European Review for Medical and Pharmacological Sciences 2023; 27: 10595-10604

Statin therapy for patients with diabetic nephropathy: balance between safety and efficacy of statin treatment for patients with impaired kidney function

A.A. JAIROUN[1], C.C. PING[1], B. IBRAHIM[2]

[1]Discipline of Clinical Pharmacy, School of Pharmaceutical Sciences, Universiti Sains Malaysia (USM), Pulau Pinang, Malaysia
[2]Faculty of Pharmacy, Universiti Malaya, Kuala Lumpur, Malaysia

Abstract. – The International Diabetes Federation estimates that by 2035, there will be 592 million people with diabetes worldwide, substantially increasing from the 382 million patients with diabetes recorded in 2013. Diabetes-related nephropathy is a leading cause of end-stage renal disease. Recently, the therapeutic use of statins in patients with chronic kidney disease (CKD) was explored in a series of meta-analyses, which revealed their potential for decreasing mortality and cardiovascular complications in this population, although not in patients undergoing hemodialysis.

The current study reviews the current state of knowledge on statin therapy regarding its safety and efficacy concerning renal outcomes in diabetic patients with CKD.

The evidence shows that statins may offer a beneficial renoprotective effect in inhibiting the progression of renal function decline. This effect is time-dependent and particularly strong in patients with type 2 diabetes and nephropathy. In addition, whether certain statin types are more beneficial than others in slowing renal function loss and reducing proteinuria remains unclear. Prior research has not examined the impact of high-intensity statin therapy on CKD patient outcomes.

Key Words:
Diabetic kidney disease, Diabetic nephropathy, Statin, Efficacy, Safety, Cardiovascular disease.

Abbreviations

AKI: Acute Kidney Injury; ALLIANCE: Aggressive Lipid-Lowering Initiation Abates New Cardiac Events; BUN: Blood Urea Nitrogen; CIN: Contrast-induced nephropathy; CKD: chronic kidney disease; CRS: cardiorenal syndrome, CVD: cardiovascular disease, DN: Diabetic nephropathy, EAS: European Atherosclerosis Society, eGFR: estimated glomerular filtration rate, ESC: European Society of Cardiology, GFR: glomerular filtration rate, HMG-CoA: Hydroxymethylglutaryl-CoA reductase inhibitors, JUPITER: Justification for the Use of Statins in Prevention, KDIGO: Kidney Disease Improving Global Outcomes, KDOQI: Kidney Disease Outcomes Quality Initiative, LDL-C: lipoprotein cholesterol, PANDA: Pediatric Anesthesia and Neuro Development Assessment, Scr: Serum Creatinine, SPARCL: Stroke Prevention by Aggressive Reduction in Cholesterol Levels, T2DM: Type 2 Diabetes Mellitus, TNT: Treating to New Targets, UEAR: Urinary Albumin Excretion Rates.

Introduction

The International Diabetes Federation[1] estimates that by 2035, there will be 592 million people with diabetes worldwide, a substantial increase from the 382 million patients with diabetes recorded in 2013. Diabetes mellitus is a common endocrine condition that is gaining prevalence. It is associated with various micro- and macrovascular complications that damage different viscera and body tissues[2]. In particular, microvascular complications and increased HbA1c are commonly identified in recently diagnosed Type 2 Diabetes Mellitus (T2DM) patients. As such, following diagnosis, it is advised that T2DM patients undergo screening for microvascular issues[3]. In individuals suffering from diabetes mellitus, controlling their glycemic levels may significantly contribute to maintaining the disease's progression. Nonetheless, achieving this goal still poses a challenge[4].

Diabetic nephropathy (DN) is one of the most severe and most common chronic complications of diabetes, being a leading contributor to end-stage renal disease[5]. Diabetic individuals are more likely to be more likely to be affected by chronic kidney disease (CKD). They are susceptible to CKD development at a rate greater than individuals who are otherwise healthy[6]. CKD is generally held to be

Corresponding Author: A.A. Jairoun, MD; e-mail: aajairoun@student.usm.my

caused by kidney damage, such as albuminuria or a reduced glomerular filtration rate (GFR), for more than three months[6]. Although CKD is a serious, independent risk factor for cardiovascular morbidity and mortality[7], it is generally given insufficient attention, leading to a lack of diagnosis and treatment, especially among patients with diabetes[8-13].

The most frequent complication among patients with CKD is dyslipidemia due to renal dysfunction, which further causes renal damage and diminished renal function, characterized by a steady decline in the eGFR[14]. Previous research[15-17] has determined several mechanisms that may drive kidney damage in patients with DN. For example, hyperlipidemia may be a crucial factor in DN progression (e.g., either utilizing mesangial cells' being exposed to lipotoxicity or through the contribution of DN in intrarenal atherosclerosis).

