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Effect of statins on ventricular tachyarrhythmia, cardiac arrest, and sudden cardiac death: a meta-analysis of published and unpublished evidence from randomized trials

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Aims The effect of statin treatment on ventricular arrhythmic complications is uncertain. We sought to test whether statins reduce the risk of ventricular tachyarrhythmia, cardiac arrest, and sudden cardiac death.

Methods and results We searched MEDLINE, EMBASE, and CENTRAL up to October 2010. Randomized controlled trials comparing statin with no statin or comparing intensive vs. standard dose statin, with more than 100 participants and at least 6-month follow-up were considered for inclusion and relevant unpublished data obtained from the investigators. Twenty-nine trials of statin vs. control (113 568 participants) were included in the main analyses. In these trials, statin therapy did not significantly reduce the risk of ventricular tachyarrhythmia [212 vs. 209; odds ratio (OR) = 1.02, 95% confidence interval (CI) 0.84–1.25, $P = 0.87$] or of cardiac arrest (82 vs. 78; OR = 1.05, 95% CI 0.76–1.45, $P = 0.84$), but was associated with a significant 10% reduction in sudden cardiac death (1131 vs. 1252; OR = 0.90; 95% CI 0.82–0.97, $P = 0.01$). This compared with a 22% reduction in the risk of other 'non-sudden' (mostly atherosclerotic) cardiac deaths (1235 vs. 1553; OR = 0.78, 95% CI 0.71–0.87, $P < 0.001$). Results were not materially altered by inclusion of eight trials (involving 41 452 participants) of intensive vs. standard dose statin regimens.

Conclusion Statins have a modest beneficial effect on sudden cardiac death. However, previous suggestions of a substantial protective effect on ventricular arrhythmic events could not be supported.

Keywords Statins • Ventricular arrhythmia • Sudden death • Meta-analysis

Introduction

About half of all deaths due to heart disease manifest as sudden cardiac arrest or sudden cardiac death, many of which occur out of hospital before acute medical help can be reached.[1] While acute coronary events are the major underlying cause of sudden cardiac death, many of these are thought to be primarily caused by ventricular tachyarrhythmia.[2–4] Despite the clear public health relevance of fatal arrhythmic events, strategies for their prediction and prevention remain challenging.[5]

During recent years, a number of observational studies have suggested that raised inflammatory markers are associated with a higher future risk of ventricular tachyarrhythmia and sudden cardiac death in a variety of clinical settings.[6–9] This, together with evidence indicating that statins reduce inflammation[10] as well as experimental findings on other biological effects of statins unrelated to their LDL-cholesterol-lowering effects, has raised the hope that such treatment may, in addition to its undisputed anti-atherosclerotic effects, have some direct anti-arrhythmic effects.[11–13] Potential pathophysiological mechanisms for such an effect may include plaque stabilisation, changes to the transmembrane ion channel conduction, anti-oxidant and anti-proliferative effects, and decrease in the parasympathetic tone.[12] Supportive evidence for such an anti-arrhythmic effect of statins comes from

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a number of non-randomized studies[14–17] and meta-analysis of such studies,[18] showing an association between statin use and reduced risk of ventricular arrhythmic events. However, reliable evidence from randomized clinical trials is not available, partly because many large-scale statin trials have not published information on such events or were not individually sufficiently powered to test this hypothesis.[5]

To reach a more precise estimate of effects, we set out to perform a meta-analysis of all large-scale trials of a statin vs. a control, or of a more vs. a less intensive statin regimen, which have collected, but not necessarily published, data on ventricular arrhythmic events. In particular, we sought to estimate the effects separately on ventricular tachyarrhythmia, cardiac arrest, and sudden cardiac death.

Methods

Search strategy for identification of relevant studies

Study methods have been published previously.[19] In brief, we searched MEDLINE (January 1966 to October 2010), EMBASE (January 1985 to October 2010), and the Cochrane Central Register of Controlled Trials (up to October 2010) for articles with a subject term 'hydroxymethylglutaryl-coenzyme A reductase inhibitor' or any of the following terms: 'hydroxymethylglutaryl-co a reductase inhibitor', 'statin', 'fluvastatin', 'pravastatin', 'lovastatin', 'simvastatin', 'atorvastatin', or 'rosuvastatin'. The search was limited to randomized controlled trials with no language restrictions.

Review methods and selection criteria

Two reviewers independently screened all titles and abstracts for randomized controlled trials with either a parallel or factorial design, with at least one comparison of a statin vs. a control regimen or a more vs. less intensive statin regimen, and with 100 or more participants followed for at least 6 months. All such trials were considered potentially eligible; there were no restrictions placed on participant characteristics or study outcomes. We also hand-searched the reference lists of these studies to ensure that other relevant articles, such as meta-analyses of statin trials or other types of articles related to statins and cardiac arrhythmias, were not missed. After removing duplicate reports, full-text articles of all remaining reports were examined.

Data abstraction

An electronic data abstraction form was used to capture the following information: study name or investigator's name; recruitment period; mean follow-up duration; year of publication of the primary findings; randomized treatment comparisons; summary information about the studied population (number of participants, mean age, number of men, and prevalence of myocardial infarction or heart failure at randomization); the primary outcome of the study; the mean LDL-cholesterol level at randomization and at 1-year follow-up (or end of the study if follow-up duration was less than a year) by treatment allocation; and the number of patients with any of the following events: ventricular tachycardia or fibrillation (i.e. ventricular tachyarrhythmia), resuscitated cardiac arrest, sudden cardiac death, and all cardiac death. In trials where such events had not previously been reported, we asked the investigators to abstract the relevant numbers from their routine records of adverse events. We also asked the investigators to provide information about the definition used for the outcomes of interest. However, since most of these outcomes had not been pre-specified or adjudicated, no unique definition could be provided. Non-responders were sent at least one reminder after about three weeks.

