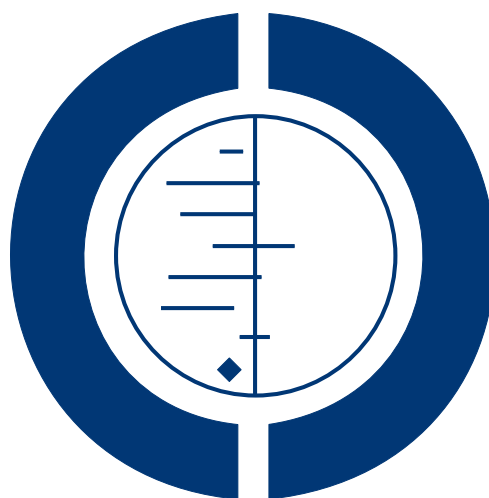


HMG CoA reductase inhibitors (statins) for dialysis patients (Review)

Navaneethan SD, Shrivastava R



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[Intervention Review]

HMG CoA reductase inhibitors (statins) for dialysis patients

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ABSTRACT

Background

Cardiovascular disease accounts for more than half the number of deaths among dialysis patients. The role of HMG CoA reductase inhibitors (statins) in the treatment of hyperlipidemia in dialysis patients is unclear and their safety has not been established.

Objectives

To assess the benefits and harms of statins in peritoneal dialysis (PD) and hemodialysis patients (HD).

Search strategy

We searched MEDLINE (1966-July 2003), EMBASE (1980-July 2003), the Cochrane Central Register of Controlled trials (CENTRAL, in *The Cochrane Library* - issue 2, 2004), the Cochrane Renal Group's specialized register (April 2004) and handsearched reference lists of textbooks, articles and scientific proceedings.

Selection criteria

Randomized controlled trials (RCTs) and quasi-RCTs comparing statins with placebo, no treatment or other statins in dialysis patients.

Data collection and analysis

Two reviewers independently assessed trial quality and extracted data. Statistical analyses were performed using the random effects model after testing for heterogeneity. The results were expressed as mean difference (MD) for continuous outcomes and risk ratio (RR) for dichotomous outcomes with 95% confidence intervals (CI).

Main results

Six studies involving 357 participants were identified - three studies had both continuous ambulatory peritoneal dialysis (CAPD) and HD participants, two included only HD participants and one study only included CAPD participants. Studies were all of short duration and morbidity and mortality were not assessed. Average total cholesterol decreased significantly with statins compared to placebo in all dialysis patients (MD -53.70 mg/dL (1.40 mmol/L), 95% CI -66.95 to -40.54). Similarly, average LDL cholesterol decreased significantly with statins in comparison to placebo in all patients (MD -55.40 mg/dL (1.44 mmol/L), 95% CI -69.90 to -40.90) as did average triglycerides (-33.72 mg/dL (0.37 mmol/L), 95% CI -54.16 to -13.28). There was a significant increase in average HDL cholesterol levels (MD 4.84 mg/dL (0.13 mmol/L), 95% CI 0.28 to 9.40) with statins compared to placebo in HD but not in CAPD patients. One trial compared statins to the hypolipidemic agent probucol and found no significant differences between the two treatment groups.

HMG CoA reductase inhibitors (statins) for dialysis patients (Review)

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Authors' conclusions

Statins used for 12 weeks decreased cholesterol levels in dialysis patients similar to the general population. Included studies were of short duration and therefore the efficacy of statins in decreasing the cardiovascular, cerebrovascular events and mortality rates is still unclear. The safety of statins needs to be addressed in the current ongoing clinical trials.

PLAIN LANGUAGE SUMMARY

Statins reduce total cholesterol and triglycerides in dialysis patients to a level similar to the general population

Dialysis patients are at high risk of heart disease and have high cholesterol levels. Statins have been shown to decrease cholesterol levels and mortality in the general population. The aim of this review was to see if a similar effect could be shown in dialysis patients. This review showed that statins decreased total cholesterol and triglyceride levels to a level similar to that seen in the general population. Their long-term efficacy in decreasing the death rates and their side effect profile in dialysis patients still needs to be studied.

BACKGROUND

By the end of year 2001, the United States had a prevalence of 1400 end-stage renal disease (ESRD) patients per million population (total 300,000 patients), and 22.8 billion US dollars were spent on treatment for dialysis and kidney transplant patients. The prevalence of ESRD has increased throughout the world with an increase in the number undergoing dialysis. For instance, from 1998-2001 there was an 85% increase in the prevalence in Thailand, 25% increase in Poland, and 19% increase in Russia (USRDS 2003). Despite the large amount being spent on treating ESRD, the number of deaths has increased from nearly 40,000 deaths/year in 1992 to 70,000 deaths/year in 2000 in United States alone (USRDS 2003). Cardiovascular disease accounts for more than 50% of these deaths (Wanner 1991; USRDS 2003). Dialysis patients with concomitant cardiovascular disease have a higher all-cause mortality compared to the general population. Prevalence of traditional cardiovascular risk factors like diabetes and hypertension are also higher in the ESRD patients when compared to the general population. In the study by Longenecker, based on these traditional risk factors, the projected 5-year atherosclerotic cardiovascular disease risk based on Framingham Risk Equation was 13% in ESRD patients when compared to 6% in the general population (Longenecker 2002). The incidence of acute myocardial infarction among diabetic patients increases from 75/1000 patient-year to 129/1000 patient-year by the fourth year. Also the use of dialytic modalities varies significantly worldwide. Australia and New Zealand have the highest percentage (40-50%) of patients on continuous ambulatory peritoneal dialysis/continuous cyclic peritoneal dialysis (CAPD/CCPD) (ANZDATA 2003), whereas 80% of US dialysis patients undergo hemodialysis (HD). This may also influence the cardiovascular outcomes (USRDS 2003).

