

RESEARCH

Statins and prevention of infections: systematic review and meta-analysis of data from large randomised placebo controlled trials

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Abstract

Objective To evaluate whether the potential of statins to lower the risk of infections as published in observational studies is causal.

Design Systematic review and meta-analysis of randomised placebo controlled trials.

Data sources Medline, Embase, and the Cochrane Library.

Study selection Randomised placebo controlled trials of statins (up to 10 March 2011) enrolling a minimum of 100 participants, with follow-up for at least one year.

Data extraction Infection or infection related death.

Results The first study selection yielded 632 trials. After screening of the corresponding abstracts and full text papers, 11 trials totalling 30 947 participants were included. 4655 of the participants (2368 assigned to statins and 2287 assigned to placebo) reported an infection during treatment. Meta-analysis showed no effect of statins on the risk of infections (relative risk 1.00, 95% confidence interval 0.96 to 1.05) or on infection related deaths (0.97, 0.83 to 1.13).

Conclusion These findings do not support the hypothesis that statins reduce the risk of infections. Absence of any evidence for a beneficial effect in large placebo controlled trials reduces the likelihood of a causal effect as reported in observational studies.

Introduction

Statins (hydroxymethyl glutaryl coenzyme A (HMG-CoA) reductase inhibitors), drugs used to lower cholesterol levels, are prescribed frequently and their cardiovascular benefits are widely accepted in medical practice. In addition to cholesterol lowering effects, statins have anti-inflammatory and immunomodulatory properties, so called pleiotropic effects.

Such effects might be beneficial in the management of infections.¹⁻³

Whether statins can help to prevent infection is still debated. Since 2006, population based observational studies have reported associations between statins and a reduced risk of infectious outcomes such as pneumonia and sepsis and infection related mortality, with preventive effects up to 76%.⁴⁻¹⁰ However, the possibility of biased estimations of effect, which are inherent in observational studies, cannot be excluded. Recently, some investigators suggested that the protective associations reported in many of these studies could reflect bias from “healthy user” effects—that is, that statin users tend to have less severe comorbidity and better functional status than non-users and are more likely to practise other healthy behaviours. Despite extensive efforts to minimise all types of confounding and other biases, the effects of statins on risk of infection are inconclusive.^{11 12}

We hypothesised that if a preventive effect of statins on the risk of infections existed it should be detectable in the data of large placebo controlled trials. Considering the placebo controlled nature of such trials this would mean a true effect. We carried out a systematic review and meta-analysis of placebo controlled trials of statins to evaluate whether the beneficial association between statins and infections published in observational studies is causal.

Methods

We carried out a systematic review and meta-analysis of published trials according to the preferred reporting items for

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Details of contact with authors

Details of participants' characteristics

systematic reviews and meta-analyses (PRISMA) guidelines.¹³ A systematic search of Medline in PubMed, Embase, and the Cochrane Library database (the Cochrane central register of controlled trials) for studies reporting an infection as an adverse event or cause of death related to statin use was done from inception to 10 March 2011. To identify further articles we hand searched references and the related citations in PubMed.

We included randomised controlled trials reported in English only. Search terms, MeSH subject headings, and limits were “hydroxymethylglutaryl-CoA reductase inhibitors”, “anticholesteremic agents”, “statin”, “simvastatin”, “rosuvastatin”, “pravastatin”, “atorvastatin”, “fluvastatin”, “cerivastatin”, “pitavastatin”, “lovastatin”, “placebo controlled”, and “randomised controlled trial”.

Inclusion and exclusion criteria

All captured publications were screened according to predefined selection criteria. We included all randomised controlled trials with a statin as active treatment and a placebo as comparator. Eligible studies had a follow-up period of at least 12 months, a minimum of 100 participants, and reported on infections or infection related mortality. We excluded duplicate publications—that is, two or more studies that investigated the same sample.

After the first automated query in the databases, we used a three step process for screening. Firstly, we screened the abstracts. Secondly, we screened the remaining publications on the basis of the corresponding full text publication for reports on adverse events and causes of death. Finally, we screened the articles with information on adverse events and mortality for reports on the occurrence of infections or infection related mortality.

