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Meta-Analysis of Lipid-Lowering Therapy in Maintenance Dialysis Patients

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Key Words
Statin · Cholesterol · Atherosclerosis · Dialysis · Meta-analysis · Ezetimibe · Cardiovascular · Lipid-lowering therapy

Abstract
Background/Aims: The use of lipid-lowering therapy (LLT) in patients on chronic dialysis is contentious. Here we present an aggregate data meta-analysis of randomised controlled trials (RCTs) comparing long-term LLT versus placebo in dialysis patients. ***Method:*** A search of Medline, Google Scholar, COCHRANE database, EMBASE, and cardiovascular and nephrology society proceedings was performed. Criteria for inclusion were RCTs of LLT versus placebo, in which LLT was demonstrated to significantly reduce low-density lipoprotein cholesterol, >12 months of follow-up, and at least one cardiovascular or mortality endpoint in an independently reported dialysis population. Meta-analysis was performed for atherosclerotic cardiovascular events, stroke and mortality using a random-effects method for odds ratio (OR) of risk. ***Results:*** Three studies were included with 7,051 patients (3,541 treatment and 3,510 placebo). Twenty-five percent of the LLT patients suffered an atherosclerotic cardiovascular event versus 27% for placebo. The OR was 0.89 (95% CI: 0.80–0.99, p = 0.04). For stroke (haemorrhagic and non-haemorrhagic combined), the figures were 6.2% (LLT) versus 5.7% (placebo) [OR = 1.11 (95% CI: 0.85–1.46, p = 0.45)]. For all-cause mortality, the figures were 40 versus 42% [OR = 0.97 (95% CI: 0.88–1.06, p = 0.49)]. ***Conclusion:*** There was an overall significant reduction in risk for atherosclerotic cardiovascular events in dialysis patients treated with LLT compared to placebo. There was a numerical but not a statistical reduction in mortality. There was no statistically significant increase in risk of stroke as has been previously reported.

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Introduction

The use of lipid-lowering therapy (LLT) in patients on chronic dialysis is contentious [1–3]. The Study of Heart and Renal Protection (SHARP) suggested benefit, with equal efficacy in chronic kidney disease (CKD) and dialysis patients [4]. This was by way of showing a statistically significant benefit of LLT versus placebo in a combined treatment group of 9,270 dialysis and non-dialysis CKD patients, allied to a non-significant test of heterogeneity between the two sub-populations. Because the cardiovascular risk profiles of CKD and dialysis patients differ [5–9], it can be argued that these two groups should not be evaluated together, irrespective of the findings of SHARP. The German Diabetes and Dialysis Study [Die Deutsche Diabetes Dialyse Studie (4D)] randomised 1,255 patients with type 2 diabetes, all on haemodialysis, to either atorvastatin or placebo and found a significantly lower rate of

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cardiac events but higher rate of strokes in the treatment arm [10]. There was no overall difference in outcome between the groups. Similarly, AURORA (A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival) randomised 2,776 haemodialysis patients to rusovastatin or placebo and found no difference in the combined endpoint of fatal or non-fatal major cardiovascular events, nor in any individual component thereof [11].

Given the number of patients that would be required to adequately power a conclusive randomised controlled trial (RCT) [4], the nephrology community is unlikely to see such data emerge for some time if at all. Because of this, we must rely on meta-analysis to adjudicate between the differing results of these studies. However, existing meta-analyses of LLT in dialysis patients have thus far provided no further insight [12–15]. This is for two reasons. Firstly, these meta-analyses have included safety and efficacy studies which have very limited follow-up periods of 8–24 weeks. With such short observation one may not expect to see any of the long-term benefit of chronic LLT use. Second, these analyses have limited themselves to studies using only statin therapy. This meant the exclusion of SHARP, the largest RCT of LLT in CKD and which showed a significant reduction in low-density lipoprotein (LDL) cholesterol for patients on LLT versus placebo. Furthermore, previous meta-analysis data from the general population demonstrates a 'remarkably consistent' relationship between LDL cholesterol reduction and cardiovascular risk reduction, irrespective of the agent used [16].

