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RESEARCH

Effect of statins on atrial fibrillation: collaborative meta-analysis of published and unpublished evidence from randomised controlled trials

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ABSTRACT

Objective To examine whether statins can reduce the risk of atrial fibrillation.

Design Meta-analysis of published and unpublished results from larger scale statin trials, with comparison of the findings against the published results from smaller scale or shorter duration studies.

Data sources Medline, Embase, and Cochrane's CENTRAL up to October 2010. Unpublished data from longer term trials were obtained through contact with investigators.

Study selection Randomised controlled trials comparing statin with no statin or comparing high dose versus standard dose statin; all longer term trials had at least 100 participants and at least six months' follow-up.

Results In published data from 13 short term trials (4414 randomised patients, 659 events), statin treatment seemed to reduce the odds of an episode of atrial fibrillation by 39% (odds ratio 0.61, 95% confidence interval 0.51 to 0.74; P<0.001), but there was significant heterogeneity (P<0.001) between the trials. In contrast, among 22 longer term and mostly larger trials of statin versus control (105 791 randomised patients, 2535 events), statin treatment was not associated with a significant reduction in atrial fibrillation (0.95, 0.88 to 1.03; P=0.24) (P<0.001 for test of difference between the two sets of trials). Seven longer term trials of more intensive versus standard statin regimens (28 964 randomised patients and 1419 events) also showed no evidence of a reduction in the risk of atrial fibrillation (1.00, 0.90 to 1.12; P=0.99).

Conclusions The suggested beneficial effect of statins on atrial fibrillation from published shorter term studies is not supported by a comprehensive review of published and unpublished evidence from larger scale trials.

INTRODUCTION

Atrial fibrillation is the most common form of cardiac arrhythmia in clinical practice and its prevalence increases with age.[1] In England and Wales, for instance, it has been estimated that about 0.7% of men and 0.4% of women aged 45-54 are affected, but these proportions rise to about 9% and 7%, respectively, by age 75-84.[2] Moreover, because of increases in life expectancy in most countries, as well as consequent increases in the prevalence of heart failure, the overall global burden from atrial fibrillation is likely to increase substantially in the coming decades. Although not acutely life threatening, the haemodynamic compromise and increased risk of stroke associated with chronic atrial fibrillation[1 3] can cause severe morbidity and mortality (especially among older people[4] and those with heart failure[5]). Atrial fibrillation is therefore responsible for much impairment of quality of life[6] and causes a substantial burden to health services,[7] but there is little reliable evidence from large scale randomised controlled trials about how to prevent it.[8]

Recently, there has been some evidence for the protective role of statins in reducing the risk of atrial fibrillation. In particular, one meta-analysis identified six trials involving 386 events (165 statin *v* 221 control) and suggested that statins could reduce the risk of atrial fibrillation by 61% (95% confidence interval 15% to 82%).[9] A second meta-analysis comprising six trials (five of which were included in the first meta-analysis), however, yielded a more modest (and non-significant) point estimate of 24% (−5% to 45%; 177 statin *v* 220 control).[10] In both meta-analyses, the findings from the included trials were highly heterogeneous, and the highly selected populations of patients in these trials raised questions about the applicability of the findings to much larger populations at risk of atrial fibrillation. Thus, many experts have called for more research, acknowledging that the conduct of large scale randomised statin trials with atrial fibrillation as the primary outcome could pose numerous practical, financial, and ethical challenges.[8] In the absence of such trials, the wealth of available information from many large scale randomised controlled trials that have collected but not necessarily published information on atrial fibrillation offers an opportunity to test the hypothesis generated by the previous meta-analyses.

We investigated whether longer term treatment with statins can reduce the risk of atrial fibrillation in a wide range of people by performing a meta-analysis of published and unpublished findings from all larger scale statin trials, many of which were conducted in populations at risk of atrial fibrillation because of underlying cardiac disease.

METHODS

Search strategy for identification of relevant studies

We searched Medline (January 1966 to October 2010), Embase (January 1985 to 2010 week 40), and the Cochrane Central Register of Controlled Trials (Cochrane Library, issue 4, 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 randomised controlled trials with no language restrictions.

Review methods and selection criteria

Two reviewers independently screened all titles and abstracts for randomised controlled trials with either a parallel or factorial design, at least one comparison of a statin versus a control regimen or a more versus less intensive statin regimen, and a total of 100 or more randomised participants followed up for at least six months. There were no restrictions on participants' characteristics or study outcomes. We also hand searched the reference lists of these studies to ensure that we did not miss other relevant articles, such as meta-analyses of statin trials or other types of articles related to statins and cardiac arrhythmias. After removing duplicate reports, we examined full text articles of all remaining reports (fig 1).

Data abstraction

For each trial, we recorded the study's or investigator's name; mean duration of follow-up; year of publication of the primary findings; randomised treatments; summary information about the studied population (number of participants, mean age, number of men, and prevalence of myocardial infarction or heart failure at randomisation); and the primary outcome of the study. The number of patients with at least one reported episode of atrial fibrillation was recorded. In trials where information on atrial fibrillation had not previously been published, we asked the investigators to abstract the relevant numbers from their routine records of adverse events. Non-responders were sent a reminder after about three weeks and, when possible, were then contacted by telephone.