A relationship exists between decreased eGFR and cardiovascular disease (CVD), even without the influence of other risk factors[18]. Hence, promptly implementing lipid-regulating therapy in CKD patients is essential and established practice. According to the updated Kidney Disease Improving Global Outcomes (KDIGO) lipid management guidelines for CKD treatment, statins are recommended for patients with CKD who are not dependent on dialysis, are aged 50 years and above, and have an eGFR not above 60 mL/min/1.73 m^2 or a minimum urinary albumin-to-creatinine ratio of 30 mg/g, regardless of their serum cholesterol level. This is in line with the recommendations of the 2016 ESC/EAS guidelines[19,20].

Statins [3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors] are an established class of safe antihyperlipidemic drugs that are widely used owing to their effectiveness in lowering the low-density lipoprotein cholesterol (LDL-C) level[21]. Statins are drugs employed as the main therapeutic medications in averting cardiovascular problems mortality amongst CVD patients and are used as the primary therapeutic medications in averting cardiovascular problems and mortality amongst CVD patients as well as those at an increased likelihood of developing the disease, and have been recognized as the most effective lipid-regulating treatment[22,23]. Beyond their lipid-regulating properties, statins have pleiotropic effects, such as plaque stabilization and anti-inflammation, yielding excellent cardiovascular protection for such populations.

While human and animal research has shown that statins are beneficial in preventing cardiovascular events[24], albuminuria[25], and diabetic glomerulosclerosis[26], there is no consensus on their efficacy in enhancing renal function in patients with DN to date. Recent studies[25,27,28] have indicated the renoprotective effects of statins, including a beneficial impact on pathologic albuminuria and a slowing of eGFR decline. Clinical trials[7,13], have shown no correlation between statin use and eGFR improvement. In addition, despite some studies[21,25,29,30], showing the beneficial effects of statins on albuminuria, such product has been found in other studies[31,32]. Similarly, according to some research, statins may improve the eGFR[33,34]; however, according to a meta-analysis, they do not have a significant impact on this matter[21]. This conflicting evidence regarding the effect of statin therapy on eGFR among individuals with DN may be due to reporting bias. This stems from variations in the study cohort/populations, study design and methodologies utilized across these studies. Recently, the therapeutic use of statins in patients with CKD was explored in a series of meta-analyses, which revealed their potential for decreasing mortality and cardiovascular complications in this population, although not in patients undergoing hemodialysis[35-40]. The current study analyses the state of scientific knowledge on statin medication in terms of its efficacy and safety with an eye toward renal outcomes in diabetic patients with CKD.

Efficacy and Safety of Statin Therapy in Patients with Chronic Kidney Disease (CKD)

Studies[41] have shown that statin therapy leads to a reduction in major vascular events in a wide range of individuals. Long-term statin therapy reduces mortality in patients with a history of cardiovascular disease without an account and has a protective effect on the kidneys in patients with CKD. Statins are associated with reducing the probability of mortality and myocardial infarction in addition to other coronary artery diseases and coronary artery diseases such as cerebral palsy. Statins in patients with mild to moderate CKD have the effect of preventing and reducing cardiovascular risk[42].

All-Cause Mortality

According to Yan et al[43] meta-analysis, where data were available for 9,393 statin therapy patients, 730 died during the follow-up period. The analysis showed reduced mortality in CKD patients on statin therapy, but CI did not include

any effect[43]. Barylski et al[44] investigated statins in CKD patients, not on dialysis, reducing the risk of death from all causes and stroke. However, in dialysis patients, statins did not significantly affect the risk of death from all causes and stroke[44]. However, Jung et al[45] research has shown that a reduction in the risk of death from all causes occurs in adult patients on maintenance dialysis when using statin therapy combined with ezetimibe. Kim et al[46] research has shown that reducing the risk of death from all causes occurs in CKD patients who use statins regardless of whether they are on dialysis and other risk factors.

Stroke

High-intensity statin therapy reduces the incidence of myocardial infarction, according to a meta-analysis[43]. According to Chung et al[47], statins reduce the risk of death from all causes but do not decrease the risk of ischemic hemorrhage stroke. Analyzes suggest that atorvastatin may improve function in patients with CKD who have previously had a stroke or transient ischemic attack and may prevent GFR decline in patients with DM and previous stroke[48]. Patients using statin therapy have a reduced risk of cardiovascular disease as kidney disease progresses from the early stages to the last stage of kidney disease. Statins have been associated with a higher incidence of stroke in patients with end-stage renal disease[49].

Myocardial Infarction and Heart Failure

Yan et al[43] meta-analysis did not show straightforward prevention of myocardial infarction in patients on high statin therapy. In the context of decreasing the incidence of heart failure, there is no discernible distinction between invasive and non-invasive statin medications[43]. According to Ercan[50], statin treatment significantly reduces mortality in patients with end-stage renal disease with acute myocardium compared with those who did not use statins. Smith et al[51] also showed that statins positively affect patients with lower levels of kidney disease.