With this in mind, it would be of benefit to establish meta-analysis of the use of LLT in dialysis patients where the criteria for inclusion are that studies be an RCT with adequate follow-up to establish a possible difference in outcome between treatment and placebo, and that inclusion be determined by a demonstrable improvement in LDL cholesterol in the treatment arm relative to placebo, not solely on the agent being used. Here we present an aggregate data meta-analysis of such RCTs, evaluating their effect on cardiovascular events and mortality.

Table 1. Breakdown of major atherosclerotic cardiovascular events in included studies where this was not a pre-defined endpoint

	Treatment	Placebo
AURORA [11]		
Participants	1,389	1,384
Death from coronary heart disease (definite)	143	156
Death from ischaemic stroke	14	17
Death from unclassified stroke	9	4
Definite non-fatal myocardial infarction	74	100
Non-fatal ischaemic stroke	43	38
Non-fatal unclassified stroke	3	1
Revascularisation	148	152
Total	434	468
4D [10]		
Participants	619	636
Fatal myocardial infarction	23	33
Death after intervention for CHD	3	4
Other death due to CHD	1	5
Non-fatal myocardial infarction	70	79
PTCA	34	45
CABG	24	30
Other intervention	1	0
All ischaemic stroke	47	33
All unclassified stroke	10	6
Total	213	235

Values represent numbers. CHD = Coronary heart disease; PTCA = percutaneous transluminal coronary angioplasty; CABG = coronary artery bypass graft.

Method

Trial Selection

A search of Medline, Google Scholar, the COCHRANE Library, Scopus, Web of Science, EMBASE, and cardiovascular and nephrology society proceedings from January 1, 2000 to December 31, 2012 was performed. The search terms used were: 'randomised controlled trial AND (one of: haemodialysis, end stage renal disease, ESRD, end stage kidney disease, ESKD, dialysis) AND (one of: lipid-lowering therapy, statin, atorvastatin, simvastatin, fluvastatin, rosuvastatin, ezetimibe, fibrate, fenofibrate, cholesterol)'. Criteria for study inclusion were RCT of LLT versus placebo in which LLT was demonstrated to statistically significantly reduce LDL cholesterol, a minimum of 12 months of follow-up on therapy, and at least one clinical cardiovascular endpoint reported in dialysis patients as an independent group. Two operators performed searches independently (D.G., J.P.R.). All searches were performed using full text analysis in those studies identified as an RCT.

Analysis

This was a pooled data meta-analysis. Because there were differences in characteristics between each study population (haemodialysis vs. peritoneal dialysis, diabetes vs. non-diabetic subjects), a random-effects model was used, with duration of therapy included as an additional modifier.

Statistical significance was considered in all cases at the level $\alpha < 0.05$. Atherosclerotic cardiovascular events was chosen as the first endpoint for analysis to establish whether, with adequate power, a dialysis-specific study of LLT versus placebo would be likely

