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Interventions in the management of serum lipids for preventing stroke recurrence (Review)

Manktelow BN, Potter JF

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[Intervention Review]

Interventions in the management of serum lipids for preventing stroke recurrence

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ABSTRACT

Background

Studies have shown that interventions which reduce total and low-density lipoprotein cholesterol levels also reduce coronary heart disease (CHD) and stroke events in those with a history of CHD. However, it is uncertain whether treatment to alter cholesterol levels can prevent recurrence of either stroke or subsequent cardiovascular events and whether differences in outcomes exist between classes of lipid-lowering therapy. This is an update of a Cochrane review first published in 2002.

Objectives

To investigate the effect of altering serum lipids pharmacologically for preventing subsequent cardiovascular disease and stroke recurrence in patients with a history of stroke.

Search methods

We searched the Cochrane Stroke Group Trials Register (last searched December 2008), the Cochrane Central Register of Controlled Trials (*The Cochrane Library* Issue 3, 2008), MEDLINE (1966 to December 2008) and EMBASE (1980 to December 2008). We contacted pharmaceutical companies known to produce a lipid-lowering agent for information on relevant publications or unpublished work.

Selection criteria

Unconfounded randomised trials of participants aged 18 years and over with a history of stroke or transient ischaemic attack (TIA).

Data collection and analysis

Two review authors independently selected trials, assessed quality and extracted data.

Main results

We included eight studies involving approximately 10,000 participants. The active interventions were pravastatin, atorvastatin, simvastatin, clofibrate, and conjugated oestrogen. Fixed-effect analysis showed no overall effect on stroke recurrence but statin therapy alone had a marginal benefit in reducing subsequent cerebrovascular events in those with a previous history of stroke or TIA (odds ratio (OR) 0.88, 95% confidence interval (CI) 0.77 to 1.00). There was no evidence that such intervention reduced all-cause mortality or sudden death (OR 1.00, 95% CI 0.83 to 1.20). Three statin trials showed a reduction in subsequent serious vascular events (OR 0.74, 95% CI 0.67 to 0.82).

Authors' conclusions

There is evidence that statin therapy in patients with a history of ischaemic stroke or TIA significantly reduces subsequent major coronary events but only marginally reduces the risk of stroke recurrence. There is no clear evidence of beneficial effect from statins in those with previous haemorrhagic stroke and it is unclear whether statins should be started immediately post stroke or later. In view of this and the evidence of the benefit of statin therapy in those with a history of CHD, patients with ischaemic stroke or TIA, with or without a history of established CHD, should receive statins.

PLAIN LANGUAGE SUMMARY

Interventions in the management of serum lipids for preventing stroke recurrence

There is evidence of a reduction in subsequent serious vascular events from statin therapy in patients with a history of ischaemic stroke or transient ischaemic attack (TIA). Studies have shown that interventions for reducing either total serum cholesterol or low density lipoprotein cholesterol levels reduce the risk of coronary heart disease (CHD) and stroke events in people with a history of CHD. However, for stroke patients the relation between the level of serum cholesterol and cholesterol subfractions with the risk of future stroke or cardiovascular events is unclear. This review, which includes eight studies involving approximately 10,000 participants, shows statin therapy, but not other lipid-lowering measures, reduces the risk of subsequent major vascular events and a marginal benefit in decreasing stroke events, but not all-cause mortality in those with a history of ischaemic cerebrovascular disease.

BACKGROUND

A close association between serum lipid levels and the incidence of coronary heart disease (CHD) has been well proven in middle-aged and elderly people. The UK Joint Working Party called the evidence that patients with established CHD benefit from cholesterol reduction "exceptionally strong" and recommended that all patients with established coronary artery disease should have their serum cholesterol reduced to at least below 5.0 mmol/l (Wood 1998). The British Hypertension Society (Williams 2004) and Joint British Society guidelines on prevention of cardiovascular disease (JBS2 2005) make similar recommendations. However, the relation between plasma cholesterol and cholesterol sub-fractions with cerebrovascular disease is much more controversial. Two meta-analyses of observational data on the relation between serum lipid levels and stroke highlight the uncertainty in the relation between serum lipids and stroke recurrence: one of the studies involved 61 observational cohorts of 900,000 individuals (PSC 2007) and the other 13 cohorts of 125,000 Asian participants (ESCHD 1998). The Prospective Studies Collaborative found no positive association between cholesterol and stroke (including cerebral infarction, cerebral haemorrhage and unclassified stroke) apart from a weak link in those in early middle age (40 to 59 years of age). In the study of Asian populations, no clear relation between cholesterol levels and stroke was found, though there was a trend towards a lower risk of non-haemorrhagic and an increased risk of haemorrhagic stroke with decreasing cholesterol levels.

Direct evidence from randomised trials involving agents that alter serum lipid levels to prevent first-time strokes (i.e. primary stroke prevention) is also lacking (Atkins 1993; Hebert 1995). However, meta-analyses of the accumulated data do suggest that HMG-CoA reductase inhibitors, i.e. statins, may reduce primary stroke incidence (Blauw 1997; Bucher 1998; Byington 2001; Crouse 1997; Di Mascio 2000; Hebert 1997). The Cholesterol Treatment Trialists' Collaboration (CTT 2005) reported a reduction in non-haemorrhagic stroke incidence with LDL cholesterol reduction but not in haemorrhagic strokes. Other evidence suggests that reducing total serum cholesterol levels may paradoxically increase the risk of a haemorrhagic stroke (Law 2003).

If the relation between serum lipids and primary stroke incidence is unclear, the association between stroke recurrence and serum cholesterol is even more uncertain (McNaughton 2002). There is no consistent evidence available yet as to whether lipid levels post stroke are a risk factor for recurrence and whether treatment to alter levels is of benefit in terms of prevention for either stroke recurrence or any subsequent cardiovascular event. Indeed, there is observational evidence that higher serum cholesterol concentrations in the immediate post-stroke period are associated with increased survival (Dyker 1997; Sandercock 2001; Vauthey 2000). A similar confused picture exists between the relation of blood lipids in the non-acute post-stroke period and stroke recurrence. The mainly cohort studies to date have either taken people who have experienced an unspecified cerebrovascular event (Jorgensen 1997) or included only haemorrhagic strokes (Neau 1997; Passero 1995), while a further group considered minor ischaemic events, including transient ischaemic attacks (TIAs), as well as acute ischaemic strokes (Candelise 1986; Eliasziw 1995; Marshall 1961; Moroney 1997; Prencipe 1998; Sorensen 1989; van Latum 1995). However, there is added confusion in that stroke classification, both initial and subsequent, had not been taken into account and the measures of serum lipid levels differed between reports (i.e. some have used total serum cholesterol, others triglycerides or lipoprotein sub-fraction levels). In addition, some studies have used lipid levels taken in the acute stroke period on which to base the outcome analysis, whereas others have taken measurements made weeks to months after the event. There is evidence that lipid levels in the immediate post-stroke period differ from those taken some weeks after the event, with levels falling in the post-stroke period (Butterworth 1997; Mendez 1987).

It is also unclear from observational studies whether total serum cholesterol levels, cholesterol sub-fractions or triglyceride levels are directly related to cerebrovascular disease or whether they are acting as markers for co-morbid conditions, such as CHD, and that it is the latter that is associated with stroke recurrence, not lipid levels per se.

This is an update of a Cochrane review, first published in 2002, which investigates the effects of the treatments that alter serum lipid levels in patients who have had a cerebral infarct, haemorrhage, minor stroke or TIA with stroke recurrence as an outcome measure, taking into account three recently published trials that have specifically looked at the effects of statin therapy in those with a previous history stroke or TIA.

OBJECTIVES

To investigate the effects of treatments that alter serum lipid levels in patients who have had a cerebral infarct, haemorrhage, unspecified stroke type, minor stroke or TIA in relation to the outcome measure of stroke recurrence.

METHODS

Criteria for considering studies for this review

Types of studies

Published or unpublished unconfounded randomised trials of interventions in the treatment of serum lipid levels for the prevention of stroke recurrence.

Types of participants

Patients over 18 years of age with a history of ischaemic or haemorrhagic stroke, including TIA, who were eligible for randomisation.