Effects on Lipid Levels

Information on the effect of statin-intensive therapy on lowering LDL cholesterol levels is available in four pivotal trials TNT[52], JUPITER[53], SPARCL[48], and PANDA[54]. A mean change in LDL cholesterol levels from baseline to the end of follow-up was achieved at the last physician visit when atorvastatin 80 mg was used, where the decrease was 17.5 mg/dL. In comparison, the reduction at 10 mg atorvastatin was 2.7 mg/dL in patients with CKD. Rosuvastatin 20 mg may reduce LDL cholesterol levels by approximately 50 mg/dL in patients with CKD. Intensive statin therapy has better effects on lowering LDL cholesterol than placebo[43].

Effect of Statins on Change in Kidney Function (Renal Function) and Urinary Protein Excretion/Proteinuria

High-intensity statin therapy does not show substantial superiority in increasing high-dose GFR. However, other research[53] has yielded the opposite result. In the JUPITER study[53] for individuals who had an eGFR < 60 ml/min/1.73 m² the median eGFR levels after 12 months were recorded as 53.0 and 52.8 ml/min/1.73 m² in the groups receiving rosuvastatin and placebo respectively. The PANDA research[53] has shown that after adjusting for initial kidney function, gender, age, smoking, etc., statins do not significantly affect renal function. The PANDA study[54] included the albumin/creatinine ratio, cystine C, serum creatinine, albumin excretion, and creatinine clearance. Data from the PANDA study showed no association between renal protection and high-intensity statin therapy. Therefore, it is challenging to come up with conclusions about the implications of high-intensity statin treatment on renal function, and a further investigation that will produce evidence of sufficient quality is necessary[43].

Effect of Statins on Albuminuria

Zhang et al[55] research has shown that statins reduce proteinuria, albuminuria, and clinical death but do not slow the progression to the last stage of kidney disease. According to a meta-analysis by Douglas et al[56], statins lead to reduced albuminuria and proteinuria. However, there is evidence that statins (pravastatin) do not affect albuminuria in CKD patients[57]. Shen et al[58] study showed that statins reduce albuminuria in T2DM patients with diabetic nephropathy. Although meta-analyzes report the beneficial effects of statins on pathological albuminuria, more extensive studies are needed to assess these results' validity and determine whether statins can reduce the progression to end-stage renal disease[59].

Effect of Statins on Estimated Glomerular Filtration Rate (eGFR)

In a meta-analysis[60] involving 33 studies, 21 reported the effect of statins on GFR. The analysis showed that statins were not associated with a change in GFR compared with the control[60].

There was significant heterogeneity in the critical studies, and sensitivity analysis suggested that the overall conclusion was unstable. For investigations conducted earlier than 2010, where the patients' mean ages were above 65 and pravastatin and atorvastatin were administered, subgroup evaluation demonstrated a significant association between statin consumption and increased GFR. However, using fluvastatin has been associated with a lower GFR than in the control group[60,61].

Effect of Statins on Urinary Albumin Excretion Rates (UAER)

The pooled results suggest that statin use is associated with lower urinary albumin excretion than controls[60]. In research comprising Asian populations, simvastatin, and fluvastatin medication were administered. However, statins produced little to no effect on urinary albumin excretion. Moreover, pravastatin has led to high urinary albumin excretion in patients followed for 12 months or more[60]. According to Shen et al[58], statin analyses have a beneficial effect on UEAR. There was a statistically significant decrease in UEAR in the statin-treated group compared to the control group[58].

Effect of Statins on Serum Creatinine (Scr)

According to a meta-analysis by Lv et al[61], statins may decrease Scr. However, the summary result of the Zhao et al[59] meta-analysis showed no significant differences in new Scr between the control and statin groups.

Effect of Statins on Blood Urea Nitrogen (BUN)

According to Shen et al[58], statin analyses do not statistically affect BUN compared to the control group. In the research of Nasri et al[62], significant kidney damage occurred in patients receiving 150 mg/kg/day atorvastatin, while no significant kidney damage occurred in patients receiving 10 mg/kg/day or 50 mg/kg/day.

Safety Evaluation

High-intensity statin therapy has no clear association with an increased incidence of serious adverse events. Combined analyses did not show a significant difference in the overall incidence rate of adverse events, although the incidence was higher in the statin group compared to the control group. According to a meta-analysis[43], myopathy occurred in only ten patients, while rhabdomyolysis occurred in three patients with CKD. Compared to the control, the association between statin intensive care and rhabdomyolysis and myopathy is unclear. Among patients from the TNT[52], SPARCL[48], and ALLIANCE[63] studies, we had one patient with creatine phosphokinase abnormalities. However, the incidence of statin side effects is very low, and the pooled results do not show a significant difference between the control and statin groups. Yet, insufficient evidence dispels the suspicion that high-intensity statin therapy can cause serious side effects[43]. According to the SPARCL study, persistent elevations in hepatic transaminases were common in patients receiving atorvastatin therapy compared to controls. However, rates were low and similar in CKD and non-CKD patients. Patients with CKD and those without CKD had elevated levels of creatine phosphokinase. Statin's adverse effects on the musculoskeletal system were minimal[48].