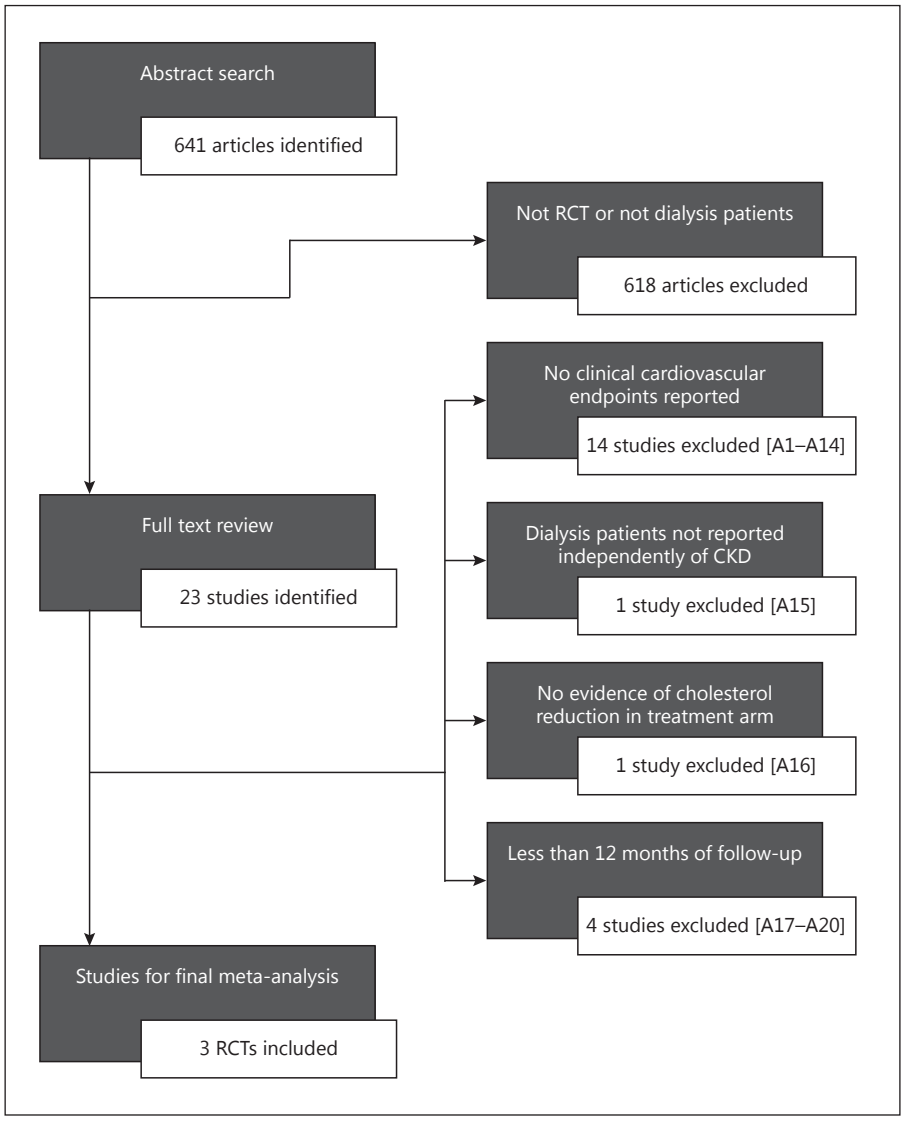

Fig. 1. Study selection process (references can be found in the online suppl. material; www.karger.com/doi/10.1159/000357676).

to replicate the findings of the heterogeneity study in SHARP [4]. Atherosclerotic cardiovascular events included fatal and non-fatal myocardial infarction, fatal and non-fatal non-haemorrhagic stroke, and arterial revascularisation procedures excluding dialysis vascular access procedures. Further analyses of each individual component of this endpoint were then undertaken (myocardial infarction, non-haemorrhagic stroke, revascularisation procedures). We acknowledge that the pooled data was unlikely to be powered adequately to determine such a difference.

A second set of analyses was performed to further investigate the increased risk of stroke reported in 4D [10]. We analysed the endpoints of all strokes, non-haemorrhagic strokes, and haemorrhagic strokes, including both fatal and non-fatal events in each case. This set of analyses would determine whether the finding of 4D was repeated in meta-analysis and provide some evidence as to the nature of the increased risk.

The final analyses performed were to determine whether any improvement in outcome or increased risk of stroke led to a difference in mortality associated with LLT in dialysis patients. Cardiovascular and all-cause mortality were analysed. Cardiovascular death was defined as any death due to any cardiac causes or stroke as determined by individual trial steering committees.

In all analyses, 2 operators independently adjudicated whether the endpoints satisfied the criteria for inclusion in each analysis (D.G., J.P.R.). Where contention arose, decision was by consensus after discussion. Analysis was performed using MIX software version 1.7 [17–20].

Results

Of the 641 articles identified using the search terms, 618 were excluded for either not being RCTs or for not including patients on dialysis. Of the remaining 23 RCTs,

Table 2. Characteristics of the studies selected for the final analyses

Study	Year	Population	n	Follow-up	Treatment	Control	LDL reduction
4D [10]	2005	diabetic haemodialysis	1,255	mean 3.9 years	atorvastatin 20 mg	placebo	–42% at 1 month
AURORA [11]	2009	haemodialysis	2,776	median 3.8 years	rusovastatin 10 mg	placebo	–43% at 3 months
SHARP [4]	2011	haemodialysis, peritoneal dialysis[a]	3,023	median 4.9 years[b]	simvastatin 20 mg + ezetimibe 10 mg	placebo	–39% at 12 months[b]

LDL reduction is for treatment arm and represents change from baseline at specified follow-up. [a] Study also included patients with CKD not on dialysis who are not reported here. [b] Results for whole cohort including those patients not on dialysis.