The primary lipid abnormality in both HD and CAPD patients is hypertriglyceridemia. This is due to the decreased activity of a lipoprotein lipase caused by the presence of a lipoprotein lipase inhibitor and reduction in apo-C-II activity (Senti 1992). There is also a mildly elevated LDL cholesterol level with a marked predominance of highly atherogenic small dense LDL particles in these patients. Low HDL cholesterol with a resultant increase in the LDL/HDL ratio and elevated lipoprotein (a) contributes to the atherosclerotic complications in HD patients (Cheung 1993; Cressman 1992). CAPD patients have more atherogenic lipid profile than HD patients. CAPD patients have significantly lower HDL cholesterol, increased LDL/HDL ratio, and have higher lipoprotein (a) levels due to the loss of large amounts of proteins in the dialysate fluid (Kronenberg 1995; Siamopoulos 1995). Also, CAPD patients have higher total cholesterol due to absorption of glucose from the dialysate solution contributing to the enhanced atherosclerosis in these patients (Appel 1991).

Numerous treatment modalities have been tried in the dialysis population including dietary therapy, high-flux membranes in HD patients and hypolipidemic drug therapy. Dietary modification is the initial treatment for the hypercholesterolemic patients in the general population and has also been shown to be effective in reducing the cholesterol levels in dialysis patients. However dietary manipulation in these patients may be difficult as they have complex, pre-existing dietary requirements related to dialysis. For patients on HD, reducing the total fat intake to less than 40% of total energy is difficult as it may result in decreased overall energy intake. Compliance is also a major issue. Thus dietary therapy alone is usually insufficient to achieve near normal lipid levels, necessitating pharmacotherapy (Saltissi 2001). The use of high-flux membranes in HD patients improves the lipid abnormalities

comparable to the extent with dietary treatment but not to the extent as hypolipidemic drugs (Blankestijn 1995; House 1998).

HMG CoA reductase inhibitors (statins) have been shown to be effective in both primary and secondary prevention of cardiovascular events in high-risk patients in the general population (NCEP 2001). They reduce newly synthesized serum cholesterol ester transfer activity, lecithin, cholesterol acetyltransferase (LCAT) activity, and serum LDL, IDL, lipoprotein, and apolipoprotein concentrations and may increase HDL cholesterol levels (Wanner 1991; PERFECT Study 1997). A recent cohort study (United States Renal Data System Morbidity and Mortality Study wave 2 (USRDS DMMS-2)), concluded that statin use was associated with reduced cardiovascular and total deaths in dialysis patients (Seliger 2002). Numerous clinical trials have analyzed their safety and efficacy in reducing the serum cholesterol to or near to acceptable levels in HD and CAPD patients (Harris 2002; Li 1993; Nishikawa 1999; Saltissi 2002; Wanner 1991). A literature search revealed a meta-analysis conducted in 1995 that analyzed the efficacy of various treatment modalities including statins in pre-dialysis, dialysis and transplant patients (Massy 1995). This meta-analysis included non-randomized controlled trials (RCTs) and included studies using different cut-off values for the serum cholesterol levels, and many were undertaken before the introduction of Adult Treatment Panel III guidelines for hyperlipidemia (NCEP 2001). Most of the RCTs analyzing the efficacy of statins in dialysis patients were done in the past 10 years. In addition, the impact on mortality and safety were not assessed. Therefore, a systematic review was needed to analyze whether statins help to decrease cholesterol levels in dialysis patients and decrease the cardiovascular, cerebrovascular events and mortality rates in these patients without significant adverse effects.

OBJECTIVES

This review aimed to look at the benefits (reduction in the cholesterol levels, all cause mortality, cardiovascular and cerebrovascular, mortality, cardiovascular and cerebrovascular events) and harms (elevated liver enzymes, rhabdomyolysis) of statins in dialysis patients.

METHODS

Criteria for considering studies for this review

Types of studies

All RCTs and quasi-RCTs of at least 12 weeks duration looking at benefits and harms of statins in dialysis patients. The first period of randomized crossover studies was to be included.

Types of participants

Inclusion criteria

All diabetic and non-diabetic ESRD patients, more than 18 years of age, undergoing dialysis (HD or peritoneal dialysis (PD)) for at least six months regardless of their baseline cholesterol level.

Exclusion criteria

Patients with active liver disease or impaired liver function, elevated creatine phosphokinase, on multiple lipid lowering agents and on other medications that might interfere with statins.

Types of interventions

Studies analyzing the use of statins in dialysis patients compared to a placebo or no drug treatment for at least three months (end of treatment values), studies comparing statins and other lipid lowering agents for at least three months and the studies comparing different statins in dialysis patients were considered for inclusion.

Types of outcome measures

1. Effect on serum total cholesterol, LDL cholesterol, HDL cholesterol, triglyceride levels and liver function tests (LFT).
2. All cause, cardiovascular, and cerebrovascular mortality.
3. Cardiovascular and cerebrovascular event rates (non-fatal myocardial infarction (MI) including revascularization rates, stroke).
4. Adverse events: elevated liver enzymes, creatine phosphokinase levels or rhabdomyolysis, withdrawal rates.

Search methods for identification of studies

Electronic searches

Relevant trials were obtained from the following sources (see additional Table 1 - *Electronic search strategies*):

1. The Cochrane Renal Group's specialized register of RCTs for any "New" records not yet incorporated in the specialized register (last search April 2004)
2. Cochrane Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library*, Issue 2, 2004
3. MEDLINE and Pre-MEDLINE 1966 - July 2003 - to ensure all trials have been identified.
4. EMBASE 1980 - July 2003 - to ensure all trials have been identified

This was combined with the Cochrane highly sensitive search strategy for identifying RCTs in MEDLINE (Dickersin 1994), and

a similar strategy for EMBASE (Lefebvre 1996). Please see the Cochrane Renal Group Module for details of these strategies.

Searching other resources

1. Reference lists of nephrology textbooks, review articles and relevant trials.
2. Reference lists of abstracts from nephrology scientific meetings (ASN, EDTA, World Congress of Nephrology, Asian Pacific Congress of Nephrology).

Data collection and analysis

The reviewers (SN, RS) screened all abstracts obtained through the MEDLINE, EMBASE, Renal Group Specialized register and CENTRAL independently. Studies relevant to dialysis and hypercholesterolemic drugs were identified. Studies that might include relevant data or information on trials involving HMG Co-A reductase inhibitors were retained initially. Full texts of these studies were obtained as needed to determine whether the studies were eligible for the review. Studies published in non-English language journals were translated before assessment for inclusion. Reviewers (SN, RS) independently extracted data from the eligible studies using standard data extraction forms. Where more than one publication of one trial existed, only the publication with the most complete data was included. Any further information required from the original author was requested and any relevant information obtained was included in the review. Disagreements among the reviewers (SN, RS) were resolved in consultation with Cochrane Renal Group editorial office.

