CARI Guidelines: Management of cholesterol-lowering therapy in people with chronic kidney disease

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CARI Guidelines: Caring for Australians and New Zealanders with Kidney impairment

Contact

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Summary of recommendations

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3. Guideline recommendations

Strong recommendation Updated evidence, no change in recommendation

We recommend that people with chronic kidney disease (eGFR ≥15 ml/min/1.73m^2) and an absolute cardiovascular risk of 10% or higher should receive statin therapy (with or without ezetimibe) to reduce the risk of cardiovascular events and death.

Remark: Moderate certainty of the evidence

Strong recommendation Reviewed, no new evidence

We recommend Aboriginal and Torres Strait Islander Peoples and Māori with chronic kidney disease (reduced GFR and/or albuminuria/proteinuria) and an absolute cardiovascular risk of 5% or higher should receive statins (with or without ezetimibe) to prevent cardiovascular events and death.

Remark: Low certainty of the evidence

4. Ungraded suggestions for clinical care

Good practice statement Updated

Patients with albuminuria (A2 3—300 mg/g and A3 >300 mg/g) should receive statins (with or without ezetimibe)

Good practice statement New

Patients with chronic kidney disease (reduced GFR and/or albuminuria/proteinuria) and absolute cardiovascular risk of 5% to 10% should discuss the potential therapeutic use of a statin therapy with their healthcare providers.

Good practice statement Reviewed, no new evidence

Clinicians should ensure that patients and their carer/family learn about the effects that statin therapy with or without ezetimibe has to prevent cardiovascular events and death.

5. Suggestions for future research

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7. Appendix 1. Guideline development methodology

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1. Guideline information

Version number: 2
Date written: September 2021, Last search: 28th April 2022 (one new study being considered)
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This guideline is an update of the Early Chronic Kidney Disease Guideline subtopic: Medical therapies to reduce chronic kidney disease progression and cardiovascular risk: lipid lowering therapy

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2. Background

Chronic kidney disease (CKD) is a public health concern, with an estimated global prevalence of around 10-13% worldwide *[10][13]*, with a steady prevalence rate in Australia and Aotearoa New Zealand. CKD accounts for about 10% of all deaths *[14]* and over 1.1 million hospitalisations annually in Australia, and is a known risk factor for cardiovascular disease *[81]*. Patients with CKD (15-60 ml/min/1.73m^2) have similar risks of death and cardiovascular events as people with existing cardiovascular disease. The management of CKD is facing increasing healthcare costs, with an estimated approximate cost of $1 billion to the Australian healthcare system every year *[16]*, and 1% of the health budget in Aotearoa New Zealand *[18]*. Timely identification and application of appropriate medical therapies are essential to address rising healthcare expenses and may reduce the progression of CKD and cardiovascular disease risk by up to 50% *[21]*.

Traditional and non-traditional cardiovascular risk factors are prevalent in people with CKD. An estimated 60% of people with CKD have elevated serum cholesterol and triglycerides *[23]*. Abnormal lipid levels contribute to the development of cardiovascular disease and may contribute to the progression of CKD *[25][26]*. Clinical trials of lipid lowering therapy have established the cardioprotective effects of statin therapy *[42][61][72]*, and statin therapy combined with ezetimibe in patients with CKD, in both primary and secondary prevention. However, the effect of statin therapy with or without ezetimibe on CKD progression remains largely unknown *[29]*.

The objective of this guideline is to review the evidence of lipid lowering therapy and provide recommendations for clinical care regarding use of statin therapy with or without and ezetimibe in adults with CKD. Please note that this is an update of a previously published CARI Guideline topic *[30]* that was part of the wider CARI early chronic kidney disease guideline *[33]*. Fibrate therapy with or without statin therapy was considered outside the scope of this guideline. The guideline development methods are listed in Appendix 1.

3. Guideline recommendations

Strong recommendation

Updated evidence, no change in recommendation

We recommend that people with chronic kidney disease (eGFR ≥15 ml/min/1.73m^2) and an absolute cardiovascular risk of 10% or higher should receive statin therapy (with or without ezetimibe) to reduce the risk of cardiovascular events and death.

Moderate certainty of the evidence

Evidence To Decision

Benefits and harms

Statin therapy versus placebo/standard of care

The updated Cochrane systematic review to May 2020 included 52 randomised controlled trials *[92]*. The search has been updated on a weekly basis, with one additional study *[107]* identified since May 2020 The review found that for critical patient outcomes, compared to placebo with standard of care, statins probably decrease stroke and myocardial infarction (7 fewer, 95% CI 4 to 9 fewer per 1000 patient years). However, there was probably little or no effect on stroke alone (5 fewer, 95%CI 5 fewer to 1 more per 1000 patient years), and hospitalisation due to heart failure (7 fewer, 95%CI 14 fewer to 7 more per 1000 patient years).

For important outcomes, statins compared to placebo with standard of care, decrease major cardiovascular events (32 fewer, 95%CI 38 to 24 fewer per 1000 patients), decrease death (10 fewer, 95%CI 14 to 5 fewer per 1000 patients), and probably decrease cardiovascular mortality (6 fewer, 95%CI 7 to 3 fewer per 1000 patients). Statins also probably improve creatinine clearance slightly (MD 1 higher, 95%CI 0.44 to 1.55 mL/min higher) compared to placebo. However, there was probably no effect on kidney failure (0 fewer, 95%CI 0 to 0 fewer per 1000 patients) and elevated serum creatinine kinase concentration (rhabdomyolysis) (0 fewer, 95%CI 2 fewer to 5 more per 1000 patients). Additionally, statins compared to placebo were found to have little or no effect on cancer (0 fewer, 95%CI 3 fewer to 5 more per 1000 patients), and to decrease LDL cholesterol (MD 0.029 mmol/L lower, 95%CI 0.034 to 0.024 mmol/L lower).

Statin therapy plus ezetimibe versus statin therapy alone

A search of the medical literature was conducted in August 2020, eight randomised controlled trials compared statins plus ezetimibe with statins alone in patients with CKD. There was no reporting of the critical outcomes stroke, myocardial infarction, and hospitalisation for heart failure in these trials. For important outcomes, the combination of ezetimibe and a statin probably had little or no effect on death (2 fewer, 95%CI 6 fewer to 2 more per 1000 patient years) or major cardiovascular events (6 fewer, 95%CI 12 to 0 fewer per 1000 patient years), and may have had no effect on cardiovascular mortality (1 more, 95%CI 2 fewer to 2 more per 1000 patient years). There was limited reporting of side-effects of statins combined with ezetimibe. From the studies, we are unable to determine if there was an effect on kidney failure or rhabdomyolysis. No studies reported on cancer, memory loss, onset of diabetes, fatigue or life participation.

The SHARP trial is currently the best available evidence for the combination therapy of statins with ezetimibe. The trial found that the combination of statins and ezetimibe reduced major atherosclerotic events and non-haemorrhagic strokes compared to placebo *[75]*.