Updated search for short term trials

The two previous meta-analyses (both published in 2008)[9 10] included statin trials that had previously published results on atrial fibrillation. Because these meta-analyses were themselves a few months old by the time our search for the longer term trials began, we also performed an updated search for any smaller published statin trials that had reported on atrial fibrillation and were published since the data search in the previous meta-analyses up to October 2010. Unpublished data from trials that did not have at least 100 participants randomised and at least six months' follow-up were not sought.

Assessment of risk of bias

To identify potential sources of bias in the reported events of atrial fibrillation (according to the Cochrane Statistical Methods Group and the Cochrane Bias Methods Group) we considered sequence generation, concealment of allocation sequence, blinding, incomplete outcome data, selective outcome reporting, and any other potential sources of bias. Risk of bias at the individual trial level and across the two sets of trials was categorised into low, unclear, and high.

Statistical analysis

Our primary hypothesis was to test whether longer term treatment with statins reduces the risk of atrial fibrillation. We therefore considered the shorter term trials included in the two previous meta-analyses (as well as any further short term trials) separately from the longer term statin trials. Although the previous two meta-analyses had no restriction on the size or duration of the trials included, none of the trials included in those meta-analyses (or the six found subsequently) had a planned treatment duration of more than six months and a sample size of 100 or more participants, so our electronic searches identified a non-overlapping group of longer term trials. Our primary analyses were restricted to trials of statin versus control (that is, placebo or usual care). As the anti-inflammatory effect of statins—one of the key mechanisms for their potential anti-arrhythmic effects[11 12]—might be more pronounced in high dose statin treatment,[13] we also carried out secondary analyses based on the trials that had compared a more intensive versus a standard statin regimen.

For every trial, we calculated the "observed minus expected" statistic (O−E) and its variance (V) from the number of patients who developed atrial fibrillation and the total number of patients in each treatment group, using standard formulas for 2×2 contingency tables. 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, and its continuity corrected 95% confidence interval is given by $\exp(G/V \pm (0.5/V + 1.96/\sqrt{V}))$.[14] Odds ratios are given with 95% confidence intervals for the overall results and with 99% confidence intervals (replacing 1.96 in the formula above by 2.576) for individual trial results and subgroup results. We assessed the heterogeneity between the different hypothesis testing trials 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

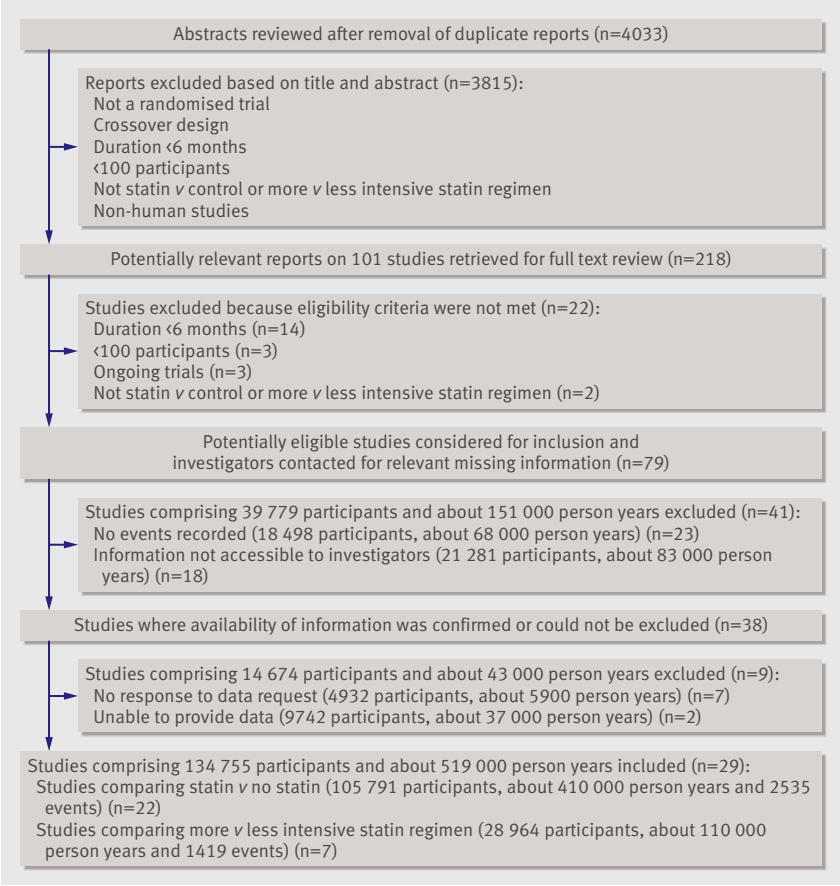

Fig 1 | **Search retrieval process for studies of statins**

freedom equal to one less than the number of trials. In forest plots, trials are shown in order of the amount of statistical information they contribute to the overall result. The summary odds ratios from the two sets of trials were compared with a standard χ^2 test (on 1 degree of freedom).

To assess the potential for a differential effect of statins on atrial fibrillation in different clinical settings, we performed two separate subgroup analyses among the statin versus control trials. One assessed the effect of statins separately among trials in which reports were known to have been of first diagnosed episodes of atrial fibrillation, trials in which reports were known to have been recurrences of previously diagnosed paroxysmal atrial fibrillation, and trials in which it was unknown whether reports were first diagnosed or recurrent events. The other subgroup analysis tested whether the effect of statins might differ in people at different underlying risk of atrial fibrillation by looking at the treatment effects separately for three groups of trials, according to the predominant type of participants: patients without previous coronary heart disease, patients with previous coronary heart disease, and patients with known heart failure or end stage renal disease. (Trials that largely included patients with heart failure or end stage renal disease were considered together because of the large clinical overlap between these two groups of patients: heart failure is highly prevalent in people with kidney failure,[15] and both groups are at increased risk of atrial fibrillation.[16 17])

Statistical analyses were done with R version 2.2.1.[18] All statistical tests were two sided, and all analyses were done on an intention to treat basis.