Types of interventions

We investigated all interventions designed to control serum lipid levels. This included drugs (e.g. statins, fibrates, niacin) and diet (e.g. fibre) given at any dose and for any duration. We classified fish oils as either a drug or diet intervention according to the method of administration.

Types of outcome measures

Primary outcome

- All ischaemic or haemorrhagic strokes.

Secondary outcomes

- Fatal and disabling stroke events.
- All-cause mortality, including sudden deaths.

- Serious vascular events (non-fatal stroke, non-fatal myocardial infarction (MI), vascular death).
- All cardiovascular events (fatal and non-fatal MI, congestive cardiac failure, symptomatic peripheral vascular disease).

Search methods for identification of studies

See the 'Specialized register' section in the Cochrane Stroke Group module.

We searched the Cochrane Stroke Group Trials Register, which was last searched by the Review Group Co-ordinator in December 2008, the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* Issue 3, 2008), MEDLINE (1966 to December 2008) (Appendix 1) and EMBASE (1980 to December 2008). We also contacted the following pharmaceutical companies known to produce a lipid-lowering agent and asked them to provide information on publications or unpublished work relevant to this review.

- Bristol Myers Squibb Pharmaceuticals Ltd (pravastatin, cholestyramine);
- Fournier Pharmaceuticals Ltd (fenofibrate);
- Merck Sharp & Dohme Ltd (simvastatin);
- Parke-Davis Research Laboratories (atorvastatin, gemfibrozil);
- Pharmacia and Upjohn Ltd (acipimox, colestipol);
- Reckitt and Colman Products Ltd (soluble fibre);
- Roche Products Ltd (bezafibrate);
- Sandoz Pharmaceuticals (fluvastatin);
- Sanofi Winthrop (ciprofibrate);
- Zeneca Pharmaceuticals (clofibrate).

Data collection and analysis

We independently assessed the trials identified. We obtained the full text of all studies where there was no evidence from the abstract that any of the selection criteria were not met by the study. We then confirmed which trials met the selection criteria, with all decisions on the inclusion of a trial being reached by consensus. If we could not reach agreement, we agreed to seek appropriate external advice for a final decision, although this was not necessary in this review. Where necessary, we contacted study authors for clarification. We also planned to contact study authors if information on the primary outcome was missing; however, this was not necessary.

We recorded details of the methodological quality of the included trials. In particular, we extracted details of randomisation, blinding, and participants withdrawn or lost to follow up. We did not use a scoring system for study quality. We included trials with an inadequate method of randomisation (i.e. where allocation could be anticipated or interfered with) because of the possible identification of older trials that were undertaken prior to currently accepted standards of trial design. However, we planned to perform sensitivity analyses by repeating any analysis excluding these studies, but this was not necessary.

We planned to exclude trials of drug interventions without full concealment of treatment allocation from both patients and clinicians, but we did not identify any such trials. Trials of diet interventions should be blind to any person making outcome assessments. We also planned to exclude confounded trials (i.e. trials where an additional active treatment is administered to one of the groups in a non-factorial design), but we did not identify any such trials.

We carried out data extraction independently, and agreed to resolve any disagreements using the procedure outlined above, but we did not disagree on any aspects of data extraction. We estimated the overall treatment effect by the Peto odds ratio (OR) from a fixed-effect model. We carried out all statistical analysis using the Cochrane Review Manager software, Review Manager 5.0 (RevMan 2008).

If possible, we planned to perform subgroup analyses to investigate the effect of the following.

1. Baseline cerebrovascular disease type:
   a. all strokes and TIAs;
   b. all acute strokes;
   c. all acute ischaemic strokes and TIAs (not done);
   d. all acute ischaemic strokes (not done);
   e. all haemorrhagic strokes (not done).
2. Intervention type:
   a. any drug versus control;
   b. statins (any dose) versus control (not done);
   c. statins (high dose) versus control (not done);
   d. non-statin drugs versus control;
   e. diet versus none (not done).
3. Previous cardiovascular event (not done).
4. Optimal cholesterol control versus standard control (not done).

We had planned to perform a meta-regression to investigate the effect of lipid changes actually achieved if unbiased estimates had been obtainable. There was also insufficient information for an assessment of potential side effects from treatment.

RESULTS

Description of studies

We identified eight trials that met all of the inclusion criteria. Five of the studies investigated statins: pravastatin (CARE; LIPID), simvastatin (HPS; FASTER); and atorvastatin (SPARCL). Two looked at the use of clofibrate (Acheson 1972; VACSA 1973), and the eighth used oestrogen as Premarin (VASCA 1966). However, the data used here from three studies (CARE; LIPID; HPS) are sub-group analyses from the trials.

Of the trials where data from subgroups of the trial population were analysed, one trial only included patients with a history of MI or unstable angina (LIPID), another only recruited those who had had an acute MI (CARE), whereas the third included adults with coronary disease, other occlusive arterial disease or diabetes (HPS). The remaining trials also differed in their study populations. One study included patients who had experienced a cerebral infarct or TIA (VACSA 1973), whereas another only included those whose symptoms lasted over 12 hours (VASCA 1966). The other trials recruited patients with any history of stroke or TIA as the inclusion event (Acheson 1972; SPARCL), but certain sub-groups of stroke were excluded at entry in some trials, e.g. cardio-embolic strokes in SPARCL. In the FASTER study, statin treatment was started within 24 hours of onset of a minor stroke or TIA. Data on the time from

stroke onset to randomisation were not reported in the trials but was in the order of several weeks to years. The effect this may have had in terms of outcome measures was also not recorded.

In addition, the studies differed in the length of follow up of the patients. The shortest reported length of follow up was 90 days for the FASTER study, followed by the VASCA trial, with an average follow up of under 17 months (VASCA 1966). This increased to up to four years in one trial (Acheson 1972), and up to four and a half years in another (VACSA 1973). The four more recent trials reported that patients were followed for six years (LIPID, a median of five years (range 4.0 to 6.2 years) (CARE), a median of 4.9 years (SPARCL) and a mean of five years (HPS).

Risk of bias in included studies

All the trials identified were unconfounded parallel group randomised trials.

It was unclear whether allocation concealment was adequate in two trials (Acheson 1972; VACSA 1973) as details are not reported: neither study used an intention-to-treat analysis. Eleven patients were excluded from the former (Acheson 1972): three because the diagnosis was incorrect and a further eight because they refused to co-operate during the follow-up period. The other trial (VACSA 1973) excluded nine participants; eight were randomised to a hospital not continuing in the study, and one was illegible because of a concurrent malignancy. In neither case was it stated to which treatment group each of these participants had been randomised.

One trial matched patients pairwise according to identified potential risk factors: clinical status, duration of disease, age, sex, degree of hypertension, and serum cholesterol level (within 50 mg/100ml) (Acheson 1972).

Another trial reported a slightly higher rate of cardiovascular disorders in the control group at baseline (VASCA 1966) and some differences between the treatment groups were reported in a further study (VACSA 1973), although it is not stated whether these were felt to be clinically important. The final studies (CARE; FASTER; HPS; LIPID; SPARCL) reported that, for the entire study populations in each trial, the two treatment groups were similar with respect to stroke risk factors.

Effects of interventions

All ischaemic or haemorrhagic strokes

Seven of the studies reported stroke recurrence as an outcome measure for those with a previous history of stroke or TIA. Overall, using a fixed-effect analysis there was no evidence, at the 5% significance level, for a difference in outcome between the treatment and placebo groups. There was, however, some evidence of a difference between the two treatment groups (statins and fibrates: P = 0.03).

The treatment effects from the two trials of fibrates tended to favour the control group although this was not statistically significant (odds ratio (OR) 1.48, 95% confidence interval (CI) 0.94 to 2.30). For the studies involving statins only, there was borderline statistical difference favouring the active treatment group compared with the placebo groups in stroke recurrence (OR 0.88, 95% CI 0.77 to 1.00) (five studies) with no evidence of heterogeneity in the results (P = 0.25). However, analysis by type of subsequent stroke (two studies) showed evidence for a protective effect of statins for ischaemic stroke (OR 0.78, 95% CI 0.67 to 0.92) (Analysis 1.4) but evidence for an increased risk of haemorrhagic stroke (OR 1.72, 95% CI 1.20 to 2.46) (Analysis 1.5).

