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ORIGINAL ARTICLE

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Australian and New Zealand Living Guideline cholesterol-lowering therapy for people with chronic kidney disease (CARI Guidelines): Reducing the evidence-practice gap

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Abstract

Aim: People with chronic kidney disease experience high rates of cardiovascular disease. Cholesterol-lowering therapy is a mainstay in the management but there is uncertainty in the treatment effects on patient-important outcomes, such as fatigue and rhabdomyolysis. Here, we summarise the updated CARI Australian and New

CARI Guidelines Steering Committee: Names as listed in the acknowledgements.

David W. Johnson and Robert Walker contributed equally to the design and review of the guidelines; both were Co-Convenors for the Guideline Working Group.

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Zealand Living Guidelines on cholesterol-lowering therapy in chronic kidney disease.

Methods: We updated a Cochrane review and monitored newly published studies weekly to inform guideline development according to international standards. The Working Group included expertise from nephrology, cardiology, Indigenous Health, guideline development and people with lived experience of chronic kidney disease.

Results: The guideline recommends people with chronic kidney disease (eGFR ≥15 mL/min/1.73 m^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 (strong recommendation, moderate certainty evidence). The guidelines also recommends a lower absolute cardiovascular risk threshold (≥5%) for Aboriginal and Torres Strait Islander Peoples and Māori with chronic kidney disease to receive statin therapy (with or without ezetimibe) (strong recommendation, low certainty evidence). The evidence was actively surveyed from 2020–2023 and updated as required. No changes to guideline recommendations were made, with no new data on the balance and benefits of harms.

Conclusions: The development of living guidelines was feasible and provided the opportunity to update recommendations to improve clinical decision-making in real-time. Living guidelines provide the opportunity to transform chronic kidney disease guidelines.

KEYWORDS
cholesterol lowering therapy, chronic kidney disease, clinical practice guideline

Summary at a glance

In people >30 with chronic kidney disease not requiring dialysis and a 5-year cardiovascular risk ≥10% cholesterol-lowering therapy is effective at preventing death and cardiovascular events with minimal harms. Indigenous populations should receive cholesterol-lowering therapy at a lower absolute cardiovascular risk (≥5%) due to a higher burden of cardiovascular disease.

1 | SCOPE AND PROCESSES OF THE GUIDELINE

This Guideline is an update of the Guideline subtopic: Medical therapies that was part of the wider CARI Early Chronic Kidney Disease Guideline.[1] The Guideline was transitioned to a Living Guideline according to expert methodological standards[2,3] due to high rates of cardiovascular morbidity and mortality for patients with chronic kidney disease (CKD), uncertainty regarding treatment effects on critical and important outcomes, and new emerging evidence.

The scope of this Guideline was cholesterol-lowering therapy in adults with CKD (not receiving dialysis) with a focus on Indigenous and non-Indigenous Australian and New Zealand adults over 30 years of age. The intended users include primary care providers, consumers and their caregivers, clinical specialists, nephrologists, health care practitioners, program managers, and policymakers. The Guideline was overseen by a multidisciplinary guideline panel including three consumers with lived experience of cholesterol-lowering therapy. The Guideline provides recommendations concerning statin therapy and ezetimibe in adults with CKD after a systematic examination of the underlying evidence. The Cochrane review, HMG CoA reductase inhibitors (statins) for people with CKD not requiring dialysis, has been updated as a Living Systematic Review and has formed the underlying evidence synthesis for the Living Guideline, following standards set by Cochrane.[4] An additional search was done on the use of ezetimibe therapy, in addition to the systematic review and was included in the evidence review for the Guideline. This was outside of the scope of the Cochrane review, but after discussions, the workgroup felt ezetimibe therapy needed to be included in the guideline. Eight studies were identified from the search, and the certainty of evidence was assessed using GRADE, which covers the domains of study limitations (Cochrane risk of bias 1.0 tool), inconsistency, indirectness, imprecision, and publication bias (Figure 1). Further details are available in the supplementary files.[5,6]

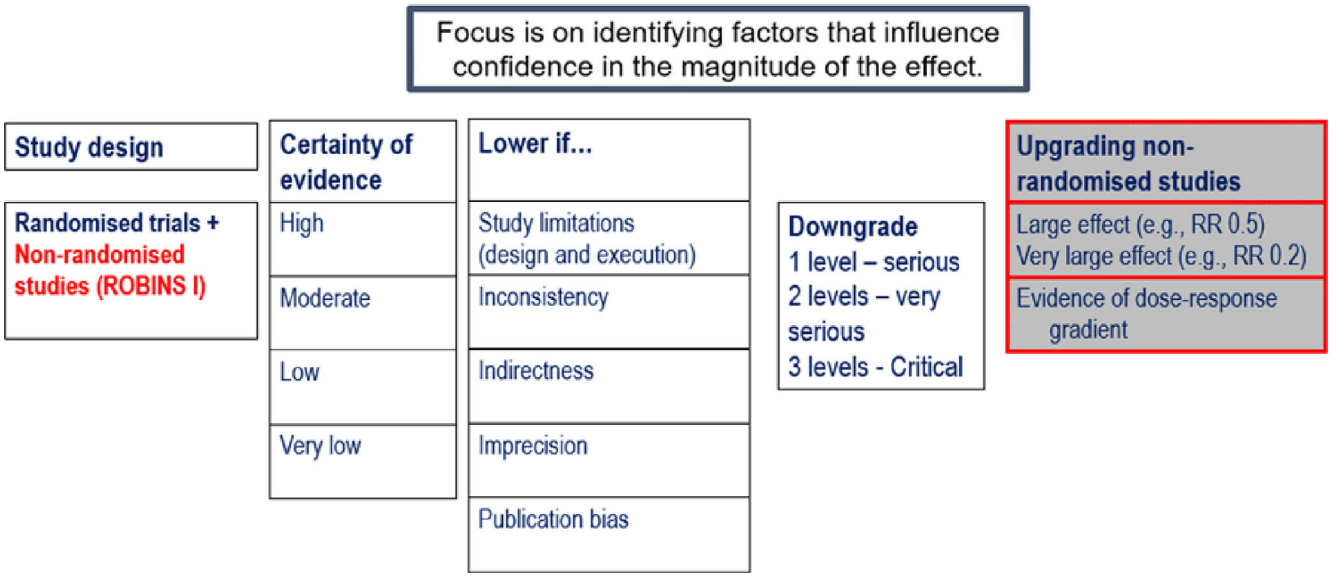

FIGURE 1 Factors that influence confidence in the magnitude of the effect.

The guidelines were first finalized in January 2021, and weekly evidence surveillance occurred through searching the medical literature database from the inception of the guideline update (May 2020) to 25th January 2023. There were 662 reports of studies screened throughout the weekly evidence surveillance period. An updated review of the evidence was circulated to the guideline Working Group when newly incorporated evidence changed the balance of benefits and harms and the certainty of the evidence, which occurred once in September 2021. The Working Group reviewed the updated evidence to either update or maintain the recommendations as needed, with no changes to recommendations required in September 2021. Lifestyle modification and fibrate therapy were considered beyond the scope of the Guideline. The full methods can be found as an Appendix S1 to the guidelines on the CARI Guidelines website.

The updated Guidelines is hosted on the CARI Guidelines website and digitally on MAGICapp (https://app.magicapp.org/#/guideline/EgJmpn).

TABLE 1 Critical and important outcomes for evidence review.