RESULTS

Shorter term trials

The two previous meta-analyses[9 10] contained data on seven trials,[19-25] yielding a total of 3608 randomised patients and about 1050 person years of follow-up (0.3 years per patient). In addition, we identified six further statin trials that had published data on atrial fibrillation (but were not eligible to be considered as long term trials) (table 1).[26-31] With the exception of one trial, all shorter term trials were restricted to patients in whom cardiac surgery or electrical cardioversion was planned. Most short term trials used sensitive event capturing methods and included short episodes of atrial fibrillation on continuous electrocardiographic monitoring as relevant study outcomes regardless of presence or absence of symptoms. The potential risk of bias was judged to be high in four of the trials and unclear in a further four.

In the 13 shorter term trials combined (4414 patients, 1129 person years of follow-up), a report of atrial fibrillation on at least one occasion during follow-up occurred among 659 patients (fig 2). Within these trials, treatment with statins was associated with a reduced odds of atrial fibrillation, by 39% (275 (12.5%) in the statin group versus 384 (17.4%) in the control group (odds ratio 0.61, 95% confidence interval 0.51 to 0.74; P<0.001; fig 2). There was significant heterogeneity between the trials (χ^2=43.4, df=12, P<0.001), caused in part by one study with an extreme relative reduction in the odds of atrial fibrillation (14 (35%) *v* 36 (90%); continuity corrected χ^2=23.2, df=1, P<0.001).[21] Even within the 12 other trials, however, we observed a highly significant 34% reduction in the odds of atrial fibrillation (261 *v* 348; 0.66, 0.55 to 0.81), albeit still with significant heterogeneity between these 12 trials (χ^2=26.9, df=11, P<0.001). In the largest trial, there was no significant reduction in risk (93 (6.0%) *v* 96 (6.2%) events; P=0.86).[20] Exclusion of the four trials in which the potential for bias was thought to be high had little effect on the estimated odds ratio in the remaining nine trials (249 *v* 345; 0.62, 0.51 to 0.76).

Longer term trials

Out of 4033 abstracts reviewed, we retrieved 218 papers describing 101 longer term trials for further examination, 79 of which met the inclusion criteria (fig 1). Of these 79 trials, atrial fibrillation was not recorded in 23 (18 000 patients and 68 000 person years) and data were not readily available to the investigators in 18 (21 000 patients, 83 000 person years). Of the remaining 38 trials, all except nine were included in the current meta-analysis (there was no response to our request for data for seven trials (4900 patients, 5900 person years), and information was not available in two trials because of restrictions on sharing

Table 1 | Summary of characteristics of short term trials on effect of statins

Study	Mean follow-up (years)	Country / region	Intervention/ control	Main inclusion criteria	Event capturing methods	No in intervention/ control	Mean age (years)	Male (%)	Previous MI (%)	Potential risk of bias
Tveit et al, 2004[19]	0.12	Norway	Pravastatin 40 mg/no treatment	Cardioversion	Serial ECG recording	51/51	68	87	—	Unclear
MIRACL, 2004[20]	0.31	Multinational	Atorvastatin 80 mg/placebo	Acute coronary syndrome	Serial ECG recording	1538/1548	65	65	25	Low
Dernellis et al, 2005[21]	0.42	Greece	Atorvastatin 20-40 mg/placebo	Paroxysmal atrial fibrillation	48 hour ambulatory ECG once during follow-up	40/40	52*	65	—	Unclear
ARMYDA-3, 2006[22]	0.08	Italy	Atorvastatin 40 mg/placebo	Planned cardiac surgery	Continuous ECG monitoring for 6 days followed by daily ECG recording until discharge	101/99	66	74	43	Low
Chello et al, 2006[23]	0.06	Italy	Atorvastatin 20 mg/placebo	Planned CABG	Postoperative monitoring	20/20	65	78	—	Unclear
Ozaydin et al, 2006[24]	0.25	Turkey	Atorvastatin 10 mg/no treatment	Cardioversion	24 hour ambulatory ECG monitoring at 1 and 3 month follow-up	24/24	62	60	0	High
Garcia-Fernandez et al, 2006[25]	0.08	Spain	Atorvastatin 80 mg/no treatment	Cardioversion	ECG recording at 3 months or clinical event	27/25	—	—	—	High
Song et al, 2008[26]	0.02	Korea	Atorvastatin 20 mg/no treatment	Planned CABG	Continuous ECG monitoring until discharge	62/62	63	40	7	High
Mannacio et al, 2008[27]	0.05	Italy	Rosuvastatin 20 mg/placebo	Planned CABG	Postoperative monitoring	100/100	73	60	23	Low
Tamayo et al, 2008[28]	0.39	Spain	Simvastatin 20 mg/no treatment	Planned CABG	Postoperative monitoring	22/22	68	65	0	High
Almroth et al, 2009[29]	0.13	Sweden	Atorvastatin 80 mg/placebo	Cardioversion	Serial ECG recording	118/116	65	76	—	Low
Xia et al, 2009[30]	0.25	China	Rosuvastatin 20 mg/no treatment	Cardioversion	24 hour ambulatory ECG monitoring	32/32	61	98	—	Unclear
Ji et al, 2009[31]	0.04	China	Atorvastatin 20 mg/placebo	Planned CABG	Continuous ECG monitoring 7 days followed by daily ECG recording until discharge	71/69	66	49	—	Low

MI=myocardial infarction; ECG=electrocardiography; CABG=coronary artery bypass graft surgery.
*Median.

unpublished data (10 000 patients, 37 000 person years)). Of the 29 included trials,[13 32-58] six provided data on atrial fibrillation in the published reports[32 48 49 54 57] and investigators in the remaining 23 provided the data on request. There were no obvious systematic differences between the trials that were and were not included.