Assessment of risk of bias

To identify potential sources of bias in the reported events, we considered the following domains for each trial individually: (i) selection bias (random sequence generation and allocation concealment); (ii) performance bias (blinding of participants and study investigators for the outcomes of interest); (iii) detection bias (blinding of outcome assessors); (iv) attrition bias (incomplete outcome data); (v) reporting bias (selective outcome reporting). Risk of bias for each domain was categorized into low, unclear or high. This information was used to make judgements about the overall risk of bias for each study. We followed the Cochrane Collaboration's recommendation to make judgements based on whether the ranking of the level of bias across domains could have led to any material bias on the outcomes of interests and, if it could, what the direction of the bias would likely be.[20]

Statistical analysis

To test the primary hypothesis that statins might reduce the risk of particular arrhythmic events, the main analyses were restricted to the trials of a statin vs. a control regimen (i.e. placebo or usual care). However, since the anti-inflammatory effect of statins—one of the key mechanisms for their potential anti-arrhythmic effects—have been suggested to be more pronounced in high-dose statin therapy,[21] secondary analyses based on additional trials that had compared a more intensive vs. a standard statin regimen were also performed.

For each trial, the 'observed minus expected' statistic ($o - e$) and its variance (v) were calculated from the number of patients who developed each arrhythmic event and the total number of patients in each treatment group. These ($o - e$) values, one from every trial, were summed to produce a grand total (G), with variance (V) equal to the sum of their separate variances. The value $\exp(G/V)$ is Peto's 'one-step' estimate of the odds ratio (OR) and its continuity corrected 95% confidence interval (CI) is given by $\exp(G/V \pm [0.5/V + 1.96/\sqrt{V}])$.[22] Heterogeneity between the individual trials was assessed by calculating $S - G^2/V$, where S is the sum of $[o - e]^2/v$ for each trial, and testing this statistic against a χ^2 distribution with degrees of freedom equal to one less than the number of trials. Tests for trend in the magnitude of the log OR when trials were ordered by their statistic size (i.e. v) were also performed.

To test whether there was a differential effect of statins on sudden cardiac death compared with other 'non-sudden' cardiac death, we estimated the effects on each separately (in the trials in which both outcomes were reported), comparing the two estimates using a standard χ^2 test on 1 degree of freedom.

The difference in LDL cholesterol achieved between randomized groups in the trials of a more intensive vs. a standard dose statin regimen was typically much lower than that achieved in the trials of statin vs. control. If the magnitude of any true relative risk reduction was related to this difference, a standard meta-analysis of the results in the different trials could be misleading. Therefore, in addition to the main analyses, supplementary 'LDL-weighted' analyses were also performed to provide the estimate of the OR per 1.0 mmol/L reduction in LDL cholesterol.

Results

Figure 1 summarizes the search retrieval process. Out of 4034 abstracts reviewed, 219 papers describing 102 trials were retrieved for further examination, of which 83 met the inclusion criteria. Of these, 37 trials were included in the analysis (most of the others reported that such events were not recorded in the trial). Twenty-nine trials (including 113 568 randomized participants and