Outcome	Rating
Non-fatal stroke	Critical
Non-fatal myocardial infarction	Critical
Hospitalization 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

2 | BACKGROUND

Chronic Kidney Disease (CKD) has a steady prevalence rate in Australia and Aotearoa New Zealand and is a known risk factor for cardiovascular disease.[7] People with CKD (eGFR 15–60 mL/min/1.73 m^2) have similar risks of death and cardiovascular events as people with existing cardiovascular disease. The management of CKD incurs increasing healthcare costs.[8,9] Timely identification and application of effective medical therapies may reduce the progression of CKD and cardiovascular disease risk by up to 50%[10] and help to reduce rising healthcare costs.

Abnormal profiles of serum cholesterol and triglycerides are prevalent in people with CKD,[11] and may accelerate the development of cardiovascular disease and progression of CKD.[12,13] The cardioprotective effects of statin therapy for both primary and secondary prevention in patients with CKD have been well established,[14–16] as has statin therapy combined with ezetimibe.[16] However, the effect of statin therapy with or without ezetimibe on the progression of CKD remains largely unknown.[17]

This CARI Living Guideline aims to review the current synthesized evidence of lipid-lowering therapy based on critical and important outcomes identified by the Guideline panel (Table 1). It also aims to develop recommendations for clinical care regarding the use of statin therapy with or without ezetimibe in adults with CKD and update these recommendations as new information emerges.

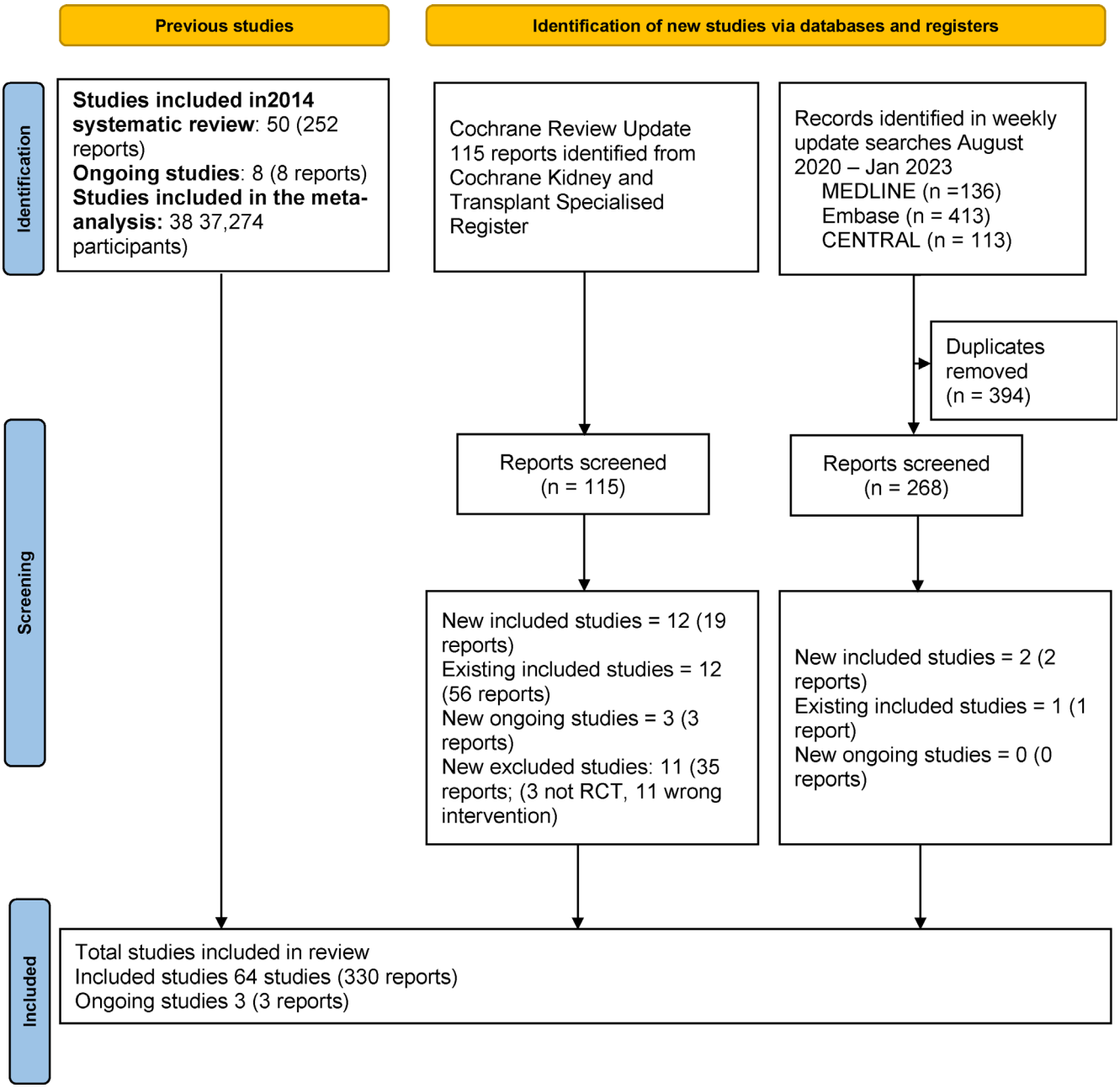

FIGURE 2 PRISMA diagram of included studies.

3 | GUIDELINE RECOMMENDATIONS

a. We recommend that people >30 years old with chronic kidney disease not receiving dialysis and a 5-year absolute cardiovascular risk of 10% or higher should receive statin therapy (with or without ezetimibe) to reduce the risk of cardiovascular events and death *(Strong recommendation, moderate certainty evidence)*.

- Australian CVD risk calculator: https://www.cvdcheck.org.au/calculator.
- New Zealand CVD Risk calculator: https://www.nzssd.org.nz/cvd/.

3.1 | Rationale

Our evidence review identified 64 relevant randomized controlled trials (Figure 2). Statin therapy compared to placebo/standard care found substantial cardiovascular benefit and few demonstrable harms (Table 2; Figure 3). Limited data are available on important harms in people with CKD, such as rhabdomyolysis. Few data on patient-important outcomes, such as fatigue and life participation, are available. Trials in the general population have found statin therapy to be safe[18] and similar effects might be expected in people with mild to moderate CKD.

TABLE 2 Summary of findings table—statin therapy versus placebo.