Tables 2 and 3 show the characteristics of the 29 longer term trials. Twenty two trials (including 105 791 randomised participants and 410 000 person years of follow-up) compared a statin with a control regimen and seven trials (including 28 964 randomised participants and 110 000 person years of follow-up) compared a more intensive with a standard statin regimen. Event information was mostly based on routinely collected data on adverse events, with the exception of six trials that used periodic electrocardiography, including at the end of the study,[32 35 38 41 42 48] and one study that used a prespecified definition of atrial fibrillation based on pacemaker interrogation.[49] Nine trials confirmed reports of atrial fibrillation.[32 35 38 41 42 48 49 54] Of these, seven recorded baseline information about the presence or absence of atrial fibrillation (either as a clinical history or on ECG evidence) and hence could confirm that the numbers provided were first diagnosed occurrences of atrial fibrillation[32 35 38 41 42 48 49] or definite recurrences of known paroxysmal atrial fibrillation.[48] In all other trials, such information was not available, so a subset of the reported events could represent symptomatic recurrences of previously diagnosed atrial fibrillation. The potential risk of bias in the longer term trials was judged to be low in all but one trial.[49] Exclusion of this trial had no effect on the results (as it contributed just 13 events).

The primary analyses were restricted to the 22 longer term trials that compared a statin with a control regimen. In these trials, 2535 patients experienced an episode of atrial fibrillation. Statin treatment did not significantly reduce the risk of atrial fibrillation (1240 (2.3%) statin *v* 1295 (2.5%) control, odds ratio 0.95, 0.88 to 1.03; P=0.24), and there was no evidence that the effect of statin treatment varied within these trials (heterogeneity χ^2=21.9, df=21, P=0.40; fig 2). An uncorrected test of the combined results from the 13 short term and 22 long term trials would not be statistically appropriate because seven out of the 13 shorter term trials generated the hypothesis being tested in the longer term trials (which could lead to a point estimate, confidence interval, and P value that are appreciably biased).[59 60] Consequently, the suggestion of a small reduction in risk when all 35 trials are considered together (0.89, 0.82 to 0.95; P=0.002) should be interpreted with caution.

In the seven longer term trials that examined a more intensive compared with a standard statin regimen, there was no evidence that higher dose statin reduced