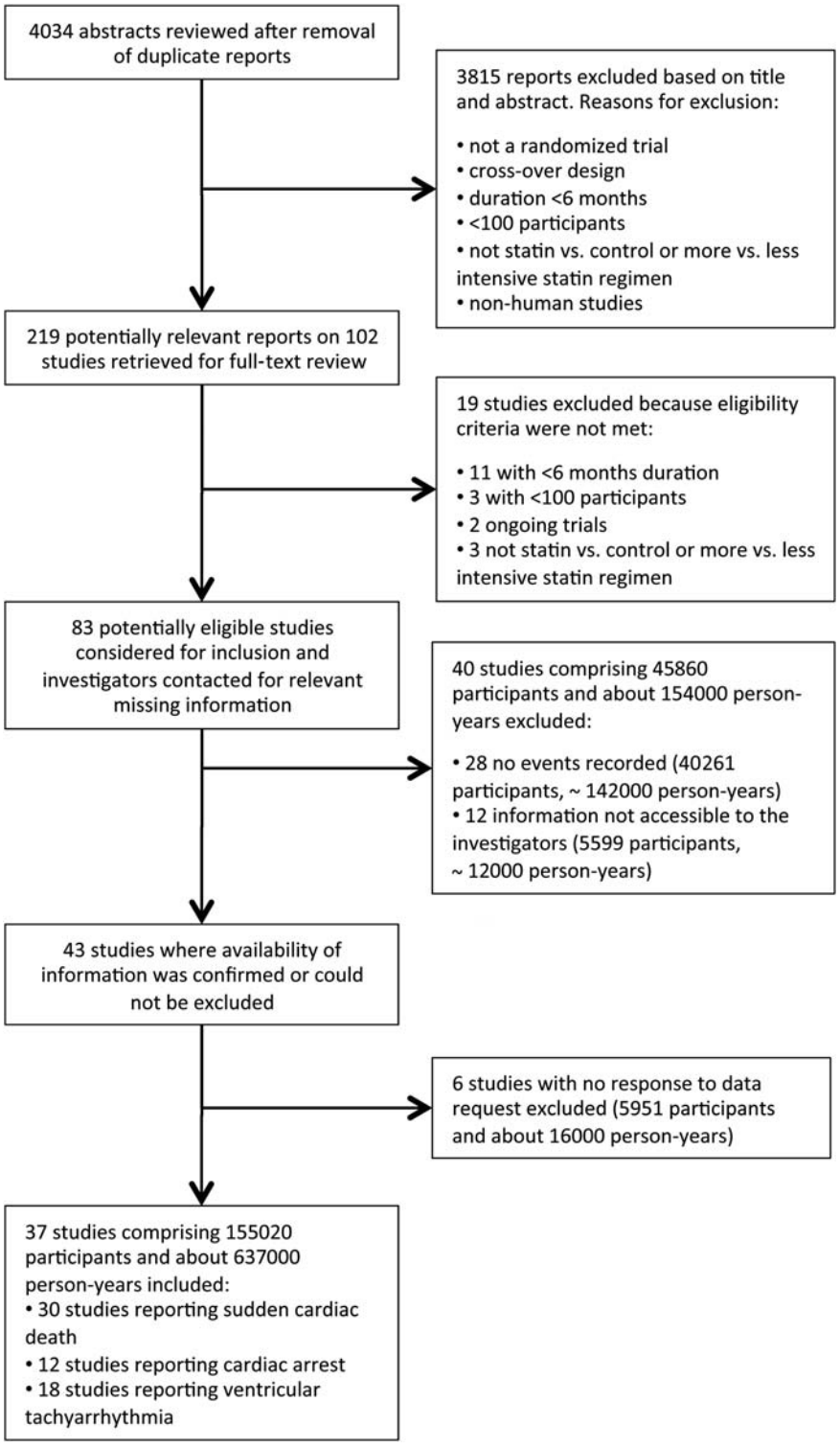

Figure 1 Flow diagram of search retrieval process.

Table 1 Summary of trials' characteristics

Study	Year of publication of main results	Mean follow-up (years)	Country/ region	Treatment comparison		LDL-c difference[a] (mmol/L)	Population characteristics				
				Intervention	Control regimen		Main inclusion criteria	Total number of participants	Mean age (years)	Male (%)	Prior MI (%)
Statin vs. control regimen											
PMSG-CR[23]	1993	0.5	Multinational	P 20–40 mg	Placebo	1.22	MI, angina or other risk factors	1062	55	77	34
4S[24]	1994	5.2	Nordics	S 40 mg	Placebo	1.77	MI or angina	4444	58	81	79
MAAS[25]	1994	4.0	Europe	S 20 mg	Placebo	1.40	Confirmed CHD plus other risk factors	381	56	88	55
PLAC-1[26]	1995	2.3	USA	P 40 mg	Placebo	1.22	Confirmed CHD	408	57	78	44
PREDICT[27]	1997	0.5	France	A 10 mg	Placebo	1.03	Post PCI	695	58	83	37
AFCAPS/ TexCAPS[28]	1998	5.3	USA	L 20–40 mg	Placebo	0.94	Primary prevention	6605	58	85	0
LIPID[29]	1998	5.6	Australia, New Zealand	P 40 mg	Placebo	1.03	History of MI or UA	9014	62	83	64
GISSI-P[30]	2000	1.9	Italy	P 20–40 mg	No treatment	0.35	Recent MI	4271	60	86	100
HPS[31]	2002	5.0	UK	S 40 mg	Placebo	1.29	Vascular disease or diabetes	20 536	64	75	41
LIPS[32]	2002	3.1	Europe, Canada, Brazil	F 80 mg	Placebo	0.92	Post PCI	1677	60	84	44
FLORIDA[33]	2002	1.0	USA	F 40 mg	Placebo	1.20	MI	540	61	83	100
ASCOT-LLA[34]	2003	3.2	Nordics and UK	A 10 mg	Placebo	1.07	Hypertension plus other risk factor	10 305	65	81	0
ALERT[35]	2003	5.1	Multinational	F 40 mg	Placebo	0.84	Renal transplant recipients	2102	50	66	34
CARDS[36]	2004	3.9	UK, Ireland	A 10 mg	Placebo	1.14	Type 2 diabetes plus other risk factor	2838	62	68	0
PREVEND IT[37]	2004	3.8	Netherlands	P 40 mg	Placebo	1.00	Microalbuminuric patients	864	51	65	0
ALLIANCE[38]	2004	4.3	USA	A 10–80 mg	Usual care	1.16	CHD	2442	61	82	58
PCAB[39]	2005	4.5	Japan	P 10–20 mg	Usual care	0.49	After CABG	335	59	85	62
4D[40]	2005	3.9	Germany	A 20 mg	Placebo	0.89	Diabetic haemodialysis patients	1255	66	54	18
NEDIAT[41]	2005	2.9	Sweden	A 10 mg	Placebo	0.71	CKD Stages 4 and 5	143	70	69	24
MEGA[42]	2006	5.3	Japan	P 10–20 mg	No treatment	0.67	Primary prevention	7832	58	30	0
ASPEN[43]	2006	4.3	Multinational	A 10 mg	Placebo	0.99	Type 2 diabetes	1864	61	66	17
SPARCL[44]	2006	4.9	Multinational	A 80 mg	Placebo	1.43	Stroke or TIA, no CHD	4731	63	60	0
CLARIDI[45]	2006	1.0	Belgium, Greece	A 80 mg	Placebo	1.68	CHD with internal cardioverter defibrillator	106	67	94	87