Outcome		Absolute effect estimates			
Timeframe	Study results and measurements	Placebo or standard of care	Statin therapy	Certainty of the evidence (Quality of evidence)	Plain text summary
Myocardial infarction	Relative risk: 0.55 (CI 95% 0.42–0.73) Based on data from 9475 patients in 10 studies[a] Follow up Mean 39 months	**15** per 1000	**8** per 1000 Difference: **7 fewer per 1000** (CI 95% 9 fewer–4 fewer)	**Moderate** Due to serious risk of bias[b]	Statins probably decreases fatal and non-fatal myocardial infarction
Stroke	Relative risk: 0.64 (CI 95% 0.37–1.08) Based on data from 9115 patients in 7 studies[c] Follow up Mean 40 months	**13** per 1000	**8** per 1000 Difference: **5 fewer per 1000** (CI 95% 8 fewer–1 more)	**Moderate** Due to serious inconsistency[d]	Statins probably has little or no difference on fatal and non-fatal stroke
Hospitalization due to heart failure	Relative risk: 0.7 (CI 95% 0.37–1.32) Based on data from 579 patients in 1 studies[e] Follow up 54 months	**22** per 1000	**15** per 1000 Difference: **7 fewer per 1000** (CI 95% 14 fewer–7 more)	**Low** Due to serious imprecision, Due to serious risk of bias[f]	There were too few who experienced the hospitalization due to heart failure, to determine whether statins made a difference
Major cardiovascular events	Relative risk: 0.72 (CI 95% 0.66–0.79) Based on data from 36 156 patients in 14 studies[g] Follow up Mean 46 months	**113** per 1000	**81** per 1000 Difference: **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) Based on data from 28 723 patients in 12 studies[h] Follow up Mean 40 months	**48** per 1000	**38** per 1000 Difference: **10 fewer per 1000** (CI 95% 14 fewer–5 fewer)	**High**	Statins decreases all-cause mortality
Cardiovascular mortality	Relative risk: 0.77 (CI 95% 0.69–0.87) Based on data from 19 182 patients in 8 studies[i] Follow up Mean 39 months	**24** per 1000	**18** per 1000 Difference: **6 fewer per 1000** (CI 95% 7 fewer–3 fewer)	**Moderate** Due to serious risk of bias[j]	Statins probably decreases cardiovascular mortality
Kidney failure	Relative risk: 0.98 (CI 95% 0.91–1.05) Based on data from 6704 patients in 3 studies[k] Follow up Mean 34 months	**2** per 1000	**2** per 1000 Difference: **0 fewer per 1000** (CI 95% 0 fewer–0 fewer)	**Moderate** Due to serious risk of bias[l]	Statins probably has little or no difference on end-stage kidney disease
Rhabdomyolysis	Relative risk: 3.07 (CI 95% 0.13–75.37) Based on data from 2618 patients in 2 studies[m] Follow up Mean 64 months	**2** per 1000	**6** per 1000 Difference: **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[n]	We are uncertain whether statins increase or decrease elevated creatinine kinase (rhabdomyolysis)

(Continues)

TABLE 2 (Continued)

Outcome		Absolute effect estimates			
Timeframe	Study results and measurements	Placebo or standard of care	Statin therapy	Certainty of the evidence (Quality of evidence)	Plain text summary
Onset of diabetes	(CI 95% -)	Difference: **fewer**			No studies were found that looked at onset of diabetes
Memory loss	(CI 95% -)	Difference: **fewer**			No studies were found that looked at memory loss
Cancer	Relative risk: 1.03 (CI 95% 0.82–1.3) Based on data from 5581 patients in 2 studies[o] Follow up Mean 44 months	**15** per 1000 Difference: **0 fewer per 1000** (CI 95% 3 fewer–5 more)	**15** per 1000	**Moderate** Due to serious imprecision[p]	Statins probably has little or no difference on cancer
Creatinine clearance	Measured by: Scale: - Based on data from 4112 patients in 17 studies[q] Follow up Mean 14 months	**45** mL/min Mean Difference: **MD 1 higher** (CI 95% 0.44 higher–1.55 higher)	**46** mL/min Mean	**Moderate** Due to serious risk of bias[r]	Statins probably improves end of treatment creatinine clearance
Life participation	Measured by: Scale: -	Difference: **null lower**			No studies were found that looked at life participation
Fatigue	Measured by: Scale: -	Difference: **null lower**			No studies were found that looked at fatigue
LDL cholesterol	Measured by: Scale: - Based on data from 2183 patients in 24 studies[s] Follow up Mean 13 months	**3.90** mmol/L Mean Difference: **MD 1.13 lower** (CI 95% 1.33 lower–0.93 lower)	**3.90** mmol/L Mean	**Low** Due to serious risk of bias, Due to serious inconsistency[t]	Statins may have little or no difference on LDL cholesterol

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

References

[1] Tunnicliffe DJ, Palmer SC, Cashmore BA, et al. HMG CoA reductase inhibitors (statins) for people with chronic kidney disease not requiring dialysis. Cochrane Database Syst Rev. 2023;11(11):Cd007784.
[4] Wong G, Staplin N, Emberson J, Baigent C, Turner R, Chalmers J, Zoungas S, Pollock C, Cooper B, Harris D, Wang JJ, Mitchell P, Prince R, Lim WH, Lewis J, Chapman J, Craig J: Chronic kidney disease and the risk of cancer: an individual patient data meta-analysis of 32,057 participants from six prospective studies. BMC Cancer 2016;16 488.
[6] Chonchol M, Cook T, Kjekshus J, Pedersen TR, Lindenfeld J: Simvastatin for secondary prevention of all-cause mortality and major coronary events in patients with mild chronic renal insufficiency. American Journal of Kidney Diseases 2007;49(3):373-382.
[9] Kendrick J, Shlipak MG, Targher G, Cook T, Lindenfeld J, Chonchol M: Effect of lovastatin on primary prevention of cardiovascular events in mild CKD and kidney function loss: a post hoc analysis of the Air Force/Texas Coronary Atherosclerosis Prevention Study. American Journal of Kidney Diseases 2010;55(1):42-49.
[10] Koren MJ, Davidson MH, Wilson DJ, Fayyad RS, Zuckerman A, Reed DP: Focused atorvastatin therapy in managed-care patients with coronary heart disease and CKD. American Journal of Kidney Diseases 2009;53(5):741-750.
[13] Kimura G, Kasahara M, Ueshima K, Tanaka S, Yasuno S, Fujimoto A, Sato T, Imamoto M, Kosugi S, Nakao K: Effects of atorvastatin on renal function in patients with dyslipidemia and chronic kidney disease: assessment of clinical usefulness in CKD patients with atorvastatin (ASUCA) trial. Clinical and Experimental Nephrology 2017;21(3):417-424.
[14] Bianchi S, Bigazzi R, Caiazza A, Campese VM: A controlled, prospective study of the effects of atorvastatin on proteinuria and progression of kidney disease. American Journal of Kidney Diseases 2003;41(3):565-570.
[16] Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, Neil HAW, Livingstone SJ, Charlton-Menys V, DeMicco DA, Fuller JH: Effects of atorvastatin on kidney outcomes and cardiovascular disease in patients with diabetes: an analysis from the Collaborative Atorvastatin Diabetes Study (CARDS). American Journal of Kidney Diseases 2009;54(5):810-819.