Certainty of the Evidence

Moderate

The overall certainty of the evidence for the recommendation is moderate (downgraded one level due to serious study limitations or serious inconsistency or serious imprecision for critical outcomes). For critical outcomes (myocardial infarction, stroke, hospitalisation due to heart failure), the certainty of the evidence was moderate when sufficient data were available. Evidence for treatment effects on important outcomes, such as death and major cardiovascular events, was adjudicated as moderate to high certainty. There was limited reporting of harms in randomised controlled trials.

The critical outcomes exhibited moderate certainty of the evidence due to risk of bias for myocardial infarction and serious inconsistency for stroke (due to heterogeneity). There were limited data for the critical outcome hospitalisation due to heart failure, and hence we are unable to determine the difference between the statins and placebo for this outcome. For important

outcomes, the certainty of the evidence was high for death and major cardiovascular events, but moderate for cardiovascular mortality and kidney failure due to study limitations. For safety outcomes, the quality of the evidence for cancer was moderate due to few events, and very low for elevated serum creatinine kinase concentration (rhabdomyolysis) due to study limitations, serious inconsistency and serious imprecision. Other safety outcomes, such as onset of diabetes, fatigue and memory loss, were not reported in studies.

For the comparison of statins with ezetimibe to statins alone the certainty of the evidence was low. There were no data reported for the critical outcomes of myocardial infarction, stroke, and hospitalisation due to heart failure. There was moderate certainty of the evidence for important outcomes, death and major cardiovascular events (study limitations), and low certainty of the evidence for cardiovascular mortality (study limitations and serious imprecision). The certainty of the evidence for important side effects, such as cancer and rhabdomyolysis, were unclear due to the limited reporting in randomised controlled trials.

Values and preferences

No substantial variability expected

A systematic review *[104]* of 32 qualitative studies examining the attitudes of patients at risk of cardiovascular disease (not exclusively CKD) on taking statins, identified that statins provided patients with reassurance in managing their health. Patients also felt that statins were easy to incorporate into their daily lives. However, there were some barriers to statin use, including the benefits of statins not being visible, leading to a questioning of the utility of the therapy. Some patients expressed that they did not feel unwell enough to be on treatment, and statins signified that they were sick.

There is limited published evidence on the preferences and values of patients on the combination of ezetimibe and statins. A qualitative systematic review and meta-synthesis of the general patient population found that, an increase in the number of medicines was described as a sign of losing control. However, patients saw taking the prescribed number and dosage of medication as vital to their health *[93]*.

Patients in the Work Group expressed similar attitudes to those identified in the literature. They felt statins were beneficial to patients, and prescribed medication was crucial to maintaining health. However, patients emphasised the need for better education from healthcare providers on the effects that statins or ezetimibe on preventing cardiovascular events and death.

Resources and other considerations

Statin therapy in Australia is publicly funded through the Pharmaceutical Benefits Scheme. For patients with highest absolute risk of cardiovascular events, statins are subsidised regardless of cholesterol concentration. However, for people with lower cardiovascular risk, cholesterol thresholds remain a part of the criteria for subsidy. Statin therapy (atorvastatin, simvastatin, pravastatin) is publicly subsidised in Aotearoa New Zealand. Generic versions of statins are available in Australia at relatively low cost.

The Study of Heart and Renal Protection (SHARP) Trial cost-effectiveness analysis *[94]* found that the use of statins in patients with stage 3b and 4 CKD was cost effective, with costs below USD 80,000 for every quality adjusted life year (QALY). This equated to less than AUD100,000 and less than NZD 80,000 using the Organisation for Economic Co-operation and Development (OECD) purchasing power parities. Cost-effectiveness was more apparent in patients with more severe forms of kidney disease and patients with increased cardiovascular risk. However, cost-effectiveness was not demonstrated in patients with stage 5 CKD not on dialysis. The criterion for cost-effective was less than USD 100,000 for every quality adjusted life year (QALY), and for very cost effective less than USD 50,000 for every QALY. Additionally, other studies have illustrated the cost-effectiveness of statins in the secondary prevention in Australia *[105]*, and in patients with 10% or higher absolute risk of cardiovascular disease in 5 years Cobiac LJ *[106]*.

The use of ezetimibe is subsidised in Australia for people with diabetes and coronary heart disease whose cholesterol is inadequately controlled by a statin. In New Zealand, ezetimibe is publicly funded for patients with absolute risk of cardiovascular disease of at least 15% over 5 years, elevated cholesterol (2 mmol/L), and intolerance of statin use.

The SHARP Trial cost-effectiveness analysis *[26]*, using a criterion for cost-effective as less than USD 100,000 for every QALY and that for very cost effective as less than USD 50,000 for every QALY, found that the addition of ezetimibe to statins

was cost-effective compared to statins. Statins with the addition of ezetimibe were cost-effective across all stages of CKD included in the trial (stage 3b, stage 4, stage 5 [not on dialysis]), and all stages of absolute cardiovascular risk (<10%, 10-20%, >20%).

Rationale

There are substantial benefits of statins compared to placebo/standard of care and very few associated harms. However, data from randomised controlled trials in patients with CKD are sparse on important harms, such rhabdomyolysis, and patient reported outcomes, such as fatigue and life participation. General population primary prevention trials have found that statins are relatively safe *[98]* and similar effects might be expected in patients with mild to moderate CKD.

Statins are acceptable interventions to patients in the general population, including patients with CKD, and are considered an important safeguard to protect cardiovascular health. Furthermore, statins are publicly subsided and cost-effective in Australia and Aotearoa New Zealand.

The balance of benefits and harms of the combination of statin therapy and ezetimibe is largely derived from the SHARP study *[69]*. SHARP observed that the combination of statins and ezetimibe reduced major atherosclerotic events and non-haemorrhagic stroke compared to placebo. However, this result pertained to data from one study, and only a few small randomised controlled trials comparing statins with ezetimibe to statins alone in patients with CKD have been published. These studies found no incremental benefit of the addition to statins and ezetimibe, with no differences in critical and important outcomes and only limited reporting of safety data and patient reported outcomes.

There has been little or no examination on patients' preferences and values related to treatment using ezetimibe. Patients in the general population see the addition of a drug as a sign of deteriorating health *[93]*. Ezetimibe is publicly subsidised with qualifying criteria and is cost-effective in Australia and New Zealand.

In the judgement of the Work Group, dosing of statin therapy and ezetimibe should be based upon dosages that have received regulatory approval. There is a lack of evidence of benefit from titration of statin therapy or ezetimibe to a specific LDL-cholesterol target *[108]*. Higher doses of treatment may result in an increased risk of adverse events.

Based on these data and the inequities of access to lipid-lowering therapy, including place of residence and gender, evident in the general population *[99][100]*, the Work Group felt that most patients with CKD not requiring dialysis with greater than 10% absolute cardiovascular risk would benefit and would take a statin (with or without ezetimibe) to reduce their risk of cardiovascular events and death.