Study quality

The quality of studies included in the review was assessed independently by (SN) and (RS) without blinding to authorship or journal using the checklist developed for the Cochrane Renal Group. The quality items assessed were allocation concealment, intention-to-treat analysis, completeness to follow-up and blinding of investigators, participants and outcome assessors.

Quality checklist

Allocation concealment

- *Adequate* (A): Randomization method described that would not allow investigator/participant to know or influence intervention group before eligible participant entered in the study
- *Unclear* (B): Randomization stated but no information on method used is available

- *Inadequate* (C): Method of randomisation used such as alternate medical record numbers or unsealed envelopes; any information in the study that indicated that investigators or participants could influence intervention group

Blinding

- *Blinding of investigators*: Yes/No/not stated
- *Blinding of participants*: Yes/No/not stated
- *Blinding of outcome assessor*: Yes/No/not stated
- *Blinding of data analysis*: Yes/No/not stated

The above are considered not blinded if the treatment group can be identified in >20% of participants because of the side effects of treatment.

Intention-to-treat analysis

- Yes: Specifically reported by authors that intention-to-treat analysis was undertaken and this was confirmed on study assessment.
- No: Not reported and lack of intention-to-treat analysis confirmed on study assessment. (Patients who were randomised were not included in the analysis because they did not receive the study intervention, they withdrew from the study or were not included because of protocol violation)
- Not stated

Completeness to follow-up

Percentage of participants excluded or lost to follow-up.

Statistical assessment

The studies were combined quantitatively when it was appropriate. Meta-analyses were performed to analyze the efficacy of statins in all dialysis patients, and HD and PD patients separately. Separate analyses were done for total cholesterol, LDL cholesterol, HDL cholesterol, and triglyceride levels. For dichotomous outcomes (all-cause mortality, cardiovascular or cerebrovascular mortality), results were to be expressed as risk ratio (RR) with 95% confidence intervals (CI). Where continuous scales of measurement were used to assess the effects of treatment (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides), the mean difference (MD) by comparing the end of treatment values was used. Data was pooled using the random effects model. Heterogeneity among the included trials was analyzed using chi-square testing and the I² test. A value of >50% in I² testing indicates substantial heterogeneity among the included studies.

Subgroup analysis was planned to explore the possible sources of heterogeneity. It was planned to assess the efficacy of statins in decreasing cholesterol at different doses and the incidence of adverse events at various doses. We also planned to analyze the efficacy of

statins at different treatment duration (e.g. at 12 weeks, 6 months, 1 year) that might cause heterogeneity, however these could not be done as there were only a few studies. Adverse effects, especially elevated LFT and withdrawal rates were tabulated and assessed with descriptive techniques, as they were likely to be different for the various agents used. Where possible, the risk ratio (RR) with 95% CI was calculated for elevated LFT and withdrawal rates, either compared to no treatment or to another agent.

It was planned that if sufficient RCTs were identified, an attempt would be made to examine for publication bias using a funnel plot (Egger 1997).

RESULTS

Description of studies

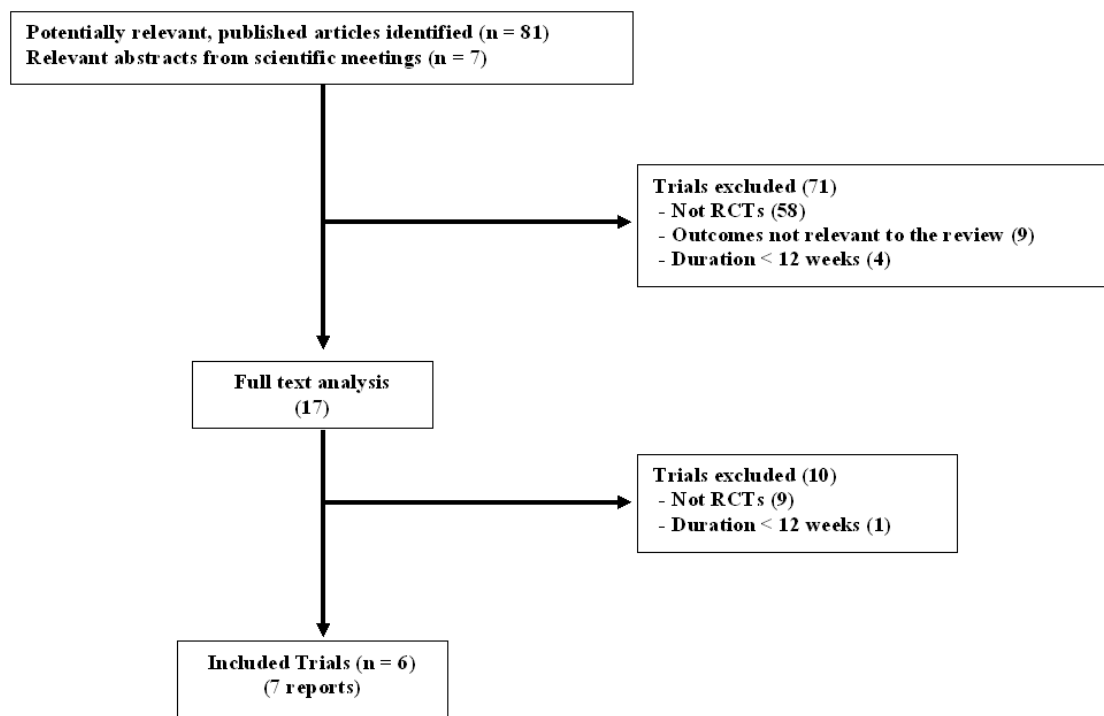
See: [Characteristics of included studies](#); [Characteristics of excluded studies](#); [Characteristics of ongoing studies](#).

