Medical therapies to reduce chronic kidney disease progression and cardiovascular risk: lipid lowering therapy

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GUIDELINES

a. We recommend that patients with early chronic kidney disease (stage 1-3) should be treated with statin therapy (with or without ezetimibe) to reduce the risk of atherosclerotic events (1A).

UNGRADED SUGGESTIONS FOR CLINICAL CARE

There are no ungraded statements.

IMPLEMENTATION AND AUDIT

Kidney Check Australia Taskforce (KCAT) education programs should incorporate these updated guidelines. Audits of primary health care providers, similar to the BEACH study, should be commissioned to evaluate awareness of these guidelines.

Relevant education programs (KCAT) and guidelines (Heart Foundation) should incorporate these recommendations. Audits of primary health care providers should be commissioned to evaluate awareness of these guidelines and use (type and dose) of anti-lipaemic therapies. Relevant education programs (KCAT) and guidelines (Diabetes Australia) should incorporate these recommendations. Audits of primary health care providers should be commissioned to evaluate awareness of these guidelines and to monitor relevant key performance indicators, including HbA1c, and cardiovascular and renal outcomes.

BACKGROUND

Chronic kidney disease (CKD) represents a major, rapidly growing, public health burden worldwide. In Australia, CKD affects approximately 1 in 7 (or more than 2 million) adults over the age of 25, and contributes to nearly 10% of all deaths and over 1.1 million hospitalisations annually. [1, 2] Several studies, in various populations [3-22], have demonstrated that:

- CKD is a potent, independent cardiovascular (CV) risk factor, with CV events occurring between 10 to 100 times more frequently in the CKD population, and
- CKD has a multiplicative impact on other chronic diseases.

CKD is expensive. In 2000-01, the estimated total recurrent health expenditure on CKD in Australia was $647 million. [23] A recent analysis of the health economic impact of end-stage kidney disease (ESKD) in Australia estimated that, at the end of 2007, hospital dialysis cost around $189 million per year. [24]

Taken together, CKD is a significant contributor of morbidity and mortality, and represents a major expense to the health care system. Early intervention with appropriate medical therapies is essential to address this public health burden and may reduce the progression of CKD and CV risk by up to 50%. [25] The objective of this guideline is to review currently available evidence in this regard and provide appropriate clinical recommendations. Recommendations in other guidelines, and the evidence underpinning these recommendations, have also been reviewed.

Clinical trials have clearly established the use of lipid-lowering therapy, particularly using statins, in both primary and secondary prevention of CV disease in the general population[26-28] Given that CKD is associated with increased absolute cardiovascular risk and alterations in lipid metabolism, one might reasonably expect that the benefit of anti-lipaemic agents would exceed that found in the general population. Despite this, studies in the dialysis population are disappointing[29-31] Furthermore, it has been observed that there may be an inverse association between lipid levels and mortality in the pre-dialysis population[32] The objective of this guideline is to review currently available evidence with regards to lipid-lowering therapy in patients with early (stages 1-3) CKD. The effect of lipid-lowering agents on CKD progression has been previously discussed in the CARI Guideline on Lipids (http://www.cari.org.au/CKD_Prevent_List_Published/Lipids.pdf) and will be briefly discussed here in the context of recent clinical updates.

SEARCH STRATEGY

Databases searched: Text words for chronic kidney disease were combined with MeSH terms and text words for hypolipidaemic agents, statins, fibrates, ezetimibe and lipid lowering. The search was carried out in Medline (1994 – October 2009) and the Cochrane library. No language restrictions were placed on the search. The conference proceedings of the American Society of Nephrology from 1994 - 2011 were also searched for trials. A search update was conducted in Medline (2009 – May 2012) using the same MeSH terms and text words.

Date of search/es: October 2009, May 2012

WHAT IS THE EVIDENCE?