Besides the predefined search strategy, one reviewer (HLvdH) considered trials that had been excluded in the final step for not reporting infections as of potential importance when extensive data on other adverse events were available. The principal investigators of these trials were then contacted for supplementary data.

Data extraction

One reviewer (HLvdH) extracted the data. From each eligible publication data were captured on first author, year of publication, title, journal, study population, primary study outcome, duration of follow-up, number of participants in each group (statin and placebo groups), and type and dose of statin studied. From each included study HLvdH extracted data on the occurrence of infections as adverse events and data on infection related mortality.

Quality and risk of bias assessment

Using the Cochrane risk of bias tool we screened all captured trials for quality of study design, including randomisation, blinding, withdrawal, and dropouts.¹⁴ Because we studied unexpected “adverse” events in this systematic review we focused our assessment on quality of reporting adverse events and withdrawal of treatment in both study arms. Withdrawal of treatment was considered to rule out the possibility that differences in denominators may explain differences in calculated infection rates.

Statistical analysis

Statistical analysis of the dichotomous variables was carried out using relative risk as the summary statistic. We used random effect modelling by DerSimonian-Laird for analysis and reported

results in a forest plot with 95% confidence intervals. The relative risks represented the risk of an adverse event happening during study interval in participants taking a statin compared with those taking a placebo. When possible we carried out subgroup analyses and stratified the results for type of statin, statin dosage, patients’ characteristics, and type of infection. A relative risk of less than 1 would favour the statin treated population; we considered the point estimate of the relative risk to be significant at the $P < 0.05$ level if the confidence interval did not include the value 1. Heterogeneity was analysed using the Cochran Q test (χ^2) and I^2 statistics as a complement to the Q test.^{15 16} I^2 is the proportion of total variation observed between the trials attributable to differences between trials rather than to sampling error (chance), with values less than 30% representing low variation, less than 60% moderate variation, and greater than 60% high variation. Analyses were done with PASW Statistics 18.0 for Windows (SPSS). We carried out additional sensitivity analysis to explore the influence of the quality and risk of bias found in the included trials.

Results

The first database query yielded 607 publications (fig 1). Another 25 studies were identified by hand searching. After removal of duplicates, the remaining 587 articles were screened on the basis of the title and abstract. Only 135 trials fulfilled the inclusion criteria. These trials were further evaluated for reporting on the incidence of adverse events and mortality. Of the 39 trials reporting adverse events and causes of death, 10 publications had information on infections. Additionally, 13 trials were certified as potentially relevant and the authors were contacted for primary and supplementary information (see web extra). Of these 13 trials, only one study group provided additional information. In total, the final selection comprised 11 trials. Analyses were carried out on these 11 trials.

Baseline characteristics

Table 1 summarises the baseline characteristics of the included trials. The 11 trials randomised 30 947 participants: 14 103 (45.6%) received statin therapy and 16 844 (54.4%) received placebo. The average follow-up was 3.3 (range 1-5.1) years. The mean age of the patients was 63 (range 48 to 73) years (see web extra).

Of the 11 randomised controlled trials, one was not double blinded (table 2). Three of the trials stated they were randomised but did not give the specific method of sequence generation, although they did state that investigators and participants were blinded to the process of randomisation. Except for one trial,¹⁷ study quality was satisfactory overall and the trials were judged to be at low risk of bias (adequate sequence generation or allocation concealment, double blinding, and clear reporting of withdrawal rates and loss to follow-up). All trials were based on intention to treat analysis of long term treatments. The original publications of the trials included in this meta-analysis reported that 1.1-34.6% of participants assigned to statins had stopped using the drugs by the end of follow-up, similar to the 1.0-44.2% of participants assigned to placebo.

Occurrence of infections

Data on infection related adverse events and infection related mortality were retrieved from the original publications, except for the GISSI-heart failure trial²¹ where the authors provided the relevant data on request. In total, 4655 patients experienced an infection during treatment, reported as an adverse event or

cause of death. Of these patients, 2368 were assigned to statins and 2287 to placebo. Table 3⁴ provides details of the individual trials. Most did not report the site of infection.