The combined search of MEDLINE, EMBASE, the Cochrane Renal Group's specialized register and CENTRAL identified 81 articles of which 66 were excluded. Seven abstracts were identified from scientific proceedings and five were excluded. The major reasons for exclusion were:

1. studies were not randomized,
2. RCTs of less than 12 weeks duration,
3. RCTs with irrelevant outcomes to this analysis.

Seventeen relevant articles were identified after reviewing the abstracts (Akciek 1996; Diepeveen 2001; Fiorini 1994; Harris 2002; Hufnagel 2000; Li 1992; Lins 2002; Nishizawa 1995; Nishikawa 1999; Malyszko 2002; PERFECT Study 1997 (2 reports); Saltissi 2002; Tani 1998; Wanner 1991; Wanner 1992; Zhu 2000). Full text assessment of these 17 articles (along with information from the authors of abstracts of scientific proceedings) resulted in six eligible studies (Diepeveen 2001; Fiorini 1994; Harris 2002; Lins 2002; PERFECT Study 1997; Saltissi 2002). A total of six studies were finally included in this meta-analysis (Figure 1).

Figure 1.



Of these six included studies, three studies included patients on both HD and PD (Diepeveen 2001; PERFECT Study 1997; Saltissi 2002). One study included PD patients alone (Harris 2002) and two studies included HD patients alone (Fiorini 1994; Lins 2002). All six trials varied in size, type of statin, duration of treatment and drug dosage. In one trial the participants had dietary intervention prior to enrolment in the study (Saltissi 2002) and only one trial included patients with normal cholesterol (Fiorini 1994).

Authors of two published studies and three abstracts were contacted for additional information and three authors replied to our requests. All the studies were designed to analyze the decrease in the lipid parameters with statins. None of these studies looked at the overall mortality, cardiovascular and cerebrovascular events and mortality that we intended to analyze.

Risk of bias in included studies

Trial quality varied among the studies (Additional Table 2 - *Quality assessment of included trials*)

Allocation concealment

Method of randomisation and allocation concealment was adequate in one study (PERFECT Study 1997) and unclear in the remaining five.

Blinding

One study blinded both the investigators and participants (PERFECT Study 1997). It is unclear if the other five studies blinded the participants, investigators or outcome assessors.

Intention-to-treat analysis

Three studies were analyzed on an intention-to-treat basis (Harris 2002; PERFECT Study 1997; Saltissi 2002).

Completeness of follow-up

There were no dropouts or loss to follow-up in one study (Fiorini 1994) and this was not mentioned in two (Diepeveen 2001; Lins 2002;). There was a 15.9% (13/82) drop out rate in the statin group and 11.7% (11/94) dropout rate in the placebo group in the study by Harris 2002. Similarly, Saltissi 2002 had a 15.7% drop out rate in both statin and placebo group. PERFECT Study 1997 had a drop out rate of 26% in the statin group versus 17% in the placebo group.

Effects of interventions

Statins versus placebo

Dialysis patients - combined hemodialysis and peritoneal dialysis (five studies)

Total cholesterol

Average total cholesterol decreased significantly with statins compared to placebo and there was significant heterogeneity between these trials (Analysis 1.1: five studies, 357 patients; MDAnalysis . -53.74 mg/dL (1.40 mmol/L), 95% CI -66.95 to -40.54; $\chi^2 = 13.34$, $P = 0.04$, $I^2 = 55.0\%$).

LDL cholesterol

There was a significant decrease in average LDL cholesterol level with statins when compared to placebo and there was significant heterogeneity between these trials (Analysis 1.2: five studies, 357 patients; MDAnalysis . -55.40 mg/dL (1.44 mmol/L), 95% CI -69.90 to -40.90; $\chi^2 = 21.32$, $P = 0.002$, $I^2 = 71.9\%$).

HDL cholesterol

The average HDL cholesterol did not increase significantly with statins in comparison to placebo and there was no significant heterogeneity between these trials (Analysis 1.3: five studies, 357 patients; MDAnalysis . 2.19 mg/dL (0.06 mmol/L), 95% CI -0.30 to 4.69; $\chi^2 = 3.92$, $P = 0.69$, $I^2 = 0\%$).

Triglycerides

Average triglycerides decreased significantly with statins in comparison to placebo and there was no significant heterogeneity between these trials (Analysis 1.4: five studies, 357 patients; MDAnalysis . -33.72 mg/dL (0.37 mmol/L), 95% CI -54.16 to -13.28; $\chi^2 = 3.92$, $P = 0.69$, $I^2 = 0\%$).

Hemodialysis patients (three studies)

Total cholesterol

Average total cholesterol decreased significantly with statins compared to placebo and there was no significant heterogeneity between these trials (Analysis 1.1.2: three studies, 86 patients; MDAnalysis . -53.44 mg/dL (1.38 mmol/L), 95% CI -77.90 to -28.98; $\chi^2 = 4.04$, $P = 0.13$, $I^2 = 50.5\%$).

LDL cholesterol

There was a significant decrease in average LDL cholesterol level with statins compared to placebo and there was no significant heterogeneity between these trials (Analysis 1.2.2: three studies, 86 patients; MDAnalysis . -47.29 mg/dL (1.22 mmol/L), 95% CI -62.01 to -32.57, $\chi^2 = 1.18$, $P = 0.56$, $I^2 = 0\%$).

HDL cholesterol

The average HDL cholesterol increased significantly with statins in comparison to placebo and there was no significant heterogeneity between these trials (Analysis 1.3.2: three studies, 86 patients;

MDAnalysis . 4.84 mg/dL (0.13 mmol/L), 95% CI 0.28 to 9.40; $\chi^2 = 1.36$, $P = 0.51$, $I^2 = 0\%$).

Triglycerides

Average triglycerides decreased with statins in comparison to placebo, however this was not significant (Analysis 1.4.2; three studies, 86 patients; MDAnalysis . -32.48 mg/dL (0.32 mmol/L), 95% CI -66.73 to 1.76; $\chi^2 = 0.88$, $P = 0.64$, $I^2 = 0\%$).