Navaneethan et al. [33] conducted a systematic review of statin therapy in patients with CKD not requiring dialysis. Twenty six RCTs and quasi-RCTs were examined (25 017 patients). Statin therapy was well-tolerated and led to significant reductions in total cholesterol (18 studies, 1677 patients: MD -41.48 mg/dL, 95% CI -49.97 to -33.99), 24-hour urine protein excretion (6 studies, 311 patients: MD -0.73 g/24 h, 95% CI -0.95 to -0.52), all-cause mortality (21 RCTs, 18,781 patients, RR 0.81, 95% CI 0.74, 0.89) and cardiovascular deaths (20 studies, 18,746 patients: RR 0.80, 95% CI 0.70 to 0.90). There was no significant improvement in creatinine clearance (11 studies, 548 patients: MD 1.48 mL/min, 95% CI -2.32 to 5.28). By comparison, a meta-analysis by Strippoli et al. [31] evaluated statin therapy in patients with CKD, which included pre-dialysis, dialysis and transplant populations. This study found no significant effect on all-cause mortality (44 studies, 23 665 patients; 0.92, 0.82 to 1.03), suggesting phenotypic differences in dialysis and pre-dialysis populations.

Separate to the Navaneethan meta-analysis, Shepherd et al. [34] conducted a sub-analysis of the TNT study, a double-blind study in which 10 001 patients with coronary heart disease were randomised to atorvastatin 80 mg/day or 10 mg/day, with a median follow-up of 5.0 years. Patients with CKD (eGFR < 60 mL/min/1.73m^2) and patients with normal eGFR who were treated with atorvastatin 80 mg had a significant reduction in the risk of major cardiovascular events (HR 0.68: 95%CI: 0.55 to 0.84; P < 0.001) and (HR 0.85; 95%CI: 0.72 to 1.00; P < 0.05) respectively, compared with atorvastatin 10mg.

Fried et al[35] published a meta-analysis of 9 randomised controlled trials, 1 quasi-randomised controlled trial and 2 randomised cross-over trials (384 patients) examining the effects of lipid-lowering agents on change in GFR in hyperlipidaemic patients with renal disease. Ten of the trials studied statins, whilst 1 assessed gemfibrozil and 1 assessed probucol. Sixty-six per cent of patients were diabetic. Lipid lowering treatment was associated with a lower rate of decline in glomerular filtration rate compared with controls (net difference 0.156 mL/min/month; 95% CI, 0.026 to 0.285 mL/min/month, *P* = 0.008). There was a tendency for a favourable effect of treatment on protein or albumin excretion. A chi square test for study heterogeneity supported the validity of pooling the results for GFR, but not for proteinuria. However, heterogeneity tests are fairly insensitive, and it seems highly questionable that separate trials of cholesterol and triglyceride lowering agents on such diverse patient groups with often very short follow-up times can really be grouped together to provide meaningful results. The other major limitation of the meta-analysis was the inclusion of non-randomised controlled trials. An updated meta-analysis by Sandhu et al[36] of 27 eligible studies with 39,704 participants found that statin therapy was

associated with significant reductions in GFR decline (1.22 ml/min/year, 95% CI 0.44-2.00) and albuminuria or proteinuria (standardized mean difference 0.58 units, 95% CI 0.17-0.98). This systematic review was subsequently superseded by that of Navaneethan et al. [33] who found that statin therapy was associated with significant reductions 24-hour urine protein excretion (6 studies, 311 patients: MD -0.73 g/24 h, 95% CI -0.95 to -0.52), but not in creatinine clearance (11 studies, 548 patients: MD 1.48 mL/min, 95% CI -2.32 to 5.28).