CORONA[46]	2007	2.7	Multinational	R 10 mg	Placebo	1.61	Ischemic heart failure	5011	73	76	60
JUPITER[47]	2008	1.9	Multinational	R 20 mg	Placebo	1.09	Primary prevention	17 802	66	62	0
GISSI-HF[48]	2008	3.9	Italy	R 10 mg	Placebo	0.92	CHF	4574	68	77	32
Vrtovec *et al.*[49]	2008	1.0	Slovenia	A 10 mg	Usual care	1.91	CHF	110	63	61	59
METEOR[50]	2009	2.0	Multinational	R 40 mg	Placebo	1.79	Primary prevention	981	60	57	60
LEADe[51]	2010	1.5	Multinational	A 80 mg	Placebo	0.30	Mild-to-moderate probable Alzheimer disease	640	74	48	0
More vs. less intensive statin therapy											
A-Z[52]	2004	2.0	Multinational	S 80 mg	S 20 mg	0.30	Acute coronary syndrome	4497	61	75	17
REVERSAL[53]	2004	1.5	USA	A 80 mg	P 40 mg	0.97	>20% stenosis on routine coronary angiogram	657	56	72	0
PROVE IT[54]	2004	2.0	Multinational	A 80 mg	P 40 mg	0.65	Acute coronary syndrome	4162	58	78	18
TNT[55]	2005	4.9	Multinational	A 80 mg	A 10 mg	0.62	Clinically evident CHD	10 001	61	81	58
IDEAL[56]	2005	4.8	Nordics, Netherlands, Iceland	A 80 mg	S 20 mg	0.55	MI	8888	62	81	100
SAGE[57]	2007	1.0	Multinational	A 80 mg	P 40 mg	0.78	Elderly with CHD and evidence of ischaemia	893	72	69	46
Colivicchi *et al.*[58]	2010	0.7	Italy	A 80 mg	A 20–40 mg	0.80	Acute presentation of severe CHD	290	75	49	100
SEARCH[59]	2010	6.7	UK	S 80 mg	S 20 mg	0.39	Previous MI	12 064	64	83	100

MI, myocardial infarction; CHD, coronary heart disease; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft surgery; CKD, chronic kidney disease; TIA, transient ischaemic attack; CHF, chronic heart failure; SCD, sudden cardiac death; CA, cardiac arrest; VA, ventricular arrhythmia; UA, unstable angina; A, atorvastatin; L, lovastatin; P, pravastatin; R, rosuvastatin; S, simvastatin.
[a]LDL-cholesterol differences are based on average differences between the two groups at 1 year (or the closest time to 1 year if 1 year data unavailable).

Table 2 Risk of bias for reported events of sudden death, cardiac arrest, and ventricular tachyarrhythmia

	Outcome available in the published literature			Selection bias	Performance bias	Detection bias	Attrition bias		Intention-to-treat analysis	Reporting bias	Overall risk of bias
	SCD	CA	VT				Description of withdrawals and losses to follow-up	Overall risk of attrition bias			
Statin vs. control regimen											
PMSG-CR[23]	Yes	—	—	Unclear	Low	Low	Yes	Low	Yes	Low	Low
4S[24]	Yes	Yes	—	Unclear	Low	Low	Yes	Low	Yes	Low	Low
MAAS[25]	Yes	—	—	Low	Low	Low	No	Low	Yes	Low	Low
PLAC-1[26]	Yes	Yes	—	Unclear	Low	Low	Yes	Low	Yes	Low	Low
PREDICT[27]	Yes	—	—	Low	Low	Low	Yes	Low	Yes	Low	Low
AFCAPS/ TexCAPS[28]	Yes	—	—	Low	Low	Low	Yes	Low	Yes	Low	Low
LIPID[29]	Yes	—	—	Low	Low	Low	Yes	Low	Yes	Low	Low
GISSI-P[30]	Yes	—	No	Unclear	Low	Low	Yes	Low	Yes	Low	Low
HPS[31]	Yes	No	No	Low	Low	Low	Yes	Low	Yes	Low	Low
LIPS[32]	Yes	—	—	Low	Low	Low	Yes	Low	Yes	Low	Low
FLORIDA[33]	Yes	—	—	Unclear	Low	Low	Yes	Low	Yes	Low	Low
ASCOT-LLA[34]	—	—	Yes	Low	Low	Low	Yes	Low	Yes	Low	Low
ALERT[35]	No	—	—	Low	Low	Low	Yes	Low	Yes	Low	Low
CARDS[36]	Yes	—	—	Low	Low	Low	Yes	Low	Yes	Low	Low
PREVEND IT[37]	No	—	—	Low	Low	Low	No	Low	Yes	Low	Low
ALLIANCE[38]	No	Yes	No	Unclear	Low	Low	Yes	Low	Yes	Low	Low
PCAB[39]	Yes	—	No	Low	Low	Low	Yes	Low	Yes	Low	Low
4D[40]	Yes	—	No	Low	Low	Low	Yes	Low	Yes	Low	Low
NEDIAT[41]	No	—	—	Low	Low	Low	Yes	Low	Yes	Low	Low
MEGA[42]	Yes	—	No	Low	Low	Low	Yes	Low	Yes	Low	Low
ASPEN[43]	No	No	No	Low	Low	Low	Yes	Low	Yes	Low	Low
SPARCL[44]	—	Yes	—	Low	Low	Low	Yes	Low	Yes	Low	Low
CLARIDI[45]	—	—	Yes	Unclear	Low	Low	No	Low	Yes	Low	Unclear
CORONA[46]	Yes	Yes	Yes	Low	Low	Low	Yes	Low	Yes	Low	Low
JUPITER[47]	No	—	—	Low	Low	Low	Yes	Low	Yes	Low	Low
GISSI-HF[48]	Yes	—	Yes	Low	Low	Low	Yes	Low	Yes	Low	Low
Vrtovec *et al.*[49]	Yes	—	—	Unclear	Low	Low	No	Unclear	Yes	Low	Unclear
METEOR[50]	—	—	No	Low	Low	Low	Yes	Low	Yes	Low	Low
LEADe[51]	Yes	—	No	Low	Low	Low	Yes	Low	Yes	Low	Low

More vs. less intensive statin therapy											
A-Z[52]	Yes	—	—	Low	Low	Yes	Low	Yes	Low	Low	
REVERSAL[53]	—	No	No	Low	Low	Yes	Low	Yes	Low	Low	
PROVE IT[54]	Yes	No	No	Low	Low	Yes	Low	Yes	Low	Low	
TNT[55]	No	Yes	No	Unclear	Low	Yes	Low	Yes	Low	Low	
IDEAL[56]	No	Yes	No	Low	Low	Yes	Low	Yes	Low	Low	
SAGE [57]	—	Yes	—	Low	Low	Yes	Low	Yes	Low	Low	
Colivicchi *et al.*[58]	No	—	—	Unclear	Low	Yes	Low	Yes	Low	Low	
SEARCH[59]	—	—	No	Low	Low	Yes	Low	Yes	Low	Low	