Peritoneal dialysis patients (three studies - CAPD patients)

Total cholesterol

Average total cholesterol decreased significantly with statins compared to placebo and there was significant heterogeneity between these trials (Analysis 1.1.1; three studies, 164 patients; MDAnalysis . -64.16 mg/dL (1.66 mmol/L), 95% CI -86.81 to -41.51; $\chi^2 = 5.16$, $P = 0.08$, $I^2 = 61.2\%$).

LDL cholesterol

There was a significant decrease in average LDL cholesterol level with statins in comparison to placebo and there was significant heterogeneity between these trials (Analysis 1.2.1; three studies, 164 patients; MDAnalysis . -76.44 mg/dL (1.98 mmol/L), 95% CI -106.12 to -46.77; $\chi^2 = 10.49$, $P = 0.005$, $I^2 = 80.9\%$).

HDL cholesterol

The average HDL cholesterol did not increase significantly with statins in comparison to placebo and there was no significant heterogeneity between these trials (Analysis 1.3.1; three studies, 164 patients; MDAnalysis . -1.17 mg/dL (0.03 mmol/L), 95% CI -9.21 to 6.87; $\chi^2 = 3.68$, $P = 0.16$, $I^2 = 45.7\%$).

Triglycerides

Average triglycerides decreased significantly with statins in comparison to placebo and there was no significant heterogeneity between these trials (Analysis 1.4.1; three studies, 164 patients; MDAnalysis . -44.11 mg/dL (0.49 mmol/L), 95% CI -75.32 to -12.90; $\chi^2 = 1.92$, $P = 0.38$, $I^2 = 0\%$).

Statins versus other hypolipidemic agents

We found only one study comparing statins with other hypolipidemic agents (Fiorini 1994). This study showed no significant difference in total cholesterol, LDL cholesterol, HDL cholesterol or triglycerides with the use of statins compared to probucol.

Adverse events

Withdrawal rates and elevated LFT were the only adverse events reported (Harris 2002; PERFECT Study 1997; Saltissi 2002).

There were no significant differences in withdrawal rate (Analysis 3.1) or elevated LFT (Analysis 3.2) for CAPD or HD patients.

Quality of life

None of the studies reported quality of life measures.

Publication bias

We were not able to evaluate publication bias with a funnel plot or other methods due to the small number of trials.

DISCUSSION

We found that statins decreased average total cholesterol by 54 mg/dL (1.40 mmol/L) in dialysis patients (CAPD 64 mg/dL (1.66 mmol/L); HD 53 mg/dL (1.38 mmol/L)). LDL cholesterol was similarly reduced by an average of 55 mg/dL (1.44 mmol/L) (CAPD 76 mg/dL (1.98 mmol/L); HD 47 mg/dL (1.22 mmol/L)). In dialysis patients triglycerides were significantly decreased by 34 mg/dL (0.37 mmol/L). This decrease was significant in CAPD patients (CAPD 44 mg/dL (0.49 mmol/L) but not in HD patients. There was significant increase in HDL cholesterol in HD patients (4.84 mg/dL (0.13 mmol/L) but not in CAPD patients (1.17 mg/dL (0.03 mmol/L)). None of these studies assessed the role of statin potency to decrease cardiovascular events, cerebrovascular events and mortality which are the important outcomes, and ones we had intended to analyze. Also the safety profile of statins in dialysis patients is not well studied. Statins are widely used in the primary and secondary prevention of coronary artery disease in the general population and have been shown to decrease total cholesterol by an average 40-60 mg/dL and LDL cholesterol by 35-50 mg/dL with an increase of HDL by 2-5 mg/dL in the general population (Downs 1998; Shepherd 1995). This decrease in total cholesterol and LDL cholesterol resulted in a reduction of cardiovascular and cerebrovascular events (4S study 1994; Downs 1998; LIPID study 1998). Thus this review supports the widely held belief that statins would have a similar effect in decreasing total cholesterol levels in dialysis patients, even though their long-term utility is still not established.

Dosing of statins in chronic kidney disease and the general population is similar, as they do not undergo renal excretion (Appel 2002; Stern 1997). Thus, reduction of total cholesterol levels in patients on dialysis may be similar to those of non-uremic patients. Hypertriglyceridemia is the major lipid abnormality in ESRD patients and it increases the highly atherogenic, small, dense LDL particles thereby increasing the cardiovascular risk (Quaschnig 1999). Hypertriglyceridemia has also been shown to be a significant risk factor for coronary artery disease. Our meta-analysis showed that

statins produced significant reduction in triglyceride levels in dialysis patients in general, and CAPD patients in particular. Thus statins may have an additional benefit in those patients on CAPD. In addition, elevated LDL and total cholesterol levels, low HDL cholesterol and the resultant increased LDL/HDL ratio are other contributing factors to the atherosclerotic complications in dialysis patients (Cheung 1993; Cressman 1992). This meta-analysis showed that statins significantly reduced LDL cholesterol in both HD and CAPD patients. The effect on HDL was only statistically significant in HD patients. Whether the decrease in triglycerides, total cholesterol, and LDL cholesterol persisted, and whether the decrease translated into reduced morbidity and mortality remains unanswered.

Exact decreases in cholesterol levels with different doses could not be assessed as the studies were of different duration and used different statins with different dosage. However this meta-analysis showed a statistically significant decrease in cholesterol level with the use of statins for 12 weeks in both CAPD and HD patients. A low baseline cholesterol level in the presence of low albumin has been described as a predictor of high cardiovascular mortality. Hypercholesterolemia in normo-albuminemic patients have higher cardiovascular mortality rates, similar to the general population (Iseki 2002; Liu 2004). We were not able to analyze the efficacy of statins separately in normo-albuminemic and hypoalbuminemic patients due to insufficient data.