There was also no evidence of a treatment effect on stroke recurrence for those with a previous history of stroke only (OR 0.97, 95% CI 0.71 to 1.31) (four studies) and, although both statin studies showed a tendency toward a protective effect (OR 0.73, 95% CI 0.44 to 1.22), there was no evidence of heterogeneity amongst all of the studies included with the overall results (P = 0.30) nor for difference between the type of intervention (P = 0.19).

All-cause mortality, including sudden deaths

Despite the reduction in serious cardiovascular events with statin therapy, there was no evidence that intervention reduced all-cause mortality in patients with a history of stroke or TIA (OR 1.00, 95% CI 0.83 to 1.20) (Analysis 1.2) (three studies) and no evidence that treatment type influenced this outcome (test for subgroup differences P = 0.52), but this is based on only one trial in the statin group and two in the fibrate group.

For patients with a history of stroke only, OR 1.16, 95% CI 0.69 to 1.95 (one study).

Serious vascular events

There was strong evidence for a reduction in subsequent vascular events in patients with a history of stroke or TIA with lipid-lowering therapy: OR 0.77, 95% CI 0.70 to 0.84, P < 0.0001 (four studies). This effect was due to the positive results from the two large trials of statins (HPS; SPARCL), though not from the early statin intervention trial (FASTER). For patients with a history of stroke or TIA , subsequent serious vascular events were significantly reduced (OR 0.74, 95% CI 0.67 to 0.82) in those on statins in the three studies where data were available.

For patients with a history of stroke only, the results were only available from a trial of oestrogen where no beneficial effect was seen: OR 1.03, 95% CI 0.72 to 1.48.

The effects of treatment on outcome measures could not be calculated in relation to lipid level changes between treatment and control groups for any of the outcome measures. The decision was taken post hoc to analyse the data according to non-statin drug type (i.e. fibrate and oestrogen) where possible. This was done to provide more information but should be interpreted in the light of it being a post hoc decision.

DISCUSSION

Since publication of the previous Cochrane analysis in 2002, there have been three important trials of the effects of altering lipid levels pharmacologically post stroke on stroke recurrence, development of serious vascular events, and death, all of which have involved the use of statins. The Heart Protection Study (HPS) enrolled 3280 patients aged 40 to 80 years, 64% with a history of ischaemic stroke and 46% with TIA (those with cerebral haemorrhage were excluded) and a baseline total cholesterol (TC) > 3.5 mmol/l with a mean of 5.9 mmol/l. They were randomised to simvastatin 40 mg daily or placebo and followed up for 4.8 years. The SPARCL trial was the first to assess the effects of a statin (atorvastatin 80 mg daily) exclusively in stroke patients, enrolling 4731 participants aged over 18 years

with cerebral infarction (67%), TIA (30%) and cerebral haemorrhage (2%). Baseline TC was < 5.5 mmol/l and follow up was for 4.9 years. Most recently the FASTER study was published, having been prematurely stopped because of recruitment problems. This trial recruited minor stroke and TIA patients within 24 hours of symptom onset, of whom 199 patients were randomised to simvastatin 40 mg and 193 to placebo with a 90-day follow up. Overall the trials involving both statins and fibrates failed to demonstrate that therapy reduced stroke recurrence in patients with a history of cerebrovascular disease, although the trials showed some degree of heterogeneity in terms of the outcome measure between the different drug classes.

The two trials that excluded TIA patients, randomising only patients with a history of stroke and CHD, to pravastatin or placebo (CARE; LIPID) similarly failed to offer point estimates of treatment effect favouring the use of statins. However, these were both small subgroup analyses from large trials, and included only 821 patients. The estimated odds ratio for treatment effect had a wide confidence interval (OR 0.73, 95% CI 0.44 to 1.22). However, these two statin-based trials comprised patients who had a history of CHD and who are likely to be prescribed statins to reduce the risk of further heart disease irrespective of their effectiveness in preventing further stroke episodes. These two trials were also limited in their applicability as the study population was aged 75 years or under but did include patients with TIA.

The results from the important HPS study show evidence of benefit from statin therapy in the sub-group of patients with a history of cerebrovascular disease in preventing subsequent major vascular events (i.e. major coronary event and coronary or non-coronary revascularisation) but, interestingly, not stroke. There was evidence that those with a history of cerebrovascular disease were more likely to develop subsequent cerebral haemorrhage with simvastatin than those without a stroke history. However, these data are also limited by the relatively small number of stroke events in this sub-group and that the results apply only to those under the age of 80 years, who have had an ischaemic, but not haemorrhagic, stroke or TIA and who are not severely disabled after their initial stroke. We were unable to differentiate further between stroke subtype, e.g. large artery events versus lacunar and cardio-embolic events, as well as between infarct and haemorrhagic strokes. The effect of statin treatment on major vascular event rates were not reported in the CARE and LIPID studies. No other lipid-lowering trials to date have shown this benefit in study populations, including both those with and without a history of cerebrovascular disease (ALLHAT 2002; PROSPER 2002). The PROSPER Trial (PROSPER 2002) investigated the effects of pravastatin in older people (aged 70 to 82 years) with a history of, or risk factors for, vascular disease (of whom 11% had a previous stroke) and although it showed evidence of a reduction in the risk of subsequent coronary artery disease there was no evidence of a benefit in stroke reduction (the data relating to those with a history of stroke have not been presented separately). Similarly, major vascular event rates were not reported in the stroke sub-group of the CARE and LIPID studies. The ALLHAT (ALLHAT 2002) and ASCOT (ASCOT 2003) studies also showed no evidence for a reduction in stroke, nor in coronary heart disease, although in this trial the patients in the usual care group experienced an 11% fall in cholesterol levels. Subgroup analyses from these trials of patients with a previous history of cerebrovascular disease may add further information but are not currently available.

The SPARCL study is unique in that it is the first trial of statins solely in stroke patients without evidence of CHD and included those with a history of cerebral haemorrhage, though the numbers in this group were too small to allow for useful analysis. However, those with presumed cardio-embolic stroke including those with atrial fibrillation were excluded, reducing the generalisability of the results as this might be expected to involve at least 20% of the stroke population. Non-fatal or fatal stroke were significantly reduced by atorvastatin, though this was mainly due to a reduction in fatal stroke; however, although the odds of ischaemic stroke were reduced by 22% with atorvastatin, the odds of cerebral haemorrhage were significantly increased by 66%. This is the only study to date that has shown drug induced changes in serum lipids are associated with a reduction in stroke risk. Active treatment also reduced the odds of any coronary event by 42% and the odds of all major cardiovascular events by 20%.

It is impossible to assess in this review if the effects of time from stroke or TIA onset to treatment influences subsequent events as these data are not available, though the range is large, from weeks to years. The FASTER Trial data, however, may indicate that very early intervention (within 24 hours of symptom onset) with statins following stroke could have an adverse effect, there being a non-significant increase in stroke recurrence for the simvastatin-treated patients; this needs further clarification.

Amongst the eight trials that have aimed to alter lipid levels following stroke or TIA, three different classes of drugs have been used: the majority have used statins (CARE; FASTER; HPS; LIPID; SPARCL); two used fibrates (Acheson 1972; VACSA 1973) and one oestrogen (VASCA 1966). However, because of the way the data are presented it is difficult to directly compare outcome measures between trials for all stroke events (the outcome measure where most information is available). There was some evidence for differences in outcome between drug groups: statin therapy resulting in a borderline significant 12% reduction in the odds of subsequent cerebrovascular events compared to a 48% increase in odds with fibrates. Even in the statin trials, there was a diversity of effect on stroke sub-type, with a significant 72% increase in the odds of cerebral haemorrhage with treatment which partially offset the 22% reduction in odds for ischaemic stroke (there being a 10:1 ratio of ischaemic to haemorrhagic events as would be expected). For serious vascular events, a similar difference was seen between statins and fibrates, although the numbers are much smaller than for stroke recurrence; again statins resulted in a 26% reduction in the odds compared with a 27% increase with fibrates, although data were limited to the VACSA trial for the latter drug group. It was not possible to assess if these effects were similar for those who had a previous history of stroke only as opposed to TIA: the data from trials that enrolled only stroke patients, as opposed to those with recruiting either stroke or TIA, appear not to differ in outcomes. Statin therapy, however, appeared to have no benefit in reducing all-cause mortality.