Clinical Question/ PICO

Population: People with chronic kidney disease (eGFR ≥15 mL/min/1.73m^2)
Intervention: Statin therapy
Comparator: Placebo or standard of care

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo or standard of care	**Intervention** Statin therapy	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Myocardial infarction 9 Critical	Relative risk 0.55 (CI 95% 0.42 — 0.73) Based on data from 9,475 participants in 10 studies. [1] (Randomized controlled) Follow up: Mean 39 months.	**15** per 1000 Difference:	**8** per 1000 **7 fewer per 1000** (CI 95% 9 fewer — 4 fewer)	**Moderate** Due to serious risk of bias [2]	Statins probably decreases fatal and non-fatal myocardial infarction

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo or standard of care	**Intervention** Statin therapy	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Stroke 9 Critical	Relative risk 0.64 (CI 95% 0.37 — 1.08) Based on data from 9,115 participants in 7 studies. [3] (Randomized controlled) Follow up: Mean 40 months.	13 per 1000 Difference:	8 per 1000 **5 fewer per 1000** (CI 95% 8 fewer — 1 more)	**Moderate** Due to serious inconsistency [4]	Statins probably has little or no difference on fatal and non-fatal stroke
Hospitalisation due to heart failure 9 Critical	Relative risk 0.7 (CI 95% 0.37 — 1.32) Based on data from 579 participants in 1 studies. [5] (Randomized controlled) Follow up: 54 months.	22 per 1000 Difference:	15 per 1000 **7 fewer per 1000** (CI 95% 14 fewer — 7 more)	**Low** Due to serious imprecision, Due to serious risk of bias [6]	There were too few who experienced the hospitalisation due to heart failure, to determine whether statins made a difference
Major cardiovascular events 6 Important	Relative risk 0.72 (CI 95% 0.66 — 0.79) Based on data from 36,156 participants in 14 studies. [7] (Randomized controlled) Follow up: Mean 46 months.	113 per 1000 Difference:	81 per 1000 **32 fewer per 1000** (CI 95% 38 fewer — 24 fewer)	**High**	Statins decreases major cardiovascular events
Death 6 Important	Relative risk 0.8 (CI 95% 0.7 — 0.9) Based on data from 28,723 participants in 12 studies. [8] (Randomized controlled) Follow up: Mean 40 months.	48 per 1000 Difference:	38 per 1000 **10 fewer per 1000** (CI 95% 14 fewer — 5 fewer)	**High**	Statins decreases all-cause mortality
Cardiovascular mortality 6 Important	Relative risk 0.77 (CI 95% 0.69 — 0.87) Based on data from 19,182 participants in 8 studies. [9] (Randomized controlled) Follow up: Mean 39 months.	24 per 1000 Difference:	18 per 1000 **6 fewer per 1000** (CI 95% 7 fewer — 3 fewer)	**Moderate** Due to serious risk of bias [10]	Statins probably decreases cardiovascular mortality
Kidney failure 6 Important	Relative risk 0.98 (CI 95% 0.91 — 1.05) Based on data from 6,704 participants in 3 studies. [11] (Randomized controlled) Follow up: Mean 34 months.	2 per 1000 Difference:	2 per 1000 **0 fewer per 1000** (CI 95% 0 fewer — 0 fewer)	**Moderate** Due to serious risk of bias [12]	Statins probably has little or no difference on end-stage kidney disease
Rhabdomyolysis 6 Important	Relative risk 3.07 (CI 95% 0.13 — 75.37) Based on data from 2,618 participants in 2 studies. [13] (Randomized controlled)	2 per 1000 Difference:	6 per 1000 **4 more per 1000** (CI 95% 2 fewer	**Very low** Due to serious risk of bias, Due to serious inconsistency, Due to serious	We are uncertain whether statins increases or decreases elevated creatinine kinase (rhabdomyolysis)

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo or standard of care	**Intervention** Statin therapy	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
	Follow up: Mean 64 months.		— 149 more)	imprecision [14]	
Onset of diabetes 4 Important					No studies were found that looked at onset of diabetes
Memory loss 4 Important					No studies were found that looked at memory loss
Cancer 3 Not Important	Relative risk 1.03 (CI 95% 0.82 — 1.3) Based on data from 5,581 participants in 2 studies. [15] (Randomized controlled) Follow up: Mean 44 months.	**15** per 1000 Difference:	**15** per 1000 **0 fewer per 1000** (CI 95% 3 fewer — 5 more)	**Moderate** Due to serious imprecision [16]	Statins probably has little or no difference on cancer
Creatinine clearance 6 Important	Based on data from 4,112 participants in 17 studies. [17] (Randomized controlled) Follow up: Mean 14 months.	**45** mL/min (Mean) Difference:	**46** mL/min (Mean) **MD 1 higher** (CI 95% 0.44 higher — 1.55 higher)	**Moderate** Due to serious risk of bias [18]	Statins probably improves end of treatment creatinine clearance
Life participation 4 Important					No studies were found that looked at life participation
Fatigue 4 Important					No studies were found that looked at fatigue
LDL cholesterol 3 Not Important	Based on data from 2,183 participants in 24 studies. [19] (Randomized controlled) Follow up: Mean 13 months.	**3.9** mmol/L (Mean) Difference:	**3.9** mmol/L (Mean) **MD 1.13 lower** (CI 95% 1.33 lower — 0.93 lower)	**Low** Due to serious risk of bias, Due to serious inconsistency [20]	Statins may have little or no difference on ldl cholesterol

1. Systematic review [1] with included studies: [17], [48], [22], [62], [63], [34], [42], [9], [11], [50]. **Baseline/comparator:** Primary study. **Supporting references:** [80],

2. **Risk of Bias: serious.** Inadequate sequence generation/ generation of comparable groups, resulting in potential for selection bias. **Inconsistency: no serious. Indirectness: no serious. Publication bias: no serious.**
3. Systematic review [1] with included studies: [22], [62], [11], [17], [42], [48], [50]. **Baseline/comparator:** Primary study. **Supporting references:** [82],
4. **Inconsistency: serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
5. Systematic reviewwith included studies: [11]. **Baseline/comparator:** Primary study. **Supporting references:** [82],
6. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Inadequate sequence generation/ generation of comparable groups, resulting in potential for selection bias. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Only data from one study. **Publication bias: no serious.**
7. Systematic review [1] with included studies: [67], [69], [11], [62], [61], [50], [47], [42], [6], [38], [63], [9], [48], [22]. **Baseline/comparator:** Primary study. **Supporting references:** [81],
8. Systematic review [1] with included studies: [50], [42], [62], [17], [61], [48], [11], [6], [76], [22], [47], [63]. **Baseline/comparator:** Primary study. **Supporting references:** [81],
9. Systematic review [1] with included studies: [48], [63], [76], [62], [9], [11], [47], [61]. **Baseline/comparator:** Primary study. **Supporting references:** [81],
10. **Risk of Bias: serious.** Inadequate sequence generation/ generation of comparable groups, resulting in potential for selection bias. **Inconsistency: no serious. Indirectness: no serious. Publication bias: no serious.**
11. Systematic review [1] with included studies: [48], [17], [69]. **Baseline/comparator:** Primary study. **Supporting references:** [83],
12. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency: no serious. Indirectness: no serious. Publication bias: no serious.**
13. Systematic reviewwith included studies: [9], [6]. **Baseline/comparator:** Control arm of reference used for intervention.
14. **Risk of Bias: serious.** Inadequate sequence generation/ generation of comparable groups, resulting in potential for selection bias. **Inconsistency: serious.** Point estimates vary widely. **Indirectness: no serious. Imprecision: serious.** Low number of patients. **Publication bias: no serious.**
15. Systematic review [1] with included studies: JUPITER 2007, 4S 1993. **Baseline/comparator:** Systematic review. **Supporting references:** [4],
16. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious. Publication bias: no serious.**
17. Systematic review [1] with included studies: Hommel 1992, Sawara 2008, Ohsawa 2015, Yasuda 2004, [58], [74], [36], [41], [52], ESPLANADE 2010, Verma 2005, Nielsen 1993, [35], [19], [50], Lee 2002, ASUCA 2013. **Baseline/comparator:** Control arm of reference used for intervention.
18. **Risk of Bias: serious.** Inadequate sequence generation/ generation of comparable groups, resulting in potential for selection bias, Inadequate concealment of allocation during randomization process, resulting in potential for selection bias. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
19. Systematic review [1] with included studies: Zhang 1995, LORD 2006, ESPLANADE 2010, Lee 2002, Tonolo 1997, PREVEND IT 2000, Aranda 1994, Hommel 1992, Di Lullo 2005, Nielsen 1993, Ohsawa 2015, Abe 2011c, Lam 1995, Verma 2005, UK-HARP-I 2005, Sawara 2008, Goicoechea 2006, Mori 1992, Imai 1999, Fried 2001, Nakamura 2002, Yasuda 2004, Bianchi 2003, Panichi 2005. **Baseline/comparator:** Control arm of reference used for intervention.
20. **Risk of Bias: serious.** Incomplete data and/or large loss to follow up. **Inconsistency: serious.** The magnitude of statistical heterogeneity was high, with I^2: 92%.. **Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**

