic coronary artery disease (OR 0.96, 95% CI 0.80–1.14), all-cause mortality was reduced among patients with acute coronary syndromes treated with more intensive statin regimens (OR 0.75, 95% CI 0.61–0.93). Compared with lower intensity regimens, more intensive regimens were associated with small absolute increases in rates of drug discontinuation (2.5%), elevated levels of aminotransferases (1%) and myopathy (0.5%), and there was no difference in noncardiovascular mortality. All 7 trials reported events by randomization arm rather than by LDL level achieved. About half of the patients treated with more intensive statin therapy did not achieve an LDL level of less than 2.0 mmol/L, and none of the trials tested combination therapies.

Interpretation: Our analysis supports the use of more intensive statin regimens in patients with established coronary artery disease. There is insufficient evidence to advocate treating to particular LDL targets, using combination lipid-lowering therapy to achieve these targets or for using more intensive regimens in patients without established coronary artery disease.

Une version française de ce résumé est disponible à l'adresse www.cmaj.ca/cgi/content/full/178/5/576/DC1

Dyslipidemia is the most important modifiable risk factor for myocardial infarction worldwide,[1] and serum cholesterol levels are directly related to mortality from coronary artery disease in all populations studied.[2–4] Over the past decade, randomized controlled trials enrolling a wide variety of patients have confirmed that for every 1-mmol/L reduction in serum low-density lipoprotein (LDL) cholesterol achieved by statin therapy, the relative risks of cardiovascular events and mortality are reduced (by 21% and 12% respectively).[5]

Statins exert their beneficial effects primarily by reducing the level of LDL cholesterol,[6] and the reductions in the relative risk of cardiovascular events achieved by statin therapy appears to be similar regardless of baseline cholesterol levels.[5] As a result, attention has increasingly focused on defining optimal target LDL levels, particularly in patients at highest risk (i.e., those with coronary artery disease). Based on the observational studies mentioned above,[2,3] the apparent lack of a lower threshold for statin benefit in the randomized controlled trials, and recent trials reporting greater benefits with more intensive statin regimens (compared with less intensive regimens), Canadian[7] and American[8] guidelines for secondary prevention now recommend target LDL levels below 2.0 mmol/L in patients with coronary artery disease. On the other hand, European guidelines specify a target LDL of 2.5 mmol/L in these patients.[9] Questions have been raised about the safety and incremental benefits of more intensive statin regimens.[10–12]

We performed a systematic review and meta-analysis to critically examine the evidence for the safety, efficacy (LDL lowering) and clinical effectiveness from trials comparing more intensive statin therapy with less intensive statin therapy in patients with coronary artery disease.

Methods

Eligibility criteria

We included randomized clinical trials that compared different regimens of statin therapy intensity in adult patients with coronary artery disease and that reported cardiovascular events or mortality. We excluded studies that were only published in abstract form. We also excluded trials that com-

pared different intensities of statin therapy but that used much lower statin doses in the control arm than currently used in clinical practice (such as the Post-CABG [Coronary Artery Bypass Graft] Trial conducted in the mid-1990s).[13]

Study identification and selection

A librarian searched MEDLINE (from 1966), EMBASE (from 1988) and the Cochrane Central Registry of Controlled Trials using relevant subject headings, chemical abstract registry names and text–word searching for statins or hydroxymethyl-glutaryl-CoA reductase inhibitors (for search terms, see on-line Appendix 1 available at www.cmaj.ca/cgi/content/full/178/5/576/DC2). The search was conducted on August 10, 2006, and it was updated July 19, 2007. We also conducted a "cited-reference search" in Web of Science for all eligible papers, reviewed the reference lists of all included studies and review articles, and contacted content experts.

Data extraction and quality assessment

K.J. and F.A.M. independently screened all citations, abstracted data and assessed methodologic quality. Disagreements were resolved by consensus. All of the included trials reported composite primary outcomes, but because these differed among studies, they were not appropriate for meta-analysis. Instead, we extracted the individual outcomes from each study that were objectively defined and common among studies (e.g., death, myocardial infarction, stroke).

Data analysis

We extracted intention-to-treat data about cardiovascular events or death, and we used RevMan 4.2 (Update Software Ltd., Oxford, United Kingdom) to perform the meta-analysis of studies reporting the same outcome. We used the DerSimonian and Laird random-effects model to calculate odds ratios (OR) and the I^2 statistic to assess heterogeneity for each outcome of interest.[14]

Results

Study selection and evaluation

Our search identified 429 citations, of which 7 trials fulfilled our eligibility criteria (kappa = 0.70 for agreement on study eligibility) (Figure 1).[15–21] We excluded 2 potentially eligible trials that compared different intensities of statin therapy: 1 trial enrolled only patients with familial hypercholesterolemia[22] and 1 enrolled a wide variety of patients of whom the majority (54%) did not have coronary artery disease.[23]