Selection bias is based on random sequence generation and allocation concealment; performance bias includes blinding of participants and study investigators for the outcomes of interest; detection bias includes blinding of outcome assessors; attrition bias includes the possibility of incomplete outcome data; and reporting bias includes the possibility of selective outcome reporting. Selection bias is a feature of the trial design. Performance and detection bias are overall low, given that most data were collected without any prior knowledge of the investigators of the tested hypothesis in this study at the time of event collection. All analyses in this report are based on intention-to-treat and we further mitigated the possible effect of any attrition bias and reporting bias at individual trial level by collection of additional unpublished data. SCD, sudden cardiac death; CA, cardiac arrest; VT, ventricular tachyarrhythmia.

~445 000 person-years of follow-up) compared statin vs. control[23–51] and eight trials (including 41 452 randomized participants and ~192 000 person-years of follow-up) compared more vs. less intensive LDL lowering with statins (*Table 1*).[52–59] Twelve of the included trials had not published information on ventricular arrhythmic events previously (eight trials of statin vs. control [35,37,38,41,43,47,50,51] and five trials of more vs. less intensive statin therapy),[53,55,56,58,59] and for another seven of the included trials, information from the published literature was complemented by additional unpublished data obtained from the investigators (six statin vs. control [30,31,36,39,40,42] and one more intensive vs. standard dose statin trials).[54] One study was available only as a conference proceeding.[45] The average achieved 1-year difference in mean LDL cholesterol between randomized treatment arms was 1.13 mmol/L for the trials of statin vs. control and 0.53 mmol/L for the trials that compared a high dose of a statin with a standard dose. The risk of bias was judged to be unclear for two trials and low for all other trials (*Table 2*).

Ventricular tachyarrhythmia

Only two trials had previously published information on ventricular tachyarrhythmia[34,46] with another two having presented such findings at a scientific meeting.[45,48] Unpublished information on ventricular tachyarrhythmia was provided from investigators for an additional 14 trials.[30,31,38–40,42,43,50,51,53–56,59] Overall, these 18 trials reported 672 patients with at least one episode of ventricular tachyarrhythmia. In the primary analysis of 13 statin vs. control trials, statin therapy did not reduce the risk of ventricular tachyarrhythmia significantly (212 vs. 209; OR = 1.02, 95% CI 0.84–1.25, $P = 0.87$; *Figure 2*). This result was not materially affected when all trials were considered together (OR = 1.06; 95% CI 0.91–1.24; $P = 0.48$; *Figure 2*). There was no significant heterogeneity within the trials of statin vs. control (and no good evidence of heterogeneity within the trials of more vs. less intensive therapy), no evidence of trend according to the study size, and no evidence that the effect sizes differed significantly between the two types of trials.

Cardiac arrest

Twelve trials reported a total of 254 cardiac arrests[24,26,31,38,43,44,46,53–57] (eight of these trials had previously published such information).[24,26,38,44,46,55–57] In the seven statin vs. control trials for which cardiac arrest data were available, statin therapy did not reduce the risk of cardiac arrest significantly (82 statin vs. 78 control, OR = 1.05; 95% CI 0.76–1.45; $P = 0.84$; *Figure 3*), although the CI was wide due to the relatively few numbers of events. Including the additional five trials of intensive vs. standard dose had little effect on the estimated effect size (overall OR = 0.98; 95% CI 0.76–1.27; $P = 0.92$; *Figure 3*). There was no evidence that the effect sizes differed significantly within either type of trial or between the two types of trials, and no evidence of trend according to study size.

Sudden cardiac death

Thirty trials reported a total of 2874 sudden cardiac deaths (nine trials had not previously published such information).[35,37,38,41,43,47,55,56,58] In the 25 statin vs. control trials for