[22] Fried LF, Forrest KY, Ellis D, Chang Y, Silvers N, Orchard TJ: Lipid modulation in insulin-dependent diabetes mellitus: effect on microvascular outcomes. Journal of Diabetes and its Complications 2001;15(3):113-119.
[23] Gheith OA, Sobh MA-K, Mohamed KE-S, El-Baz MA, El-Husseini F, Gazarin SS, Ahmed HA-E-H, Rasem MW, Amer GM: Impact of treatment of dyslipidemia on renal function, fat deposits and scarring in patients with persistent nephrotic syndrome. Nephron 2002;91(4):612-619.
[24] Goicoechea M, de Vinuesa SG, Lahera V, Cachofeiro V, Gómez-Campderá F, Vega A, Abad S, Luño J: Effects of atorvastatin on inflammatory and fibrinolytic parameters in patients with chronic kidney disease. Journal of the American Society of Nephrology: JASN 2006;17(12 Suppl 3):S231-S235.
[26] Collins R, Armitage J, Parish S, Sleigh P, Peto R: MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. Lancet 2003;361(9374):2005-2016.
[29] Imai Y, Suzuki H, Saito T, Tsuji I, Abe K, Saruta T: The effect of pravastatin on renal function and lipid metabolism in patients with renal dysfunction with hypertension and hyperlipidemia. Pravastatin and Renal Function Research Group. Clinical and Experimental Hypertension 1999;21(8):1345-1355.
[30] Ridker PM, MacFadyen J, Cressman M, Glynn RJ: Efficacy of rosuvastatin among men and women with moderate chronic kidney disease and elevated high-sensitivity C-reactive protein: a secondary analysis from the JUPITER (Justification for the Use of Statins in Prevention-an Intervention Trial Evaluating Rosuvastatin) trial. Journal of the American College of Cardiology 2010;55(12):1266-1273.
[35] Lemos PA, Serruys PW, de Feyter P, Mercado NF, Goedhart D, Saia F, Arampatzis CA, Soares PR, Ciccone M, Arquati M, Cortellaro M, Rutsch W, Legrand V: Long-term fluvastatin reduces the hazardous effect of renal impairment on four-year atherosclerotic outcomes (a LIPS substudy). The American Journal of Cardiology 2005;95(4):445-451.
[36] Fassett RG, Robertson IK, Ball MJ, Geraghty DP, Coombes JS: Effect of atorvastatin on kidney function in chronic kidney disease: a randomised double-blind placebo-controlled trial. Atherosclerosis 2010;213(1):218-224.
[38] Nakamura H, Mizuno K, Ohashi Y, Yoshida T, Hirao K, Uchida Y: Pravastatin and cardiovascular risk in moderate chronic kidney disease. Atherosclerosis 2009;206(2):512-517.
[40] Nakamura T, Ushiyama C, Hirokawa K, Osada S, Inoue T, Shimada N, Koide H: Effect of cerivastatin on proteinuria and urinary podocytes in patients with chronic glomerulonephritis. Nephrology, Dialysis, Transplantation 2002;17(5):798-802.
[46] Panichi V, Paoletti S, Mantuano E, Manca-Rizza G, Filippi C, Santi S, Taccola D, Donadio C, Tramonti G, Innocenti M, Casto G, Consani C, Sbragia G, Franzoni F, Galetta F, Panicucci E, Barsotti G: In vivo and in vitro effects of simvastatin on inflammatory markers in pre-dialysis patients. Nephrology, Dialysis, Transplantation 2006;21(2):337-344.
[49] Tonelli M, Isles C, Curhan GC, Tonkin A, Pfeffer MA, Shepherd J, Sacks FM, Furberg C, Cobbe SM, Simes J, Craven T, West M: Effect of pravastatin on cardiovascular events in people with chronic kidney disease. Circulation 2004;110(12):1557-1563.
[50] Asselbergs FW, Diercks GF, Hillege HL, van Boven AJ, Janssen WM, Voors AA, de Zeeuw D, de Jong PE, van Veldhuisen DJ, van Gilst WH: Effects of fosinopril and pravastatin on cardiovascular events in subjects with microalbuminuria. Circulation 2004;110(18):2809-2816.
[51] Rayner BL, Byrne M, van Zyl-Smit R: A prospective clinical trial comparing the treatment of idiopathic membranous nephropathy and nephrotic syndrome with simvastatin and diet, versus diet alone. 1996;46(4):219-224.
[55] Sawara Y, Takei T, Uchida K, Ogawa T, Yoshida T, Tsuchiya K, Nitta K: Effects of lipid-lowering therapy with rosuvastatin on atherosclerotic burden in patients with chronic kidney disease. Internal Medicine 2008;47(17):1505-1510.
[57] Baigent C, Landray MJ, Reith C, Emberson J, Wheeler DC, Tomson C, Wanner C, Krane V, Cass A, Craig J, Neal B, Jiang L, Hooi LS, Levin A, Agodoa L, Gaziano M, Kasiske B, Walker R, Massy ZA, Feldt-Rasmussen BO, Krairittichai U, Ophascharoensuk V, Fellström B, Holdaas H, Tesar V, Wiecek A, Grobbee D, de Zeeuw D, Grönhagen-Riska C, Dasgupta T, Lewis D, Herrington W, Mafham M, Majoni W, Wallendszus K, Grimm R, Pedersen T, Tobert J, Armitage J, Baxter A, Bray C, Chen Y, Chen Z, Hill M, Knott C, Parish S, Simpson D, Sleight P, Young A, Collins R: The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. Lancet 2011;377(9784):2181-2192.
[62] Tonolo G, Ciccarese M, Brizzi P, Puddu L, Secchi G, Calvia P, Atzeni MM, Melis MG, Maioli M: Reduction of albumin excretion rate in normotensive microalbuminuric type 2 diabetic patients during long-term simvastatin treatment. Diabetes Care 1997;20(12):1891-1895.
[64] Verma A, Ranganna KM, Reddy RS, Verma M, Gordon NF: Effect of rosuvastatin on C-reactive protein and renal function in patients with chronic kidney disease. The American Journal of Cardiology 2005;96(9):1290-1292.
[68] Meisinger C, Döring A, Löwel H: Chronic kidney disease and risk of incident myocardial infarction and all-cause and cardiovascular dansease mortality in middle-aged men and women from the general population. European Heart Journal 2006;27(10):1245-1250.
[69] Go AS, Chertow GM, Fan D, McCulloch CE, Hsu C-Y: Chronic kidney disease and the risks of death, cardiovascular events, and hospitalisation. The New England Journal of Medicine 2004;351 (13):1296-1305.
[70] Bansal N, Katz R, Robinson-Cohen C, Odden MC, Dalrymple L, Shlipak MG, Sarnak MJ, Siscovick DS, Zelnick L, Psaty BM, Kestenbaum B, Correa A, Afkarian M, Young B, de Boer IH: Absolute Rates of Heart Failure, Coronary Heart Disease, and Stroke in Chronic Kidney Disease: An Analysis of 3 Community-Based Cohort Studies. JAMA Cardiology 2017;2(3):314-318.
[71] Dalrymple LS, Katz R, Kestenbaum B, Shlipak MG, Sarnak MJ, Stehman-Breen C, Seliger S, Siscovick D, Newman AB, Fried L: Chronic kidney disease and the risk of end-stage renal disease versus death. Journal of General Internal Medicine 2011;26(4):379-385.

[a]Systematic review [1] with included studies: [50], [22], [30], [38], [51], [9], [13], [16], [10], [36] **Baseline/comparator** Primary study. Supporting references [68].
[b]**Risk of bias: Serious**. Inadequate sequence generation/generation of comparable groups, resulting in potential for selection bias.
[c]Systematic review [1] with included studies: [30], [38], [10], [36], [16], [13], [50] **Baseline/comparator** Primary study. Supporting references [70].
[d]**Inconsistency: Serious**.