Arguments in Favor of Statin Use

LDL cholesterol is one of the critical risk factors for cardiovascular diseases, which cause one-third of all deaths in the world. Statins are more effective than older methods for lowering LDL cholesterol levels. The effects of statins on lowering cholesterol have been documented in studies[64] evaluating the prevention of cardiovascular disease. Also, statins reduce the risk of developing new cardiovascular diseases regardless of gender, age, cholesterol level, presence of hypertension, diabetes, previous myocardial infarction, and other heart diseases[64]. Along with its effects on cardiovascular disease, statins have anti-inflammatory, antioxidant, and stabilizing characteristics. Statins are capable of enhancing kidney function by decreasing cholesterol, which could result in immediate as well as long-term benefits for renal function[65].

Prevention of Acute Kidney Injury after Cardiac Surgery

Acute Kidney Injury (AKI) is often complicated by cardiac surgery, which is multifactorial. Statins most likely inhibit inflammatory processes that occur after surgery. Patients using thyroid have lower levels of circulating C-reactive protein, myeloperoxidase, tumor necrosis factor-alpha, pro-inflammatory interleukins (IL)-8, IL-6, and IL-1, and higher concentrations of anti-inflammatory IL-10. Patients in cardiac surgery may respond differently to the dose and type of statin[66]. While high-potency statins elevate the rate of

AKI among patients in the general population, they also have renal protective properties in people who recently underwent cardiac surgery. In cardiac surgery, observational studies on renal protection of preoperative statin use have shown a reduced incidence of renal failure after surgery, or statins do not give any benefit[65]. Further, a meta-analysis[65] showed a 13% reduction in AKI in patients who had statin therapy before surgery.

Rosuvastatin has been associated with an increase in the incidence of AKI in 48 hours postoperatively. AKI was experienced by 20.8% of the patients who were prescribed atorvastatin before their surgery, compared with 19.5% of patients who were given a placebo before surgery. Furthermore, when individuals with CKD did not take statins, more of them developed AKI. There was no difference in the incidence of AKI in the control group and the high-dose atorvastatin group in 200 patients[65].

Prevention of AKI after Major Non-Cardiac Surgery

A retrospective analysis of data from patients who underwent noncardiac surgery did not show that statin therapy before surgery in routine doses for hypocholesterolemia affects the incidence of AKI, inpatient mortality, and postoperative dialysis[65,67,68]. A systematic analysis[65] has shown that preoperative statin therapy significantly reduces the risk of AKI requiring renal replacement and cumulative AKI.

Prevention of Contrast-Induced Nephropathy

Permanent and acute renal impairment may cause exposure to iodine contrast during coronary interventions. Contrast-induced nephropathy (CIN) can be accelerated by contrast volume and type, hemodynamic instability, CKD, congestive heart failure, diabetes, and age[69]. Compared with the control group, statin therapy reduces the risk of CIN. Its effectiveness in preventing CIN depends on the statin dose and is higher in patients with chronic kidney or heart disease and acute coronary syndrome.

High-dose and efficacy statins may be more effective. However, due to a lack of data, recommendations for using statins in coronary interventions with contrast iodine cannot be given[65].

Attenuation of the Cardiorenal Syndrome (CRS)

Chronic or acute kidney or heart disease can cause chronic or critical illness of another organ. For example, patients with heart failure and exacerbated GFR have higher mortality, while patients with CKD have an increased risk of heart disease, responsible for 50% of deaths[70].

The connection between these two organs is known as the CRS. CRS is significantly influenced by oxidative stress, dysfunction of endothelial cells, and inflammation in the vascular system. The progression of chronic heart and renal failure is supported by the pleiotropic effects of statins on cardiovascular processes[65].

Reduction of Major Cardiovascular Events and Mortality in CKD

Cardiovascular disease is the most common cause of premature death in the early stages of CKD[71]. Statin therapy prevents major cardiovascular events and reduces mortality in CKD patients without cardiovascular disease and not requiring dialysis. Highly effective statin therapy has been associated with a reduced risk of stroke in CKD patients[36,65].

Preventing Aminoglycoside Toxicity

The pleiotropic properties of statins were expressed only in experimental conditions, which theoretically promise to prevent aminoglycoside toxicity. A study by Ozbek et al[72], of the effect of atorvastatin on nephrotoxicity by gentamicin in rats showed that atorvastatin normalizes renal function, normalizes tissue oxidative stress parameters, and attenuates tubular necrosis in rats.

Atorvastatin reaffirmed its anti-inflammatory and antioxidant effects by decreasing the production level of nuclear factor kappa B, a mitogen-activated protein kinase, and stimulated nitric oxide synthase[72]. Also, simvastatin improves renal function and changes in renal histopathology caused by dose-dependent gentamicin in rats[65].