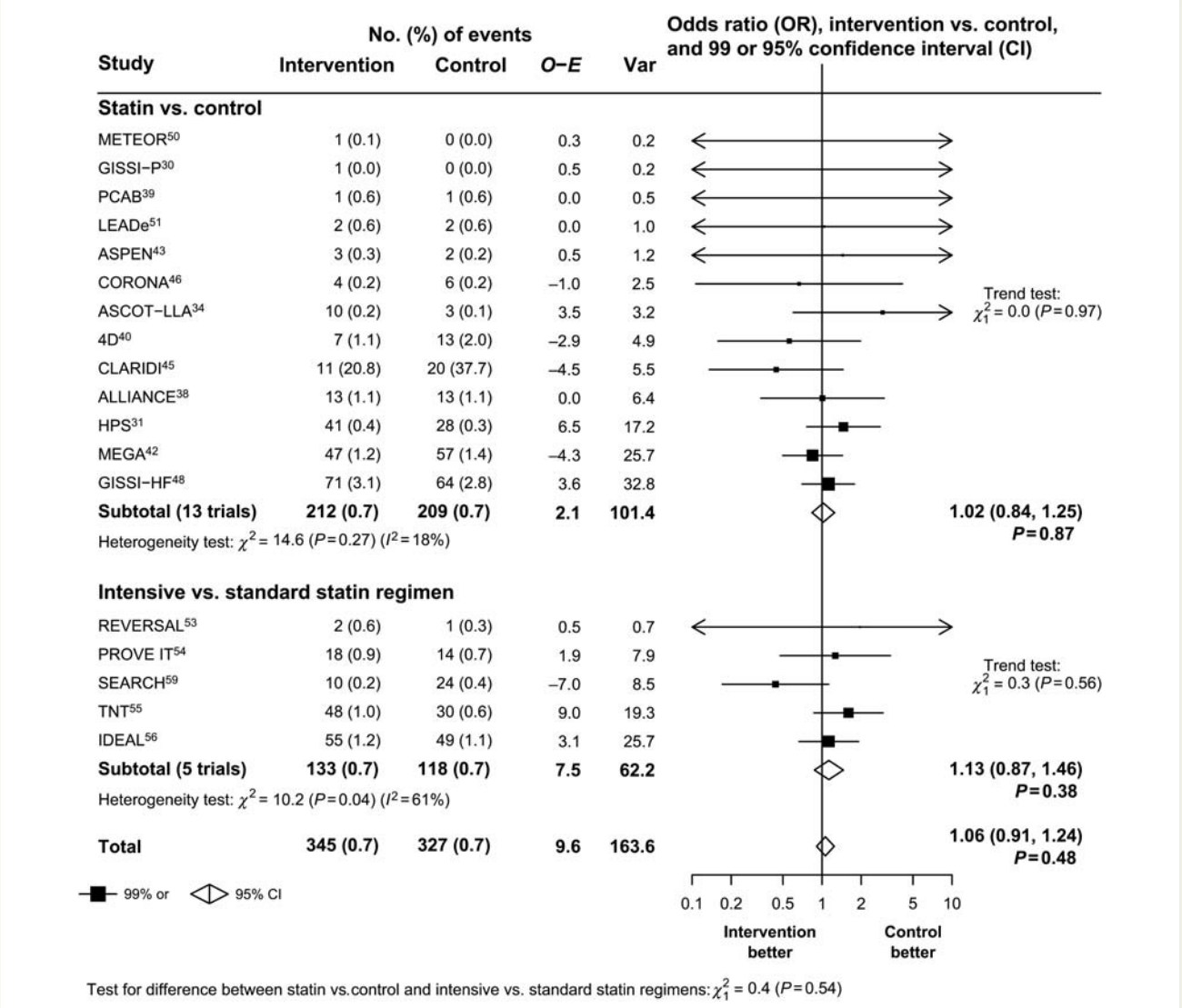

Figure 2 Effect of statin therapy on ventricular tachyarrhythmia.

which data were available, statin therapy was associated with a significant 10% proportional reduction in the risk of sudden cardiac death (1131 vs. 1252; OR = 0.90; 95% CI 0.82–0.97, $P = 0.01$) with no good evidence of heterogeneity between the trials ($P = 0.09$; *Figure 4*). Including the additional five trials of intensive vs. standard dose had little effect on the size of the estimated OR (overall OR = 0.89; 95% CI 0.82–0.96; $P = 0.002$; *Figure 4*). There was no evidence that the proportional risk reduction differed significantly between the two types of trial. In the trials of statin vs. control, there was some evidence of trend ($P = 0.01$) towards apparently larger proportional risk reductions among the smaller trials, driven by an apparent lack of benefit in two large trials of patients with heart failure, which had also failed to show any overall effect on cardiovascular outcomes.[46,48]

Of the 25 trials of statin vs. control that provided data on sudden cardiac death, 24 also provided data on all cardiac death, and hence, the numbers of patients having other (i.e. non-sudden) cardiac death could be calculated. Compared with the 10% proportional reduction in sudden cardiac death seen in these 24 trials (1115 vs. 1227; OR = 0.90, 99% CI 0.81−1.01, $P = 0.02$), there was a significant 22% proportional reduction in the risk of other 'non-sudden' cardiac death (1235 vs. 1553; OR = 0.78 99% CI 0.71–0.87; $P < 0.001$; *P*-value for difference in effect size between the two outcomes = 0.02; *Figure 5*). Consequently, statin therapy was associated with a significant 17% proportional reduction in the risk of all cardiac death (2350 vs. 2780; OR = 0.83, 95% CI 0.78–0.88; $P < 0.001$; *Figure 5*). Inclusion of the additional more vs. less intensive statin therapy trials did not materially affect the size of the estimated ORs for other non-sudden cardiac death (29 trials, 1408 vs. 1754; OR = 0.79; 95% CI 0.74–0.85; $P < 0.001$).

Adjusting the effect seen in each trial for the LDL-cholesterol difference achieved in each trial[60] had no notable impact on any of the findings (results available on request).