Recently, Baigent et al[37] published the results of a multi-centre, multi-country, double-blind, placebo-controlled RCT of 9270 patients with CKD (3023 on dialysis and 6247 not on dialysis) with no known history of myocardial infarction or coronary revascularisation randomly allocated to simvastatin 20 mg plus ezetimibe 10 mg daily (n=4650) versus matching placebo (n=4620) (Studies of Heart and Renal Protection – SHARP). Over a median follow-up of 4.9 years, patients receiving simvastatin plus ezetimibe experienced a significant reduction in LDL cholesterol (0.85 mmol/L, SE 0.02) and a 17% reduction in the risk of the primary composite outcome of first major atherosclerotic event (non-fatal myocardial infarction or coronary death, non-haemorrhagic stroke, or any arterial revascularisation procedure) (RR 0.83, 95% CI 0.74-0.94). Significant reductions were also observed in non-haemorrhagic stroke (RR 0.75, 95% CI 0.60-0.94) and revascularisation procedure (RR 0.79, 95% CI 0.68-0.93), but not in non-fatal myocardial infarction or coronary death (RR 0.92, 95% CI 0.76-1.11). The beneficial effects of statins on atherosclerotic events appeared to be proportionally similar in patients with CKD whether or not they were on dialysis. Of the patients not on dialysis, 36% had stage 3 CKD, 43% had stage 4 CKD and 20% had stage 5 CKD. For stage 3 CKD patients (n=2155), ezetimibe-simvastatin was associated with a borderline significant reduction in the primary outcome of major atherosclerotic events (RR 0.75, 95% CI 0.57-1.00). There were no significant differences between the intervention and control groups with respect to study drug discontinuations due to suspected serious adverse reactions (17 [0·4%] *vs* 12 [0·3%]), other serious adverse events (297 [6·4%] *vs* 307 [6·6%]), non-serious adverse events (165 [3·5%] *vs* 131 [2·8%]), or other reasons (1054 [22·7%] *vs* 1219 [26·4%]). The excess risk of myopathy due to ezetimibe-simvastatin was only 2 per 10,000 patients per year of treatment (9 [0.2%] vs 5 [0.1%]). Elevations in serum creatine kinase levels did not differ significantly between the two groups. There were also no differences between the intervention and control groups with respect to hepatitis, gallstones, cancer or death from any non-vascular cause. Ezetimibe-simvastatin did not reduce the risks of ESKD (RR 0·97, 95% CI 0·89–1·05) ESKD or death (RR 0·97, 0·90–1·04) or ESKD or doubling of baseline creatinine (RR 0·93, 0·86–1·01). The major limitation of the SHARP trial were that it was not adequately powered to perform sub-group analyses of CKD patients on dialysis and not on dialysis.

Less evidence is available for the effect of other hypolipidaemic agents on CKD progression and CV risk. Kshirsagar et al[38] performed a post hoc analysis of the Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT), a double-blind RCT evaluating the effect of anti-lipaemic therapy with cholestyramine on the risk of developing CHD in middle-aged men, with a mean follow-up of 94.1 months. Analysis of the 3603 patients with eGFR $\geq$ 60 ml/min/1.73m^2 demonstrated that cholestyramine led to a significant reduction in total cholesterol (from 280.2 ± 35.3 to 256.4 ± 47.3 mg/dl after 7 years, $P < 0.001$) but did not meaningfully affect renal function (MD in unadjusted eGFR 0.39 ml/min/1.73m^2, 95% CI 0.34 to 1.12, NS).

Tonelli et al. [39, 40] conducted a post hoc analysis of the Veterans' Affairs High-Density Lipoprotein Intervention Trial (VA-HIT), a double-blind RCT of gemfibrozil vs placebo in 2531 men with established CHD. Analysis of the 1046 patients with CKD (defined as creatinine clearance $\leq$ 75 ml/min using the Cockcroft-Gault equation) demonstrated that administration of gemfibrozil resulted in a reduced incidence of the primary composite outcome of coronary death or nonfatal myocardial infarction (HR 0.73; 95% CI 0.56-0.96, $P < 0.05$) with no difference in total mortality (HR 1.03; 95% CI 0.78-1.35, NS) but an increased risk of a sustained increase in serum creatinine (5.9 vs 2.8%, $P < 0.05$). The latter was defined as increases in serum creatinine $\geq$ 0.5 mg/dl higher than baseline.

In the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study[41] 9795 participants with type 2 diabetes were randomised to fenofibrate 200 mg daily or matching placebo, with a median follow-up of 5 years. The mean plasma creatinine was 77.4 (SD 15.7) and 77.7 µmol/L in the placebo and fenofibrate groups, respectively. Fenofibrate was associated with no significant reduction in the incidence of the primary composite outcome of first myocardial infarction or CHD death (HR 0.89; 95% CI 0.75-1.05, NS) and no difference in total mortality (HR 1.11; 95% CI 0.95-1.29, NS). However, there

was a small (2.6%) reduction in the rate of progression to albuminuria in patients allocated to fenofibrate (P < 0.01).

No published large scale RCTs have examined the optimal target lipid levels to which patients with early, stage 1-3, CKD should be treated.

SUMMARY OF EVIDENCE

Substantial evidence from meta-analyses and the SHARP trial indicates that statin therapy is associated with reduced cardiovascular risk and total mortality but with no significant effect on CKD progression. Statin therapy in CKD is generally well tolerated without an appreciable excess risk of myopathies, hepatitis, cancer or other adverse effects. Studies of other anti-lipaemic agents are limited.

WHAT DO THE OTHER GUIDELINES SAY?