It is not possible to obtain sufficient data on baseline lipid levels or the size of the lipid changes achieved during any of the trials in relation to outcomes. This would be useful information in order to investigate whether the potential neuroprotective effects of statins derive solely from their lipid-altering effects or by some other mechanisms, e.g. anti-inflammatory effects or endothelial protection. Some information on the recorded blood pressures of the patients and other potential risk factors for stroke recurrence,

as well as other secondary preventative measures such as aspirin use, would also have been of interest.

Many important questions are still left unanswered regarding lipid-altering therapy in the post-stroke period. It was not possible to assess the effects of any of the lipid agents on those with a previous cerebral haemorrhage (the numbers in the SPARCL study were too small and not reported separately) or TIA. It is unclear when after the cerebrovascular event therapy to alter lipid levels should be started, at what baseline lipid levels treatment should be commenced, what level of reduction should be aimed for or whether the very elderly (those aged over 80 years) stroke patient benefits to the same extent as a younger counterpart.

AUTHORS' CONCLUSIONS

Implications for practice

There is good evidence for a benefit of statin therapy in those under the age of 80 years with a previous non-disabling stroke or TIA (but not cerebral haemorrhage) who have baseline total cholesterol levels > 3.5 mmols/l in terms of reducing subsequent serious vascular events. The data also suggest a marginal benefit of statins in reducing future cerebrovascular events, but not overall mortality. In view of this evidence it is recommended that all ischaemic stroke or TIA patients aged at least up to 80 years should receive statin therapy as part of a secondary prevention programme

Implications for research

Further work is needed to assess the potential role of statins for those patients with a previous cerebral haemorrhage, when after the cerebrovascular event therapy to alter lipid levels should be started, at what baseline lipid levels treatment should be commenced, what level of reduction should be aimed for or whether the very elderly (those aged over 80 years) stroke patient benefits to the same extent as a younger counterpart.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Acheson 1972

Methods	Parallel group, placebo-controlled trial
Participants	106 patients (11 excluded from analysis: 3 incorrect diagnosis; 8 refused to co-operate) Country: UK Study years:1962 to 1969 Age: 43 to 76 years Male: 68%

Acheson 1972 *(Continued)*

	Inclusion: previous stroke or TIA
Interventions	Clofibrate (250 mg capsules: 4 to 6 daily for females; 6 to 8 daily for males) Placebo (corn oil for first 20 months of trial) Follow up: between 4 months and 4 years
Outcomes	Cerebral ischaemia Stroke Mortality
Notes	Matched pairs design

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

CARE

Methods	Parallel group, placebo-controlled trial
Participants	4159 patients (122 previous stroke: 211 previous stroke or TIA) Country: USA Study years: 1989 to 1996 Age: 21 to 75 years Male: 86% (whole trial) Inclusion: MI 3 to 20 months before randomisation, total cholesterol < 240 mg/dl; LDL 115 to 174 mg/dl; triglycerides ≤ 350 mg/dl
Interventions	Pravastatin (40 mg/d) Matching placebo Follow up: median 5.0 years (range 4.0 to 6.2)
Outcomes	Stroke symptoms lasting ≥ 24 hours
Notes	Sub-group analysis of trial

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

FASTER

Methods	Parallel group, placebo-controlled trial 2 x 2 factorial design with clopidogrel
Participants	392 patients Country: Canada Study years: 2003 to 2006

FASTER *(Continued)*

	Age: 40 years or older Male: 53% Inclusion: TIA or minor stroke (NIHSS < 4) within 24 hours of onset
Interventions	Simvastatin (40 mg/d) Matching placebo
Outcomes	Stroke within 90 days Major vascular event
Notes	Trial stopped early because of low recruitment

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

HPS

Methods	Parallel group, placebo-controlled trial 2 x 2 factorial design with antioxidant vitamin supplementation
Participants	20,536 patients (3280 with previous cerebrovascular event) Country: UK Study years: 1994 to 2001 Age: around 40 to 80 years Inclusion: non-fasting total cholesterol ≥ 135 mg/dL, substantial 5-year risk from CHD
Interventions	Simvastatin (40 mg/d) Matching placebo
Outcomes	Stroke Major cerebrovascular event
Notes	Sub-group analysis of 2 x 2 factorial design trial

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

LIPID

Methods	Parallel group, placebo-controlled trial
Participants	9014 patients (369 with previous stroke) Country: Australia and New Zealand Study years: 1990 to 1996 Age: 31 to 75 years Male: 83%

LIPID *(Continued)*

	Inclusion: MI or unstable angina pectoris 3 to 36 months before randomisation; total cholesterol 155 to 271 mg/dl and fasting triglicerides < 445 mg/dl
Interventions	Pravastatin (40 mg/d) Matching placebo Follow up: 6 years
Outcomes	Stroke
Notes	Sub-group analysis of trial

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

SPARCL

Methods	Parallel group, placebo-controlled trial
Participants	4731 patients Country: worldwide (205 sites) Study years: 1998 to 2001 Age: over 18 Male: 59.8% Inclusion: stroke or TIA in previous 6 months
Interventions	Atorvastatin (80 mg/d) Matching placebo Follow up: median 4.9 years
Outcomes	Fatal or non-fatal stroke
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

VACSA 1973

Methods	Parallel group, placebo-controlled trial
Participants	541 patients (9 excluded from analysis: 8 hospital withdrew; 1 concurrent malignancy) Country: USA Study years: 1966 to 1970 Age: 70 or under Male: 100%

VACSA 1973 *(Continued)*

	Inclusion: history of cerebral infarction or TIA
Interventions	Clofibrate (500 mg x 4 daily) Matching placebo Follow up: up to 4.5 years
Outcomes	Mortality Cerebral infarction Vascular event
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

VASCA 1966

Methods	Parallel group, placebo-controlled trial
Participants	582 patients Country: USA Study years: 1962 to 1965 Age: not known Male: 100% Inclusion: history of cerebral infarct with symptoms lasting at least 12 hours
Interventions	Mixed conjugated equine oestrogen (Premarin) (1.25 mg daily for 12 months then 2.5 mg) Matching placebo Follow up: average 16.7 months
Outcomes	Cerebral infarct Cerebral infarct & MI All cause mortality
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

CHD: coronary heart disease
MI: myocardial infarction
NIHSS: National Institutes of Health Stroke Scale
TIA: transient ischaemic attack