Arguments Against Statin Use

Uncertain or Undesirable Effects on Kidney Function

A large study[73] has shown a link between statin treatment and an increased incidence of chronic and autistic kidney disease. Data analysis of 143,888 patients showed that statins did not prevent AKI, moderately alleviated the decline in GFR, and reduced proteinuria in non-dialysis patients[74].

Treatment with highly effective statins is associated with a 13% increased risk of developing severe renal insufficiency that remains co-consistent in floods with CKD, diabetes, and ischemic heart disease[65,75].

Increased Risk for Rhabdomyolysis in CKD

Statins have been associated with mild skeletal muscle problems such as myalgia and increased serum creatine kinase and severe skeletal muscle problems such as rhabdomyolysis, myositis, muscle cramps, and severe muscle weakness[76]. A common factor in the development of statin-induced myopathy is CKD. Patients with CKD who experience additional important variables, including liver failure, advanced age, diabetes, etc., are more likely to develop myopathy. A patient in a case study[65] who used the right statin for three years developed CKD and described purpura fulminant and acute rhabdomyolysis.

Induction of Tubulo-Interstitial Nephritis

Studies[77] have shown an association between sub-acute tubulointerstitial nephritis and statins. A biopsy showed nephritis treated with steroids after discontinuation of statin therapy and was withdrawn. However, after statin reintroduction, nephritis occurred in the patient. Tubulointerstitial nephritis due to statin therapy probably needs to be sufficiently reported because it insidiously develops in patients not prone to AKI[65].

Controversy Regarding Statin Use in CKD

In patients with CKD, the effects of statins are uncertain. The use of statins in all patients with CKD was proposed by KDOQI in 2003[78]. KDOQI suggested using statins targeting LDL cholesterol levels below 100 mg/dL regardless of dialysis[78,79]. A sharp decrease reduced the incidence of major atherosclerotic events in LDL cholesterol with daily therapy with simvastatin plus ezetimibe. However, this therapy did not slow the five-year progression of kidney disease in many patients with advanced CKD. Although rosuvastatin and atorvastatin significantly reduced LDL cholesterol, they did not substantially affect cardiovascular death, stroke, and nonfatal myocardial infarction in patients with end-stage renal disease. Patients with end-stage renal illness are unlikely to benefit from having their cholesterol reduced with statins, and they might experience statin adverse effects as a result[65].

In the updated 2012 KDOQI guidelines[78], recommendations for lowering LDL cholesterol by statins in all patients with CDK were revised, except when dialysis was initiated. Regarding therapy for patients with end-stage renal disease, clinicians need to determine whether to start statin therapy. The use of statins for the secondary prevention of cardiovascular disease may be justified in patients without DM and with longer life expectancies[65].

Conclusions

The evidence shows that statins may offer a beneficial renoprotective effect in inhibiting the progression of renal function decline. Patients who have type 2 diabetes and nephropathy are more likely to experience this impact, which is time-dependent. In addition, whether certain statin types are more beneficial than others in slowing renal function loss and reducing proteinuria remains unclear. Finally, prior research has yet to examine to what extent high-intensity statin therapy affects the clinical outcomes of patients with CKD.

Funding

The authors declared that no grants were involved in supporting this work.

Conflict of Interest

The authors declare that they have no conflict of interest to declare.

Authors' Contributions

Ammar Abdulrahman Jairoun reviewed the article design and executed article drafting and writing. Chong Chee and Baharudin Ibrahim revised the draft. The final version of the article was approved by all authors for publication.

Ethics Approval

Not applicable.

Informed Consent

Not applicable.

ORCID ID

A.A. Jairoun: 0000-0002-4471-0878.

References

1) Mactier R. Renal association clinical practice guideline development policy manual. Nephron Clin Pract 2011; 118: c13-c25.
2) Mehdar KM, Alsareii SA. The potential therapeutic effect of medium chain triglyceride oil in ameliorating diabetic liver injury in a streptozotocin-in-

duced diabetic murine model. Eur Rev Med Pharmacol Sci 2023; 27: 2428-2442.