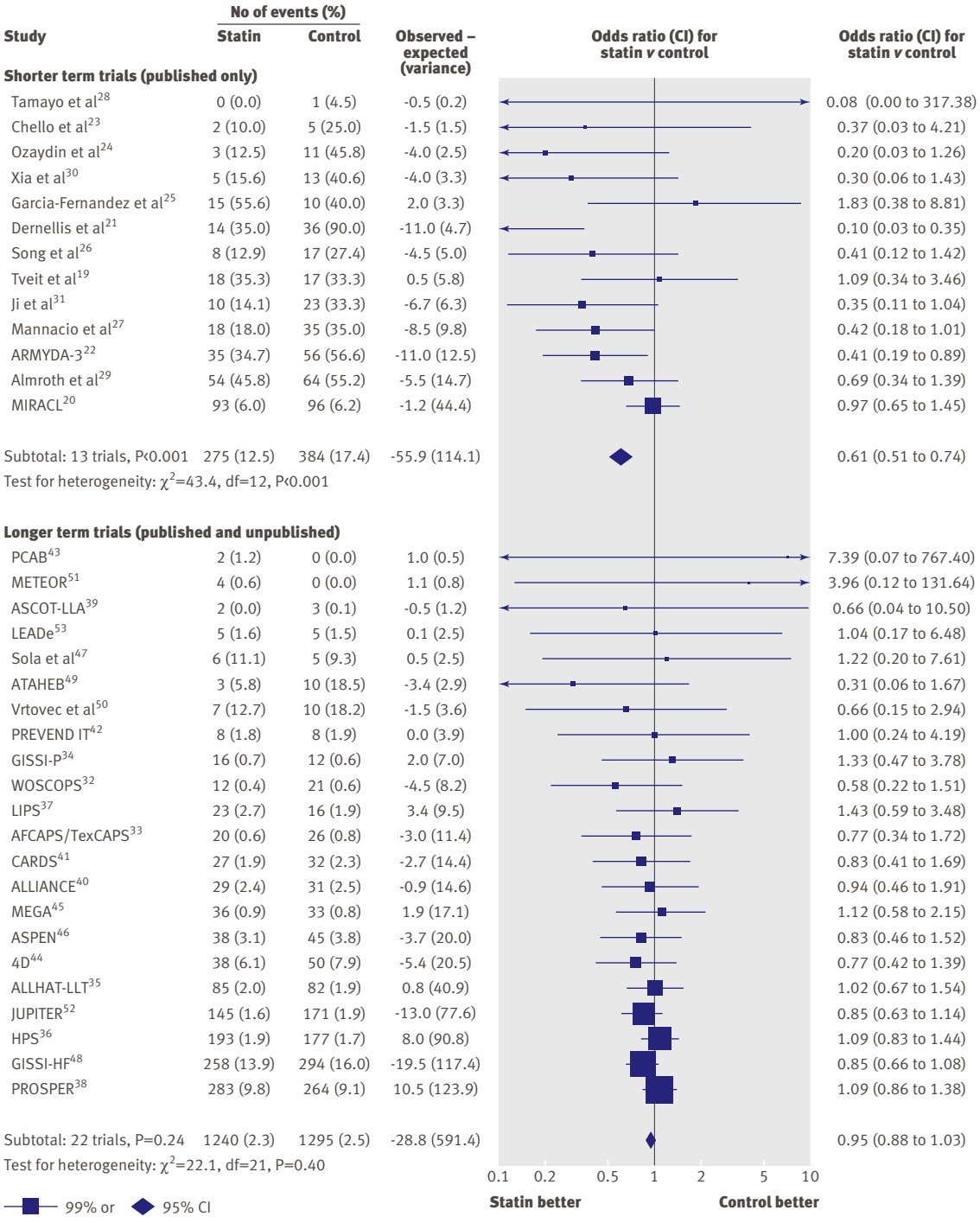

Fig 2 |Effect of statin treatment on atrial fibrillation in 13 shorter and 22 longer term trials of statin *v* control (test for difference: χ^2=18.6, df=1, P<0.001)

the risk of atrial fibrillation compared with standard dose statin (710 (4.9%) *v* 709 (4.9%), respectively; 1.00, 0.90 to 1.12; P=0.99; fig 3).

In subgroup analyses, there was no evidence that statin treatment was effective in preventing first diagnosed atrial fibrillation (574 (4.1%) statin *v* 597 (4.3%) control; fig 4), and there was no evidence that the effect of statin treatment differed in trials that studied mainly people with no previous coronary heart disease, mainly people with previous coronary heart disease, or mainly people with heart failure or advanced chronic kidney disease (χ^2=5.05, df=2, P=0.08 for heterogeneity between these three categories; fig 4). Most of the longer term trials of statin versus control reported events that were not adjudicated, but when the analyses were restricted to those seven trials that had independently confirmed the events,[32 35 38 41 42 48 49] there was also no significant reduction in the risk of atrial fibrillation (676 (4.7%) statin *v* 711 (5.0%) control; 0.94, 0.84 to 1.05; P=0.29).

Table 2 | Summary of characteristics of longer term (with at least six months' follow-up) hypothesis testing trials: statin versus control regimen

Study	Mean follow-up (years)	Country/ region	Intervention/control	Main inclusion criteria	Event capturing methods	No in intervention/ control	Mean age (years)	Male (%)	Previous MI (%)	Potential risk of bias
WOSCOPS, 1995[32]	4.8	UK	Pravastatin 40 mg/placebo	Primary prevention	Periodic ECG recording	3302/3293	55	100	0	Low
AFCAPS/ TexCAPS, 1998[33]	5.3	USA	Lovastatin 20-40 mg/placebo	Primary prevention	Unpublished AE reports	3304/3301	58	85	0	Low
GISSI-P, 2000[34]	1.9	Italy	Pravastatin 20 mg/no treatment	Recent MI	Unpublished AE reports	2138/2133	60	86	100	Low
ALLHAT-LLT, 2002[35]	4.8	North America	Pravastatin 40 mg/usual care	Hypertension plus other risk factor	Periodic ECG recording	4327/4255	66	51	0	Low
HPS, 2002[36]	5.0	UK	Simvastatin 40 mg/placebo	Vascular disease or diabetes	Unpublished AE reports	10 269/10 267	64	75	41	Low
LIPS, 2002[37]	3.1	Europe, Canada, Brazil	Fluvastatin 80 mg/placebo	Post PCI	Unpublished AE reports	844/833	60	84	44	Low
PROSPER, 2002[38]	3.2	Scotland, Ireland, Netherlands	Pravastatin 40 mg/placebo	Elderly with vascular disease or high risk	Periodic ECG recording, unpublished	2891/2913	75	48	13	Low
ASCOT-LLA, 2003[39]	3.2	Nordics, UK, Ireland	Atorvastatin 10 mg/placebo	Hypertension plus other risk factors	Unpublished AE reports	5168/5137	65	81	0	Low
ALLIANCE, 2004[40]	4.3	USA	Atorvastatin 10-80 mg/usual care	CHD	Unpublished AE reports	1217/1225	61	82	58	Low
CARDS, 2004[41]	3.9	UK, Ireland	Atorvastatin 10 mg/placebo	Type 2 diabetes plus other risk factor	Unpublished AE reports	1428/1410	62	68	0	Low
PREVEND IT, 2004[42]	3.8	Netherlands	Pravastatin 40 mg/placebo	Microalbuminuric patients	Unpublished AE reports	433/431	51	65	0	Low
PCAB, 2005[43]	4.5	Japan	Pravastatin 10-20 mg/usual care	After CABG	Unpublished AE reports	168/167	59	85	62	Low
4D, 2005[44]	3.9	Germany	Atorvastatin 20 mg/placebo	Haemodialysis patients with diabetes	Unpublished AE reports	619/636	66	54	18	low
MEGA, 2006[45]	5.3	Japan	Pravastatin 10-20 mg/no treatment	Primary prevention	Unpublished AE reports	3866/3966	58	32	0	Low
ASPEN, 2006[46]	4.3	Multinational	Atorvastatin 10 mg/placebo	Type 2 diabetes	Unpublished AE reports	1211/1199	61	66	16	Low
Sola, 2006[47]	1.0	USA	Atorvastatin 20 mg/placebo	Non-ischaemic CHF	Unpublished AE reports	54/54	54	34	0	Low
GISSI-HF, 2008[48]	3.9	Italy	Rosuvastatin 10 mg/placebo	CHF	Serial ECG recording and AE reports	1855/1835	68	77	32	Low
ATAHEB, 2008[49]	1.0	Taiwan	Atorvastatin 20 mg/usual care	Pacemaker for bradyarrhythmias	Pacemaker interrogation	52/54	71	45	0	High
Vrtovec et al, 2008[50]	1.0	Slovenia	Atorvastatin 10 mg/usual care	CHF	Unpublished AE reports	55/55	63	61	59	Low
METEOR, 2008[51]	2.0	Multinational	Rosuvastatin 40 mg/placebo	Low risk for cardiovascular event	Unpublished AE reports	702/282	57	60	0	Low
JUPITER, 2008[52]	1.8	Multinational	Rosuvastatin 20 mg/placebo	Primary prevention	Unpublished AE reports	8901/8901	66	62	0	Low
LEADe, 2010[53]	1.5	Multinational	Atorvastatin 80 mg/placebo	Mild to moderate probable Alzheimer's disease	Unpublished AE reports	314/326	74	48	0	Low