Statin treatment and outcome events

In meta-analysis the use of statins was not associated with a decrease in the risk of infection related adverse events compared with placebo (relative risk 1.00, 95% confidence interval 0.96 to 1.05; $P=0.93$, fig 2⁴). Heterogeneity of the included studies was low ($I^2=5.5\%$). Similarly, statins were not associated with a reduction in the risk of infection related mortality (0.97, 0.83 to 1.13; $P=0.71$, fig 3⁴). The included studies also showed low heterogeneity ($I^2=18.8\%$). In sensitivity analysis the exclusion of data from the trial lacking double blinding¹⁷ did not significantly alter the results for infection related mortality (0.98, 0.84 to 1.14).

Discussion

In this systematic review and meta-analysis of data from randomised placebo controlled trials of statins, we found no evidence to support the hypothesis that statins decrease the risk of infection. We pooled the data of 30 947 participants, giving a relative risk of 1.00 for infections and 0.97 for infection related mortality. Absence of any evidence towards a beneficial effect of statins on risk of infection in large placebo controlled statin trials does not support a causal protective association between statins and infections as reported in observational studies.

Comparison with other studies

Our results differ from those of most of the observational studies that examined use of statins and risk of infections. Since 2006, observational studies have reported a possible beneficial effect of statins on risk of infection.^{43 44} Many such studies showed beneficial effects, but a study by Majumdar et al was the first to introduce the so called healthy user effect as a possible source of bias in these studies. Although these researchers studied the effects of statins on prognosis of infections, their findings that analyses with more thorough adjustment, including for functional status, showed no association might also extend to prevention of infections.¹¹ In 2009 a study reported that statin use was not associated with a decreased risk of pneumonia when adjusted for measures of functional or cognitive state.¹² More recently, statins have been linked to an increased risk of infection after stroke and no evidence of an effect on risk of invasive mould infection.^{45 46}

A major methodological difference between these studies and our study may explain the divergent results. Most importantly, and inherent to the study design, observational studies are always at risk of unmeasured confounding. A major strength of our meta-analysis of data from only randomised controlled trials is the absence of such bias. The so called healthy user effect, for example, should be absent when allocation to statin treatment or to placebo is determined by chance. Given that our study showed an effect size of about zero provides evidence that previous findings from observational studies indeed might be biased.

Although it is likely that results from the trials were correct and analyses from observational studies were biased, the reverse scenario is also plausible. Firstly, the reporting of infections was limited and most researchers did not provide additional data on request. Therefore we might have included a non-representative sample of statin trials for infectious outcomes. However, the lack of effect reported in the published

trials would be biased only in the unlikely scenario of preferential publication of null findings. Secondly, we cannot rule out the possibility that statins still might be beneficial in some categories of patients. Although our meta-analysis provided no suggestion for a specific subgroup with reduced risk of infection, this might be missed because randomised trials in general include "healthier" people with fewer comorbidities and drugs used concurrently. On the other hand, most of the participants in this meta-analysis had renal disease and diabetes, two known risk factors for infections, and comparable to the type of patients largely present in many of the observational studies showing a large beneficial effect, whereas our study found a null effect. Also, the mean age of the patients in the present meta-analysis did not differ from the available observational studies (63 years v 63 years).

In the present study we focused on the effects of statins on risk of infection. We know that a large amount of observational data exists suggesting acute statin effects to improve the prognosis of infection. In our opinion, prevention and treatment effects are both important, but they are clearly different. It is not inconceivable that statins influence the inflammatory response in the acute phase of infection without affecting the overall risk of acquiring infection. According to Clinicaltrials.gov, several randomised clinical trials of statins in the setting of sepsis and pneumonia are currently under way. The findings from these trials will help to answer what statins can add to our shared effort to improve the prognosis of infection.