Linking evidence to practice: Various studies have shown that LDL cholesterol levels remain >130 mg/dL in >50% of the dialysis population and are considered to be having coronary artery disease equivalents. However statins were prescribed to only 10-20% of patients (Harris 2002; Longenecker 2002; Seliger 2002). Most of these studies were done prior to 2001. The prescribing pattern of statins has changed and the rates might have increased in the past few years. Based on a data analysis from USRDS, the use of statins decreased cardiovascular-specific death and total mortality in dialysis patients (Seliger 2002). NKF-KDOQI guideline recommends treatment with statins in dialysis patients with LDL >100 mg/dL after therapeutic lifestyle changes and diet modification (K/DOQI 2003). These guidelines are based on the best available evidence about statins in the general population, a few retrospective studies and data analysis in dialysis patients due to the lack of RCTs in the dialysis population. The pleiotropic effects of statins have been established and shown to play a major role in reducing mortality in the general population (Farmer 2000). Thus the role of statins in hyperlipidemic patients has been justified in dialysis patients and the use of statins is increasing. Ongoing studies (4D Study 2004; AURORA Study 2003; HARP Study 1999; SHARP Study 2003) are designed to analyze the efficacy of statins in decreasing the mortality in dialysis patients. Results of these studies are expected in next few years and might give a better understanding to the role of statins in this population, including their safety.

Strengths and limitations: This is the first systematic review analyzing the efficacy of statins in dialysis patients. Only RCTs were included to increase the quality of evidence. The sample size of included studies was small and the studies were of short duration. Adverse event rates were not reported in all studies and a reasonable analysis could not be done. Efficacy of various doses of statins is unclear. The results should be interpreted in the light of these limitations.

AUTHORS' CONCLUSIONS

Implications for practice

Statins decreased cholesterol levels in dialysis patients to levels similar to those seen in the general population when treated for 12 weeks. The impact of this decrease on mortality rates amongst patients on dialysis is unclear which is key to the treatment of hyperlipidemia in these patients. Safety of statins in these patients could not be determined. This meta-analysis validates the use of statins in hyperlipidemic dialysis patients with appropriate monitoring of adverse effects until the results of ongoing RCTs are available and can be incorporated into this review.

Implications for research

Well-designed multi-center RCTs are needed to analyze the efficacy of statins in decreasing mortality and morbidity (all-cause, cardiovascular, cerebrovascular) rather than just looking at the efficacy in decreasing cholesterol levels. These studies should include patients with and without cardiovascular or cerebrovascular disease, and with and without elevated cholesterol levels and analyze the benefits of statins. Both HD and PD patients should be included and analyzed in subgroups. Studies should be of longer duration and should address the safety of statins in dialysis patients. These studies should also try to analyze the cut-off level for LDL cholesterol levels that might decrease mortality rates in dialysis patients. This might be different for dialysis patients from general population.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Diepeveen 2001

Methods	Country: Netherlands Randomised: Yes Method of allocation: Unclear Withdrawals: Unclear Intention to treat: Unknown Publication Type: Abstract in scientific meeting	
Participants	Number randomised: 23 HD and 25 PD patients Age: HD-53(18) yr, PD-47(14) yr Sex: Both Inclusion criteria: Unknown Exclusion criteria: Unknown	
Interventions	23 HD and 25 PD patients were randomised to receive A: Alfa-tocoferol+atorvastatin B:Alfa tocoferol+placebo C: Atrovastatin +placebo D: Placebo + Placebo. Study Duration: 12 weeks	
Outcomes	1 .Lipid parameters (TC, LDL, HDL, TG)	
Notes	Study included 4 arms and we compared C and D.(see interventions)	
Risk of bias		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Fiorini 1994

Methods	Country: Italy Randomised: Yes Method of randomisation: Unclear intention to treat: unclear	
Participants	Number randomised:12 Age:Exp 64(14)yr; Placebo 62.8(10) Sex: Both Inclusion criteria: Patients on HD for at least 6 months,hypertriglyceridemia,normal or increased cholesterol's levels, normal or reduced HDL level:LDL/HDL ratio was raised. Exclusion criteria: Diabets Mellitus,liver failure,therapy with beta-blockers,thiazides,androgens and lipid lowering drugs	

Fiorini 1994 (Continued)

Interventions	Exp: Simvastatin 20mg/day Control: Probucol Duration:6 months	
Outcomes	1. Lipid parameters (TC, TG, LDL, HDL, LDL/HDL, Apo-A) 2. Liver function tests, CK levels	
Notes		
Risk of bias		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Harris 2002

Methods	Country: UK Randomised: Yes Method of allocation: Unclear Withdrawals: Numbers and reason described Intention to treat: yes	
Participants	Number Randomised:116 CAPD patients. (Exp-82, Placebo-95) Age: Exp:56.7(15.4) yr; Placebo: 57.5(13.5) yr Sex: Both Inclusion Criteria: CAPD or APD for at least 3 months, TC>200mg/dl, LDL >135 mg/dl,dyslipidemia uncontrolled by other lipid lowering therapy for at least 4 weeks. Exclusion criteria: Active liver disease or Increased ALT or AST (>3 X ULN), concurrent therapy with immunosuppressants, uncontrolled DM, patient receiving other lipid lowering agents, patients with history of PTCA, CABG within 3 months, alcohol abuse, clinical evidence of inflammatory muscle disease and total cholesterol >310 mg/dL)	
Interventions	Exp: Atorvastatin 10mg and dose increased to 40 mg as needed to achieve LDL<135 mg/dL Duration:16 weeks	
Outcomes	1.Lipid parameters (TC, LDL, HDL, TG) 2.Clinical adverse events along with ALT, AST, CK monitoring	
Notes		
Risk of bias		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Lins 2002

Methods	Country: Belgium Randomised: Yes Method of randomisation: Unclear Withdrawals: Not reported Intention to Treat: Unknown Publication Type: Abstract in scientific meeting.
Participants	Number Randomised: 42 Hemodialysis patients (Exp 23, Placebo-19) Age: Exp 63.8 (12.3) yr; Placebo 65.2 (9.3) yr Sex: Both Inclusion Criteria: Total cholesterol >210 mg/dl and total TG >500 mg/dl Exclusion criteria: Not mentioned
Interventions	Exp: Atorvastatin forced 4-weekly titration of 10 to 20 and to 40 mg once daily. Study duration: 12 weeks.
Outcomes	1. Lipid parameters (TC, TG, LDL, HDL) and apoproteins (A-I, A-II,B,E,CIII) 2. Adverse events (Specific details unknown)
Notes	Study awaiting publication.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