ECG: electrocardiography; AE=adverse event; MI=myocardial infarction; CHD=coronary heart disease; CABG=coronary artery bypass graft surgery; CHF=chronic heart failure; PCI=percutaneous coronary intervention.

DISCUSSION

Despite previous suggestions, this meta-analysis of published and unpublished information from larger scale trials found no evidence for the use of statins in the prevention of atrial fibrillation. During recent years, statins have emerged as one of the most effective treatments to reduce the burden of cardiovascular disease worldwide.[61] Because of their remarkably good safety profile and declining costs, there has been some interest in the potential use of statins as direct anti-arrhythmic or anti-inflammatory drugs.[12 62] Various hypothetical mechanisms for such effects, mostly unrelated to their effects on low density lipoprotein particles (though still possibly dose related), have been proposed. The suggestion that such "pleiotropic effects" reduce atrial fibrillation by as much as one third, however, is not supported by our meta-analysis.

Interpretation of apparently contradictory findings

While several methodological and clinical differences between the shorter term and longer term trials preclude a meaningful combination of the results, they could help us understand the discrepant findings.

Table 3 | Summary of characteristics of longer term (with at least six months' follow-up) hypothesis testing trials: more intensive versus less intensive statin treatment

Study	Mean follow-up (years)	Country/ region	Intervention/control	Main inclusion criteria	Event capturing methods	No in intervention/ control	Mean age (years)	Male (%)	Previous MI (%)	Potential risk of bias
A-Z, 2004[54]	2.0	Multinational	Simvastatin 80 mg/20 mg	Acute coronary syndrome	Published AE reports	2265/2232	61	76	17	Low
REVERSAL, 2004[13]	1.5	USA	Atorvastatin 80 mg/ pravastatin 40 mg	>20% stenosis on routine coronary angiogram	Unpublished AE reports	328/329	56	72	0	Low
PROVE IT, 2004[54]	2.0	Multinational	Atorvastatin 80 mg/ pravastatin 40 mg	Acute coronary syndrome	Published AE reports	2099/2063	58	78	18	Low
TNT, 2005[55]	4.9	Multinational	Atorvastatin 80 mg/10 mg	Clinically evident CHD	Unpublished AE reports	4995/5006	61	81	58	Low
IDEAL, 2005[56]	4.8	Nordics, Netherlands, Iceland	Atorvastatin 40-80 mg/ simvastatin 20-40 mg	Myocardial infarction	Unpublished AE reports	4439/4449	62	81	100	Low
Schmermund et al, 2006[57]	1	Germany	Atorvastatin 80 mg/10 mg	No obstructive CHD	Published AE report	235/234	61	75	0	low
Colivicchi et al, 2010[58]	0.7	Italy	Atorvastatin 80 mg/20-40 mg	Acute presentation of severe CHD	Unpublished AE reports	144/146	75	48.6	100	Low

MI=myocardial infarction; AE=adverse event; CHD=coronary heart disease.

Firstly, the two sets of trials differed in methods of detection and verification of the outcome. The shorter term trials generally used more sensitive methods for event capturing than the longer term trials. For example, brief asymptomatic periods of atrial fibrillation that were detected on continuous cardiac monitoring were classified as events in some shorter term studies. In contrast, events in many of the longer term studies were based on clinical reports collected from adverse event forms that are more likely to be relevant to patients. In most longer term trials, atrial fibrillation was not a prespecified end point, and this might have resulted in underestimation of the true number of events and hence larger random errors in those particular studies.[63] Such passive collection of event information is unlikely to have introduced any bias because under-reporting would be likely to occur similarly in each treatment group. The events in the longer term trials were also not generally adjudicated, but even when the analysis was restricted to those seven trials of statin versus control that had independently confirmed the events,[32 35 38 41 42 48 49] there was no suggestion of a reduction in the risk of atrial fibrillation, indicating that lack of complete event adjudication is unlikely to have had a major impact on the results.