Strengths and limitations of the study

Strengths of our study include the effort to minimise confounding and the alternative approach used. Firstly, we carried out a thorough systematic review of all placebo controlled trials of statins for data on the presence of infections. This was followed by a meta-analysis to analyse unbiased statin effects on the risk of acquiring infections. This alternative approach provides a unique chance to explore the heterogeneity among the observational studies on the subject. This approach has also been applied to explore the reporting of statins and their effects on risk of fracture.⁴⁷

Our study also has some limitations. Mainly, of the 632 publications screened only 11 trials reported on the incidence of infections. Therefore we were unable to carry out subgroup analyses for statin dose, type of statin, patients' characteristics, and type of infection. Secondly, we have no information on the validity of the infectious outcomes, as these were not predefined study outcomes. We do, however, feel confident that infections are major events that would be noticed. Furthermore, if validity was impaired we would expect this to be non-differential and not to lead to an inaccurate estimate of the relative risk of infection.

Conclusions and policy implications

Our systematic review and meta-analysis of data on infectious outcomes in large placebo controlled statin trials did not provide evidence to support the hypothesis that statins decrease the risk of infections. On the basis of previous observational studies, many investigators have called for randomised trials of statins for the prevention of infections. Our finding of an absence of any protective effect shows that results from the observational studies might be biased and that the arguments for setting up such a trial are weakened. Besides this, given our observed effect size of about zero, the sample size and follow-up time required for adequate power to show a difference would be approximately infinite. Furthermore, such a trial could entail

withholding statin treatment for a long period from people with an indication for such treatment. In our opinion, such a study would be unethical. According to Clinicaltrials.gov, numerous randomised clinical trials with long term use of statins are planned or recruiting patients. A better approach could be to push reporting of infectious outcomes in detail whenever statin trials are undertaken. This would have better prospects for identifying subgroups in whom there may be effects worthy of additional testing in a focused randomised trial.

Contributors: EMWvdG conceived and designed the study. HLvdH acquired the data, carried out the statistical analysis, and drafted the manuscript. HLvdH had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis and is the guarantor. All authors were involved in interpretation of results and drafting and revising the manuscript. All authors approved the final submitted version.

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Ethical approval: Not required.

Data sharing: No additional data available.

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What is already known on this topic

Hydroxymethyl glutaryl coenzyme A reductase inhibitors, or statins, are widely used to prevent and treat cardiovascular disease
 Statins have diverse anti-inflammatory and immunomodulatory effects
 Observational studies have reported a decreased risk of infections for people taking statins, but biased estimations in these studies cannot be ruled out

What this study adds

In this systematic review and meta-analysis of randomised placebo controlled trials, statins had no effect on the risk of infections
 The absence of any evidence towards a beneficial effect of statins on risk of infection in large placebo controlled trials potentially negates the causal effect reported in observational studies

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Tables

Table 1 | Baseline characteristics of randomised controlled trials of statins included in analysis of infections and infection related mortality

Study	Details of participants	Primary outcome	Drug and daily dose (mg)	Median follow-up (years)	Mean age (years)
Fellstrom 2009 ¹⁸	2773 undergoing haemodialysis	Time to major cardiovascular event	Rosuvastatin 10 mg v placebo	3.2	64
Kjekshus 2007 ¹⁹	5011 with coronary heart disease	Composite of cardiovascular event (fatal or non-fatal)	Rosuvastatin 10 mg v placebo	2.7	73
Amerenco 2006 ²⁰	4731 with previous stroke or transient ischaemic attack	Time to non-fatal or fatal stroke	Atorvastatin 80 mg v placebo	4.9	63
GISSI-HF 2008 ²¹	4574 with chronic heart failure	Time to death or admission for cardiovascular event	Rosuvastatin 10 mg v placebo	3.9	68
Wanner 2005 ²²	1255 with diabetes undergoing haemodialysis	Composite of cardiovascular events and death from cardiac causes	Atorvastatin 20 mg v placebo	4	66
Stegmayr 2005 ¹⁷	143 with renal disease	All cause mortality, myocardial infarction, coronary artery bypass surgery, percutaneous transluminal coronary angioplasty	Atorvastatin 10 mg v placebo	2	68
Holdaas (ALERT extension*) 2005 ²³	1652 after renal transplant	First major adverse cardiac event	Fluvastatin 40 mg v placebo	6.7	48
Serruys 2002 ²⁴	1677 with chronic heart disease	Time to major adverse cardiac event	Fluvastatin 80 mg v placebo	3.9	60
Newman 2008 ²⁵	2838 with diabetes	Time to major adverse cardiac event	Atorvastatin 10 mg v placebo	3.9	62
Study of Heart and Renal Protection† 2010 ²⁶	5245 with renal disease	Composite of major atherosclerotic events (myocardial infarction, death from coronary heart disease, stroke)	Simvastatin 20 mg v placebo	1	61
Bone 2007‡ ²⁷	626 postmenopausal women	Percentage change from baseline in lumbar (L1-4) spine bone mineral density	Atorvastatin 10-80 mg v placebo	1	59

*Publication of two year extension of original study. ALERT trial had a follow-up of 5.1 years, which was included in average.