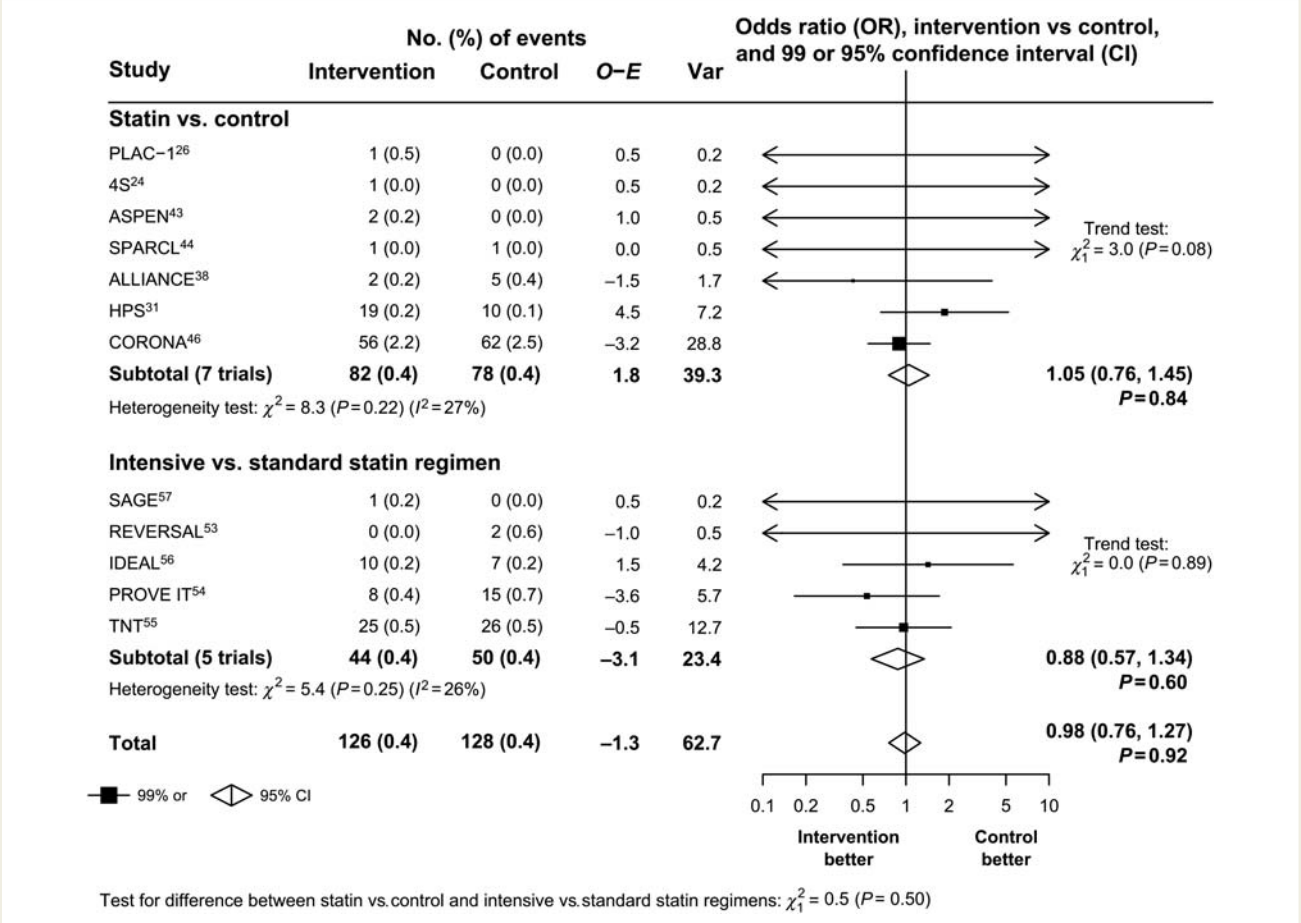

Figure 3 Effect of statin therapy on cardiac arrest.

Discussion

This study is the most comprehensive meta-analysis of the effect of statin therapy on ventricular arrhythmic events collecting both published and unpublished information from a large set of randomized controlled trials. While we found no evidence that statin therapy significantly reduced the risk of ventricular tachyarrhythmia or of cardiac arrest, the risk of sudden cardiac death was reduced by 10% compared with a reduction in the risk of other (non-sudden) cardiac deaths of about 20%.

Are these findings compatible with a direct anti-arrhythmic effect of statins? Sudden cardiac death is a clinical syndrome that can be caused either *primarily* by arrhythmia, i.e. a primary electrical event, or by acute coronary events *complicated* by arrhythmia.[3,4] In clinical studies, it is difficult to distinguish between the two causative mechanisms (and some non-cardiac events may in fact have been misclassified as sudden cardiac death). However, autopsy studies suggest that in the general population, at least a third of people diagnosed with sudden cardiac death will have evidence of acute coronary occlusion with a further third showing evidence of plaque erosion.[2,61–63] Since statins reduce the risk of acute coronary events, one might expect a reduction in sudden cardiac death due solely to effects on lipid-lowering. It is unclear what magnitude risk reduction this might translate to however and, consequently, we cannot exclude the possibility of some direct anti-arrhythmic effect of statins existing. However, the observation that the reduction in risk of sudden cardiac death was only half of that for other (mostly atherosclerotic) cardiac death, together with the lack of evidence for any effect on ventricular tachyarrhythmia, does not lend much support to any clinically relevant direct ventricular anti-arrhythmic benefit.

Our findings contrast with the previous suggestion that statins reduce the risk of ventricular tachyarrhythmia by about one-third.[14–18,45] This could be due to residual confounding and other inherent biases in the previous non-randomized studies[14–18] together with large random errors in the one small randomized controlled trial to have directly tested this hypothesis.[45] Similarly, in a previous meta-analysis of randomized controlled trials of 10 trials and only 750 events, it was estimated that statins reduce the risk of sudden cardiac death by about one-fifth.[64] However, that meta-analysis included only published results and in total included only about one-third as many sudden cardiac deaths as the current study (which also sought to include unpublished data, thereby avoiding the biases that can be introduced by the favourable publication of apparently promising findings).[65,66]