PERFECT Study 1997

Methods	Country: New Zealand Randomised: 4 Factorial design Method of allocation: code maintained by a person separate to the study Blinding: double blind (patient and investigator) Withdrawals: not stated Intention to treat: Yes Follow-up: 6 months Publication Type: Journal article
Participants	Combined HD and CAPD patients Age: mean (\pm SD) 50 \pm 15 y Sex (M/F): 32/21 Inclusion criteria: Not stated Exclusion criteria: Definite indication for statin or ACEi, known allergy to either drug, planned transplant from LRD in next 12 months, congestive heart failure, severe valve disease, supine systolic BP , 100 mmHg or significant postural hypotension, uncontrolled hypertension, hepatitis B or C positive, AST or ALT > twice upper limit or normal, treatment with cyclosporin or a fibrate, life threatening illness or serious debilitating disease other than CRF

PERFECT Study 1997 (Continued)

Interventions	Statin group - Simvastatin plus placebo enalapril (b) n = 24 10 mg daily Placebo group - Placebo simvastatin plus placebo enalapril (d) n = 29	
Outcomes	1.Lipid parameters (TC, LDL, HDL, TG)	
Notes	Study had four arms a) Simvastatin plus enalapril b) Simvastatin plus placebo enalapril c) Placebo simvastatin plus enalapril d) Placebo simvastatin plus placebo enalapril	
Risk of bias		
Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Saltissi 2002

Methods	Country: Australia Randomised: Yes Method of allocation: Unclear Withdrawals: Number and reason described Intention to treat: Yes
Participants	Number randomised: 34 HD and 23 CAPD patients HD: 22 - Exp drug and 12 Placebo CAPD:16-Exp drug and 7-Placebo Age: HD: Exp 59.5 (13.9)yr ;Placebo 62.8 (9.6) yr CAPD: Exp 55.3 (13.3)yr; Placebo 61.0 (7.6) yr Sex: Both Inclusion Criteria: HD or CAPD for 9 months, Non-HDL >135mg/dl, LDL >116mg/dl, TG <600mg/dl Exclusion Criteria: Impaired hepatic function, elevated CPK, Myocardial insufficiency, uncontrolled diabetes mellitus, active infection, malignancy and treatment with other lipid lowering agents
Interventions	117 patients who met inclusion criteria were treated with Australian National Heart foundation lipid lowering diet for 6 weeks. Patients who did not achieve the desired LDL, TC were randomised in 2:1 fashion. EXP: Simvastatin 5mg and dose was increased to 20 mg as needed to achieve Non-HDL <135 mg/dL Duration:24 weeks
Outcomes	1. Lipid parameters (TC, LDL, HDL, TG, Lp(a), Apo A1). 2. Clinical adverse experiences along with ALT, AST and CK monitoring

Saltissi 2002 (Continued)

Notes		
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Akcicek 1996	Prospective cohort study
Hufnagel 2000	Prospective cohort study
Li 1992	Study duration was less than 12 weeks
Malyszko 2002	Prospective cohort study
Nishikawa 1999	Prospective cohort study
Nishizawa 1995	Prospective cohort study
Tani 1998	Prospective cohort study
Wanner 1991	Prospective cohort study
Wanner 1992	Prospective cohort study
Zhu 2000	Prospective cohort study

Characteristics of ongoing studies [ordered by study ID]

4D Study 2004

Trial name or title	The Determination of cardiovascular endpoints in niDDm Dialysis patients study (4D Study)
Methods	
Participants	Patients on hemodialysis for less than 2 years and with diabetes
Interventions	Atrovastatin 20 mg/day vs placebo

4D Study 2004 (Continued)

Outcomes	Primary outcome:Cardiovascular mortality Secondary outcome:Allcause mortality,non-fatal cardiovascular events,fatal and non-fatal cerebrovascular disease,and the mean percentage change in lipid profile from baseline
Starting date	2004
Contact information	Christoph Wanner, M.D., Department of Medicine,Division of Nephrology,University Clinic,Josef-Schneider-str.2,97080,Wuzburg,Germany
Notes	Webiste: http://www.atorvatrials.nl/inet/atorvatrials/ep/contentView.do?contentType=2&contentId=11859&BV_SessionID=@@@2008980246.1092724318@@@&BV_EngineID=cccfadcmfdgelegcefcfnndfjmdffi.0

AURORA Study 2003

Trial name or title	AURORA: A study to evaluate the use of rosuvastatin in subjects on regular haemodialysis: an assessment of survival and cardiovascular events
Methods	
Participants	2700 subjects will be randomised at approx 190 sites from Australia, Canada and Europe. It is anticipated that 300 patients will be recruited from 20 centres within the UK. It is expected that each centre will randomise between 10-20 patients. Subjects will be selected from Secondary care centres, according to the inclusion and exclusion criteria. This may involve the Investigator/Research Nurse at the site screening medical records to identify potentially suitable subjects. Potentially suitable subjects may also be identified via routine clinics at the hospital
Interventions	Subjects will be randomly assigned to either rosuvastatin treatment (10 mg/day) or placebo with a 1:1 randomisation ratio (ie, 150 placebo controls)
Outcomes	(1) time from randomisation to death from any cause (2) time from randomisation or major cardiovascular event (non-fatal stroke, non-fatal myocardial infarction or cardiovascular death)
Starting date	May 2003
Contact information	Dr Alan Jardine University Department of Medicine and Therapeutics Western Infirmary Glasgow G11 6NT UK Telephone: 0141 211 2000 Fax: 0141 339 2800 Email: a.g.jardine@clinmed.gla.ac.uk
Notes	