Table 3. Patient participant numbers and events for dialysis patients only in each of the selected studies

Study	n		MACE		Non-haemorrhagic stroke		Coronary events		Revascularisation	
	treatment	control	treatment	control	treatment	control	treatment	control	treatment	control
4D [10]	619	636	213 (34)	235 (37)	57 (9)	39 (6)	93 (15)	112 (18)	62 (10)	79 (12)
AURORA [11]	1,389	1,384	434 (31)	468 (34)	69 (5)	60 (4)	217 (16)	256 (18)	148 (11)	152 (11)
SHARP [4]	1,533	1,490	230 (15)	246 (17)	44 (2)	64 (4)	90 (6)	81 (5)	146 (10)	151 (10)
Study	n		All stroke		Haemorrhagic stroke		Cardiovascular death		All-cause mortality	
	treatment	control	treatment	control	treatment	control	treatment	control	treatment	control
4D [10]	619	636	59 (10)	44 (7)	5 (1)	8 (1)	148 (24)	162 (25)	297 (48)	320 (50)
AURORA [11]	1,389	1,384	94 (7)	81 (6)	25 (2)	21 (2)	324 (23)	324 (23)	636 (46)	660 (48)
SHARP [4]	1,533	1,490	66 (4)	74 (5)	22 (2)	10 (1)	172 (11)	161 (11)	507 (33)	480 (32)

Numbers given are the numbers of endpoint events in the specified trial and arm. Numbers in parentheses are the percentage of patients in the specified trial arm who reached the endpoint.

Table 4. Summary of meta-analyses

	Major atherosclerotic cardiovascular events	Coronary events	Revascularisation procedures	Non-haemorrhagic strokes	All strokes	Haemorrhagic strokes	Cardiovascular deaths	All-cause mortality
OR	0.89	0.88	0.92	1.05	1.11	1.29	0.99	0.97
95% CI	0.80–0.99	0.74–1.04	0.79–1.07	0.65–1.70	0.85–1.46	0.72–2.31	0.88–1.12	0.88–1.06
Significance (p)	0.04	0.13	0.26	0.83	0.45	0.39	0.88	0.49
Overall effect (z)	2.07	1.53	1.12	0.21	0.75	0.85	0.15	0.69

20 were excluded. This was most often for not having clinical cardiovascular endpoints (n = 14) and the follow-up duration being too short (n = 4). In both circumstances these were generally safety and efficacy studies of 4–24 weeks' duration, with lipid profile or surrogate cardiovascular endpoints. The full breakdown of the study selection process is presented in figure 1. There were 3 studies included for the meta-analysis, with 7,051 patients (3,541 treatment and 3,510 placebo) [4, 10, 11]. Endpoint data from SHARP were provided directly by the Oxford Trials Unit except for major atherosclerotic cardiovascular events (MACE), which was taken from the SHARP trial website. Data from 4D and AURORA were taken from the published manuscripts and the breakdown of events from these studies is found in table 1.

There was a consistent reduction of LDL cholesterol across the studies, with a range of 35–43% irrespective of treatment regime. None of the studies showed a significant change in LDL cholesterol at follow-up in the pla-

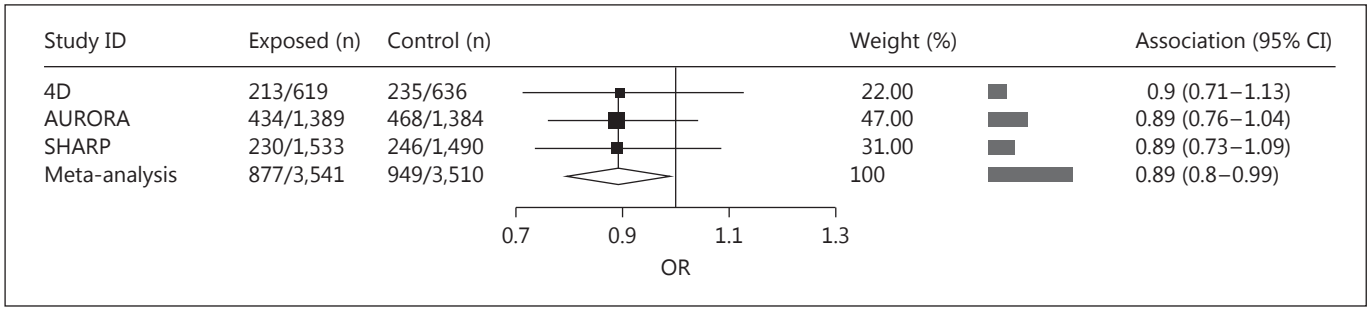

Fig. 2. Forest plot of endpoint 1: fatal and non-fatal atherosclerotic cardiovascular events.