Secondly, the absolute risk of atrial fibrillation and the clinical condition of the patients included in the two sets of trials were quite different. Notwithstanding the differences in methods of event capturing used between the trials, the average underlying absolute risk of atrial fibrillation was higher in patients included in the shorter term trials than in those included in the longer term trials because of differences in selection criteria. While there is no a priori reason to suggest that absolute risk should influence the relative effect of treatment, it might sometimes help to explain some of the heterogeneity observed if, for example, it is associated with other biological or clinical factors that influence treatment effects. In the context of atrial fibrillation, future risk depends largely on the degree of atrial structural alterations (that is, atrial remodelling).[64] If anything, drugs that are effective for the treatment of atrial fibrillation in people at low risk with a structurally normal heart might be expected

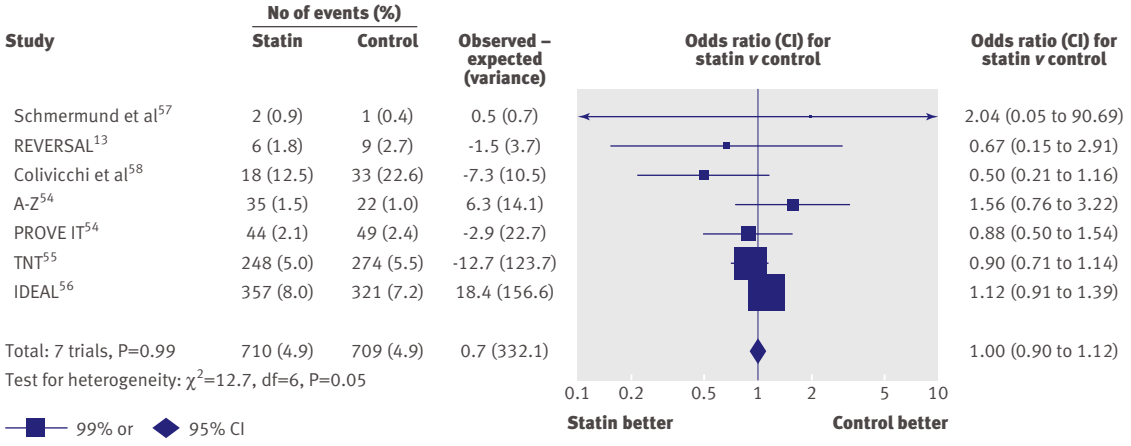

Fig 3 | Effect of statin treatment on atrial fibrillation in seven longer term trials of more intensive *v* standard statin regimens

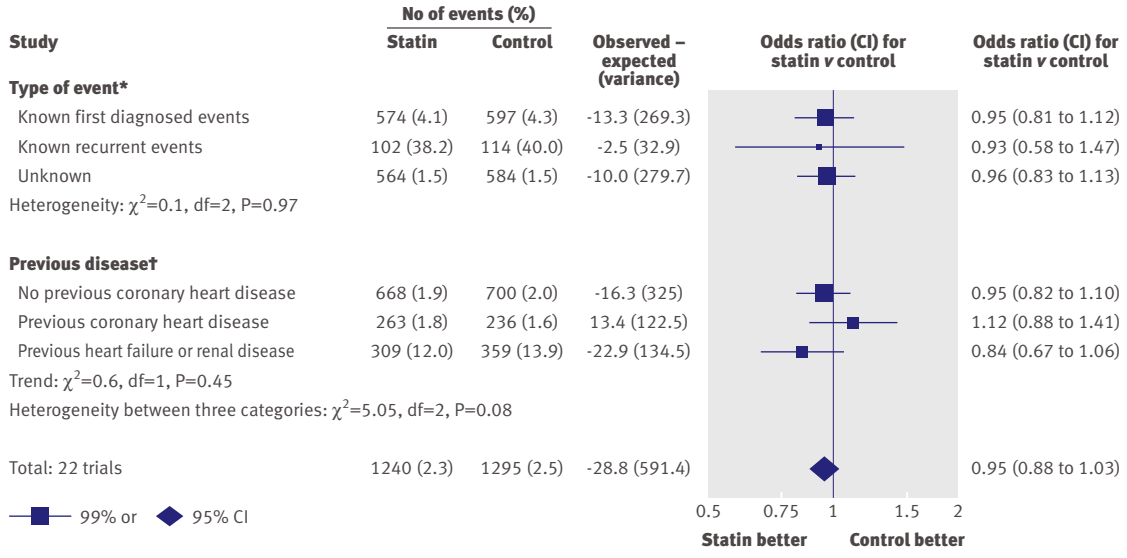

Fig 4 | Effect of statin treatment on atrial fibrillation in 22 longer term trials of statin *v* control, by subgroups of trial population. *Six trials could confirm that reported atrial fibrillation events were new (that is, incident) cases,[32 35 38 41 42 49] and one trial[48] provided atrial fibrillation events in both those with and without history of paroxysmal atrial fibrillation at baseline. †No previous coronary heart disease[32 33 35 38 39 41 42 45 46 49 51-53]; previous coronary heart disease[34 36 37 40 43]; previous heart failure or renal disease[44 47 48 50]