Characteristics of ongoing studies *[ordered by study ID]*

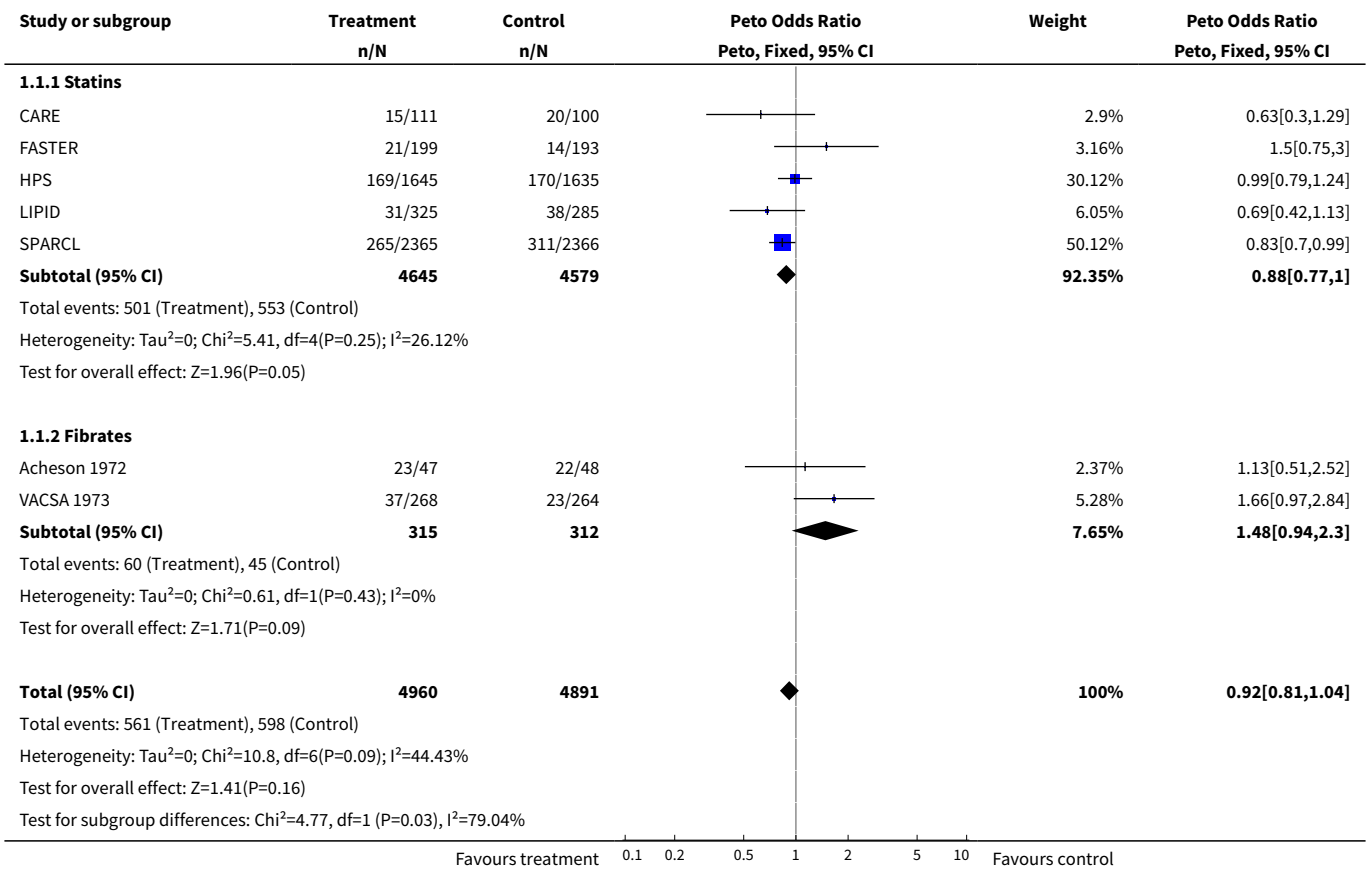
J-STARS	
Trial name or title	Japan Statin Treatment Against Recurrent Stroke
Methods	
Participants	Ischaemic stroke, hyperlipidemia and total cholesterol 180 to 240 mg/dL, without statin in last 30 days Age: 45 to 80 years
Interventions	Pravastatin 10 mg/day or placebo
Outcomes	Primary: cerebrovascular events Secondary: stoke subtype, cardiovascular event, stroke death, cerebrovascular and cardiovascular death
Starting date	1 March 2004
Contact information	Dr Masayasu Matsumoto, Hiroshima University mack@hiroshima-u.ac.jp
Notes	Expected completion February 2014

DATA AND ANALYSES

Comparison 1. Intervention versus control: history of stroke or TIA

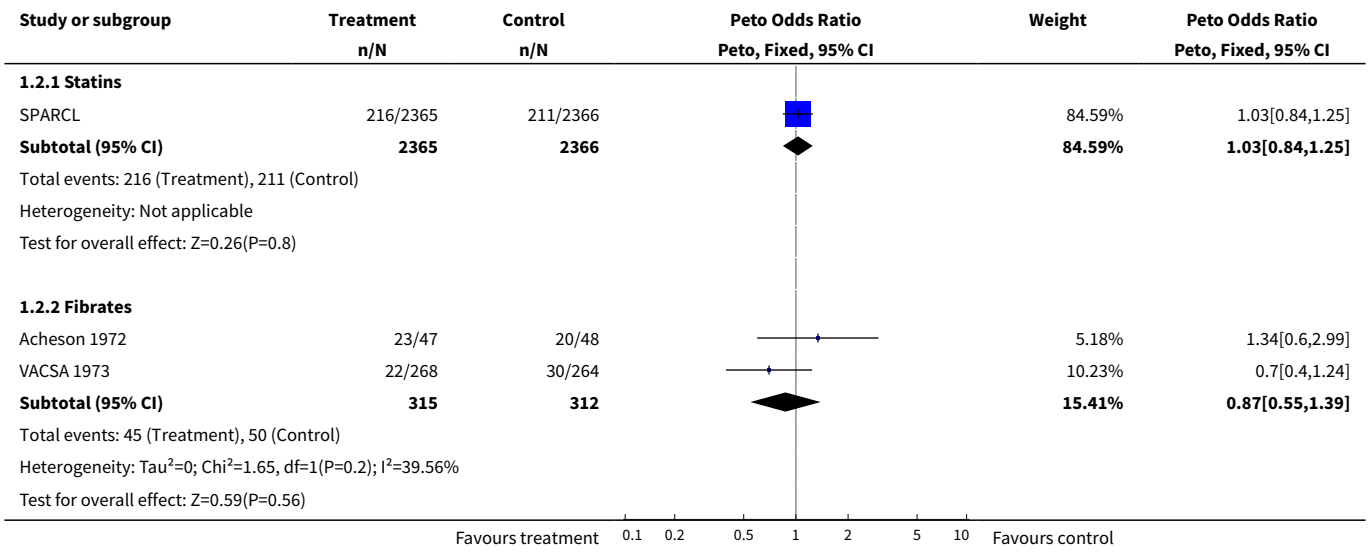
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All ischaemic or haemorrhagic strokes	7	9851	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.92 [0.81, 1.04]
1.1 Statins	5	9224	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.88 [0.77, 1.00]
1.2 Fibrates	2	627	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.48 [0.94, 2.30]
2 All-cause mortality, including sudden deaths	3	5358	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.00 [0.83, 1.20]
2.1 Statins	1	4731	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.03 [0.84, 1.25]
2.2 Fibrates	2	627	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.87 [0.55, 1.39]
3 Serious vascular events	4	8935	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.77 [0.70, 0.84]
3.1 Statins	3	8403	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.74 [0.67, 0.82]
3.2 Fibrates	1	532	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.27 [0.84, 1.89]
4 Ischaemic strokes	2	8011	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.78 [0.67, 0.92]
5 Haemorrhagic strokes	2	8011	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.72 [1.20, 2.46]

Analysis 1.1. Comparison 1 Intervention versus control: history of stroke or TIA, Outcome 1 All ischaemic or haemorrhagic strokes.

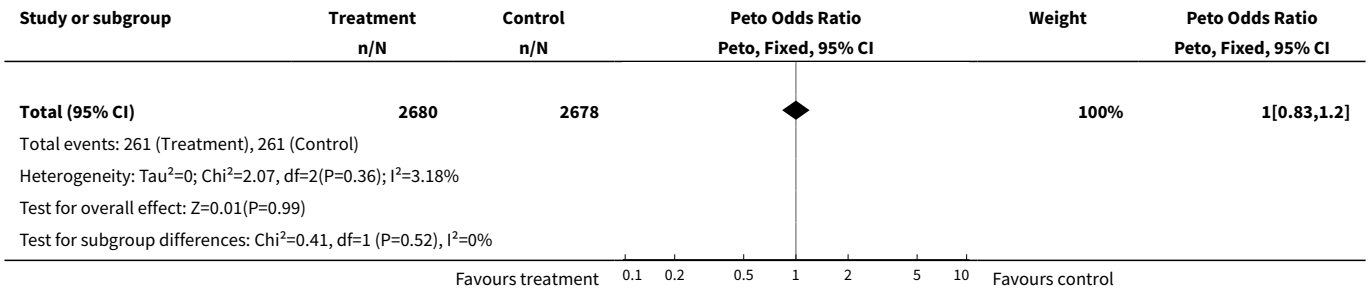


Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
1.1.1 Statins					
CARE	15/111	20/100		2.9%	0.63[0.3,1.29]
FASTER	21/199	14/193		3.16%	1.5[0.75,3]
HPS	169/1645	170/1635		30.12%	0.99[0.79,1.24]
LIPID	31/325	38/285		6.05%	0.69[0.42,1.13]
SPARCL	265/2365	311/2366		50.12%	0.83[0.7,0.99]
Subtotal (95% CI)	**4645**	**4579**		**92.35%**	**0.88[0.77,1]**
Total events: 501 (Treatment), 553 (Control)					
Heterogeneity: Tau^2=0; Chi^2=5.41, df=4(P=0.25); I^2=26.12%					
Test for overall effect: Z=1.96(P=0.05)					
1.1.2 Fibrates					
Acheson 1972	23/47	22/48		2.37%	1.13[0.51,2.52]
VACSA 1973	37/268	23/264		5.28%	1.66[0.97,2.84]
Subtotal (95% CI)	**315**	**312**		**7.65%**	**1.48[0.94,2.3]**
Total events: 60 (Treatment), 45 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.61, df=1(P=0.43); I^2=0%					
Test for overall effect: Z=1.71(P=0.09)					
Total (95% CI)	**4960**	**4891**		**100%**	**0.92[0.81,1.04]**
Total events: 561 (Treatment), 598 (Control)					
Heterogeneity: Tau^2=0; Chi^2=10.8, df=6(P=0.09); I^2=44.43%					
Test for overall effect: Z=1.41(P=0.16)					
Test for subgroup differences: Chi^2=4.77, df=1 (P=0.03), I^2=79.04%					