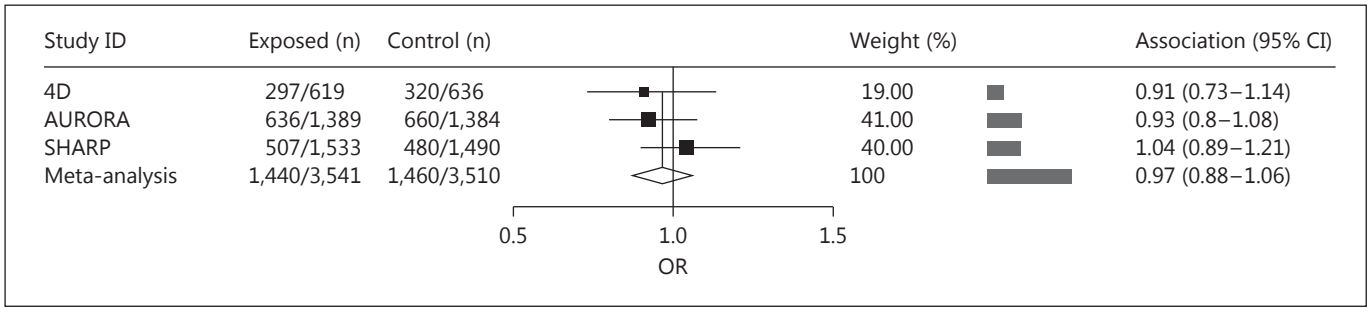

Fig. 3. Forest plot of endpoint 2: coronary events.

cebo arm. Study characteristics are presented in table 2. Event rates of each analysis are summarised in table 3, and the statistical outputs of the meta-analyses are summarised in table 4.

Endpoint 1: Fatal and Non-Fatal Atherosclerotic Cardiovascular Events

There were 877 events in 3,541 LLT patients (24.8%) versus 949 events in 3,510 placebo patients (27.0%). The odds ratio (OR) in LLT versus placebo was 0.89 and reached statistical significance (95% CI: 0.80–0.99, p = 0.04; fig. 2).

Endpoint 2: Coronary Events

There were 400 coronary events in 3,541 LLT patients (11.6%) versus 449 events in 3,510 placebo patients (12.8%). The OR in LLT versus placebo was 0.88 (95% CI: 0.74–1.04, p = 0.13; fig. 3).

Endpoint 3: Revascularisation Procedures

There were 356 revascularisation procedures in 3,541 LLT patients (10.0%) versus 382 in 3,510 placebo patients (10.9%). The OR in LLT versus placebo was 0.92 (95% CI: 0.79–1.07, p = 0.26; fig. 4).

Endpoint 4: Fatal and Non-Fatal Non-Haemorrhagic Strokes

There were 170 non-haemorrhagic strokes in 3,541 LLT patients (4.8%) versus 163 in 3,510 placebo patients (4.6%). The OR in LLT versus placebo was 1.05 (95% CI: 0.65–1.70, p = 0.83; fig. 5).

Endpoint 5: All Strokes

There were 219 strokes in 3,541 LLT patients (6.2%) versus 199 in 3,510 placebo patients (5.7%). The OR in LLT versus placebo was 1.11 (95% CI: 0.85–1.46, p = 0.45; fig. 6).

Endpoint 6: Fatal and Non-Fatal Haemorrhagic Strokes

There were 52 haemorrhagic strokes in 3,541 LLT patients (1.5%) versus 39 in 3,510 placebo patients (1.1%). The OR in LLT versus placebo was 1.29 (95% CI: 0.72–2.31, p = 0.39; fig. 7).