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Clinical Question/ PICO

Population: People with chronic kidney disease (eGFR 15 - 90 mL/min/1.73m^2)
Intervention: Statin therapy plus ezetimibe
Comparator: Statin therapy

Outcome Timeframe	**Study results and measurements**	**Comparator** Statin therapy	**Intervention** Statin therapy plus ezetimibe	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Myocardial infarction 9 Critical					No studies were found that looked at myocardial infarction
Stroke 9 Critical					No studies were found that looked at stroke
Hospitalisation of heart failure 9 Critical					No studies were found that looked at myocardial infarction

Outcome Timeframe	**Study results and measurements**	**Comparator** Statin therapy	**Intervention** Statin therapy plus ezetimibe	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Death 6 Important	Relative risk 0.95 (CI 95% 0.85 — 1.06) Based on data from 3,761 participants in 1 studies. [1] (Randomized controlled) Follow up: 18 months.	38 per 1000 Difference:	36 per 1000 **2 fewer per 1000** (CI 95% 6 fewer — 2 more)	**Low** Due to serious risk of bias, Due to serious imprecision [2]	Statins + ezetimibe may have little or no difference on all-cause mortality
Cardiovascular death 6 Important	Relative risk 1.06 (CI 95% 0.87 — 1.29) Based on data from 3,761 participants in 1 studies. [3] (Randomized controlled) Follow up: 18 months.	18 per 1000 Difference:	19 per 1000 **1 more per 1000** (CI 95% 2 fewer — 5 more)	**Low** Due to serious risk of bias, Due to serious imprecision [4]	Statins + ezetimibe may have little or no difference on cardiovascular mortality
Major cardiovascular events 6 Important	Relative risk 0.87 (CI 95% 0.78 — 0.97) Based on data from 3,761 participants in 1 studies. [5] (Randomized controlled) Follow up: 18 months.	113 per 1000 Difference:	98 per 1000 **15 fewer per 1000** (CI 95% 25 fewer — 3 fewer)	**Low** Due to serious risk of bias, Due to serious imprecision [6]	Statins + ezetimibe may decrease 3-point MACE
Rhabdomyolysis 6 Important	Relative risk 1.16 (CI 95% 0.42 — 3.18) Based on data from 3,761 participants in 1 studies. [7] (Randomized controlled) Follow up: 18 months.	2 per 1000 Difference:	2 per 1000 **0 fewer per 1000** (CI 95% 1 fewer — 4 more)	**Very low** Due to serious risk of bias, Due to very serious imprecision [8]	We are uncertain whether statins + ezetimibe increases or decreases rhabdomyolysis
Kidney failure 6 Important	Relative risk 1.08 (CI 95% 0.16 — 7.49) Based on data from 152 participants in 1 studies. [9] (Randomized controlled) Follow up: Mean 15 months.	2 per 1000 Difference:	2 per 1000 **0 fewer per 1000** (CI 95% 2 fewer — 13 more)	**Very low** Due to serious risk of bias, Due to very serious imprecision [10]	We are uncertain whether statin therapy plus ezetimibe increases or decreases kidney failure
Onset of diabetes 4 Important					No studies were found that looked at onset of diabetes
Memory loss 4 Important					No studies were found that looked at memory loss
Cancer 3 Not Important					No studies were found that looked at cancer

Outcome Timeframe	**Study results and measurements**	**Comparator** Statin therapy	**Intervention** Statin therapy plus ezetimibe	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Fatigue 4 Important					No studies were found that looked at fatigue
Life participation 4 Important					No studies were found that looked at life participation

1. Systematic reviewwith included studies: [85]. **Baseline/comparator:** Primary study.
2. **Risk of Bias: serious.** Inadequate sequence generation/ generation of comparable groups, resulting in potential for selection bias, Inadequate concealment of allocation during randomization process, resulting in potential for selection bias. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Only data from one study. **Publication bias: no serious.**
3. Systematic reviewwith included studies: [85]. **Baseline/comparator:** Primary study.
4. **Risk of Bias: serious.** Inadequate sequence generation/ generation of comparable groups, resulting in potential for selection bias, Inadequate concealment of allocation during randomization process, resulting in potential for selection bias. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Only data from one study. **Publication bias: no serious.**
5. Systematic reviewwith included studies: [85]. **Baseline/comparator:** Control arm of reference used for intervention.
6. **Risk of Bias: serious.** Inadequate sequence generation/ generation of comparable groups, resulting in potential for selection bias, Inadequate concealment of allocation during randomization process, resulting in potential for selection bias. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Only data from one study. **Publication bias: no serious.**
7. Systematic reviewwith included studies: [85]. **Baseline/comparator:** Control arm of reference used for intervention.
8. **Risk of Bias: serious.** Inadequate sequence generation/ generation of comparable groups, resulting in potential for selection bias, Inadequate concealment of allocation during randomization process, resulting in potential for selection bias. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Wide confidence intervals, Only data from one study. **Publication bias: no serious.**
9. Systematic reviewwith included studies: [90]. **Baseline/comparator:** Control arm of reference used for intervention.
10. **Risk of Bias: serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Wide confidence intervals, Only data from one study. **Publication bias: no serious.**

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Strong recommendation

Reviewed, no new evidence

We recommend Aboriginal and Torres Strait Islander Peoples and Māori with chronic kidney disease (reduced GFR and/or albuminuria/proteinuria) and an absolute cardiovascular risk of 5% or higher should receive statins (with or without ezetimibe) to prevent cardiovascular events and death.