Study characteristics

Table 1 presents key characteristics from the 7 trials (reporting data from 29 395 patients with coronary artery disease)
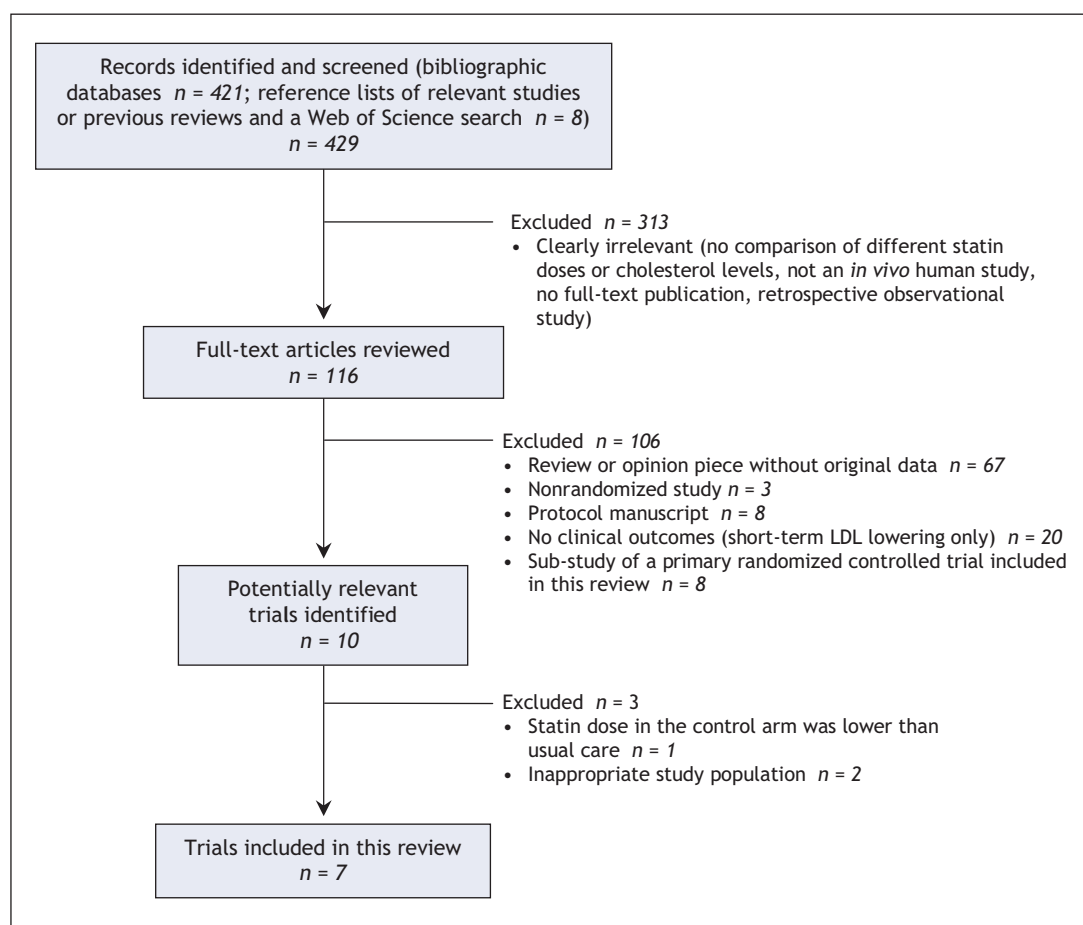

Figure 1: Flow of trials through the selection process.

Table 1: Characteristics of 7 randomized controlled trials comparing different intensities of statin therapy included in the systematic review