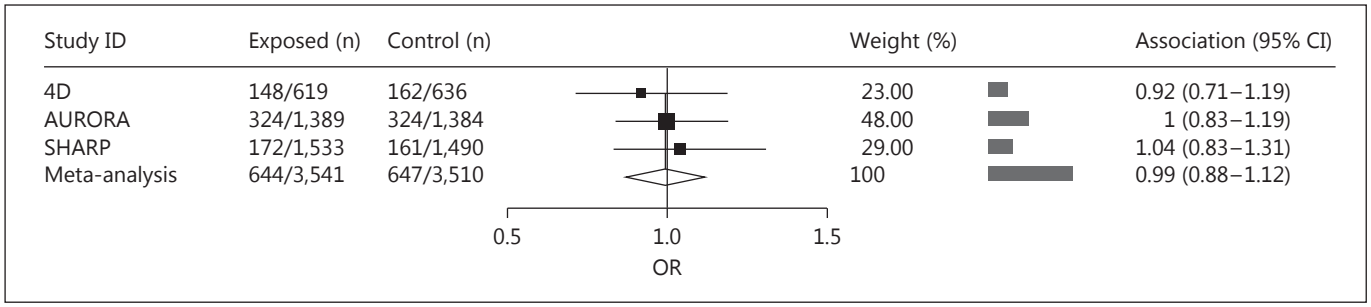

Fig. 4. Forest plot of endpoint 3: revascularisation procedures.

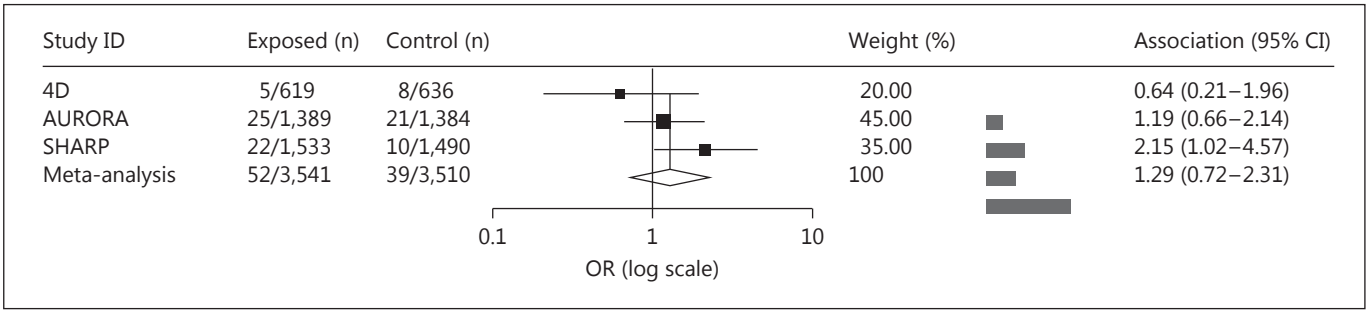

Fig. 5. Forest plot of endpoint 4: fatal and non-fatal non-haemorrhagic strokes.

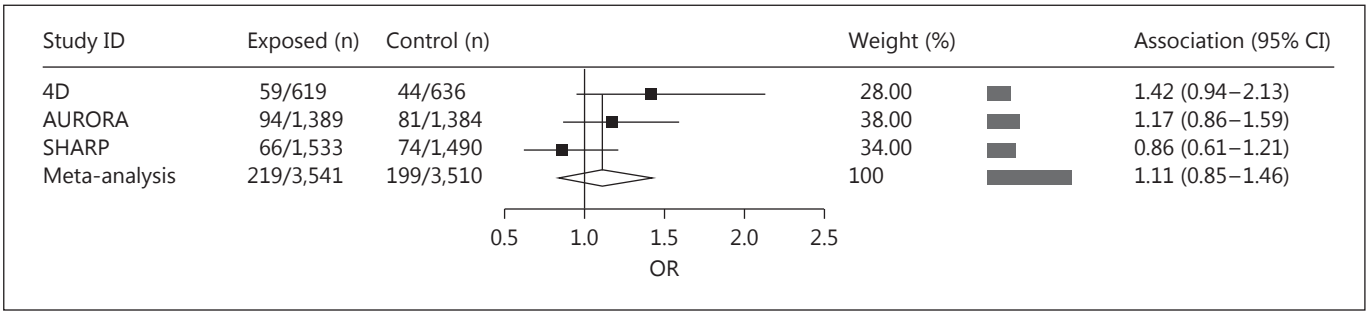

Fig. 6. Forest plot of endpoint 5: all strokes.