Low certainty of the evidence

Evidence To Decision

Benefits and harms

Substantial net benefits of the recommended alternative

No randomised controlled trials have examined statins with or without ezetimibe in indigenous people with CKD, and no pre-specified subgroups of indigenous people have been reported in trials. However, the benefits of statins with or without ezetimibe highlighted in our systematic review of patients with CKD *[92]* are expected to be no different in Aboriginal and Torres Strait Islanders people and Māori people.

Certainty of the Evidence

Low

The certainty of the evidence is indirect as the evidence is derived from general CKD population trials. These general CKD population randomised control trials found moderate certainty of the evidence of benefit and minimal harms of statins with or without ezetimibe. The certainty of the evidence has downgraded from moderate to low because of the indirectness of the evidence.

Values and preferences

There is a paucity of evidence on the perspectives and preferences of Indigenous people on lipid-lowering therapy. The Work Group did not include any patients or caregivers of Aboriginal or Torres Strait Islander Peoples, or Māori. However, the Work Group did include Indigenous Health Advancement experts, including nurses and General Practitioners who considered the findings from the qualitative evidence synthesis of the general population *[93]* may be relevant to Indigenous Peoples.

Resources and other considerations

Statins in Australia are publicly funded through the Pharmaceutical Benefits Scheme. Eligibility criteria of statins for Aboriginal or Torres Strait Islander Peoples is different to non-Indigenous people.
“any Indigenous person with diabetes mellitus, and patients with lower than the highest absolute cardiovascular risk a lipid criteria of (total cholesterol >6.5 mmol/L or total cholesterol 5.5 mmol/L and HDL cholesterol 1 mmol/L).”
Generic versions of statins are available in Australia at a relatively low cost. Despite the availability of generic versions of statins, many Aboriginal and Torres Strait Islander people are disadvantaged due to health inequities. These may be high out-of-pocket costs. However, the Closing the Gap – Pharmaceutical Benefit Scheme Co-payment Measure may support Aboriginal and Torres Strait Islanders People with chronic kidney disease to access statin therapy at a lower cost. Statins (atorvastatin, simvastatin, pravastatin) are publicly subsidised for all patients in New Zealand.
There is no Aboriginal or Torres Strait Islander eligibility criteria qualifier for the use of ezetimibe in Australia. In New Zealand, ezetimibe is publicly funded through special authority for patients with an absolute risk of cardiovascular disease of at least 15% over 5 years, elevated cholesterol (2 mmol/L), and intolerance of statin use.

As highlighted previously, statins with or without ezetimibe, are cost-effective in Australia and New Zealand *[94]*. The use of statins in both General Practice and Aboriginal Community Controlled Health Services in the general population are cost-effective *[95]*.

Rationale

Aboriginal and Torres Strait Islander Peoples in Australia and Māori in Aotearoa New Zealand are at increased risk of cardiovascular disease due to increased exposure to risk factors for cardiovascular complications *[109][110]*. The underlying evidence on benefits

and harms, patient preferences and values, and cost-effectiveness is derived from general CKD population studies.

The Work Group considered that these data would apply to Indigenous Peoples with CKD. Other clinical practice guidelines recommend cardiovascular risk assessments are undertaken at least ten years earlier for Indigenous Peoples than for non-Indigenous people *[96][100]*. Given that recommendation a. does not include an age limit, the Work Group proposed a lower absolute cardiovascular risk (≥5%) for Aboriginal and Torres Strait Islander Peoples and Māori due to higher rates of cardiovascular disease in this population.

Despite the low certainty of the evidence, the higher prevalence of absolute cardiovascular risk and less access to lipid-lowering therapy in Indigenous people guided the recommendation. The Work Group felt that Indigenous people with CKD and 5% absolute risk of cardiovascular disease would benefit from receiving statins with or without ezetimibe to prevent cardiovascular events and death.

Clinical Question/ PICO

Population: People with chronic kidney disease (eGFR ≥15 mL/min/1.73m^2)
Intervention: Statin therapy
Comparator: Placebo or standard of care

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo or standard of care	**Intervention** Statin therapy	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Myocardial infarction 9 Critical	Relative risk 0.55 (CI 95% 0.42 — 0.73) Based on data from 9,475 participants in 10 studies. [1] (Randomized controlled) Follow up: Mean 39 months.	15 per 1000 Difference:	8 per 1000 **7 fewer per 1000** (CI 95% 9 fewer — 4 fewer)	**Moderate** Due to serious risk of bias [2]	Statins probably decreases fatal and non-fatal myocardial infarction
Stroke 9 Critical	Relative risk 0.64 (CI 95% 0.37 — 1.08) Based on data from 9,115 participants in 7 studies. [3] (Randomized controlled) Follow up: Mean 40 months.	13 per 1000 Difference:	8 per 1000 **5 fewer per 1000** (CI 95% 8 fewer — 1 more)	**Moderate** Due to serious inconsistency [4]	Statins probably has little or no difference on fatal and non-fatal stroke
Hospitalisation due to heart failure 9 Critical	Relative risk 0.7 (CI 95% 0.37 — 1.32) Based on data from 579 participants in 1 studies. [5] (Randomized controlled) Follow up: 54 months.	22 per 1000 Difference:	15 per 1000 **7 fewer per 1000** (CI 95% 14 fewer — 7 more)	**Low** Due to serious imprecision, Due to serious risk of bias [6]	There were too few who experienced the hospitalisation due to heart failure, to determine whether statins made a difference
Major cardiovascular events 6 Important	Relative risk 0.72 (CI 95% 0.66 — 0.79) Based on data from 36,156 participants in 14 studies. [7] (Randomized controlled) Follow up: Mean 46 months.	113 per 1000 Difference:	81 per 1000 **32 fewer per 1000** (CI 95% 38 fewer — 24 fewer)	**High**	Statins decreases major cardiovascular events
Death	Relative risk 0.8 (CI 95% 0.7 — 0.9)	48 per 1000	38 per 1000	**High**	Statins decreases all-cause mortality