Kidney Disease Outcomes Quality Initiative: No recommendation.
UK Renal Association: No recommendation.
Canadian Society of Nephrology:[42]

1.9.1 Statin therapy should be initiated in patients with stage 1-3 CKD according to existing lipid guidelines for the general population.

1.9.2 In patients with stage 1-3 CKD, clinicians should consider titrating statin dose according to lipid guidelines for the general population.

1.9.4 Gemfibrozil 1200 mg daily may be considered as an alternative to statin treatment in patients with stage 1-3 CKD who are at intermediate or high cardiovascular risk with concomitant low levels of HDL cholesterol (< 1.0 mmol/L).

1.9.5 Fasting triglycerides > 10 mmol/L at any stage of CKD should be treated by recommending lifestyle changes and adding gemfibrozil or niacin, as required, to reduce the risk of acute pancreatitis. Current data do not support treating hypertriglyceridemia per se as a cardiovascular risk reduction strategy.

European Best Practice Guidelines: No recommendation.
International Guidelines:
Kidney Check Australia Taskforce:[43]
CKD is associated with substantial abnormalities of lipid metabolism, including increased low-density lipoproteins, triglycerides, very-low-density lipoproteins, and lipoprotein (a), and reduced levels of high-density lipoprotein cholesterol. Dyslipidaemia is more severe in patients with proteinuria, particularly those with nephrotic syndrome. Dyslipidaemia should be treated as per cardiovascular disease recommendations and targets.
Management

- Dietary advice
- Statins (dose reduction not necessary)

Target

- Total < 4.0 mmol/L
- LDL < 2.5 mmol/L

National Institute for Clinical Excellence (NICE):[44]

R57 The use of statin therapy for the primary prevention of CVD in people with CKD should not differ from its use in people without CKD and should be based on existing risk tables for people with and without diabetes. It should be understood that the Framingham risk tables significantly underestimate risk in people with CKD.

R58 Offer statins to people with CKD for the secondary prevention of CVD irrespective of baseline lipid values.

Scottish Intercollegiate Guidelines Network (SIGN): [45]
Statin therapy should be considered in all patients with stage 1-3 chronic kidney disease, with a predicted 10-year cardiovascular risk $\geq$ 20%.

SUGGESTIONS FOR FUTURE RESEARCH

A randomised controlled trial should be performed to determine the relative safety and efficacy of statins compared with statins combined with ezetimibe in CKD patients.

CONFLICT OF INTEREST

Richard Phoon has a level II b. conflict of interest for receiving speaker fees and honoraria from several companies related to anaemia, CKD-MBD and cardiovascular disease between 2008 and 2012.

David Johnson has a level II b. conflict of interest for receiving speaker honoraria and advisor's fees from several companies related to anaemia, CKD-MBD, hypertension and cardiovascular disease between 2008 and 2012.

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APPENDICES

Table 1. Characteristics of included studies

Study ID	N	Study design	Participants	Follow up	Comments and results
Navaneethan et al (2009) [33]	26 studies (25,017 patients)	Systematic review	To evaluate the benefits and harms of statins in CKD patients who were not receiving renal replacement therapy		• Statins significantly decreased: - total cholesterol (18 studies, 1,677 patients: MD -41.48 mg/dL, 95%CI: -49.97 to -33.99) - LDL cholesterol (16 studies, 1,605 patients: MD -42.38 mg/dL, 95%CI: -50.71 to -34.05) • Statins also decreased: - the risk of all-cause and cardiovascular mortality (21 RCTs, 18,781 patients: RR 0.81, 95%CI: 0.74 to 0.89) and (20 studies, 18,746 patients: RR 0.80, 95%CI: 0.70 to 0.90) respectively. - 24-hour urinary protein excretion (6 studies, 311 patients: MD -0.73 g/24h, 95%CI: -0.95 to -0.52) • Statins did not significantly improve creatinine clearance (11 studies, 548 patients: MD 1.48 mL/min, 95%CI: -2.32 to 5.28)
Strippoli et al (2008) [31]	50 trials (30,144 patients)	Meta-analysis	To analyse the benefits and harms of statins in patients with chronic kidney disease (pre-dialysis, dialysis, and transplant populations)		• Compared with placebo, statins significantly reduced: - total cholesterol (42 studies, 6,390 patients: MD -42.28 mg/dL, 95%CI: -47.25 to -37.32) - LDL cholesterol (39 studies, 6,216 patients: MD -43.12 mg/dL, 95%CI: -47.85 to -38.40) - Proteinuria (6 studies, 311 patients: MD -0.73 g/24h, 95%CI: -0.95 to -0.52) • Statins also reduced fatal cardiovascular events (43 studies, 23,266 patients: RR 0.81, 95%CI: 0.73 to 0.90) and non-fatal cardiovascular events (8 studies, 22,863 patients: RR 0.78, 95%CI: 0.73 to 0.84) • Statins did not have a significant effect on all-cause mortality (44 studies, 23,665 patients: RR 0.92, 95%CI: 0.82 to 1.03)
Shepherd et al (2008) (TNT Study) [34]	10,001	RCT	Participants 35 to 75 years old with coronary heart disease (CHD) were randomised to 80 mg/day or 10 mg/day atorvastatin	5 years (median)	• 351/3,107 (11.3%) patients with CKD experienced a major cardiovascular event compared with 561/6,549 (8.6%) patients with normal eGFR (hazard ratio [HR] 1.35; 95%CI: 1.18 to 1.54; P < 0.0001) • Atorvastatin 80mg reduced the relative risk of major cardiovascular events by 32% in patients with CKD (HR 0.68; 95%CI: 0.55 to 0.84; P = 0.0003) and by 15% in patients with normal eGFR (HR 0.85; 95%CI: 0.72 to 1.00; P = 0.049) compared with atorvastatin 10 mg