3) Yaprak B, Keskin L. Evaluation of microvascular complications in patients with new diagnosis type 2 diabetes. Eur Rev Med Pharmacol Sci 2023; 27: 1601-1608.
4) Al-Qerem W, Jarab AS, Badinjki M, Hammad A, Ling J, Alasmari F. Factors associated with glycemic control among patients with type 2 diabetes: a cross-sectional study. Eur Rev Med Pharmacol Sci 2022; 26: 2415-2421.
5) Uhlig K, MacLeod A, Craig J, Lau J, Levey AS, Levin A, Moist L, Steinberg E, Walker R, Wanner C, Lameire N, Eknoyan G. Grading evidence and recommendations for clinical practice guidelines in nephrology. A position statement from kidney disease: improving global outcomes (KDIGO). Kidney Int 2006; 70: 2058-2065.
6) National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis 2002; 39: S1-S266.
7) Hoogeveen EK, Geleijnse JM, Giltay EJ, Soedamah-Muthu SS, de Goede J, Griep LMO, Stijnen T, Kromhout D. Kidney function and specific mortality in 60-80 years old post-myocardial infarction patients: a 10-year follow-up study. PLoS One 2017; 12: e0171868.
8) Plantinga LC, Crews DC, Coresh J, Miller ER 3rd, Saran R, Yee J, Hedgeman E, Pavkov M, Eberhardt MS, Williams DE, Powe NR, Team CCS. Prevalence of chronic kidney disease in US adults with undiagnosed diabetes or prediabetes. Clin J Am Soc Nephrol 2010; 5: 673-682.
9) Middleton RJ, Foley RN, Hegarty J, Cheung CM, McElduff P, Gibson JM, Kalra PA, O'Donoghue DJ, New JP. The unrecognized prevalence of chronic kidney disease in diabetes. Nephrol Dial Transplant 2006; 21: 88-92.
10) Whaley-Connell A, Sowers JR, McCullough PA, Roberts T, McFarlane SI, Chen S-C, Li S, Wang C, Collins AJ, Bakris GL. Diabetes mellitus and CKD awareness: the kidney early evaluation program (KEEP) and national health and nutrition examination survey (NHANES). Am J Kidney Dis 2009; 53: S11-S21.
11) McClellan WM, Knight DF, Karp H, Brown WW. Early detection and treatment of renal disease in hospitalized diabetic and hypertensive patients: important differences between practice and published guidelines. Am J Kidney Dis 1997; 29: 368-375.
12) Collins AJ, Li S, Gilbertson DT, Liu J, Chen SC, Herzog CA. Chronic kidney disease and cardiovascular disease in the medicare population. Kidney Int 2003; 64: S24-S31.
13) Teramoto T. Interim analysis of the atorvastatin lipid lowering assessment survey in patients with hypercholesterolemia (ALWAYS) study. Ther Res 2011; 32: 1587-1603.
14) Jungers P, Massy Z, Khoa T, Fumeron C, Labrunie M, Lacour B, Descamps-Latscha B, Man N. Incidence and risk factors of atherosclerotic cardiovascular accidents in predialysis chronic renal failure patients: a prospective study. Nephrol Dial Transplant 1997; 12: 2597-2602.
15) Barnett KN, Ogston SA, McMurdo MET, Morris AD, Evans JMM. A 12-year follow-up study of all-cause and cardiovascular mortality among 10,532 people newly diagnosed with type 2 diabetes in Tayside, Scotland. Diabet Med 2010; 27: 1124-1129.
16) JBS3 Board. Joint British Societies' consensus recommendations for the prevention of cardiovascular disease (JBS3). Heart 2014; 100: ii1-ii67.
17) Deckert T, Poulsen JE, Larsen M. Prognosis of diabetics with diabetes onset before the age of thirty-one. II. Factors influencing the prognosis. Diabetologia 1978; 14: 371-377.
18) Hyre AD, Fox CS, Astor BC, Cohen AJ, Muntner P. The impact of reclassifying moderate CKD as a coronary heart disease risk equivalent on the number of US adults recommended lipid-lowering treatment. Am J Kidney Dis 2007; 49: 37-45.
19) Kidney Disease. Improving Global Outcomes (KDIGO) Lipid Work Group. KDIGO clinical practice guideline for lipid management in chronic kidney disease. Kidney Int Suppl 2013; 3: 259-305.
20) Catapano AL, Graham I, De Backer G, Wiklund O, Chapman MJ, Drexel H, Hoes AW, Jennings CS, Landmesser U, Pedersen TR, Reiner Ž, Riccardi G, Taskinen MR, Tokgozoglu L, Verschuren WMM, Vlachopoulos C, Wood DA, Zamorano JL. 2016 ESC/EAS guidelines for the management of dyslipidaemias: the task force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) developed with the special contribution of the European Assocciation for Cardiovascular Prevention & Rehabilitation (EACPR). Atherosclerosis 2016; 253: 281-344.
21) Mark PB, Winocour P, Day C. Management of lipids in adults with diabetes mellitus and nephropathy and/or chronic kidney disease: summary of joint guidance from the Association of British Clinical Diabetologists (ABCD) and the Renal Association (RA). Br J Diabetes 2017; 17: 64.
22) Pedersen TR, Kjekshus J, Berg K, Kjekshus J, Berg K, Haghfelt T, Faergeman O, Faergeman G, Pyörälä K, Miettinen T, Wilhelmsen L, Olsson AG, Wedel H, Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet 1994; 344: 1383-1389.
23) Heart Protection Study Collaborative Group. MRC/BHF heart protection study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet 2002; 360: 7-22.
24) National Institute for Health and Care Excellence (NICE). Lipid Modification: Cardiovascular Risk Assessment and the Modification of Blood Lipids for the Primary and Secondary Prevention of Cardiovascular Disease. NICE Guideline. National Institute for Health and Care Excellence, 2014.