Characteristic	PROVE IT–TIMI 22[15] n = 4 162	A to Z[16] n = 4 497	TNT[17] n = 10 001	IDEAL[18] n = 8 888	REVERSAL[19] n = 654	Vascular Basis[20] n = 300	SAGE[21] n = 893
Study population							
Age, yr, mean*	58	61 (median)	61	61.7	56	NR	72
Male, % of participants	78	76	81	80.9	72	86	69
Diabetes, % of participants	18	24	15	12	19	16	23
Prior coronary artery bypass graft surgery, % of participants	11	4	47	17	NR	21	29
Prior angioplasty with or without stent, % of participants	15	45	54	20	NR	64	30
Baseline LDL cholesterol, mmol/L, mean	2.74	2.89	3.9 before run-in; 2.6 after run-in	3.2	3.9	3.9	3.78
Population	Post acute coronary syndromes	Post acute coronary syndromes	Chronic coronary artery disease	Chronic coronary artery disease	Chronic coronary artery disease	Chronic coronary artery disease	Chronic coronary artery disease
Study groups (daily dose)	Pravastatin (40 mg) v. atorvastatin (80 mg)	Placebo for 4 mo then simvastatin (20 mg) v. simvastatin (40 mg for 1 mo then 80 mg)	Atorvastatin (10 mg) v. atorvastatin (80 mg)	Simvastatin (20 mg) v. atorvastatin (80 mg)	Pravastatin (40 mg) v. atorvastatin (80 mg)	Lovastatin (5 mg) v. atorvastatin (80 mg) v. Atorvastatin (80 mg) and antioxidant vitamins	Pravastatin (40 mg) v. atorvastatin (80 mg)
Duration of follow-up, yr	2	2	4.9	4.8	1.5	1	1
Primary outcome	Death, MI, unstable angina requiring hospital admission, revascularization (> 30 d after randomization), stroke	Cardiovascular death, nonfatal MI, readmission for acute coronary syndromes, stroke	Death from coronary artery disease, nonfatal MI not related to procedure, cardiac arrest with resuscitation, stroke	Death from coronary artery disease, nonfatal acute MI, cardiac arrest with resuscitation	Percentage change in atheroma volume	No. and duration of ischemic episodes on ambulatory ECG	Total duration of ischemia on ambulatory ECG
Cointerventions, % of patients							
Acetylsalicylic acid	93	98	88	79	NR	80	93
β-Blockers	85	90	55	75	NR	81	75
ACE inhibitors	69	71	28	30	NR	24	50
Treatment effect							
LDL cholesterol level achieved, more v. less intensive treatment, mmol/L	1.60 v. 2.46	1.71 v. 2.10	2.0 v. 2.6	2.1 v. 2.7	2.04 v. 2.85	2.2 v. 3.2	1.70 v. 2.52
Change from baseline, more v. less intensive treatment, % change	42 v. 10	41 v. 27	49 v. 33	34 v. 16	46 v. 25	43 v. 19	55 v. 32
Primary outcome rate, more v. less intensive treatment, %	22.4 v. 26.3	14.4 v. 16.7	8.7 v. 10.9	9.3 v. 10.4	-0.4 v. 2.7	-29 v. -61	-38 v. -37

Note: ACE = angiotensin-converting enzyme, A to Z = Aggrastat to Zocor, ECG = electrocardiogram, IDEAL = Incremental Decrease in End Points Through Aggressive Lipid Lowering, LDL = low-density lipoprotein, MI = myocardial infarction, NR = not reported, PROVE IT-TIMI 22 = Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22, REVERSAL = Reversal of Atherosclerosis with Aggressive Lipid-Lowering Therapy, SAGE = Study Assessing Goals in the Elderly, TNT = Treating to New Targets.
*Unless stated otherwise.

included in our review.[15-21] Of these trials, 2 enrolled patients after acute coronary syndromes and 5 enrolled patients with chronic coronary artery disease. The demographic characteristics of study participants were similar across the included trials. Baseline LDL cholesterol ranged between 2.74 mmol/L in the PROVE IT–TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22) trial to 3.9 mmol/L in the REVERSAL (Reversal of Atherosclerosis with Aggressive Lipid-Lowering Therapy) trial, TNT (Treating to New Targets) trial (before the run-in period, 2.6 mmol/L before randomization) and the Vascular Basis trial. Three trials were designed with continuous outcomes as their primary outcome: the Vascular Basis and the SAGE (Study Assessing Goals in the Elderly) trials reported the number of ischemic episodes[20,21] and the REVERSAL trial reported percent change in atheroma volume.[19] Four trials used clinical primary composite outcomes, but the individual components differed (Table 1).[15-18] Of note, the definitions for several of the composite cardiovascular outcomes were different in the primary publications from the PROVE-IT and the A-to-Z (Aggrastat to Zocor) trials than those used in the other trials; however, these outcomes were re-reported by the PROVE-IT and A-to-Z investigators (using the definitions from the other trials) in a secondary publication.[24] We extracted data on "myocardial infarction or coronary death" and "stroke" for PROVE-IT and A-to-Z from this follow-up publication.[24] All other outcomes were extracted from the primary study publication.

Quality of included trials

Although all 7 trials reported blinded outcome ascertainment, their Jadad scores varied from 3 to 5 (out of 5). Three trials adequately reported their method of allocation concealment (Table 2).[16,18,19]

Generalizability of included trials

Potential threats to study generalizability are reported in Table 2. For example, although the IDEAL (Incremental Decrease in End Points Through Aggressive Lipid Lowering) trial randomized over 90% of patients screened, TNT excluded almost half of those initially screened. Further, although both TNT and IDEAL included patients with stable coronary artery disease, they recruited patients from specialty clinics rather than from primary care settings. In addi-

Table 2: Quality assessment and potential risks of bias in the 7 randomized controlled trials comparing different intensity statin regimens in patients with coronary artery disease.