[e]Systematic review with included studies: [10] **Baseline/comparator** Primary study. Supporting references [70].
[f]**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; **Imprecision: Serious.** Only data from one study.
[g]Systematic review [1] with included studies: [51], [16], [26], [9], [36], [57], [55], [50], [10], [38], [49], [35], [30], [6] **Baseline/comparator** Primary study. Supporting references [69].
[h]Systematic review [1] with included studies: [36], [10], [16], [35], [6], [64], [30], [50], [51], [38], [13], [49] **Baseline/comparator** Primary study. Supporting references [69].
[i]Systematic review [1] with included studies: [36], [51], [64], [50], [9], [10], [35], [49] **Baseline/comparator** Primary study. Supporting references [69].
[j]**Risk of bias: Serious.** Inadequate sequence generation/generation of comparable groups, resulting in potential for selection bias.
[k]Systematic review [1] with included studies: [36], [13], [57] **Baseline/comparator** Primary study. Supporting references [71].
[l]**Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias.
[m]Systematic review with included studies: [6], [9] **Baseline/comparator** Control arm of reference used for intervention.
[n]**Risk of bias: Serious.** Inadequate sequence generation/generation of comparable groups, resulting in potential for selection bias; **Inconsistency: Serious.** Point estimates vary widely; **Imprecision: Serious.** Low number of patients.
[o]Systematic review [1] with included studies: JUPITER 2007, 4S 1993 **Baseline/comparator** Systematic review. Supporting references [4].
[p]**Imprecision: Serious.**
[q]Systematic review [1] with included studies: ESPLANADE 2010, Verma 2005, [29], [38], [14], [23], Nielsen 1993, Hommel 1992, Lee 2002, ASUCA 2013, [46], Yasuda 2004, Ohsawa 2015, Sawara 2008, [62], [40], [24] **Baseline/comparator** Control arm of reference used for intervention.
[r]**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.
[s]Systematic review [1] with included studies: PREVEND IT 2000, Ohsawa 2015, Di Lullo 2005, Abe 2011c, Sawara 2008, UK-HARP-I 2005, Verma 2005, Lam 1995, Fried 2001, Imai 1999, Mori 1992, Goicoechea 2006, Panichi 2005, Bianchi 2003, Yasuda 2004, Nakamura 2002, Lee 2002, ESPLANADE 2010, LORD 2006, Zhang 1995, Hommel 1992, Nielsen 1993, Aranda 1994, Tonolo 1997 **Baseline/comparator** Control arm of reference used for intervention.
[t]**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%.

Statin therapy is an acceptable intervention for patients with CKD and is considered an important safeguard to protect cardiovascular health. Furthermore, statin therapy is publicly subsidized and cost-effective in Australia and Aotearoa New Zealand.

The Study of Heart and Renal Protection (SHARP) demonstrated the balance of benefits and harms of the combination of statin therapy and ezetimibe reduced major atherosclerotic events and non-haemorrhagic stroke compared to placebo.[19] However, this result pertained to data from one study and was of low certainty evidence. Only a few small randomized controlled trials have compared statin therapy with ezetimibe to statins alone in patients with CKD (Table 3). These studies found no incremental benefit of the addition of ezetimibe to statin therapy, with no evidence of differences in critical and important outcomes and only limited reporting of safety data and patient important outcomes.[20,21]

Consumers perceived the addition of another drug to current therapy as a potential indication of deteriorating health and may impact medication adherence.[22] Further research is needed to determine if this applies to the addition of ezetimibe to statin therapy in people with CKD. Ezetimibe is publicly subsidized with qualifying criteria and is demonstrated as cost-effective[23] in Australia and Aotearoa New Zealand.

In the judgement of the Guideline panel, dosing of statin therapy and ezetimibe should be based upon dosages that have received regulatory approval. Titration of statin therapy or ezetimibe to specific LDL-cholesterol targets has been recommended in other guidelines,[24] but requires further examination in people with CKD as the potential benefits and harms are uncertain due to limited available studies conducted in the CKD population.[25] As such, to date, Kidney Disease: Improving Global Outcomes has not recommended titration of statins.[26]

Based on these data and the inequities of access to lipid-lowering therapy, including remoteness and gender, evident in the general population,[27,28] the Guideline panel considered that most adults with CKD (not receiving dialysis) with 10% or higher absolute cardiovascular risk would benefit and should take statin therapy (with or without ezetimibe) to reduce their risk of cardiovascular events and death. According to the guideline, the time-period of cardiovascular disease (CVD) risk is estimated to be 5 years. Cardiovascular risk should be calculated according to updated Australian and New Zealand guidelines.[29,30] The Australian cardiovascular risk calculator can be used to determine cardiovascular risk assessment and is based on the NZ PREDICT-1° equation, developed from a large, contemporary New Zealand primary care cohort study and is different from the Framingham risk equation. The equation has been recalibrated to the Australian population and is recommended for individuals aged 45–79 years without known atherosclerotic CVD, including First Nations people. Both the New Zealand and Australian cardiovascular risk calculators include people with diabetes.[29,31] https://www.cvdcheck.org.au/calculator.

b. We recommend that Aboriginal and Torres Strait Islander Peoples and Māori with chronic kidney disease (reduced GFR and/or albuminuria/proteinuria) and a 5-year absolute cardiovascular risk of

TABLE 3 Summary of findings table—Statin therapy plus ezetimibe versus statin therapy.

Outcome		Absolute effect estimates			
Timeframe	Study results and measurements	Statin therapy	Statin therapy plus ezetimibe	Certainty of the evidence (Quality of evidence)	Plain text summary
Myocardial infarction	(CI 95% -)	Difference: **fewer**			No studies were found that looked at myocardial infarction
Stroke	(CI 95% -)	Difference: **fewer**			No studies were found that looked at stroke
Hospitalization of heart failure	(CI 95% -)	Difference: **fewer**			No studies were found that looked at myocardial infarction
Death	Relative risk: 0.95 (CI 95% 0.85–1.06) Based on data from 3761 patients in 1 studies[a] Follow up 18 months	**38** per 1000	**36** per 1000 Difference: **2 fewer per 1000** (CI 95% 6 fewer–2 more)	**Low** Due to serious risk of bias, Due to serious imprecision[b]	Statins + ezetimibe may have little or no difference on all-cause mortality
Cardiovascular death	Relative risk: 1.06 (CI 95% 0.87–1.29) Based on data from 3761 patients in 1 studies[c] Follow up 18 months	**18** per 1000	**19** per 1000 Difference: **1 more per 1000** (CI 95% 2 fewer–5 more)	**Low** Due to serious risk of bias, Due to serious imprecision[d]	Statins + ezetimibe may have little or no difference on cardiovascular mortality
Major cardiovascular events	Relative risk: 0.87 (CI 95% 0.78–0.97) Based on data from 3761 patients in 1 studies[e] Follow up 18 months	**113** per 1000	**98** per 1000 Difference: **15 fewer per 1000** (CI 95% 25 fewer–3 fewer)	**Low** Due to serious risk of bias, Due to serious imprecision[f]	Statins + ezetimibe may decrease 3-point MACE
Rhabdomyolysis	Relative risk: 1.16 (CI 95% 0.42–3.18) Based on data from 3761 patients in 1 studies[g] Follow up 18 months	**2** per 1000	**2** per 1000 Difference: **0 fewer per 1000** (CI 95% 1 fewer–4 more)	**Very Low** Due to serious risk of bias, Due to very serious imprecision[h]	We are uncertain whether statins + ezetimibe increases or decreases rhabdomyolysis
Kidney failure	Relative risk: 1.08 (CI 95% 0.16–7.49) Based on data from 152 patients in 1 studies[i] Follow up Mean 15 months	**2** per 1000	**2** per 1000 Difference: **0 fewer per 1000** (CI 95% 2 fewer–13 more)	**Very Low** Due to serious risk of bias, Due to very serious imprecision[j]	We are uncertain whether statin therapy plus ezetimibe increases or decreases kidney failure
Onset of diabetes	(CI 95% -)	Difference: **fewer**			No studies were found that looked at onset of diabetes
Memory loss	(CI 95% -)	Difference: **fewer**			No studies were found that looked at memory loss
Cancer	(CI 95% -)	Difference: **fewer**			No studies were found that looked at cancer
Fatigue	Measured by: Scale: -	Difference: **null lower**			No studies were found that looked at fatigue

(Continues)

TABLE 3 (Continued)

Outcome		Absolute effect estimates			
Timeframe	Study results and measurements	Statin therapy	Statin therapy plus ezetimibe	Certainty of the evidence (Quality of evidence)	Plain text summary
Life participation	Measured by: Scale: -	Difference: **null lower**			No studies were found that looked at life participation

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

References

[73] Stanifer JW, Charytan DM, White J, Lokhnygina Y, Cannon CP, Roe MT, Blazing MA: Benefit of Ezetimibe Added to Simvastatin in Reduced Kidney Function. Journal of the American Society of Nephrology 2017;28(10):3034-3043.