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo or standard of care	**Intervention** Statin therapy	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
6 Important	Based on data from 28,723 participants in 12 studies. [8] (Randomized controlled) Follow up: Mean 40 months.	Difference:	**10 fewer per 1000** (CI 95% 14 fewer — 5 fewer)		
Cardiovascular mortality 6 Important	Relative risk 0.77 (CI 95% 0.69 — 0.87) Based on data from 19,182 participants in 8 studies. [9] (Randomized controlled) Follow up: Mean 39 months.	24 per 1000 Difference:	18 per 1000 **6 fewer per 1000** (CI 95% 7 fewer — 3 fewer)	Moderate Due to serious risk of bias [10]	Statins probably decreases cardiovascular mortality
Kidney failure 6 Important	Relative risk 0.98 (CI 95% 0.91 — 1.05) Based on data from 6,704 participants in 3 studies. [11] (Randomized controlled) Follow up: Mean 34 months.	2 per 1000 Difference:	2 per 1000 **0 fewer per 1000** (CI 95% 0 fewer — 0 fewer)	Moderate Due to serious risk of bias [12]	Statins probably has little or no difference on end-stage kidney disease
Rhabdomyolysis 6 Important	Relative risk 3.07 (CI 95% 0.13 — 75.37) Based on data from 2,618 participants in 2 studies. [13] (Randomized controlled) Follow up: Mean 64 months.	2 per 1000 Difference:	6 per 1000 **4 more per 1000** (CI 95% 2 fewer — 149 more)	Very low Due to serious risk of bias, Due to serious inconsistency, Due to serious imprecision [14]	We are uncertain whether statins increases or decreases elevated creatinine kinase (rhabdomyolysis)
Onset of diabetes 4 Important					No studies were found that looked at onset of diabetes
Memory loss 4 Important					No studies were found that looked at memory loss
Cancer 3 Not Important	Relative risk 1.03 (CI 95% 0.82 — 1.3) Based on data from 5,581 participants in 2 studies. [15] (Randomized controlled) Follow up: Mean 44 months.	15 per 1000 Difference:	15 per 1000 **0 fewer per 1000** (CI 95% 3 fewer — 5 more)	Moderate Due to serious imprecision [16]	Statins probably has little or no difference on cancer
Creatinine clearance		45	46	Moderate Due to serious risk	Statins probably improves end of treatment

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo or standard of care	**Intervention** Statin therapy	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
6 Important	Based on data from 4,112 participants in 17 studies. [17] (Randomized controlled) Follow up: Mean 14 months.	mL/min (Mean) Difference:	mL/min (Mean) **MD 1 higher** (CI 95% 0.44 higher — 1.55 higher)	of bias [18]	creatinine clearance
Life participation 4 Important					No studies were found that looked at life participation
Fatigue 4 Important					No studies were found that looked at fatigue
LDL cholesterol 3 Not Important	Based on data from 2,183 participants in 24 studies. [19] (Randomized controlled) Follow up: Mean 13 months.	**3.9** mmol/L (Mean) Difference:	**3.9** mmol/L (Mean) **MD 1.13 lower** (CI 95% 1.33 lower — 0.93 lower)	**Low** Due to serious risk of bias, Due to serious inconsistency [20]	Statins may have little or no difference on ldl cholesterol

1. Systematic review [1] with included studies: [17], [48], [22], [62], [63], [34], [42], [9], [11], [50]. **Baseline/comparator:** Primary study. **Supporting references:** [80],
2. **Risk of Bias: serious.** Inadequate sequence generation/ generation of comparable groups, resulting in potential for selection bias. **Inconsistency: no serious. Indirectness: no serious. Publication bias: no serious.**
3. Systematic review [1] with included studies: [22], [62], [11], [17], [42], [48], [50]. **Baseline/comparator:** Primary study. **Supporting references:** [82],
4. **Inconsistency: serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
5. Systematic reviewwith included studies: [11]. **Baseline/comparator:** Primary study. **Supporting references:** [82],
6. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Inadequate sequence generation/ generation of comparable groups, resulting in potential for selection bias. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Only data from one study. **Publication bias: no serious.**
7. Systematic review [1] with included studies: [67], [69], [11], [62], [61], [50], [47], [42], [6], [38], [63], [9], [48], [22]. **Baseline/comparator:** Primary study. **Supporting references:** [81],
8. Systematic review [1] with included studies: [50], [42], [62], [17], [61], [48], [11], [6], [76], [22], [47], [63]. **Baseline/comparator:** Primary study. **Supporting references:** [81],
9. Systematic review [1] with included studies: [48], [63], [76], [62], [9], [11], [47], [61]. **Baseline/comparator:** Primary study. **Supporting references:** [81],
10. **Risk of Bias: serious.** Inadequate sequence generation/ generation of comparable groups, resulting in potential for selection bias. **Inconsistency: no serious. Indirectness: no serious. Publication bias: no serious.**
11. Systematic review [1] with included studies: [48], [17], [69]. **Baseline/comparator:** Primary study. **Supporting references:** [83],
12. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency: no serious. Indirectness: no serious. Publication bias: no serious.**
13. Systematic reviewwith included studies: [9], [6]. **Baseline/comparator:** Control arm of reference used for intervention.
14. **Risk of Bias: serious.** Inadequate sequence generation/ generation of comparable groups, resulting in potential for selection bias. **Inconsistency: serious.** Point estimates vary widely. **Indirectness: no serious. Imprecision: serious.** Low number of

patients. **Publication bias: no serious.**

15. Systematic review [1] with included studies: JUPITER 2007, 4S 1993. **Baseline/comparator:** Systematic review. **Supporting references:** [4],

16. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious. Publication bias: no serious.**

17. Systematic review [1] with included studies: Hommel 1992, Sawara 2008, Ohsawa 2015, Yasuda 2004, [58], [74], [36], [41], [52], ESPLANADE 2010, Verma 2005, Nielsen 1993, [35], [19], [50], Lee 2002, ASUCA 2013. **Baseline/comparator:** Control arm of reference used for intervention.

18. **Risk of Bias: serious.** Inadequate sequence generation/ generation of comparable groups, resulting in potential for selection bias, Inadequate concealment of allocation during randomization process, resulting in potential for selection bias. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**

19. Systematic review [1] with included studies: Zhang 1995, LORD 2006, ESPLANADE 2010, Lee 2002, Tonolo 1997, PREVEND IT 2000, Aranda 1994, Hommel 1992, Di Lullo 2005, Nielsen 1993, Ohsawa 2015, Abe 2011c, Lam 1995, Verma 2005, UK-HARP-I 2005, Sawara 2008, Goicoechea 2006, Mori 1992, Imai 1999, Fried 2001, Nakamura 2002, Yasuda 2004, Bianchi 2003, Panichi 2005. **Baseline/comparator:** Control arm of reference used for intervention.

20. **Risk of Bias: serious.** Incomplete data and/or large loss to follow up. **Inconsistency: serious.** The magnitude of statistical heterogeneity was high, with I^2: 92%.. **Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**

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52. Nakamura T, Ushiyama C, Hirokawa K, Osada S, Inoue T, Shimada N, et al. : Effect of cerivastatin on proteinuria and urinary podocytes in patients with chronic glomerulonephritis. Nephrology, Dialysis, Transplantation 2002;17(5):798-802 Pubmed

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4. Ungraded suggestions for clinical care

Good practice statement

Updated

Patients with albuminuria (A2 3—300 mg/g and A3 >300 mg/g) should receive statins (with or without ezetimibe)

Rationale

Most cardiovascular risk calculators do not include all prognostic variables, such as albuminuria and hypercholesterolemia. In patients with CKD, elevated albuminuria (A2 and A3) is predictive of death and cardiovascular events *[101][102]*. Patients with primary hypercholesterolaemia are at the highest risk of premature cardiovascular events *[103]*. Given the frailty of current cardiovascular risk calculators, the Work Group decided that patients with CKD with albuminuria or primary hypercholesterolaemia regardless of absolute cardiovascular risk would benefit from treatment with a statin with or without ezetimibe.