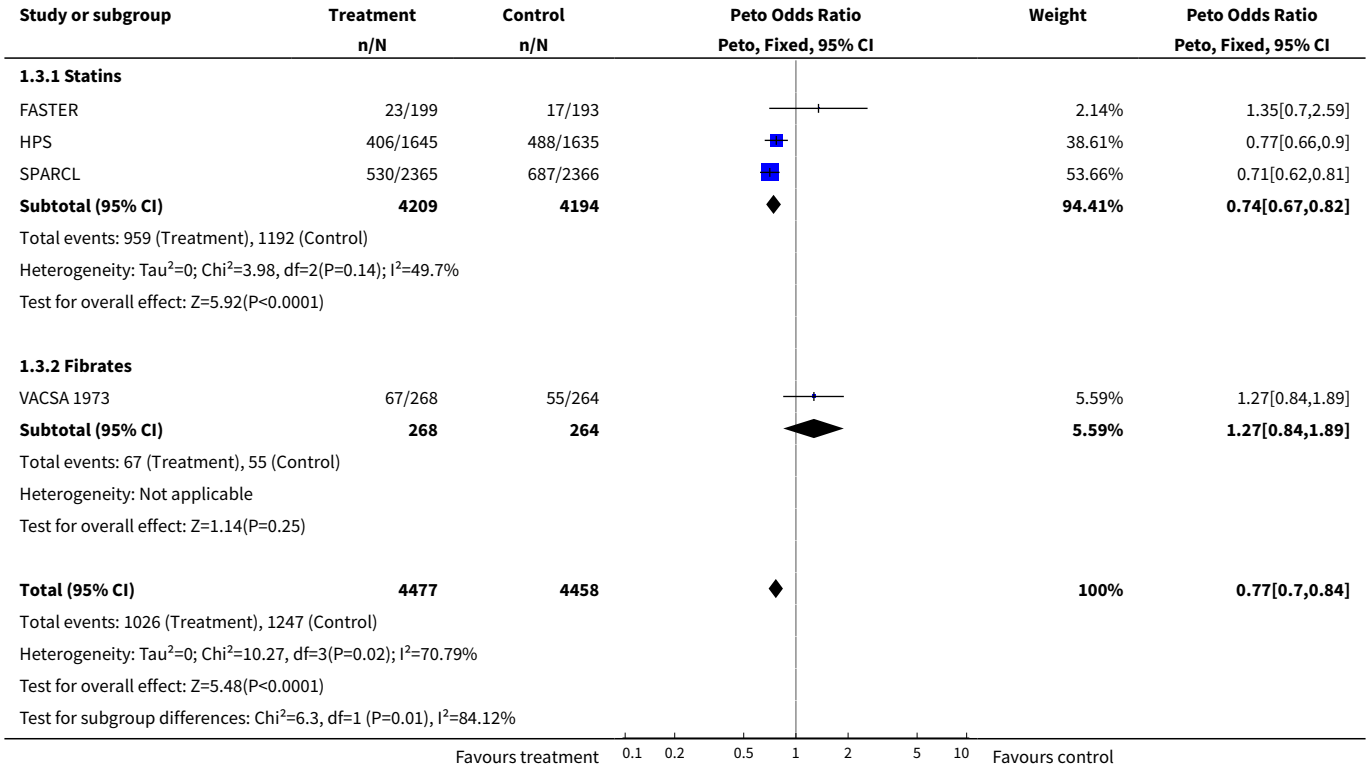
Analysis 1.2. Comparison 1 Intervention versus control: history of stroke or TIA, Outcome 2 All-cause mortality, including sudden deaths.



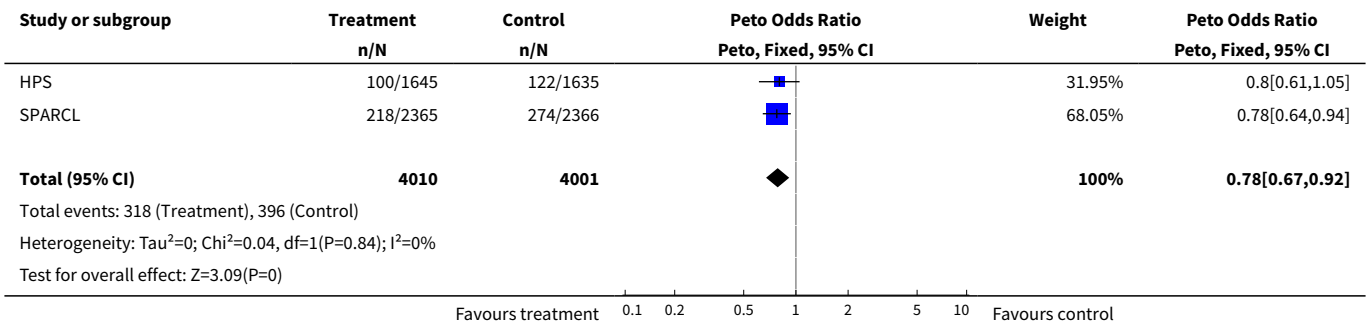
Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
1.2.1 Statins					
SPARCL	216/2365	211/2366		84.59%	1.03[0.84,1.25]
Subtotal (95% CI)	**2365**	**2366**		**84.59%**	**1.03[0.84,1.25]**
Total events: 216 (Treatment), 211 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.26(P=0.8)					
1.2.2 Fibrates					
Acheson 1972	23/47	20/48		5.18%	1.34[0.6,2.99]
VACSA 1973	22/268	30/264		10.23%	0.7[0.4,1.24]
Subtotal (95% CI)	**315**	**312**		**15.41%**	**0.87[0.55,1.39]**
Total events: 45 (Treatment), 50 (Control)					
Heterogeneity: Tau^2=0; Chi^2=1.65, df=1(P=0.2); I^2=39.56%					
Test for overall effect: Z=0.59(P=0.56)					



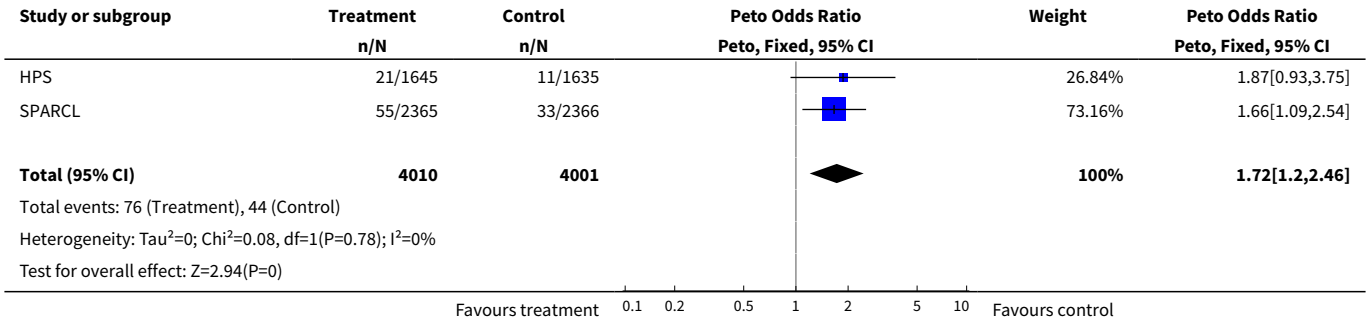
Analysis 1.3. Comparison 1 Intervention versus control: history of stroke or TIA, Outcome 3 Serious vascular events.