†After one year a re-randomisation followed and intervention changed. Study continued until four years' follow-up with intervention of placebo versus ezetimibe or simvastatin.

‡118, 121, 124, and 122 participants received atorvastatin 10 mg, 20 mg, 40 mg, and 80 mg, respectively.

Table 2 | Quality assessment of randomised controlled trials included in meta-analysis of infections

Study	Sequence generation	Allocation concealment	Adverse event monitoring	Blinding of participants and staff	Withdrawal rate (%)		Loss to follow-up (%)	
					Statin	Placebo	Statin	Placebo
Fellstrom (AURORA) ^{18 28-30}	Randomised*	Unclear	Assessment of safety and efficacy at three and six months and every six months thereafter until end of study	Double blinded	29.1	29.5	0	0
Kjekshus (CORONA) ^{19 31}	Adequate, computer random generation	Adequate	Assessment of adverse events at six weeks and three months and every three months thereafter. Additional questionnaire on muscle symptoms requested	Double blinded	19.5	21.9	NR	NR
Amarenco (SPARCL) ^{20 32 33}	Randomised*	Unclear	Assessment of adverse events and blood chemistry tests at 1, 3, 6, and 12 months and then every six months until end of trial	Double blinded	3.3	4.4	0.63	0.42
GISSI-HF ^{21 34 35}	Adequate, computer random generation	Adequate	Assessment of serious adverse events (defined as fatal, life threatening, requiring or prolonging hospital stay, permanently disabling or incapacitating, which may jeopardise participant or which may require medical or surgical intervention) related and not related to study drugs	Double blinded	1.1	1.3	0.13	0.04
Wanner (4D) ^{22 36 37}	Adequate, computer random generation	Adequate	Assessment of serious adverse events continuously, and data recording at four weeks and then every six months	Double blinded	22.9	23.6	0	0.16
Stegmayr ¹⁷	Adequate, computer random generation	Adequate	Adverse events and liver tests monitored at 1, 3, 6, 12, 18, 24, 30, and 36 months of follow-up	Not blinded	28.6	8.2	1.4	0
Holdaas (ALERT extension†) ^{23 38 39}	Adequate, computer random generation	Adequate	Assessment of clinically and laboratory adverse events, at six weeks and every six months thereafter	Double blinded	1.5	0.95	0.29	0.38
Serruys ^{24 40}	Adequate	Adequate, central allocation	Assessment of adverse events at six weeks and every six months thereafter	Double blinded	34.6	44.2	0.83	1.20
Newman, (CARDS) ^{25 41 42}	Adequate, computer random generation	Adequate	Assessment of adverse events monthly for first three months, then at six months, and thereafter every six months	Double blinded	NR	NR	0.56	1.13
Study of Heart and Renal Protection ²⁶	Randomised*	Unclear	Assessment of early adverse effects at two and six months and every six months thereafter	Double blinded	NR	NR	NR	NR
Bone ²⁷	Adequate, computer random generation	Adequate	Assessment of adverse events at occurrence	Double blinded	27.6	27.7	NR	NR

NR=not reported.

*Exact method not described.

†Publication of two year extension of original study.