[78] Landray M, Baigent C, Leaper C, Adu D, Altmann P, Armitage J, Ball S, Baxter A, Blackwell L, Cairns HS, Carr S, Collins R, Kourellias K, Rogerson M, Scoble JE, Tomson CRV, Warwick G, Wheeler DC: The second United Kingdom Heart and Renal Protection (UK-HARP-II) Study: a randomised controlled study of the biochemical safety and efficacy of adding ezetimibe to simvastatin as initial therapy among patients with CKD. American Journal of Kidney Diseases 2006;47(3):385-395.

Grading the strength of recommendations: The strength of a recommendation is graded as strong or conditional (Table 4). 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.

[a]Systematic review with included studies: [73] **Baseline/comparator** Primary study.

[b]**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; **Imprecision: Serious**. Only data from one study.

[c]Systematic review with included studies: [73] **Baseline/comparator** Primary study.

[d]**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; **Imprecision: Serious**. Only data from one study.

[e]Systematic review with included studies: [73] **Baseline/comparator** Control arm of reference used for intervention.

[f]**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; **Imprecision: Serious**. Only data from one study.

[g]Systematic review with included studies: [73] **Baseline/comparator** Control arm of reference used for intervention.

[h]**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; **Imprecision: Very Serious**. Wide confidence intervals, Only data from one study.

[i]Systematic review with included studies: [78] **Baseline/comparator** Control arm of reference used for intervention.

[j]**Risk of bias: Serious**. Inadequate concealment of allocation during randomization process, resulting in potential for selection bias; **Imprecision: Very Serious**. Wide confidence intervals, Only data from one study.

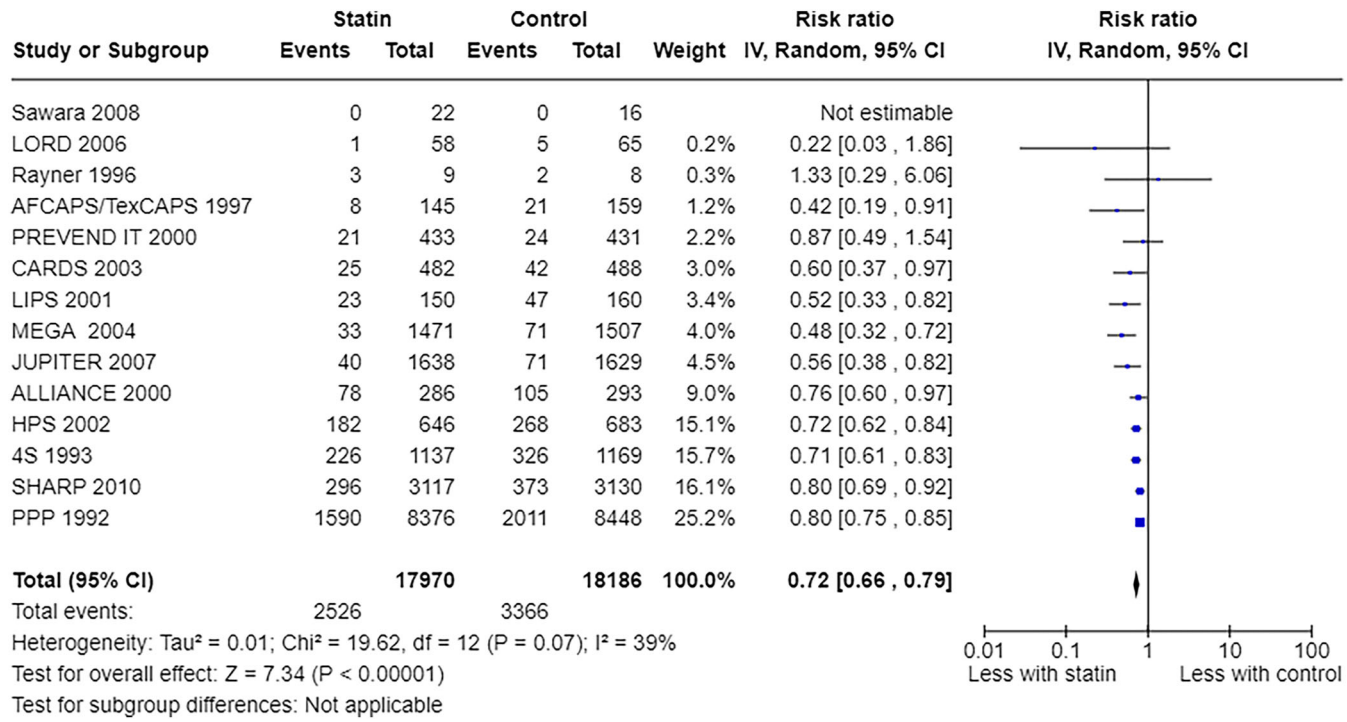

FIGURE 3 Statin therapy compared to placebo—Major cardiovascular events.

TABLE 4 CARI Guidelines nomenclature and description for grading recommendations.

	Implications		
Grade	**Patients**	**Clinicians**	**Policy**
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 recommendation can be adopted as a policy in most situations.
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 recommendation is likely to require substantial debate and involvement of stakeholders before policy can be determined.

Note: 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 5).

5% or higher within 5 years should receive statin therapy (with or without ezetimibe) to reduce cardiovascular events and death (*Strong recommendation, low certainty evidence*).

- Australian cardiovascular risk calculator: https://www.cvdcheck.org.au/calculator.
- New Zealand cardiovascular risk calculator: Cardiovascular Risk Assessment (nzssd.org.nz).

3.2 | Rationale

The ongoing impacts of colonization have increased exposure to risk factors for disease for Aboriginal and Torres Strait Islander Peoples in Australia and Māori in Aotearoa New Zealand,[32] including an increased risk of CVD.[33,34] Additionally, cardiovascular risk occurs at an earlier age in Indigenous peoples than in non-Indigenous peoples, which increases with age.[35,36] Other clinical practice guidelines recommend that cardiovascular risk assessments be conducted at least 10 years earlier for Indigenous Peoples than for non-Indigenous people.[31,37] Despite finding that no First Nations Peoples from Australia and Aotearoa, New Zealand, are included in the clinical trials, the Guideline panel considered that these data would also apply to Aboriginal and Torres Strait Islander Peoples and Māori.[4] The Guideline panel proposed a lower absolute cardiovascular risk (≥5%) for Aboriginal and Torres Strait Islander Peoples and Māori due to higher rates of CVD in this population and larger anticipated absolute benefits, with minimal risk of harm, in addition to addressing health inequities related to lower lipid-lowering therapy prescribing in primary care to First Nations Peoples in Australia and Aotearoa New Zealand.[35,36]