HARP Study 1999

Trial name or title	HARP - Heart and Renal Protection pilot study
Methods	A randomised, double-blind 2x2 factorial study assessing the safety and biochemical efficacy of simvastatin and of aspirin in patients with chronic renal impairment
Participants	Patients on hemodialysis, chronic renal failure and transplanted patients
Interventions	1. The biochemical efficacy and safety of simvastatin (20mg daily), with assessment of efficacy from change in serum lipid profile and of safety from markers of muscle and hepatic toxicity respectively; and 2. The safety of aspirin (100mgdaily) in terms of excess bleeding events, mean differences in haematological parameters, and changes in renal function. A further objective is to assess the practicability of the planned screening and follow-up procedures
Outcomes	(i) SIMVASTATIN - efficacy: Mean differences in total-and LDL-cholesterol at 3 months and 12 months after randomisation. Safety: differences in the incidence of CK> 10x upper limit of normal (ULN) and of ALT> 2xULN. Mean differences in CK and ALT. (ii) ASPIRIN - Safety: differences in the incidence of major bleeding episodes, and other bleeding episodes. Differences in incidence of acute gout, and mean differences in serum urate. Mean differences in serum creatinine. Differences in proportion with a doubling of serum creatinine or the need for renal replacement therapy (predialysis only)
Starting date	Start date: 29 March 1999 End date: 26 March 2004
Contact information	Dr Paul Altmann Oxford Renal Unit Churchill Hospital Churchill Drive Headington Oxford OX3 7LJ UK Telephone: 01865 225347 Fax: 01865 225616 Email: Paul.altmann@orh.nhs.uk
Notes	Awaiting publication

SHARP Study 2003

Trial name or title	Study of Heart and Renal protection (SHARP)
Methods	
Participants	The study will include about 9000 patients with Chronic Kidney Disease, of whom around 6000 are intended to be pre-dialysis and 3000 on dialysis at randomisation
Interventions	Simvastatin and ezetimibe versus placebo

SHARP Study 2003 (Continued)

Outcomes	Fatal and non-fatal Cardiac events, Fatal and non-fatal cerebrovascular events or revascularization
Starting date	17 November 2003
Contact information	Dr Richard D'Souza Royal Devon & Exeter Hospital (Wonford) Barrack Road Exeter Devon EX2 5DW UK Telephone: 01392 402587 Fax: 01392 402527 Email: Richard.D'Souza@rdehc-tr.swest.nhs.uk
Notes	

DATA AND ANALYSES

Comparison 1. HMG CoA reductase inhibitors (statins) versus placebo in dialysis patients

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total cholesterol (mg/dL)	5	357	Mean Difference (IV, Random, 95% CI)	-53.74 [-66.95, -40.54]
1.1 Peritoneal dialysis	3	164	Mean Difference (IV, Random, 95% CI)	-64.16 [-86.81, -41.51]
1.2 Hemodialysis	3	86	Mean Difference (IV, Random, 95% CI)	-53.44 [-77.90, -28.98]
1.3 Combined (PD and HD)	1	107	Mean Difference (IV, Random, 95% CI)	-30.77 [-52.09, -9.45]
2 LDL cholesterol (mg/dL)	5	357	Mean Difference (IV, Random, 95% CI)	-55.40 [-69.90, -40.90]
2.1 Peritoneal dialysis	3	164	Mean Difference (IV, Random, 95% CI)	-76.44 [-106.12, -46.77]
2.2 Hemodialysis	3	86	Mean Difference (IV, Random, 95% CI)	-47.29 [-62.01, -32.57]
2.3 Combined (PD and HD)	1	107	Mean Difference (IV, Random, 95% CI)	-30.77 [-47.63, -13.91]
3 HDL cholesterol (mg/dL)	5	357	Mean Difference (IV, Random, 95% CI)	2.19 [-0.30, 4.69]
3.1 Peritoneal dialysis	3	164	Mean Difference (IV, Random, 95% CI)	-1.17 [-9.21, 6.87]
3.2 Hemodialysis	3	86	Mean Difference (IV, Random, 95% CI)	4.84 [0.28, 9.40]
3.3 Combined (PD and HD)	1	107	Mean Difference (IV, Random, 95% CI)	1.93 [-1.27, 5.13]
4 Triglycerides (mg/dL)	5	357	Mean Difference (IV, Random, 95% CI)	-33.72 [-54.16, -13.28]
4.1 Peritoneal dialysis	3	164	Mean Difference (IV, Random, 95% CI)	-44.11 [-75.32, -12.90]
4.2 Hemodialysis	3	86	Mean Difference (IV, Random, 95% CI)	-32.48 [-66.73, 1.76]
4.3 Combined (PD and HD)	1	107	Mean Difference (IV, Random, 95% CI)	-15.01 [-59.12, 29.12]

Comparison 2. HMG CoA reductase inhibitors (statins) versus other hypolipemic agents in dialysis patients

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total cholesterol (mg/dL)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.1 Peritoneal dialysis	0		Mean Difference (IV, Random, 95% CI)	Not estimable
1.2 Hemodialysis	1		Mean Difference (IV, Random, 95% CI)	-11.01 [-48.95, 26.95]
2 LDL cholesterol (mg/dL)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2.1 Peritoneal dialysis	0		Mean Difference (IV, Random, 95% CI)	Not estimable

2.2 Hemodialysis	1	Mean Difference (IV, Random, 95% CI)	-20.01 [-51.87, 11.87]
3 HDL cholesterol (mg/dL)	1	Mean Difference (IV, Random, 95% CI)	Totals not selected
3.1 Peritoneal dialysis	0	Mean Difference (IV, Random, 95% CI)	Not estimable
3.2 Hemodialysis	1	Mean Difference (IV, Random, 95% CI)	5.01 [-2.38, 12.38]
4 Triglycerides (mg/dL)	1	Mean Difference (IV, Random, 95% CI)	Totals not selected
4.1 Peritoneal dialysis	0	Mean Difference (IV, Random, 95% CI)	Not estimable
4.2 Hemodialysis	1	Mean Difference (IV, Random, 95% CI)	91.00 [-5.26, 187.26]

Comparison 3. Adverse event rates in dialysis patients

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Withdrawal rate	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Peritoneal dialysis	2	199	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.07, 13.30]
1.2 Hemodialysis	1	34	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.16, 4.24]
1.3 Combined (PD and HD)	1	107	Risk Ratio (M-H, Random, 95% CI)	1.53 [0.72, 3.22]
2 Elevated liver function test	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Peritoneal dialysis	2	200	Risk Ratio (M-H, Random, 95% CI)	1.26 [0.16, 9.89]
2.2 Hemodialysis	1	34	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.11, 10.83]
2.3 Combined (PD and HD)	1	107	Risk Ratio (M-H, Random, 95% CI)	Not estimable