	PROVE IT–TIMI 22[15] n = 4 162	A to Z[16] n = 4 497	TNT[17] n = 10 001	IDEAL[18] n = 8 888	REVERSAL[19] n = 654	Vascular Basis[20] n = 300	SAGE[21] n = 893
Design	Double-blind, non-inferiority	Double-blind, superiority	Double-blind, superiority	Open-label, blinded end-point classification, superiority	Double-blind, superiority	Double-blind, superiority	Double-blind, superiority
Jadad Score*	4	5	3	3	5	4	3
Allocation concealment†	Unclear	Adequate	Unclear	Adequate	Adequate	Unclear	Unclear
Patients recruited from primary care setting	Yes‡	Yes‡	No	No	Yes†	No	Yes
Randomization, % of patients screened	Not reported	Not reported	54	92	30	50	18
Duration long enough to demonstrate effects	Yes	Yes	Yes	Yes	Questionable	Questionable	Questionable
Intention-to-treat analysis	Yes	Yes	Yes	Yes	Yes	Unclear	Yes
Run-in before randomization	No	No	Yes (8 weeks)	No	Yes (2 weeks)	No	No
Receiving statins before trial, % of patients	25	None	100	76	29 prior to wash-out	72	45

Note: PROVE IT–TIMI 22 = Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22, A to Z = Aggrastat to Zocor, TNT = Treating to New Targets, IDEAL = Incremental Decrease in End Points Through Aggressive Lipid Lowering, REVERSAL = Reversal of Atherosclerosis with Aggressive Lipid-Lowering Therapy, SAGE = Study Assessing Goals in the Elderly.
*The Jadad scale gives a methodologic score based on reported methods. Scores vary from 0 to 5, with higher scores indicating higher quality.
†Allocation concealment was classified as "adequate" if the trial described randomization procedures that ensured clinicians and participants would be unaware of potential treatment assignments (e.g., if randomization was done centrally with a random number generator and varying block size so that participating clinicians could not guess what the next treatment assignment was likely to be, and if trial participants were only assigned to a group after study recruitment and baseline data were collected).
‡For patients with acute coronary syndromes or requiring coronary angiography, hospital rather than family physician's office was defined as the primary care setting.

tion, the percentage of patients using statins before randomization varied widely among the trials. The A-to-Z trial excluded all patients who had previously received statin therapy. The TNT trial included a run-in phase such that 100% of patients had received statin therapy for at least 8 weeks before randomization.

Quantitative data syntheses

LDL-cholesterol lowering efficacy
Compared with the lower intensity arm, the higher intensity arm in each trial achieved lower LDL cholesterol levels. The differences in LDL cholesterol levels were between 0.39 and 1.0 mmol/L (weighted mean difference 0.72, 95% CI 0.60–0.84 mmol/L). An LDL cholesterol of less than 2.0 mmol/L was achieved in about 50% of patients in the more intensive statin monotherapy groups (Table 1).

All-cause mortality
The pooled analysis revealed no difference in all-cause mortality between the more or less intensive statin treatment arms in all 7 trials (OR 0.87, 95% CI 0.74–1.03). However, there was substantial heterogeneity among trials ($I^2 = 42\%$), and pooling the data obscured the fact that more intensive statin therapy was associated with a 25% reduction in mortality in patients after acute coronary syndrome (based on 353 events in 8659 patients, OR 0.75, 95% CI 0.61–0.93), but had no impact on mortality in patients with chronic coronary artery disease (based on 1333 events in 20 734 patients, OR 0.96, 95% CI 0.80–1.14).

Myocardial infarction or coronary death
More intensive statin therapy led to a statistically significant reduction in myocardial infarction or coronary death (OR 0.83, 95% CI 0.77–0.91) with no heterogeneity among trials ($I^2 = 0\%$) (Figure 2). Examining each of these components separately confirmed that the benefits were seen in patients after acute coronary syndromes or with chronic coronary artery disease and for both nonfatal myocardial infarction (based on 1772 events in 28 439 patients, OR 0.85, 95% CI 0.77–0.93) and coronary deaths (based on 839 events in 28 439 patients, OR 0.84, 95% CI 0.71–0.98).

Stroke
Although TNT was the only trial to demonstrate a significant benefit in stroke reduction, the pooled results demonstrate a statistically significant reduction in the number of strokes with more intensive statin therapy compared with less intensive therapy (OR 0.82, 95% CI 0.71–0.95) with no heterogeneity among trials ($I^2 = 0\%$) (Figure 3). The results were similar among patients with chronic coronary artery disease or with acute coronary syndromes ($p = 0.21$ for comparison between each OR).