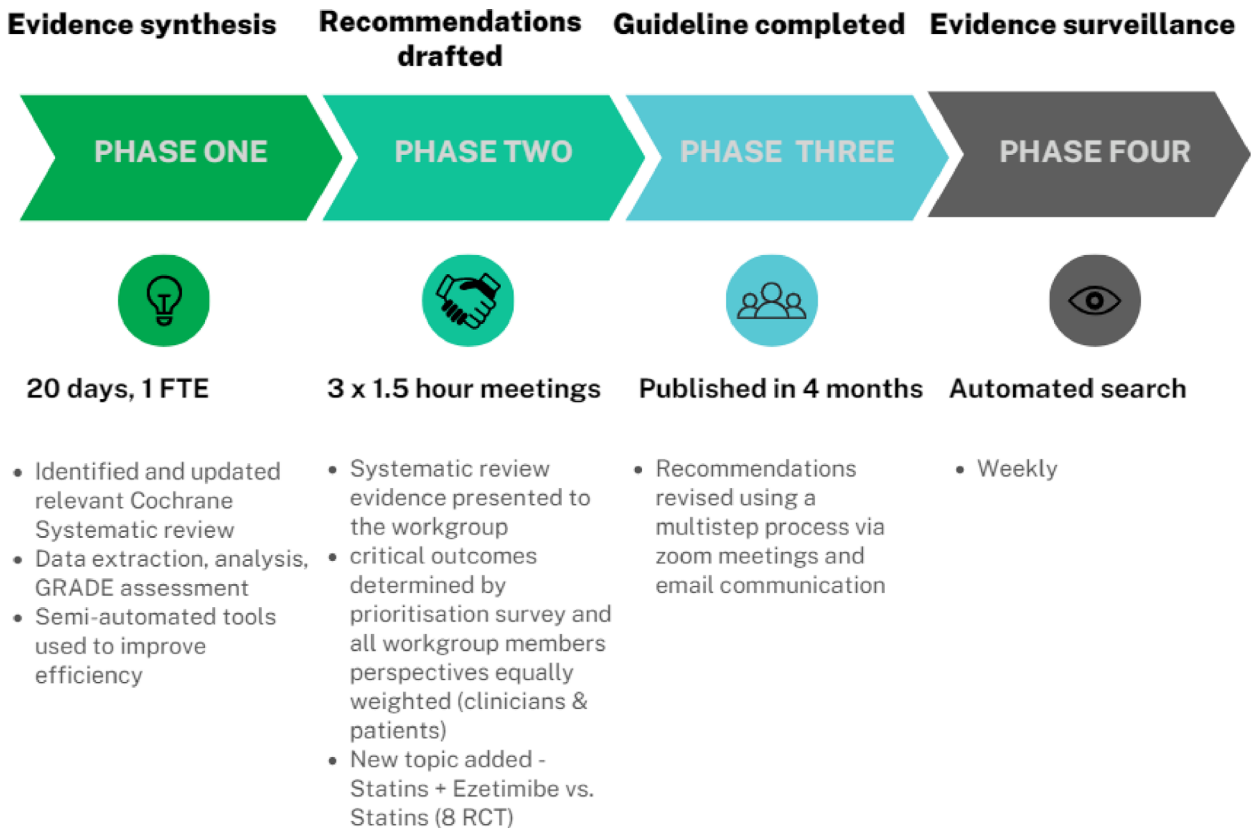

FIGURE 4 Overview of the guideline process.

TABLE 5 Classification for certainty of the evidence.

Grade	Certainty 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 substantially different.
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 with every 3 months by Cochrane Kidney and Transplant. The CARI Guidelines Evidence Review team will supplement searches with evidence surveillance conducted weekly through literature searching to identify any new emerging evidence and update the evidence review accordingly. 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.

The higher absolute cardiovascular risk and less frequent provision of lipid-lowering therapy in First Nations Peoples have guided this recommendation. The Working Group considered that First Nations Peoples with CKD and a 5% or higher absolute risk of CVD would benefit from receiving statin therapy with or without ezetimibe to prevent cardiovascular events and death.

4 | UNGRADED SUGGESTIONS FOR CLINICAL CARE

- People with albuminuria (A2 30–300 mg/g and A3 > 300 mg/g) should receive statins (with or without ezetimibe).
- Adults (≥30 years of age) with CKD (reduced GFR and/or albuminuria/proteinuria) and absolute cardiovascular risk of 5%–10% should discuss the potential therapeutic use of a statin therapy with their healthcare providers.
- Clinicians should ensure that people and their carer/family/whānau (Māori meaning for family or extended family) are provided with information on the effects of statin therapy, with or without ezetimibe, on the prevention of cardiovascular events and death.
- The Australian cardiovascular risk calculator is only validated for adults without known atherosclerotic CVD aged 30–79 years and cannot be calculated for those 18–30 years of age.[29]
- In young adults (18–29 years of age) with CKD (albuminuria and/or reduced kidney function) with the presence of type 2 diabetes, or

uncontrolled high blood pressure, or familial hypercholesterolaemia, or serum total cholesterol >7.5 mmol/L may indicate moderate to high CVD risk and treatment with a statin with or without of statin may be required.[37,38]

5 | DISCUSSION AND IMPLICATIONS

Our guidelines recommend statin with or without ezetimibe in most people with CKD with underlying cardiovascular risk. This is supported by synthesized evidence conducted to appropriate methodological standards demonstrating clear benefits from treatment. However, the data from randomized controlled trials also demonstrated important uncertainties, particularly for harms and patient-important outcomes, requiring further examination.

6 | SUGGESTIONS FOR FUTURE RESEARCH

- Long-term follow-up of randomized controlled trials to assess the safety of therapy in patients with CKD (not receiving dialysis) is 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 randomized controlled trials comparing the relative safety of statins combined with ezetimibe to statins alone in people with CKD (not receiving dialysis) should be performed.
- Randomized controlled trials examining the efficacy and safety of titration of statins in people with CKD are required.
- Outcome trials examining the use of cardiovascular imaging for determining the suitability of people with CKD (not receiving dialysis) to receive lipid-lowering therapy should be undertaken.
- Further clinical trials investigating statin use in Aboriginal and Torres Strait Islander Peoples and Māori with CKD are needed.

7 | IMPLICATIONS FOR KIDNEY DISEASE CLINICAL PRACTICE GUIDELINES

To our knowledge, these are the first clinical practice guidelines in kidney disease that have piloted living guidelines. Despite limited resources, CARI Guidelines have demonstrated the feasibility of developing living guidelines according to international standards,[2,3,39] accompanied by developing a high-quality systematic review.[32] The guideline development process was streamlined, with a focused scope agreed upon before the outset of the guidelines. The production of these guidelines was achieved through three online meetings and email communications, and utilized semi-automation where available for study selection (randomized controlled trial classifiers) and data extraction (https://www.robotreviewer.net) to support ongoing evidence surveillance (Figure 4). Despite the limited publication of new randomized controlled trials on statins in people with CKD during the study period, the methods and processes piloted for these guidelines will support further application across the development of other CARI Guidelines. Furthermore, it will reduce the 'evidence-practice gap' between evidence to implementation and support shared clinical decision making between clinicians and consumers.