Analysis 1.4. Comparison 1 Intervention versus control: history of stroke or TIA, Outcome 4 Ischaemic strokes.



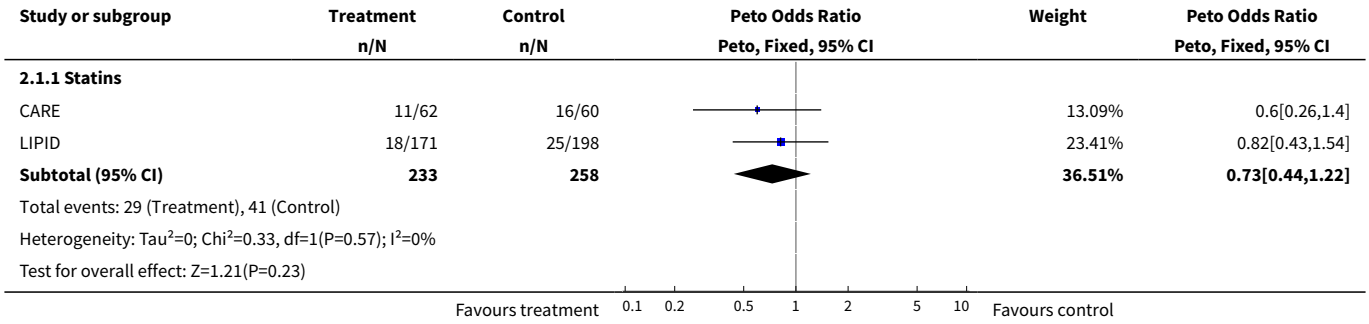
Analysis 1.5. Comparison 1 Intervention versus control: history of stroke or TIA, Outcome 5 Haemorrhagic strokes.

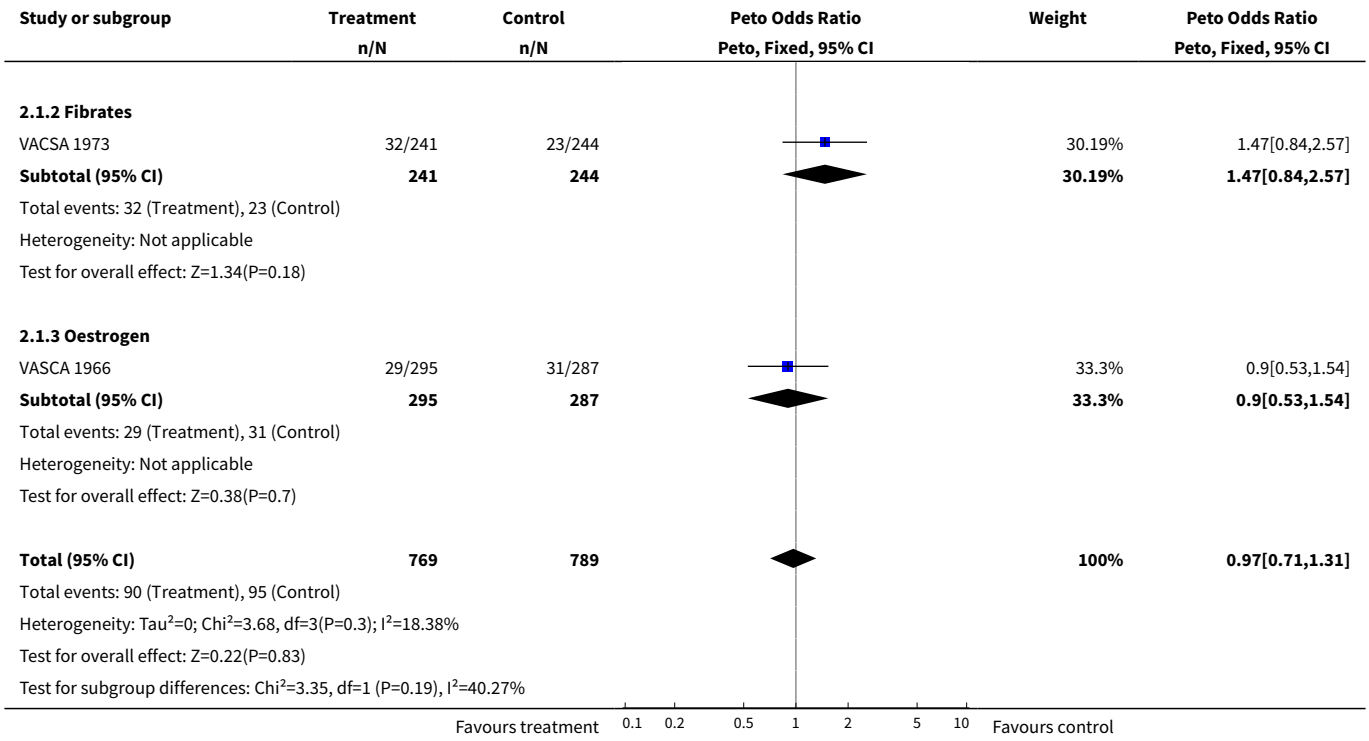


Comparison 2. Intervention versus control: history of stroke

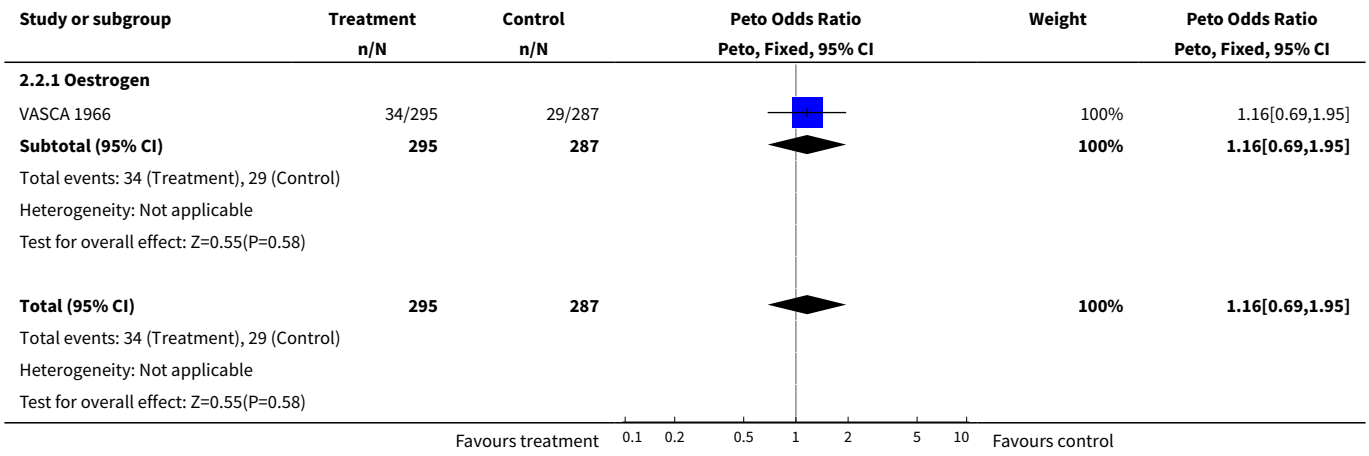
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All ischaemic or haemorrhagic strokes	4	1558	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.97 [0.71, 1.31]
1.1 Statins	2	491	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.73 [0.44, 1.22]
1.2 Fibrates	1	485	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.47 [0.84, 2.57]
1.3 Oestrogen	1	582	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.90 [0.53, 1.54]
2 All cause mortality, including sudden deaths	1	582	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.16 [0.69, 1.95]
2.1 Oestrogen	1	582	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.16 [0.69, 1.95]
3 Serious vascular events	1	582	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.03 [0.72, 1.48]
3.1 Oestrogen	1	582	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.03 [0.72, 1.48]

Analysis 2.1. Comparison 2 Intervention versus control: history of stroke, Outcome 1 All ischaemic or haemorrhagic strokes.