Endpoint 7: Cardiovascular Mortality

There were 644 cardiovascular deaths in 3,541 LLT patients (18.2%) versus 647 in 3,510 placebo patients (18.4%). The OR in LLT versus placebo was 0.99 (95% CI: 0.88–1.12, p = 0.88; fig. 8).

Endpoint 8: All-Cause Mortality

There were 1,440 deaths in 3,541 LLT patients (40.1%) versus 1,460 deaths in 3,510 placebo patients (41.6%). The OR in LLT versus placebo was 0.97 (95% CI: 0.88–1.06, p = 0.49; fig. 9).

Discussion

In this meta-analysis there was a statistically significant benefit to using LLT in reducing atherosclerotic cardiovascular events in dialysis patients. This is consistent with the implication of the test of heterogeneity between CKD and dialysis patients noted by the SHARP investigators. None of the components of MACE showed an individually statistical significance although revascularisation procedures were performed numerically less often in the treatment arm of all three studies included here.

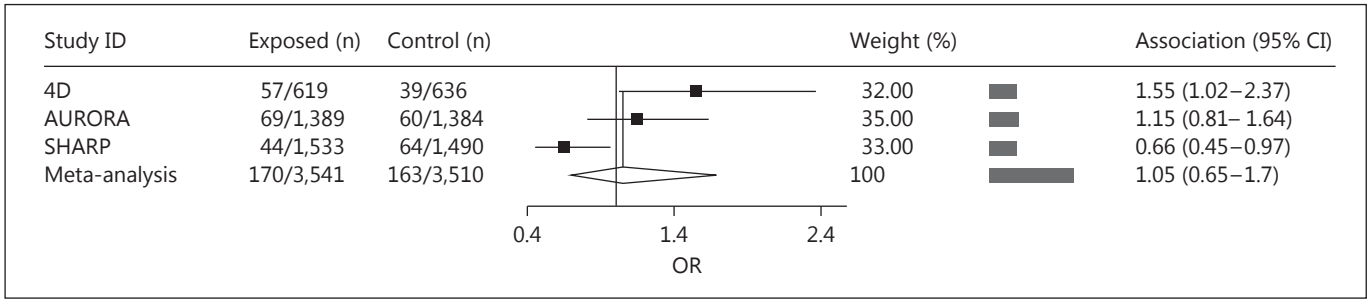

Fig. 7. Forest plot for endpoint 6: fatal and non-fatal haemorrhagic strokes.

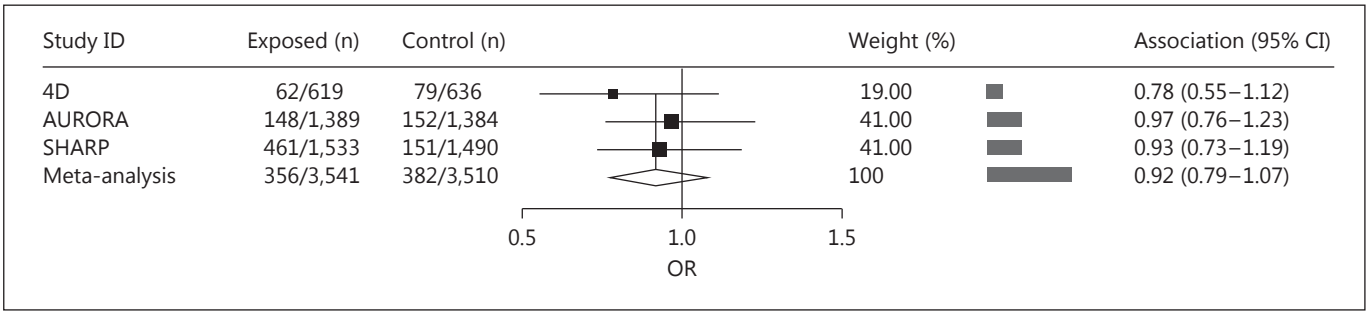

Fig. 8. Forest plot of endpoint 7: cardiovascular mortality.