Table 3| Data on infection related adverse events and infection related mortality from randomised controlled trials of statins

Study source	Infection related adverse events			Infection related mortality			Source of data
	No of events in intervention group	No of events in placebo group	Type of infection	No of events in intervention group	No of events in placebo group	Type of infection	
Fellstrom ¹⁸	976	956	Bronchitis, pneumonia, nasopharyngitis, and urinary tract infections	105	100	NR	Published
Kjekshus ¹⁹	344	370	NR	54	68	NR	Published
Amarenco ²⁰	414	439	NR	26	20	NR	Published
GISSI-HF ²¹	191	160	Respiratory tract infections, urinary tract infections, sepsis, hepatobiliary infections, and other infections	21	14	Respiratory tract infections, sepsis, and other infections	Published as well as provided by authors
Wanner ²²	NR	NR	NR	60	68	NR	Published
Stegmayr ¹⁷	NR	NR	NR	4	7	NR	Published
Holdaas (ALERT extension*) ²³	NR	NR	NR	34	35	NR	Published
Serruys ²⁴	NR	NR	NR	1	3	Sepsis	Published
Newman ²⁵	8	9	NR	NR	NR	NR	Published
Study of Heart and Renal Protection ²⁶	1	6	Infective hepatitis	NR	NR	NR	Published
Bone† ²⁷	129‡	32	Respiratory tract infections and urinary tract infections	NR	NR	NR	Published

NR=not reported.

*Causes of death by original treatment group after open label extension, in which all participants were offered fluvastatin treatment, based on intention to treat population.

†Study group receiving intervention (statin) was four times as large as placebo group.

‡Total of 25, 25, 41, and 38 participants experienced infections in groups receiving atorvastatin 10 mg, 20 mg, 40 mg, and 80 mg, respectively.