Study ID	N	Study design	Participants	Follow up	Comments and results
Fried et al (2001)[35]	13 studies (n=383)	Meta-analysis	Studies examining the effects of antilipemic agents on glomerular filtration rate and proteinuria or albuminuria in patients with renal disease	NA	• In patients who were in the lipid treatment groups, the rate of decline in glomerular filtration rate was lower compared with controls (0.156 mL/min/month; 95%CI: 0.026 to 0.285 mL/min/month; P = 0.008) • There was a significant difference in the mean weighted effect of treatment on change in urine protein or albumin excretion -0.283 (95%CI: -0.427 to -0.139; P < 0.001), however the validity of combining these results is questionable as the chi-square test for heterogeneity between the studies was statistically significant (P<0.001)
Sandhu et al (2006)[36]	27 studies (n=39,704)	Meta-analysis	Studies that evaluated statin therapy on the effect of renal function or proteinuria in adult patients without end-stage renal disease	NA	• The weighted mean difference for eGFR was statistically significant (1.22 mL/min/year slower in statin recipients; 95%CI:0.44-2.00; P = 0.002) • Subgroup analysis showed statistically significant benefits of statin therapy for participants with cardiovascular disease (0.93 mL/min/year slower than control subjects: 95%CI: 0.10 to 1.76; P = 0.03) but not for participants with diabetic or hypertensive kidney disease or with glomerulonephritis. • Standardized mean difference for the reduction in albuminuria or proteinuria was statistically significant for statin therapy (0.58 units, 95%CI: 0.17-0.98; P = 0.005)
Baigent et al (2011)[37] (SHARP Study)	9,270 (4,650 = treatment 4,620 = placebo)	RCT	Patients ≥ 40 years of age with CKD (3,023 on dialysis, 6,240 not on dialysis) Patients were randomly assigned to simvastatin (20mg) plus ezetimibe (10mg) (S+E) group or to placebo. Multicentre study, 18 countries, 380 hospitals.	4.9 years	• 17% proportional reduction in major atherosclerotic events, 526 (11.3%) in the S+E group vs 619 (13.4%) in the placebo group. RR 0.83; 95%CI: 0.74 - 0.94; log-rank P=0.0021 • Significant reductions in non-haemorrhagic stroke 131 vs 174, (RR 0.75; 95%CI: 0.60 – 0.94, P=0.01) and arterial revascularization procedures 284 vs 352 (RR 0.79; 95%CI: 0.68 – 0.93, P=0.0036) for the S+E and placebo groups, respectively. • Incidence of non-fatal myocardial infarction or death from coronary heart disease was non-significantly lower in the S+E group 213 (4.6%) vs 230 (5.0%); RR 0.92; 95%CI: 0.76 – 1.11, P=0.37. • Risk of myopathy was 2/10,000 patients/ year of treatment • No evidence of excess risk of hepatitis, gallstones, cancer or death from non-vascular causes.
Kshirsagar et al (2005) [38]	3,603	RCT	Men aged between 35 to 59 years old participated in the Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT). Participants were randomised to cholestyramine or placebo.	94.1 months	• There was no significant estimated mean difference in glomerular filtration rates between the cholestyramine and placebo groups 0.39 mL/min/1.73 m2 (95%CI: -0.32 to 1.11; P = 0.28) • However, individuals administered cholestyramine had a significant reduction in total cholesterol (from 280.2 ± 35.3 to 256.4 ± 47.3 mg/dL; P < 0.001) compared with placebo