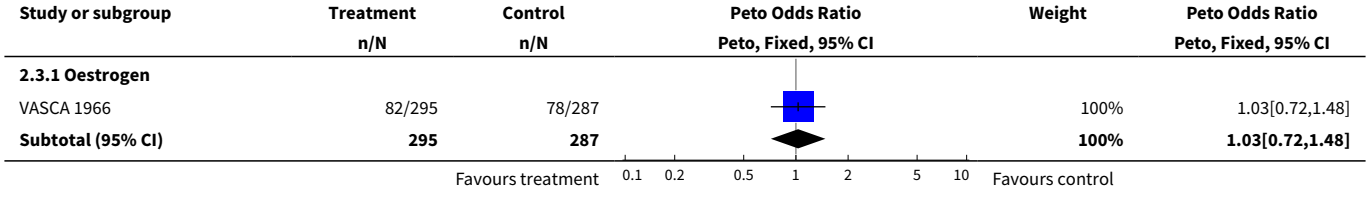


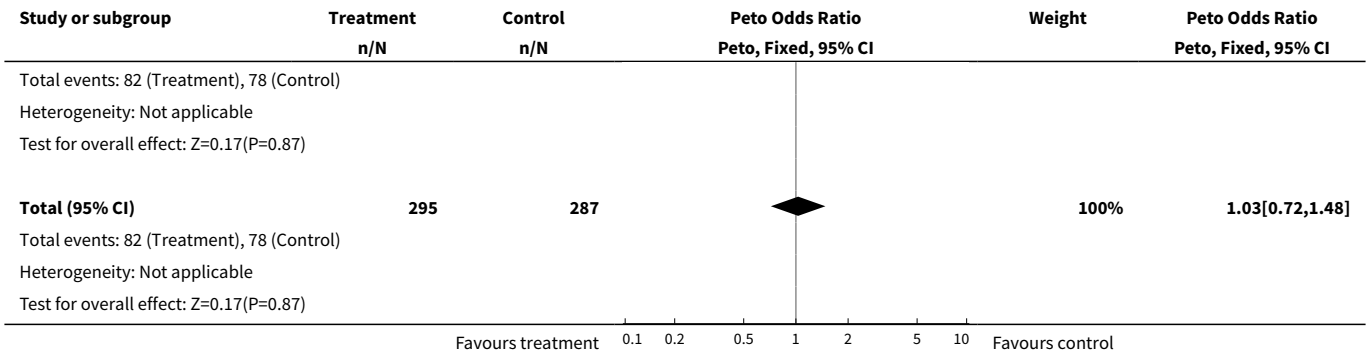


Analysis 2.2. Comparison 2 Intervention versus control: history of stroke, Outcome 2 All cause mortality, including sudden deaths.



Analysis 2.3. Comparison 2 Intervention versus control: history of stroke, Outcome 3 Serious vascular events.





APPENDICES

Appendix 1. MEDLINE search strategy

1 exp Cerebrovascular disorders/
2 stroke$.tw.
3 (cerebrovascular$ or cerebral vascular or CVA$).tw.
4 (cerebral or cerebellar or brain$ or vertebrobasilar).tw.
5 (infarct$ or isch?emi$ or thrombo$ or emboli$).tw.
6 4 and 5
7 (cerebral or intracerebral or intracranial or parenchymal).tw.
8 (brain or intraventricular or brainstem or cerebellar).tw.
9 (infratentorial or supratentorial or subarachnoid).tw.
10 7 or 8 or 9
11 (haemorrhage or hemorrhage or haematoma or hematoma).tw.
12 (bleeding or aneurysm).tw.
13 11 or 12
14 10 and 13
15 transient isch?emic attack$.tw.
16 1 or 2 or 3 or 6 or 14 or 15
17 exp Hypercholesterolemia/dt [Drug Therapy]
18 exp Hyperlipidemia/dt [Drug Therapy]
19 17 or 18
20 exp Antilipemic agents/
21 exp Anion exchange resins/
22 cholestyramine.tw.
23 colestipol.tw.
24 20 or 21 or 22 or 23
25 clofibrate.tw.
26 bezafibrate.tw.
27 ciprofibrate.tw.
28 fenofibrate.tw.
29 gemfibrozil.tw.
30 25 or 26 or 27 or 28 or 29
31 exp Hydroxymethylglutaryl-coa reductase inhibitors/
32 hmg-coa reductase inhibitor$.tw.
33 atorvastatin.tw.
34 fluvastatin.tw.
35 lovastatin.tw.
36 pravastatin.tw.
37 simvastatin.tw.
38 statin$.tw.
39 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38
40 exp Niacin/
41 nicotinic acid.tw.

42 acipimox.tw.
43 40 or 41 or 42
44 exp Fish oils/
45 fish oil$.tw.
46 omega-3 marine triglycerides.tw.
47 exp Dietary fiber/
48 soluble fib##.tw.
49 44 or 45 or 46 or 47 or 48
50 19 or 24 or 30 or 39 or 43 or 49
51 16 and 50
52 limit 51 to human
53 limit 51 to animal
54 52 and 53
55 53 not 54
56 51 not 55

FEEDBACK

Concerns regarding conclusions, 17 July 2019

Summary

Based on our brief analysis of this review and the two main trials included (SPARCL and HPS), we are not sure if the conclusion about statin use post-stroke in this Cochrane review is supported based on the following concerns:

- The authors concluded that statin therapy in patients with a history of stroke significantly reduces subsequent major coronary events. However, major coronary events was not an outcome that was looked at in this review. Perhaps, this conclusion may have been referring to findings of other studies but it does not appear to be a direct conclusion from this review.
- The review pools the stroke outcome data from various trials, which appear to have some variance in their definition of stroke. It may be difficult to determine the exact source of the numbers extracted from the individual trials and whether they best align with the review's definition of stroke. For example, in the primary outcome of all ischemic and hemorrhagic stroke (Analysis 1.1), the definition of stroke in the HPS and SPARCL study is unclear as the incidence of stroke reported in this cochrane analysis was different from the individual sum of the ischemic plus hemorrhagic stroke rates reported in the trials. If it was the individual types of stroke summed up this may inappropriately lead to double-counting some patients who had both an ischemic and a hemorrhagic stroke.
- There may be some discrepancy between the outcomes analyzed in the review and the data the authors used from the individual trials. For example, in the SPARCL trial, any cardiovascular event was defined as "any of the former" (presumably referring to stroke or TIA, major coronary event, major cardiovascular event, any coronary event and revascularization) "plus clinically significant peripheral vascular disease." This data was used for the serious vascular event analysis (Analysis 1.3) by the cochrane review authors which they defined as non-fatal stroke, non-fatal myocardial infarction and vascular death.
- Data appears to be missing for outcome 2 All-cause mortality (Analysis 1.2) in this review. Only data from the SPARCL trial was included. The original HPS study contained all-cause mortality outcome data but this was not published for the stroke subgroup. The cochrane review authors may have benefited from contacting the study investigators for this information to provide a more comprehensive analysis of this outcome.
- It is unclear whether this review encompasses all studies regarding this topic as the results of the search strategy and reasons for excluding studies were not included.
- The risk of bias assessment should be re-evaluated and an update may be warranted to align with current cochrane review standards.

(Feedback received: 13 November 2018)

Reply

None received

Contributors

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WHAT'S NEW

Date	Event	Description
17 July 2019	Feedback has been incorporated	Feedback incorporated

HISTORY

Protocol first published: Issue 2, 2000
Review first published: Issue 3, 2002

Date	Event	Description
17 December 2008	New search has been performed	The literature searches have been updated to December 2008 and three new trials have been included, giving a total of eight included studies involving approximately 10,000 participants.
17 December 2008	New citation required and conclusions have changed	With the addition of three included studies (FASTER; HPS; SPARCL), there is now evidence of a reduction in subsequent serious vascular events from statin therapy in patients with a history of ischaemic stroke or transient ischaemic attack.
27 August 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

BN Manktelow: writing of review, literature search, data extraction, data analysis.
JF Potter: writing of review, data extraction.

DECLARATIONS OF INTEREST

JF Potter has received honoraria from MSD, Sanofi and Boehringer Ingelheim for attending Advisory Boards or giving lectures at meetings sponsored by these companies.

INDEX TERMS

Medical Subject Headings (MeSH)

Cause of Death; Coronary Disease [prevention & control]; Hypercholesterolemia [*drug therapy]; Hypolipidemic Agents [*therapeutic use]; Ischemic Attack, Transient [complications]; Randomized Controlled Trials as Topic; Secondary Prevention; Stroke [*prevention & control]

MeSH check words

Humans