Figures

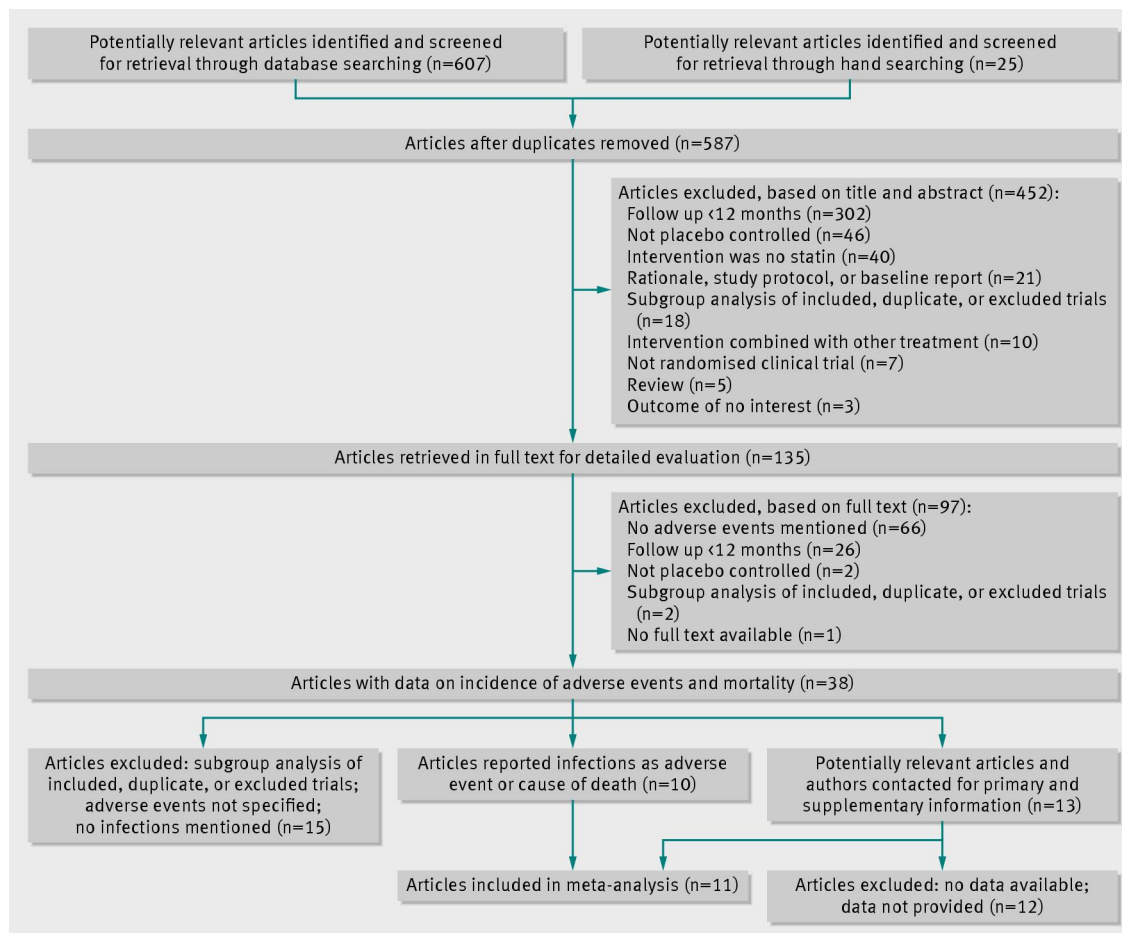


Fig 1 Flow of participants through review

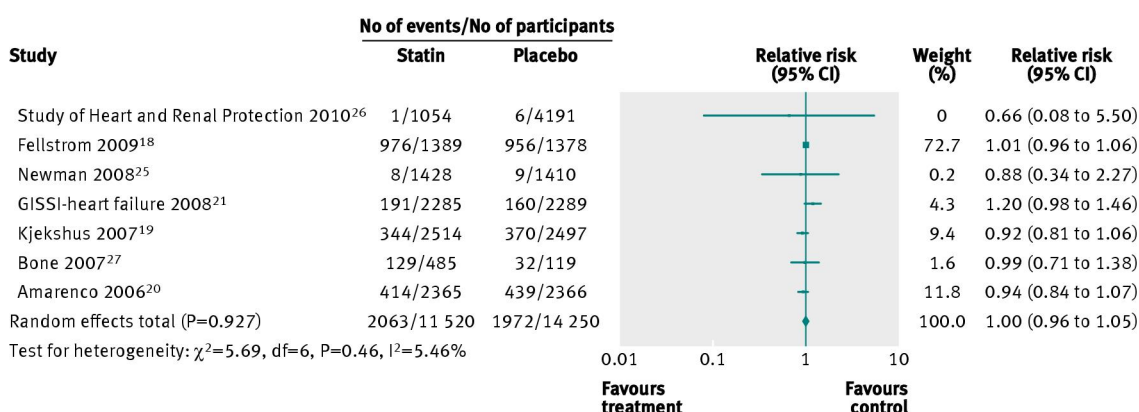


Fig 2 Meta-analysis of statin treatment and risk of infections in randomised controlled trials

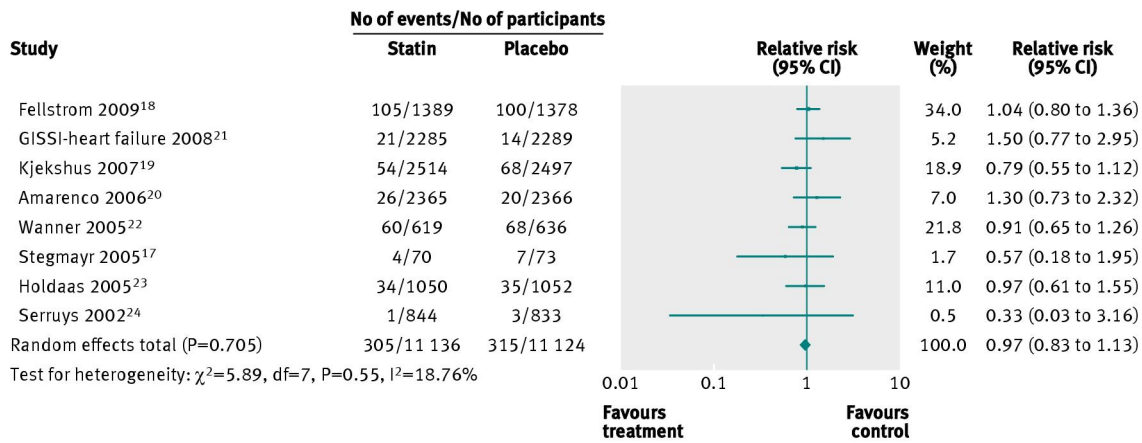


Fig 3 Meta-analysis of statins and risk of infection related mortality in randomised controlled trials