Study ID	N	Study design	Participants	Follow up	Comments and results
Tonelli et al (2004a,b) [39, 40]	2,531	RCT	Men < 74 years old with coronary heart disease were randomised to gemfibrozil or placebo in the Veterans Affairs High-Density Lipoprotein Intervention Trial	61 months (median)	• 1046 men had chronic renal insufficiency (CRI) • The change in renal function in the gemfibrozil group was not significantly different from that in the placebo group (0.49 mL/min/1.73m2/y faster; 95%CI: 0.09 slower to 1.09 faster; P = 0.10) • Incidence of coronary death or non-fatal myocardial infarction was lower in participants with CRI who received gemfibrozil compared to placebo (hazard ratio [HR] 0.73; 95%CI: 0.56 to 0.96; P = 0.02) • Gemfibrozil also reduced the risk of the combined outcome of coronary death, non-fatal myocardial infarction, or stroke (HR 0.74, 95%CI: 0.58 to 0.95; P = 0.02) • Gemfibrozil didn't reduce the need for coronary revascularization (HR 0.85, 95%CI: 0.66 to 1.10; P = 0.21) or total mortality (HR 1.03, 95%CI: 0.78 to 1.35; P = 0.85) • The risk of sustained increases in serum creatinine was increased in gemfibrozil recipients compared with placebo (5.9 vs 2.8%, P = 0.02)
Keech et al (2005) FIELD Study [41]	9,795	RCT	Participants aged 50 – 75 years with type 2 diabetes were randomly assigned to micronized fenofibrate 200 mg or placebo	5 years	• More patients in the placebo group (17%) than in the fenofibrate group (8%; P < 0.0001) commenced other lipid treatments • Fenofibrate was associated with no significant reduction in the incidence of myocardial infarction or coronary heart disease mortality (hazard ratio [HR] 0.89, 95%CI: 0.75 to 1.05; P = 0.16) • Total cardiovascular disease events were significantly reduced from 13.9% to 12.5% in the fenofibrate group (HR 0.89, 95%CI: 0.8 to 0.99; P = 0.035) but, there was no difference in total mortality (HR 1.11, 95%CI: 0.95 to 1.29; P= 0.18)

Table 1a. Characteristics of randomised trials

Study ID (author, year)	N	Study Design	Setting	Participants	Intervention (experimental group)	Intervention (control group)	Follow up (months)	Comments
Shepherd et al (2008) [34]	10,001	Randomised controlled clinical trial	Multicentre, US	Participants with coronary heart disease with or without chronic kidney disease	Atorvastatin 80mg	Atorvastatin 10mg	60	
Baigent et al (2011)[37] (SHARP Study)	9,270	Randomised controlled clinical trial	Multicentre, multinational	CKD patients aged 40 years or older whether or not on dialysis.	Simvastatin (20mg) plus Ezetimibe (10mg) daily dose	Matching placebo	4.9 years	Three arms initially to test for the safety of adding Ezetimibe.
Kshirsagar et al (2005) [38]	3,603	Randomised controlled clinical trial	Multicentre, US	Participants with type IIA hyperlipoproteinaemia	Cholestyramine	Placebo	94.1	
Tonelli et al (2004a; 2004b) [39, 40]	2,531	Randomised controlled clinical trial	Multicentre, US	Participants were men with history of coronary heart disease	Gemfibrozil	Placebo	61	
Keech et al (2005) [41]	9,795	Randomised controlled clinical trial	Multicentre, multinational	Participants with type 2 diabetes	Fenofibrate	Placebo	60	

Table 2a. Methodological quality of randomised trials

Study ID (author, year)	Method of allocation concealment *	Blinding			Intention-to-treat analysis †	Loss to follow up (%)	Comments ‡
		(participants)	(investigators)	(outcome assessors)			
Shepherd et al (2008) [34]	Not specified	Yes	Yes	Yes	Yes	0.4	Ø
Baigent et al (2011)[37] (SHARP Study)	Computer-generated	Yes	Yes	Yes	Yes	2	+
Kshirsagar et al (2005) [38]	Not specified	Yes	Yes	Yes	Yes	Unclear	Ø
Tonelli et al (2004a;2004b) [39, 40]	Permuted block design	Yes	Yes	Yes	Yes	Unclear	Ø
Keech et al (2005) [41]	Central, dynamic allocation method	Yes	Yes	Yes	Yes	0.2	+

* Choose between: central; third party (e.g. pharmacy); sequentially labelled opaque sealed envelopes; alternation; not specified.