Major cardiovascular events
Only the IDEAL, TNT, SAGE and Vascular Basis trials reported rates of major cardiovascular events (myocardial infarction, coronary death or stroke). The pooled analysis confirmed fewer major cardiovascular events in the more intensive statin treatment arm of these trials (OR 0.80, 95% CI 0.71–0.90, $I^2 = 27\%$).
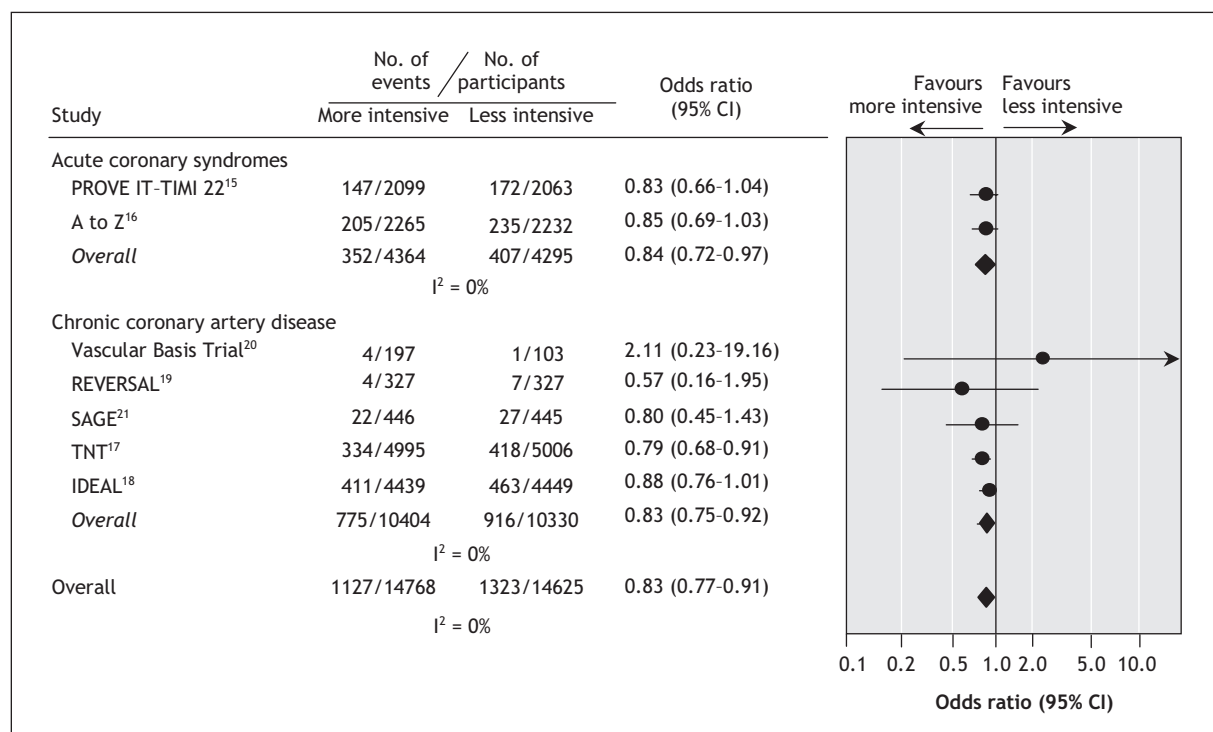

Study	No. of events / No. of participants		Odds ratio (95% CI)
	More intensive	Less intensive	
Acute coronary syndromes			
PROVE IT-TIMI 22[15]	147/2099	172/2063	0.83 (0.66-1.04)
A to Z[16]	205/2265	235/2232	0.85 (0.69-1.03)
Overall	352/4364	407/4295	0.84 (0.72-0.97)
		$I^2 = 0\%$	
Chronic coronary artery disease			
Vascular Basis Trial[20]	4/197	1/103	2.11 (0.23-19.16)
REVERSAL[19]	4/327	7/327	0.57 (0.16-1.95)
SAGE[21]	22/446	27/445	0.80 (0.45-1.43)
TNT[17]	334/4995	418/5006	0.79 (0.68-0.91)
IDEAL[18]	411/4439	463/4449	0.88 (0.76-1.01)
Overall	775/10404	916/10330	0.83 (0.75-0.92)
		$I^2 = 0\%$	
Overall	1127/14768	1323/14625	0.83 (0.77-0.91)
		$I^2 = 0\%$	

Figure 2: Risk of myocardial infarction or coronary death among patients with acute coronary syndromes or chronic coronary artery disease in 7 studies of statin therapy intensity.

Noncardiovascular mortality

Five trials[15–18,21] reported noncardiovascular mortality. There was no difference between more intensive and less intensive statin regimens in these trials (based on 670 noncardiovascular deaths in 28 439 patients, OR 0.93, 95% CI 0.69–1.25).

Discontinuation rates

Discontinuation attributed specifically to drug-related adverse events was not significantly higher with more intensive statin therapy (pooled estimate 7.8% v. 5.3% in the less intensive statin arms) (Table 3, Table 4). To add context to the safety numbers, we have included the results from the pooled analyses of the placebo-controlled randomized statin trials (in which patients received doses similar to the "less intensive arm" of the trials reviewed in this meta-analysis) in Table 4.[11]

Aminotransferase levels

Of the 6 trials that reported this outcome,[15-19,21] 5 described a significant excess risk of elevated aminotrasferase levels (aspartate aminotransferase or alanine aminotransferase levels more than 3 times the normal upper limit) with more intensive statin therapy compared with less intensive therapy (Table 3, Table 4). The pooled rates were significantly different (1.5% v. 0.4%, OR 4.14, 95% CI 2.30–7.44).[15–18,21]

Myopathy and rhabdomyolysis

Myopathic adverse events were inconsistently reported and were not significantly more frequent among patients receiving more intensive statin therapy compared with less intensive therapy (Table 3, Table 4). Although the event rates were low, all of these trials used statin monotherapy, not the combination therapy that is frequently recommended to achieve target LDL levels less than 2.0 mmol/L.