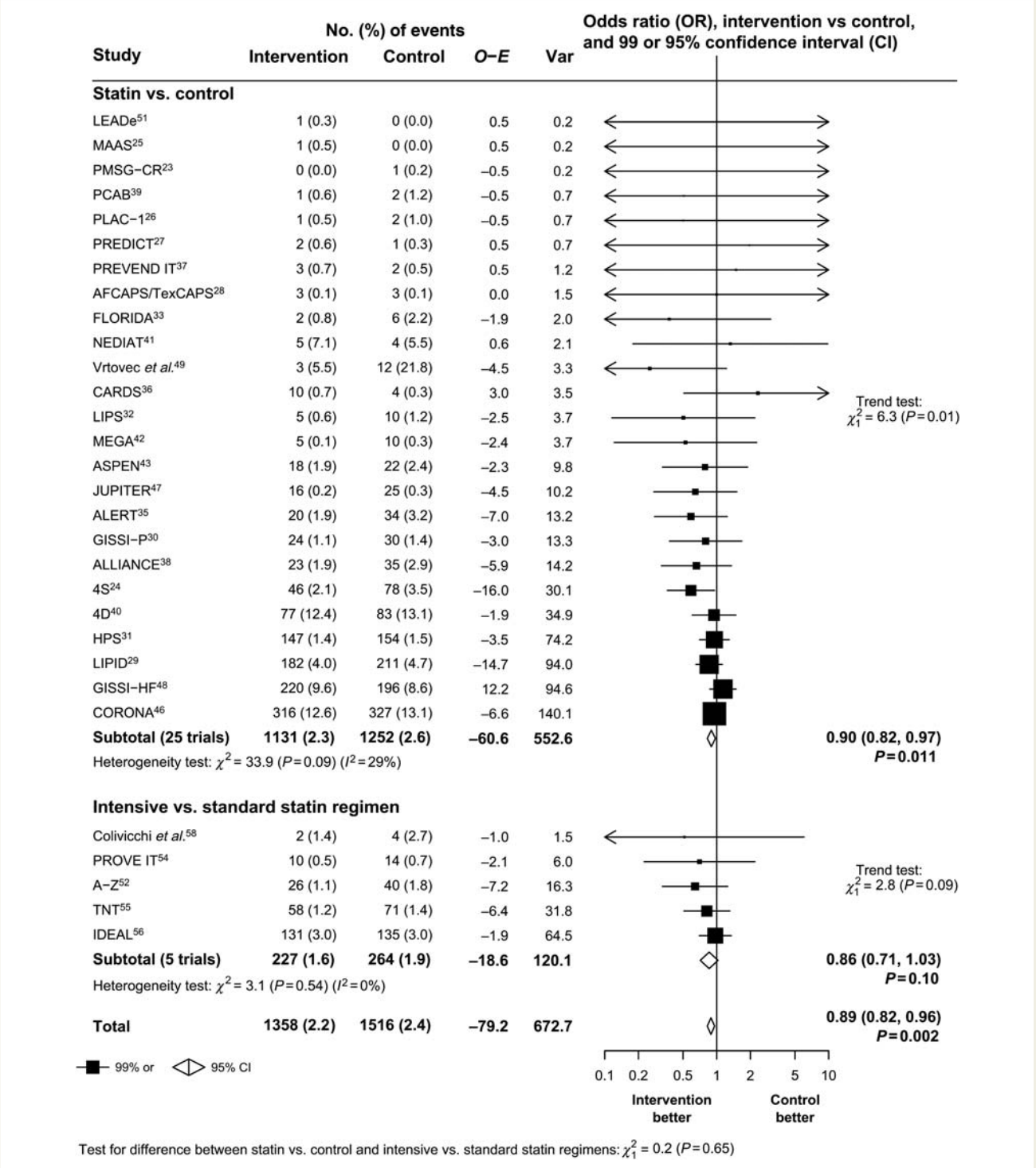

Figure 4 Effect of statin therapy on sudden cardiac death.

Study limitations

Most non-fatal arrhythmic events reported in the various included trials were collected from adverse event forms and had not undergone the same rigorous evaluation as in published reports and not based on a unified definition. Although such procedures may have resulted in underestimation of the true number of events and introduced some random errors, they are unlikely to have introduced any bias because underreporting and lack of independent confirmation of the events would be expected to have affected both study groups equally.[19,67,68] Nevertheless, the relatively limited number

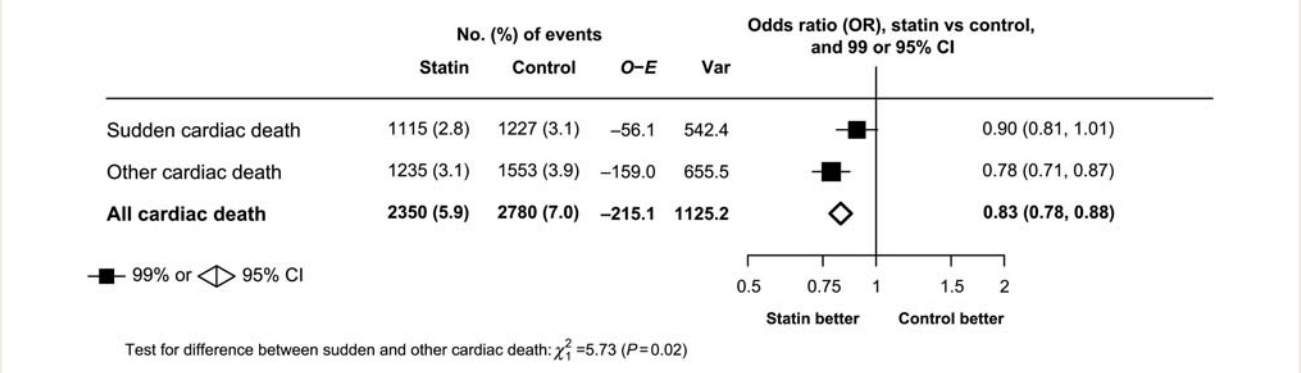

Figure 5 Effect of statin therapy on sudden cardiac death compared with other (non-sudden) cardiac death.

of cardiac arrests and ventricular tachyarrhythmia in the current report, in addition to any random errors resulting from the lack of a unified definition, means that a small benefit (or harm) of statins on these outcomes cannot be ruled out. Further evidence from adequately powered randomized controlled trials would therefore be needed to demonstrate whether any true benefits may exist.

Conclusions

Reducing LDL cholesterol with a statin reduces the risk of sudden cardiac death but the proportional benefit is small compared with that seen for other fatal cardiac events and may be explained by 'upstream' anti-atherosclerotic lipid-lowering effects. By contrast, there is no direct evidence that statins significantly reduce the risk of ventricular tachyarrhythmia.

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