25) Emerging Risk Factors Collaboration, Sarwar N, Gao P, Seshasai SRK, Gobin R, Kaptoge S, Di Angelantonio E, Ingelsson E, Lawlor DA, Selvin E, Stampfer M, Stehouwer CDA, Lewington S, Pennells L, Thompson A, Sattar N, White IR, Ray KK, Danesh J. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. Lancet 2010; 375: 2215-2222.

26) Maftei O, Pena AS, Sullivan T, Jones TW, Donaghue KC, Cameron FJ, Davis E, Cotterill A, Craig ME, Gent R, Dalton N, Daneman D, Dunger D, Deanfield J, Couper JJ, AdDIT Study Group. Early atherosclerosis relates to urinary albumin excretion and cardiovascular risk factors in adolescents with type 1 diabetes: adolescent type 1 diabetes cardio-renal intervention trial (AdDIT). Diabetes Care 2014; 37: 3069-3075.

27) Seshasai SRK, Kaptoge S, Thompson A, Di Angelantonio E, Gao P, Sarwar N, Whincup PH, Mukamal KJ, Gillum RF, Holme I, Njølstad I, Fletcher A, Nilsson P, Lewington S, Collins R, Gudnason V, Thompson SG, Sattar N, Selvin E, Hu FB, Danesh J, Emerging Risk Factors C. Diabetes mellitus, fasting glucose, and risk of cause-specific death. N Engl J Med 2011; 364: 829-841.

28) Lewis S, MacLeod M, McKnight J, Morris A, Peden N, Prescott R, Walker J, Royal College of Physicians of Edinburgh Diabetes Register Group. Predicting vascular risk in type 1 diabetes: stratification in a hospital based population in Scotland. Diabet Med 2005; 22: 164-171.

29) Cholesterol Treatment Trialists' Collaborators, Kearney PM, Blackwell L, Collins R, Keech A, Simes J, Peto R, Armitage J, Baigent C. Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis. Lancet 2008; 371: 117-125.

30) Sniderman AD, Lamarche B, Tilley J, Seccombe D, Frohlich J. Hypertriglyceridemic HyperapoB in type 2 diabetes. Diabetes Care 2002; 25: 579-582.

31) Taskinen MR, Barter PJ, Ehnholm C, Sullivan DR, Mann K, Simes J, Best JD, Hamwood S, Keech AC, FIELD Study Investigators. Ability of traditional lipid ratios and apolipoprotein ratios to predict cardiovascular risk in people with type 2 diabetes. Diabetologia 2010; 53: 1846-1855.

32) Chronic Kidney Disease Prognosis Consortium, Matsushita K, van der Velde M, Astor BC, Woodward M, Levey AS, de Jong PE, Coresh J, Gansevoort RT. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. Lancet 2010; 375: 2073-2081.

33) Winocour PH, Durrington PN, Bhatnagar D, Ishola M, Mackness M, Arrol S. Influence of early diabetic nephropathy on Very Low Density Lipoprotein (VLDL), Intermediate Density Lipoprotein (IDL), and Low Density Lipoprotein (LDL) composition. Atherosclerosis 1991; 89: 49-57.

34) Hovind P, Rossing P, Tarnow L, Smidt UM, Parving H-H. Progression of diabetic nephropathy. Kidney Int 2001; 59: 702-709.

35) Strippoli GFM, Navaneethan SD, Johnson DW, Perkovic V, Pellegrini F, Nicolucci A, Craig JC. Effects of statins in patients with chronic kidney disease: meta-analysis and meta-regression of randomised controlled trials. BMJ 2008; 336: 645-651.

36) Palmer SC, Craig JC, Navaneethan SD, Tonelli M, Pellegrini F, Strippoli GFM. Benefits and harms of statin therapy for persons with chronic kidney disease: a systematic review and meta-analysis. Ann Intern Med 2012; 157: 263-275.

37) Upadhyay A, Earley A, Lamont JL, Haynes S, Wanner C, Balk EM. Lipid-lowering therapy in persons with chronic kidney disease: a systematic review and meta-analysis. Ann Intern Med 2012; 157: 251-262.

38) Hou W, Lv J, Perkovic V, Yang L, Zhao N, Jardine MJ, Cass A, Zhang H, Wang H. Effect of statin therapy on cardiovascular and renal outcomes in patients with chronic kidney disease: a systematic review and meta-analysis. Eur Heart J 2013; 34: 1807-1817.

39) Zhang X, Xiang C, Zhou YH, Jiang A, Qin YY, He J. Effect of statins on cardiovascular events in patients with mild to moderate chronic kidney disease: a systematic review and meta-analysis of randomized clinical trials. BMC Cardiovasc Disord 2014; 14: 19.

40) Navaneethan SD, Pansini F, Perkovic V, Manno C, Pellegrini F, Johnson DW, Craig JC, Strippoli GF. HMG CoA reductase inhibitors (statins) for people with chronic kidney disease not requiring dialysis. Cochrane Database Syst Rev 2009; CD007784.