Sensitivity analyses

None of the quality variables included in Table 2 influenced the study outcomes. For example, for the most frequent outcomes (myocardial infarction or coronary death), there was no difference in effect estimates for those trials with adequate allocation concealment (OR 0.85, 95% CI 0.77–0.97) compared to those without adequate allocation concealment (OR 0.80, 95% CI 0.71–0.91). There were also no differences in the trials with run-in periods (OR 0.78, 95% CI 0.67–0.91) and those without run-in periods (OR 0.86, 95% CI 0.78–0.95).

Interpretation

Our systematic review demonstrates that, among patients with coronary artery disease, the provision of more intensive statin monotherapy (compared with less intensive statin therapy) reduces LDL cholesterol levels by a further 0.72 mmol/L. This additional reduction in LDL cholesterol resulted in 17% fewer myocardial infarctions (absolute reduction 1.4%) and 18% fewer strokes (absolute reduction 0.5%) among patients randomized to more intensive statin regimens rather than less intensive regimens. These benefits of more intensive statin monotherapy were at the expense of small absolute increases in the frequency of drug discontinuation (about 2.5%), elevated aminotrasferase levels (about 1%) and myopathy (about 0.5%) when compared with less-intensive statin therapy (only the aminotransferase elevations were statistically significant). There was no difference in noncardiovascular mortality. All-cause mortality was not reduced
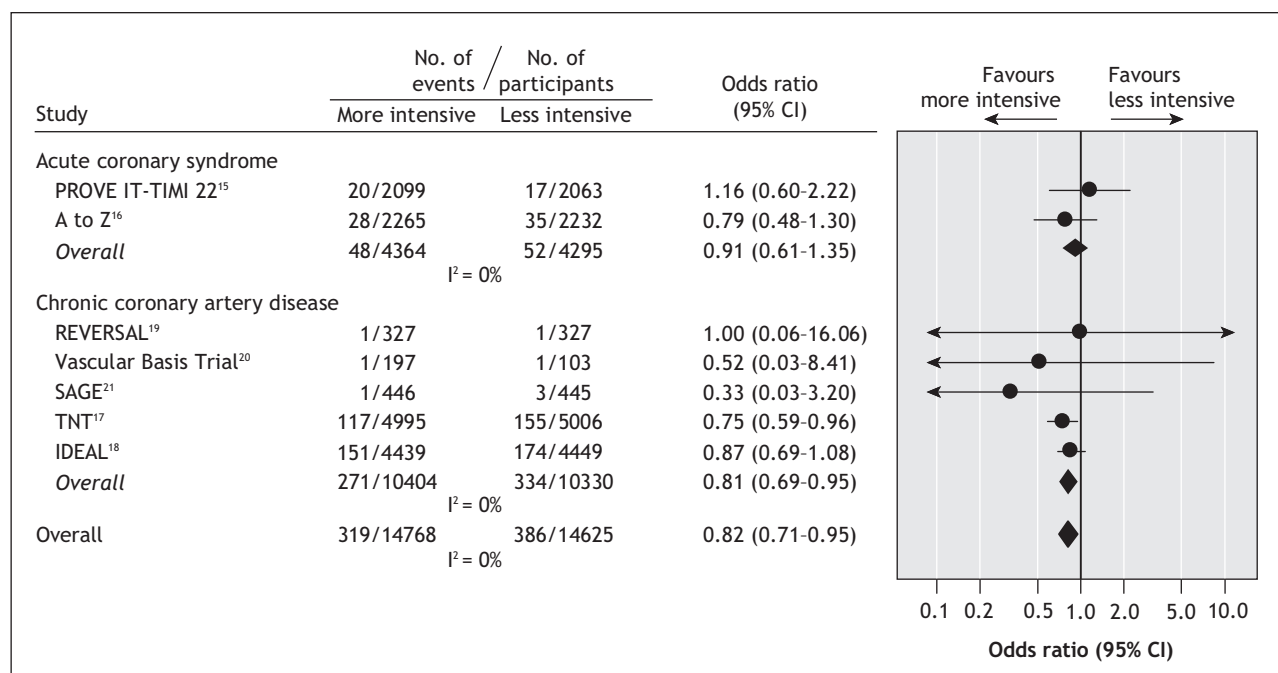