to have less effect in those with structural abnormalities, as pre-existing atrial remodelling might be irreversible or less amenable to preventive medical treatment.[65] We found no evidence that statins prevented atrial fibrillation in people with no history of heart disease, and there was no significant evidence of heterogeneity between trials that studied people at different underlying risk (fig 4). With the exception of the MIRACL trial,[20] all the shorter term trials selected either patients undergoing cardiac surgery, or electrical cardioversion, or patients with a history of atrial fibrillation. While it is unlikely that any potential pleiotropic effect of statins would be confined to these particular groups, there could be some other intermediary mechanisms that could, at least in part, account for the observed effect of statins in such settings. For example, myocardial damage is commonly encountered after coronary procedures[66] and is a potential risk factor for atrial fibrillation.[67] Therefore, a reduction in atrial fibrillation might result from just a short course of statin treatment if this abrogates myocardial tissue injury.[27 68] In contrast with those undergoing cardiac surgery, however, the attributable risk for atrial fibrillation from coronary events in less selected populations of patients, such as those included in the longer term studies, is likely to be small. Thus, in the longer term studies any beneficial effects mediated through prevention of myocardial injury would be likely to be diluted by the much larger number of events that are unrelated to acute myocardial injury.

Thirdly, differences in selection criteria between the trials meant that the proportion of people with recurrences of known atrial fibrillation was much larger in the shorter term trials than in the longer term trials. The therapeutic goals in people with paroxysmal or persistent atrial fibrillation might differ from those with no known history of atrial fibrillation, as treatment in the former group is usually expected only to delay the next episode of atrial fibrillation or the transition to a permanent state. Although any such delays might be clinically valuable, in meta-analyses of longer term studies when information about timing of the events is not available, delays in recurrences are likely to be missed if a large proportion of individuals have experienced a recurrence by the end of the study. This might also obscure any beneficial effects on prevention of first diagnosed atrial fibrillation if recurrences of atrial fibrillation constitute a large proportion of total events. In the current analyses, however, we found no evidence that statins significantly reduced atrial fibrillation in the trials in which events were known to have been first diagnosed events (fig 4). Furthermore, a pattern of early separation with a later convergence of risk curves was not reported in the longer term trials that provided a time based analysis.[35 48]

Fourthly, the differences between our findings and those of the earlier meta-analyses could be due, at least in part, to publication bias (that is, the tendency for trial results to be more likely to be published if they have strikingly positive results than if the results are negative or null).[69] Publication bias can, along with other sources of bias, produce large apparent effects when treatments are actually ineffective, particularly when included studies are based on a limited number of events (as such studies are particularly susceptible to large random errors and hence much more likely than larger studies to lead to exaggerated estimates of treatment effect). Indeed, this point is perhaps well illustrated in the current context by the null findings of the MIRACL trial,[20] which, despite being the largest study included in the earlier meta-analyses and despite being presented at a major medical conference in 2004, has

WHAT IS ALREADY KNOWN ON THIS TOPIC

Limited evidence from trials conducted in patients undergoing cardiac surgery or cardioversion suggests that statins might reduce the risk of atrial fibrillation by more than a third

WHAT THIS STUDY ADDS

A comprehensive review of both published and unpublished data from longer term trials showed no protective effect of statins on atrial fibrillation

Statins cannot currently be recommended for prevention of incident or recurrent atrial fibrillation

not to our knowledge yet been published as a full report. In addition, the impact of the results from MIRACL on the overall estimates in the two previous meta-analyses[9 10] was reduced because of the use of "random effect" approaches.

In the presence of heterogeneity, "random effect" approaches (which estimate the heterogeneity in treatment effects across trials and incorporate this variability into the estimate of the overall result) are commonly used. In certain circumstances, however, such approaches can lead to small potentially seriously biased studies gaining an inappropriately large statistical weight at the expense of larger more reliable studies.[70] In contrast, we calculated our summary effect estimates by taking a simple weighted average of the like-with-like comparisons within each trial. While this method is often referred to as being a "fixed effect" method, the terminology is unsatisfactory because it misleadingly suggests that any heterogeneity between the true effects of treatment in different trials is assumed to be zero (whereas no such unjustified assumptions are involved). However, for comparison, when we applied a standard random effect to the meta-analysis of the 13 shorter term trials, the overall event rate ratio was 0.47 (0.30 to 0.72; P<0.001) and the difference between the overall results from the shorter and longer term studies remained significant (P<0.001).

Strength and limitations

Our meta-analysis sought to obtain both published and unpublished information from all eligible trials, and the large number of events this provided gave good statistical power to detect even modest treatment effects. We might still have missed relevant event information from at least nine further trials. It is unlikely that these data would have resulted in any material change to our primary conclusions, however, because they would have been expected only to have increased the total number of person years, and hence statistical information (that is, events), by about 10%. In addition, if an important reduction in atrial fibrillation had been observed in any single trial for which data were not made available to us, it seems likely that that result would have been published (as most of these trials were completed several years ago) and would hence have been identified by our literature search.

Conclusions and implications for clinicians and future researchers

In contrast with the unequivocal evidence for the beneficial effect of statins on atherosclerotic events in a wide range of people, there is currently no compelling evidence that longer term treatment with statins prevents atrial fibrillation. While our study does not exclude a real reduction in risk of about 10%, it casts doubt over the existence of any sustained and clinically relevant beneficial effect of statins for the prevention of atrial fibrillation. The effect of statins on atrial fibrillation in particular populations of patients with selection of outcomes that are relevant to patients and healthcare providers[71] could be explored in future well designed randomised trials.

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