† Choose between: yes; no; unclear.

‡ Quality score – "How successfully do you think the study minimised bias?" Choose between: very well (+); okay (Ø); poorly (–).

Table 3a. Results and quality rating for dichotomous outcomes

Outcomes	Study ID (author, year)	Intervention group (no. of patients with events/no. of patients exposed)	Control group (no. of patients with events/no. of patients exposed)	Relative risk (RR) [95% CI]	Risk difference (RD) [95% CI]	Importance**
Major cardiovascular event (death from CHD, nonfatal myocardial infarction, fatal or nonfatal stroke)	Shepherd et al (2008) [34]	Patients with CKD 149 / 1602	Patients with CKD 202 / 1505	0.69 (0.57, 0.85)	-0.04 (-0.06, -0.02)	Critical
		Patients with normal eGFR 254 / 3225	Patients with normal eGFR 307 / 3324	0.85 (0.73, 1.00)	-0.01 (-0.03, -0.00)	
Death from coronary heart disease or non-fatal myocardial infarct	Tonelli et al (2004) [39]	93 / 508	130 / 529	0.74 (0.59, 0.94)	-0.06 (-0.11, -0.01)	Critical
Death from cardiovascular causes	Baigent et al (2011)[37] (SHARP Study)	Simvastatin+E 91 / 4630	90 / 4620	1.01 [0.76, 1.35]	0.00 [-0.01, 0.01]	Critical
Death from coronary heart disease	Keech et al (2005) [41]	110 / 4895	93 / 4900	1.18 (0.90, 1.56)	0.00 (-0.00, 0.01)	Critical
Non-fatal myocardial infarction	Baigent et al (2011)[37] (SHARP Study)	Simvastatin+E 134/ 4630	159 / 4620	0.84 [0.67, 1.05]	-0.01 [-0.01, 0.00]	Important
	Keech et al (2005) [[41]	158 / 4895	207 / 4900	0.76 (0.62, 0.94)	-0.01 (-0.02, -0.00)	
Major cardiovascular event	Tonelli et al (2004) [39]	112 / 508	154 / 529	0.76 (0.61, 0.94)	-0.07 (-0.12, -0.02)	Important
Total cardiovascular disease events	Keech et al (2005) [[41]	612 / 4895	683 / 4900	0.90 (0.81, 0.99)	-0.01 (-0.03, -0.00)	Important
Any non-haemorrhagic Stroke	Baigent et al (2011)[37] (SHARP Study)	Simvastatin+E 131/ 4630	174/ 4620	0.75 [0.60, 0.94]	-0.01 [-0.02, -0.00]	Critical

- Methodological quality, consistency across studies and directness of the evidence (generalisability/applicability).

****** The GRADE system uses the following 3 categories to rank the importance of end points:

- critical for decision making
- important but not critical for decision making
- not important for decision making (of lower importance to patients)

* NA – not applicable

Table 3b. Results and quality rating for continuous outcomes

Outcomes	Study ID (author, year)	Intervention group (mean [SD])	Control group (mean [SD])	Difference in means (95% CI)	Importance**
Total cholesterol (mg/dL)	Kshirsagar et al (2005) [38]	256.4 (47.3)	277.4 (38.2)	-21.0 (-23.81, -18.19)	Important
	Tonelli et al (2004) [39]	*NA	NA	NA	
Glomerular filtration rate	Kshirsagar et al (2005) [38]	90.0 (14.8)	89.4 (14.4)	0.60 (-0.35, 1.55)	Important
	Tonelli et al (2004) [39]	*NA	NA	NA	

- Methodological quality, consistency across studies and directness of the evidence (generalisability/applicability).

** The GRADE system uses the following 3 categories to rank the importance of end points:

- critical for decision making
- important but not critical for decision making
- not important for decision making (of lower importance to patients)

* NA – not applicable