Study	No. of events / participants		Odds ratio (95% CI)	Favours more intensive / Favours less intensive
	More intensive	Less intensive		
Acute coronary syndrome				
PROVE IT-TIMI 22[15]	20/2099	17/2063	1.16 (0.60-2.22)	
A to Z[16]	28/2265	35/2232	0.79 (0.48-1.30)	
Overall	48/4364	52/4295	0.91 (0.61-1.35)	
		I² = 0%		
Chronic coronary artery disease				
REVERSAL[19]	1/327	1/327	1.00 (0.06-16.06)	
Vascular Basis Trial[20]	1/197	1/103	0.52 (0.03-8.41)	
SAGE[21]	1/446	3/445	0.33 (0.03-3.20)	
TNT[17]	117/4995	155/5006	0.75 (0.59-0.96)	
IDEAL[18]	151/4439	174/4449	0.87 (0.69-1.08)	
Overall	271/10404	334/10330	0.81 (0.69-0.95)	
		I² = 0%		
Overall	319/14768	386/14625	0.82 (0.71-0.95)	
		I² = 0%		

Odds ratio (95% CI): 0.1 0.2 0.5 1.0 2.0 5.0 10.0

Figure 3: Risk of stroke among patients with acute coronary syndromes or chronic coronary artery disease in 7 studies of statin therapy intensity.

Table 3: Adverse events reported in trials comparing different intensities of statin therapy among patients with coronary artery disease*

Event	PROVE IT–TIMI 22[15] Low n = 2063	PROVE IT–TIMI 22[15] High n = 2099	A to Z[16] Low n = 2230	A to Z[16] High n = 2263	TNT[17] Low n = 5006	TNT[17] High n = 4995	IDEAL[18] Low n = 4449	IDEAL[18] High n = 4439	REVERSAL[19] Low n = 327	REVERSAL[19] High n = 327	SAGE[21] Low n = 445	SAGE[21] High n = 446
Adverse event leading to drug discontinuation, no. (%) of patients	56 (2.7)	69 (3.3)	191 (8.6)	216 (9.5)	265 (5.3)	360 (7.2)	186 (4.2)	426 (9.6)	22 (6.7)	21 (6.4)	46 (10.3)	48 (10.8)
Aminotrasferase level elevations, no. (%) of patients	23 (1.1)	69 (3.3)	8 (0.4)*	19 (0.9)*	9 (0.2)	60 (1.2)	5 (0.1)	43 (1.0)	5 (1.6)†	7 (2.3)†	1 (0.2)	19 (4.3)
Myalgia, no. (%) of patients	56 (2.7)	69 (3.3)	35 (1.6)	50 (2.2)	234 (4.7)	241 (4.8)	51 (1.1)	97 (2.2)	12 (3.4)	9 (2.8)	12 (2.7)	14 (3.1)
Myopathy (myalgia with creatine kinase elevation), no. (%) of patients	NR	NR	1 (0.04)	9 (0.4)	NR	NR	11 (0.3)	6 (0.1)	NR	NR	NR	NR
Rhabdomyolysis, no. (%) of patients	0	0	0	3 (0.1)	3 (0.06)	2 (0.04)	3 (0.07)	2 (0.05)	0	0	0	0

Note: PROVE IT–TIMI 22 = Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22, A-to-Z = Aggrastat to Zocor, TNT = Treating to New Targets, IDEAL = Incremental Decrease in End Points Through Aggressive Lipid Lowering, REVERSAL = Reversal of Atherosclerosis with Aggressive Lipid-Lowering Therapy, SAGE = Study Assessing Goals in the Elderly, NR = not reported.
*Adverse events were not reported in the Vascular Basis trial.
†Not all patients in these trials had regular monitoring of aminotransferase levels. The percentages presented reflect the percentage among patients who had their aminotransferase levels checked.

among patients with chronic coronary artery disease, but it was reduced by one-quarter among patients treated after acute coronary syndromes (absolute reduction 1.1%, number needed to treat 91).

Our findings have several clinical implications. First, because all of the trials compared fixed-dose regimens of more intensive statin therapy with less intensive statin therapy and because none provided a breakdown of event rates by the level of LDL cholesterol reduction achieved, the available data cannot be used to define optimal target LDL cholesterol levels. In particular, it should be noted that less than half of all patients who received more intensive statin therapy achieved LDL levels of less than 2.0 mmol/L. Nonetheless, these trials support prescribing more intensive statin regimens for patients with established coronary artery disease, particularly among those with acute coronary syndromes. A recent modeling analysis confirmed that more intensive statin therapy was very cost-effective among acute coronary syndrome survivors (US$12 900 per quality-adjusted life-year). However, the incremental cost-effectiveness among patients with chronic coronary artery disease was uncertain because the small magnitude of benefits (0.10 quality-adjusted life-year) resulted in estimates that were highly sensitive to variations in drug costs and long-term adherence.[25]

Second, it is important to highlight that these trials provide evidence for more intensive statin monotherapy. None of these trials used, or even permitted, combination therapy. Achieving lower LDL cholesterol targets will often require the use of multidrug therapy, which may result in increased risk of adverse effects, drug–drug interactions and medication nonadherence as well as increased costs for both patients and health care payors.[10,26] It is not enough that short-term trials with LDL cholesterol outcomes have demonstrated that other lipid-lowering agents can further lower LDL cholesterol when given along with statins.[27–29] Large trials are needed to establish the clinical safety and effectiveness of combination therapy.