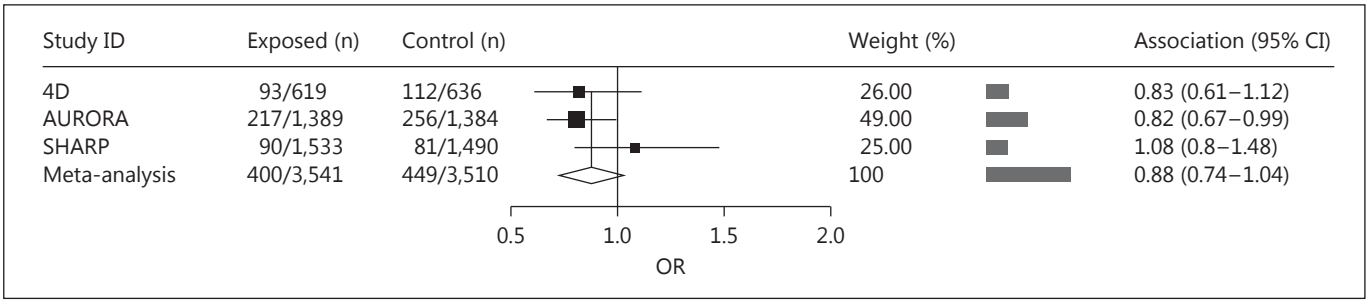

Fig. 9. Forest plot of endpoint 8: all-cause mortality.

Within the cohort of patients in the RCTs analysed here, the MACE rate was approximately 63 per 1,000 patient-years. The OR for such events in LLT patients was 0.89 compared to placebo. This is a smaller risk reduction than is seen in the general population (RR = 0.80) and in patients with CKD not on dialysis (RR = 0.83) [4, 16, 21]. This is likely to reflect the higher rate of non-atherosclerotic cardiovascular disease seen in dialysis patients, such as left ventricular hypertrophy, arterial stiffness, endothelial dysfunction, inflammation and oxidative stress [7, 22], and that sudden death, thought to be the leading cause of death in dialysis patients, is unlikely to be only a function of coronary artery disease as often in these patients as in the general population [23]. These factors also explain why there was no significant benefit to LLT use in terms of cardiovascular and all-cause mortality.

Based on the follow-up time of these studies and the event rate for MACE, we estimate that the number needed to treat for LLT to prevent one atherosclerotic event per year in the dialysis population is 103. This is unlikely to restrict the use of statins, but may have cost-effectiveness implications for more expensive second-line agents such as ezetimibe [2, 24, 25].

The previous noteworthy finding in 4D of more strokes in the LLT therapy arm was not repeated in this meta-analysis. Haemorrhagic strokes were numerically more common in LLT patients compared to placebo, but were a relatively rare event (1.2% of all patients). 'All strokes' were also numerically more common in these patients as a result, but with an OR of 1.11 and without statistical significance. Because of this, any concern over the effect of LLT on haemorrhagic stroke does not negate the overall beneficial effect of reducing atherosclerotic events in dialysis patients.

What is not clear is the long-term burden associated with fewer atherosclerotic events versus potentially more strokes. In the very least, these results show that prescribing LLT for dialysis patients should involve both a well-informed patient and clinician.

The statistical significance of an association with cardiovascular events has not been consistent between this and previous meta-analyses. This likely reflects the different definitions and selection criteria used. The analysis performed here is based on proven reductions in LDL cholesterol combined with long-term follow-up. The number of patients included in the meta-analysis is high compared to other analyses of dialysis patients independent of non-dialysis CKD. It can be argued that because of this our meta-analysis is better powered to detect a significant difference.

The shortcomings of this analysis are that the population samples differed between the RCTs, with the inclusion of diabetic and non-diabetic subjects differing, as well as the inclusion of the different dialysis modalities. It should also be noted that SHARP was a primary prevention study, excluding patients with a prior cardiovascular event, whereas 4D and AURORA were not. This is borne out by the MACE rates being at least twice as great in the latter two studies. Nonetheless, it is clear that there is a potential benefit to LLT in this setting.

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Disclosure Statement

The authors have no conflicts of interest to declare.

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