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CONFLICT OF INTEREST STATEMENT

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REFERENCES

1. Johnson DW, Atai E, Chan M, et al. KHA-CARI guideline: early chronic kidney disease: detection, prevention and management. *Nephrology (Carlton)*. 2013;18(5):340-350.
2. Cheyne S, Fraile Navarro D, Hill K, et al. Methods for living guidelines: early guidance based on practical experience. *J Clin Epidemiol*. 2023; 155:84-96.
3. El Mikati IK, Khabsa J, Harb T, et al. A framework for the development of living practice guidelines in health care. *Ann Intern Med*. 2022; 175(8):1154-1160.
4. Tunnicliffe DJ, Palmer SC, Cashmore BA, et al. HMG CoA reductase inhibitors (statins) for people with chronic kidney disease not requiring dialysis. *Cochrane Database Syst Rev*. 2023;11(11):Cd007784.
5. Andrews JC, Schünemann HJ, Oxman AD, et al. GRADE guidelines: 15. Going from evidence to recommendation 2014; determinants of a recommendation's direction and strength. *J Clin Epidemiol*. 2013; 66(7):726-735.
6. Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction 2014; GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol*. 2011;64(4):383-394.
7. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med*. 2004;351(13):1296-1305.
8. Cass AWS, Snelling P, Jones A, et al. *The Economic Impact of End Stage Kidney Disease in Australia: Projects to 2020*. Kidney Health Australia; 2010.
9. Ashton T, Marshall MR. The organization and financing of dialysis and kidney transplantation services in New Zealand. *Int J Health Care Finance Econ*. 2007;7(4):233-252.
10. Johnson DW. Evidence-based guide to slowing the progression of early renal insufficiency. *Intern Med J*. 2004;34(1–2):50-57.
11. Ellen RL, McPherson R. Long-term efficacy and safety of fenofibrate and a statin in the treatment of combined hyperlipidemia. *Am J Cardiol*. 1998;81(4a):60b-65b.
12. Drüeke TB, Nguyen Khoa T, Massy ZA, Witko-Sarsat V, Lacour B, Descamps-Latscha B. Role of oxidized low-density lipoprotein in the atherosclerosis of uremia. *Kidney Int Suppl*. 2001;78:S114-S119.
13. Schaeffner ES, Kurth T, Curhan GC, et al. Cholesterol and the risk of renal dysfunction in apparently healthy men. *J Am Soc Nephrol*. 2003; 14(8):2084-2091.
14. Ridker PM, MacFadyen J, Cressman M, Glynn RJ. Efficacy of rosuvastatin among men and women with moderate chronic kidney disease and elevated high-sensitivity C-reactive protein: a secondary analysis from the JUPITER (justification for the Use of Statins in Prevention-an Intervention Trial Evaluating Rosuvastatin) trial. *J Am Coll Cardiol*. 2010;55(12):1266-1273.
15. Shepherd J, Kastelein JJ, Bittner V, et al. Intensive lipid lowering with atorvastatin in patients with coronary heart disease and chronic kidney disease: the TNT (Treating to New Targets) study. *J Am Coll Cardiol*. 2008;51(15):1448-1454.
16. Tonelli M, Isles C, Curhan GC, et al. Effect of pravastatin on cardiovascular events in people with chronic kidney disease. *Circulation*. 2004;110(12):1557-1563.
17. Palmer SC, Navaneethan SD, Craig JC, et al. HMG CoA reductase inhibitors (statins) for people with chronic kidney disease not requiring dialysis. *Cochrane Database Syst Rev*. 2014;5:CD007784.
18. Taylor F, Huffman MD, Macedo AF, et al. Statins for the primary prevention of cardiovascular disease. *Cochrane Database Syst Rev*. 2013; 2013(1):Cd004816.
19. Baigent C, Landray MJ, Reith C, et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (study of heart and renal protection): a randomised placebo-controlled trial. *Lancet*. 2011;377(9784):2181-2192.
20. Stanifer JW, Charytan DM, White J, et al. Benefit of ezetimibe added to simvastatin in reduced kidney function. *J Am Soc Nephrol: JASN*. 2017;28(10):3034-3043.
21. Landray M, Baigent C, Leaper C, et al. The second United Kingdom Heart and Renal Protection (UK-HARP-II) study: a randomized controlled study of the biochemical safety and efficacy of adding ezetimibe to simvastatin as initial therapy among patients with CKD. *Am J Kidney Dis*. 2006;47(3):385-395.
22. Mohammed MA, Moles RJ, Chen TF. Medication-related burden and patients' lived experience with medicine: a systematic review and metasynthesis of qualitative studies. *BMJ Open*. 2016;6(2):e010035.
23. Schlackow I, Kent S, Herrington W, et al. Cost-effectiveness of lipid lowering with statins and ezetimibe in chronic kidney disease. *Kidney Int*. 2019;96(1):170-179.
24. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2019;139(25): e1082-e1143.
25. Chou R, Dana T, Blazina I, Daeges M, Jeanne TL. Statins for prevention of cardiovascular disease in adults: evidence report and systematic review for the US preventive services task force. *JAMA*. 2016; 316(19):2008-2024.
26. Tonelli M, Wanner C, Members* KDIGOLGDWG. Lipid management in chronic kidney disease: synopsis of the kidney disease: improving global outcomes 2013 clinical practice guideline. *Ann Intern Med*. 2014;160(3):182-189.
27. Stocks N, Ryan P, Allan J, Williams S, Willson K. Gender, socioeconomic status, need or access? Differences in statin prescribing across urban, rural and remote Australia. *Aust J Rural Health*. 2009;17(2): 92-96.
28. Health Mo. *Urban–Rural Health Comparisons: Key Results of the 2002/03 New Zealand Health Survey*. Ministry of Health; 2007.
29. Commonwealth of Australia as represented by the Department of Health and Aged Care. Australian guideline for assessing and managing cardiovascular disease risk; 2023.
30. Crooke M. New Zealand cardiovascular guidelines: best practice evidence-based guideline: the assessment and management of cardiovascular risk December 2003. *Clin Biochem Rev*. 2007;28(1):19-29.
31. Wells S, Riddell T, Kerr A, et al. Cohort profile: the PREDICT cardiovascular disease cohort in New Zealand primary care (PREDICT-CVD 19). *Int J Epidemiol*. 2017;46(1):22.
32. Tunnicliffe DJBS, Arnold-Chamney M, Dwyer KM, et al. *Recommendations for Culturally Safe and Clinical Kidney Care for First Nations Australians*. CARI Guidelines; 2022.
33. Vos T, Barker B, Begg S, Stanley L, Lopez AD. Burden of disease and injury in Aboriginal and Torres Strait Islander peoples: the indigenous health gap. *Int J Epidemiol*. 2009;38(2):470-477.
34. New Zealand Ministry of Health. In: Health MO, ed. *Mortality and Demographic Data, 2012*. New Zealand Government; 2015.
35. Agostino JW, Wong D, Paige E, et al. Cardiovascular disease risk assessment for Aboriginal and Torres Strait Islander adults aged under 35 years: a consensus statement. *Med J Austr*. 2020;212(9):422-427.
36. Health. Mo. *Cardiovascular Disease Risk Assessment and Management for Primary Care*. Ministry of Health; 2018.
37. Calabria B, Korda RJ, Lovett RW, et al. Absolute cardiovascular disease risk and lipid-lowering therapy among Aboriginal and Torres Strait Islander Australians. *Med J Aust*. 2018;209(1):35-41.
38. Selak V, Poppe K, Grey C, et al. Ethnic differences in cardiovascular risk profiles among 475,241 adults in primary care in Aotearoa, New Zealand. *N Z Med J*. 2020;133(1521):14-27.

39. *The Living Guidelines Handbook: Guidance for the Production and Publication of Living Clinical Practice Guidelines [Internet]*. Australian Living Evidence Consortium; 2022.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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