Third, the current literature provides limited insight into whether more intensive statin therapy should be used in patients without coronary artery disease but with multiple atherosclerotic risk factors. Although 2 small trials[22,23] have demonstrated reductions in carotid intima medial thickness in patients with familial hypercholesterolemia or other atherosclerotic risk factors, there were too few clinical events in these trials to make definitive conclusions. In light of a recent secondary analysis of the TNT trial which suggested that patients with metabolic syndrome may derive even greater benefits from more intensive statin therapy compared with patients without metabolic syndrome, this area of research should be a priority.[30]

Fourth, although the INTERHEART study and cohort studies from various regions of the world have confirmed that dyslipidemia is the most important modifiable coronary risk factor worldwide,[1–4] the trials showing the efficacy of statin therapy have largely enrolled white men. For example, in our meta-analysis 88%–97% of study participants in the 4 trials that reported participant ethnic background were white and 69%–81% were men.[15,17,19,21] Although it is unset-

Table 4: Adverse events reported in trials that compared statin regimens of different intensities and those that compared statin therapy and placebo

Event	More intensive v. less intensive statin therapy*		Less intensive statin therapy v. placebo†	
	% of patients	Odds ratio (95% CI)	% of patients	Odds ratio (95% CI)
Adverse event leading to drug discontinuation	7.8 v. 5.3	1.34 (0.98-1.83)	5.6 v. 6.1	0.92 (0.85-0.99)
Aminotrasferase level elevation	1.5 v. 0.4	4.14 (2.30-7.44)	1.4 v. 1.1	1.23 (1.06-1.42)
Myalgia	3.3 v. 2.8	1.26 (0.98-1.63)	15.4 v. 18.7	0.79 (0.76-0.83)
Myopathy (myalgia with creatine kinase elevation)	2.2 v. 1.8	1.91 (0.11-32.13)	0.9 v. 0.4	2.03 (1.55-2.67)
Rhabdomyolysis	0.05 v. 0.04	0.97 (0.29-3.24)	0.2 v. 0.1	1.36 (0.90-2.06)

Note: CI = confidence interval.
*Data were pooled from the PROVE IT-TMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22), A to Z (Aggrastat to Zocor), TNT (Treating to New Targets), IDEAL (Incremental Decrease in End Points Through Aggressive Lipid Lowering), REVERSAL (Reversal of Atherosclerosis with Aggressive Lipid-Lowering Therapy) and SAGE (Study Assessing Goals in the Elderly) trials.
†These data are from a meta-analysis of 34 placebo-controlled statin trials.[11]

tling to discover evidence grey-zones for important demographic groups, and such findings should always stimulate research to address these evidence gaps, it is important not to deny treatment to patients in these under-researched groups. For example, although individual trials were unable to confirm the benefits of statin therapy in women, a meta-analysis that pooled individual patient data from 14 trials had sufficient outcomes to confirm that statins prevented coronary events in women (OR 0.82, 95% CI 0.73–0.93).[5] Given that "most individuals with a particular condition benefit from therapies proven to be efficacious and relative treatment effects tend to be consistent across differing baseline risks,"[31] it seems reasonable to assume that groups at higher coronary risk (such as South Asians) are likely to derive the greatest absolute benefits from more intensive rather than less intensive statin therapy.

Finally, although more intensive statin therapy was well tolerated and relatively safe in the trials we reviewed, it is likely that adverse events will be more common in clinical practice for several reasons. First, trial participants are generally younger and healthier and they are more closely followed than patients in usual clinical practice. In addition, these trials excluded over half of all screened patients because of comorbidities (e.g., advanced age, renal failure, alcohol abuse, hepatic failure) or use of concomitant medications (e.g., other lipid-lowering drugs, inhibitors of the cytochrome P450 system), which may increase the risk of adverse events.[32] Second, 2 of these trials only enrolled patients after they had successfully completed a run-in period without complication.[33] Third, the time frame of these randomized trials is relatively short and underscores the importance of postmarketing surveillance studies to track complication rates and drug-discontinuation rates in usual clinical practice. The ongoing SEARCH (Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine) trial will provide much needed safety information on more intensive statin therapy (simvastatin, 80 mg/d v. 20 mg/d) over a longer timeframe (12 064 study participants, expected average follow-up of 7 years).

In summary, more intensive statin therapy is safe and well-tolerated. It provides incremental benefits over and above those of lower-intensity statin therapy in the secondary prevention of myocardial infarction and stroke in patients with known coronary artery disease, irrespective of their baseline LDL cholesterol levels. Further research is needed to define optimal LDL cholesterol targets, the role of more intensive statin therapy in patients without coronary artery disease and the role of combination therapy.

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