Good practice statement

New

Patients with chronic kidney disease (reduced GFR and/or albuminuria/proteinuria) and absolute cardiovascular risk of 5% to 10% should discuss the potential therapeutic use of a statin therapy with their healthcare providers.

Rationale

The guideline Work Group recognises that some patients with CKD and moderate absolute cardiovascular risk may benefit from statin therapy. Despite limited randomised controlled trial evidence for this population, the benefits of statin therapy far outweigh the possibility of serious adverse effects. The potential use of statin therapy in these patients should be according to clinical judgement.

Good practice statement

Reviewed, no new evidence

Clinicians should ensure that patients and their carer/family learn about the effects that statin therapy with or without ezetimibe has to prevent cardiovascular events and death.

Rationale

The systematic review of qualitative studies on attitudes to taking statin therapy identified that patients may no adhere to treatment due to the lack of visibility that statins have on patients health *[104]*. As a result, the Work Group, including patient and carer representatives emphasised the importance of education to patients, carers and family members of the effects of statin therapy and how they prevent cardiovascular events and death.

5. Suggestions for future research

- Long-term follow-up of randomised controlled trials to assess the safety of therapy in patients with CKD (eGFR ≥15 ml/min/1.73m^2) are required. New trials should be designed to assess important safety outcomes, such as rhabdomyolysis, and patient-reported outcomes, such as fatigue, life participation and memory loss.
- Further large randomised controlled trials comparing the relative safety and efficacy of statins combined with ezetimibe to statins alone in patients with CKD (eGFR ≥15 ml/min/1.73m^2) should be performed.
- Outcome trials examining the use of cardiovascular imaging for determining the suitability of patients with CKD (eGFR ≥15 ml/min/1.73m^2) to receive lipid-lowering therapy should be undertaken.

6. Conflicts of interest and funding

Conflicts of interest

David Johnson has received consultancy/honorarium from Baxter Healthcare, Fresenius Medical Care, Astra Zeneca, AWAK, Ono and Bayer; has received support for travel from Amgen, and research funding for his institution from Baxter Healthcare, Fresenius Medical Care.

Rathika Krishnasamy has received consultancy/honorarium from Baxter Healthcare; travel support from Amgen and Baxter Healthcare; and received funding for investigator-initiated research from Baxter Healthcare.

Richard Phoon has received consultancy/honorarium from AztraZeneca, NovoNordisk, Sanofi-Genzyme and support for travel from Novartis.

Rob Walker, David Tunnicliffe, Suetonia Palmer, Llyod Blythen, Brydee Cashmore, Karam Koster, Kelly Lambert, Judy Mullan, Andrea Miller, Jane Boag, Maira Patu, Natasha Trompf, Liz Riz have no conflicts of interests to declare.

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7. Appendix 1. Guideline development methodology

This is an update to a CARI Guideline on Medical therapies to reduce chronic kidney disease progression and cardiovascular risk: lipid lowering therapy published in 2012 *[30]*, that was topic in CARI early chronic kidney disease guidelines *[33]*. The guidelines were updated according to the Institute of Medicine and GRADE standards for guideline development *[?][111]*
The guideline update was transitioned to a living guideline. The topic is a priority for decision-making due to high rates of cardiovascular morbidity and mortality for patients with CKD, uncertainty regarding treatment effects on critical and important outcomes, and new emerging evidence. The objective of this project was to update evidence-based clinical practice guidelines on lipid-lowering therapy in patients with CKD (not on dialysis), and to remain currency of the guidelines by evaluating new evidence as it emerges and update the guideline as required.

Guideline scope
The scope of the guideline was informed by the previous guideline and discussed at the first face-to-face meeting with the Work Group. The scope of the guideline focused on statin and ezetimibe therapy. Other lipid-lowering therapies such as fibrates were considered outside the scope. The guideline Work Group included expertise from multiple medical disciplines, Indigenous health, Allied Health, nursing, and consumers across Australia and New Zealand.

Evidence review
In partnership with Cochrane Kidney and Transplant, the Cochrane review, HMG CoA reductase inhibitors (statins) for people with chronic kidney disease not requiring dialysis *[29]* was identified and has been transitioned to a living systematic review. This review forms the underlying evidence on the benefits and harms of statins in patients with CKD not requiring dialysis. The review was undertaken according to guidance from Cochrane on the production and publication of living systematic reviews. The review is being published concurrently and will be maintained as a living systematic review *[92]*. Additionally, Cochrane CENTRAL and MEDLINE were searched on the 31st August 2020 on ezetimibe in patients with CKD, the search strategies are provided in Appendix 2.

The Work Group completed a survey online via Qualtrics to determine the critical and important outcomes that underpinned the evidence review. Critical and important outcomes are listed in Table 1.

Table 1. Critical and important outcomes for evidence review

Outcome	Rating
Non-fatal stroke	Critical
Non-fatal myocardial infarction	Critical
Hospitalisatiojn due to heart failure	Critical
Kidney failure	Important
Death	Important
Cardiovascular death	Important
Cardiovascular events	Important
Rhabdomyolysis	Important
Cancer	Important
Fatigue	Important
Life participation	Important
Memory loss	Important
Onset of diabetes	Important
Creatinine clearance	Important
LDL cholesterol	Important

Developing the recommendations
The findings from the evidence review were presented at face-to-face meeting with the Work Group and the recommendations were drafted by the Work Group and Work Group Co-Chairs. Recommendations were revised in a multistep process during face-to-face

meetings and by email communication. The final draft was sent for external public review and peer-review. Based on feedback, the guideline was revised by the Work Group and approved the final version of the guideline.

Patient preferences and values

Three patients were Work Group members and provided insights to the lived experience of statin use in patients with chronic kidney disease. No formal evidence review was undertaken to assess patient preferences. However, key systematic reviews on the topic were identified by the Work Group and informed the development of recommendations.

Grading the strength of recommendations

The strength of a recommendation is graded as strong [1] or conditional [2] (Table 2). The strength of a recommendation was determined by the balance of benefits and harms across all critical and important outcomes, the grading of the overall quality of the evidence, patient preferences and values, equity, and resources and other considerations.

Table 2. CARI Guidelines nomenclature and description for grading recommendations

Grade	Implications - Patients	Implications - Clinicians	
Level 1 "We recommend"	Most people in your situation would want the recommended course of action and only a small proportion would not.	Most patients should receive the recommended course of action.	The in r
Level 2 "We suggest"	The majority of people in your situation would want the recommended course of action, but many would not.	Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision consistent with her or his values and preferences.	The sub sta

* Adapted from GRADE working group (www.gradeworkinggroup.org)

The overall quality of the evidence

The overall quality of the evidence was based on the certainty of the evidence for all critical and important outcomes, taking into account relative importance for each outcome to the population of interest. The overall quality of the evidence was graded (A, B, C or D) (Table 3)

Table 3. Classification for certainty of the evidence

GRADE	Certainity of the evidence	Meaning
A	High	We are confident that the true effect lies close to that of the estimate of the effect.
B	Moderate	The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is subs
C	Low	The true effect may be substantially different from the estimate of the effect.
D	Very low	The estimate of effect is very uncertain, and often will be far from the truth.

Processes for updating

The Cochrane living systematic review and evidence review on ezetimibe will updated every three months, with literature databases searched and newly identified studies incorporated into the evidence review findings. Changes in the direction of treatment effects and/or certainty of the evidence for critical and important outcomes, and any new safety concerns identified in the newly published literature will be highlighted to the Work Group to trigger a potential updating of the guideline. The guideline may be transitioned back to a traditional guideline if the evidence on critical and important outcomes remains relatively stable, based on formal cumulative meta-analysis assessment or there is no or few ongoing studies, to be assessed via www.clinicaltrials.gov.

8. Appendix 2 - Search strategies

STATINS SEARCH - 13th September 2021
CENTRAL

1. pre-dialy* or predialy*:ti,ab,kw in Clinical Trials
2. MeSH descriptor Kidney Diseases, this term only
3. chronic kidney*:ti,ab,kw in Clinical Trials
4. chronic renal*:ti,ab,kw in Clinical Trials
5. MeSH descriptor Renal Insufficiency, this term only
6. MeSH descriptor Renal Insufficiency, Chronic explode all trees
7. (CKF or CKD or CRF or CRD):ti,ab,kw in Clinical Trials
8. ur?emi*:ti,ab,kw in Clinical Trials
9. MeSH descriptor Uremia explode all trees in Clinical Trials
10. (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9)
11. MeSH descriptor Hydroxymethylglutaryl-CoA Reductase Inhibitors explode all trees
12. hydroxymethylglutaryl-CoA reductase inhibitor*:ti,ab,kw in Clinical Trials
13. HMG CoA reductase inhibitor*:ti,ab,kw in Clinical Trials
14. HMG Co A reductase inhibitor*:ti,ab,kw in Clinical Trials
15. statin*:ti,ab,kw in Clinical Trials
16. atorvastatin:ti,ab,kw or cerivastatin:ti,ab,kw or dalvastatin:ti,ab,kw or fluindostatin:ti,ab,kw in Clinical Trials
17. fluvastatin: ti,ab,kw or simvastatin:ti,ab,kw or lovastatin:ti,ab,kw or pitavastatin:ti,ab,kw in Clinical Trials
18. pravastatin:ti,ab,kw or rosuvastatin:ti,ab,kw or simvastatin:ti,ab,kw in Clinical Trials
19. meglutol:ti,ab,kw or mevinolin:ti,ab,kw or monacolin:ti,ab,kw or pravachol:ti,ab,kw or lipex:ti,ab,kw or lipitor:ti,ab,kw or zocor:ti,ab,kw or mevacor:ti,ab,kw or lescol:ti,ab,kw or baycol:ti,ab,kw in Clinical Trials
20. (#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19)
21. (#10 AND #20)

MEDLINE

1. Renal Insufficiency/
2. exp Renal Insufficiency, Chronic/
3. Kidney Diseases/
4. (chronic kidney or chronic renal).tw.
5. (CKF or CKD or CRF or CRD).tw.
6. (predialysis or pre-dialysis).tw.
7. exp Uremia/
8. uremi.tw.
9. Diabetic Nephropathies/
10. diabetic kidney disease$.tw.
11. diabetic nephropath$.tw.
12. or/1-11
13. exp Hydroxymethylglutaryl-CoA Reductase Inhibitors/
14. "hydroxymethylglutaryl-CoA reductase inhibitor$".tw.
15. ("HMG CoA reductase inhibitor$" or "HMG Co A reductase inhibitor$").tw.
16. statin$.tw.
17. atorvastatin.tw.
18. cerivastatin.tw.
19. dalvastatin.tw.
20. fluindostatin.tw.
21. fluvastatin.tw.
22. lovastatin.tw.
23. pitavastatin.tw.
24. pravastatin.tw.
25. rosuvastatin.tw.
26. simvastatin.tw.
27. (meglutol or mevinolin$ or monacolin$ or pravachol or lipex or lipitor or zocor or mevacor or lescol or baycol).tw.
28. or/13-27
29. and/12,28

EMBASE

1. Kidney Disease/
2. Chronic Kidney Disease/
3. Kidney Failure/
4. Chronic Kidney Failure/
5. Kidney dysfunction/
6. (chronic kidney or chronic renal).tw.
7. (CKF or CKD or CRF or CRD).tw.
8. (pre-dialy$ or predialy$).tw.
9. or/1-8
10. exp Hydroxymethylglutaryl Coenzyme a Reductase Inhibitor/
11. hydroxymethylglutaryl-CoA reductase inhibitor$.tw.
12. HMG CoA reductase inhibitor$.tw.
13. HMG Co A reductase inhibitor$.tw.
14. statin$.tw.
15. atorvastatin.tw.
16. cerivastatin.tw.
17. dalvastatin.tw.
18. fluindostatin.tw.
19. fluvastatin.tw.
20. lovastatin.tw.
21. pitavastatin.tw.
22. pravastatin.tw.
23. rosuvastatin.tw.
24. simvastatin.tw.
25. (meglutol or mevinolin$ or monacolin$ or pravachol or lipex or lipitor or zocor or mevacor or lescol or baycol).tw.
26. or/10-25
27. and/9,26

EZETIMIBE SEARCH - 13th September 2021
CENTRAL

1. pre-dialy* or predialy*:ti,ab,kw in Clinical Trials
2. MeSH descriptor Kidney Diseases, this term only
3. chronic kidney*:ti,ab,kw in Clinical Trials
4. chronic renal*:ti,ab,kw in Clinical Trials
5. MeSH descriptor Renal Insufficiency, this term only
6. MeSH descriptor Renal Insufficiency, Chronic explode all trees
7. (CKF or CKD or CRF or CRD):ti,ab,kw in Clinical Trials
8. ur?emi*:ti,ab,kw in Clinical Trials
9. MeSH descriptor Uremia explode all trees in Clinical Trials
10. (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9)
11. MeSH descriptor: [Ezetimibe] this term only
12. ezetimibe:ti,ab,kw
13. Zetia:ti,ab,kw
14. Ezetrol:ti,kw,ab
15. #11 or #12 or #13 or #14
16. #10 and #15

MEDLINE

1. Renal Insufficiency/
2. exp Renal Insufficiency, Chronic/
3. Kidney Diseases/
4. (chronic kidney or chronic renal).tw.
5. (CKF or CKD or CRF or CRD).tw.
6. (predialysis or pre-dialysis).tw.
7. exp Uremia/
8. uremi.tw.

9. Diabetic Nephropathies/
10. diabetic kidney disease$.tw.
11. diabetic nephropath$.tw.
12. or/1-11
13. *Ezetimibe/
14. ezetimibe*.tw.
15. Zetia.tw.
16. Ezetrol.tw.
17. or/13-16
18. randomised controlled trial.pt.
19. controlled clinical trial.pt.
20. randomized.ab.
21. placebo.ab.
22. clinical trials as topic/
23. randomly.ab.
24. (crossover or cross-over).tw.
25. Cross-over Studies/
26. trial.ti.
27. or/18-26
28. animals/ not (humans/ and animals/)
29. 27 not 28
30. 12 and 17 and 28

9.

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