41) Armitage J, Baigent C, Barnes E, Betteridge DJ, Blackwell L, Blazing M, Bowman L, Braunwald E, Byington R, Cannon C, Clearfield M, Colhoun H, Collins R, Dahlöf B, Davies K, Davis B, de Lemos J, Downs JR, Durrington P, Emberson J, Fellström B, Flather M, Ford I, Franzosi MG, Fulcher J, Fuller J, Furberg C, Gordon D, Goto S, Gotto A, Halls H, Harper C, Hawkins CM, Herrington W, Hitman G, Holdaas H, Holland L, Jardine A, Jukema JW, Kastelein J, Kean S, Keech A, Kirby A, Kjekshus J, Knatterud G, Knopp R, Koenig W, Koren M, Krane V, Landray MJ, LaRosa J, Lonn E, MacFarlane P, MacMahon S, Maggioni A, Marchioli R, Marschner I, Mihaylova B, Moyé L, Murphy S, Nakamura H, Neil A, Newman C, O'Connell R, Packard C, Parish S, Pedersen T, Peto R, Pfeffer M, Poulter N, Preiss D, Reith C, Ridker P, Robertson M, Sacks F, Sattar N, Schmieder R, Serruys P, Sever P, Shaw J, Shear C, Simes J, Sleight P, Spata E, Tavazzi L, Tobert J, Tognoni G, Tonkin A, Trompet S, Varigos J, Wanner C, Wedel H, White H, Wikstrand J, Wilhelmsen L, Wilson K, Young R, Yusuf S, Zannad F. Efficacy and safety of statin therapy in older people: a meta-analysis of individual participant data from 28 randomised controlled trials. Lancet 2019; 393: 407-415.

42) Shen H, Chen X, Lu J, Yang H, Xu Y, Zhu A, Zhang X, Ye F, Gu Y. Effects of statin therapy on chronic kidney disease patients with coronary artery disease. Lipids Health Dis 2018; 17: 84.

43) Yan YL, Qiu B, Wang J, Deng SB, Wu L, Jing XD, Du JL, Liu YJ, She Q. High-intensity statin therapy in patients with chronic kidney disease: a systematic review and meta-analysis. BMJ Open 2015; 5: e006886.

44) Barylski M, Nikfar S, Mikhailidis DP, Toth PP, Salari P, Ray KK, Pencina MJ, Rizzo M, Rysz J, Abdollahi M, Nicholls SJ, Banach M. Statins decrease all-cause mortality only in CKD patients not requiring dialysis therapy—a meta-analysis of 11 randomized controlled trials involving 21,295 participants. Pharmacol Res 2013; 72: 35-44.

45) Jung J, Bae GH, Kang M, Kim SW, Lee DH. Statins and all-cause mortality in patients undergoing hemodialysis. J Am Heart Assoc 2020; 9: e014840.

46) Kim JE, Choi YJ, Oh SW, Kim MG, Jo SK, Cho WY, Ahn SY, Kwon YJ, Ko G-J. The effect of statins on mortality of patients with chronic kidney disease based on data of the observational medical Outcomes Partnership Common Data Model (OMOP-CDM) and Korea national health insurance claims database. Front Nephrol 2022; 1: 821585.

47) Chung CM, Lin MS, Hsu JT, Hsiao JF, Chang ST, Pan KL, Lin CL, Lin YS. Effects of statin therapy on cerebrovascular and renal outcomes in patients with predialysis advanced chronic kidney disease and dyslipidemia. J Clin Lipidol 2017; 11: 422-431.e2.

48) Amarenco P, Callahan A, Campese VM, Goldstein LB, Hennerici MG, Messig M, Sillesen H, Welch KMA, Wilson DJ, Zivin JA. Effect of high-dose atorvastatin on renal function in subjects with stroke or transient ischemic attack in the SPARCL trial. Stroke 2014; 45: 2974-2982.

49) Obialo CI, Ofili EO, Norris KC. Statins and cardiovascular disease outcomes in chronic kidney disease: reaffirmation *vs.* repudiation. Int J Environ Res Public Health 2018; 15: 2733.

50) Ercan E. Statin treatment in dialysis patients after acute myocardial infarction improves overall mortality. Atherosclerosis 2017; 267: 156-157.

51) Smith DH, Johnson ES, Boudreau DM, Cassidy-Bushrow AE, Fortmann SP, Greenlee RT, Gurwitz JH, Magid DJ, McNeal CJ, Reynolds K, Steinhubl SR, Thorp M, Tom JO, Vupputuri S, VanWormer JJ, Weinstein J, Yang X, Go AS, Sidney S. Comparative effectiveness of statin therapy in chronic kidney disease and acute myocardial infarction: a retrospective cohort study. Am J Med 2015; 128: 1252.e1-1252.e11.

52) Shepherd J, Kastelein JJP, Bittner V, Deedwania P, Breazna A, Dobson S, Wilson DJ, Zuckerman A, Wenger NK. Intensive lipid lowering with atorvastatin in patients with coronary heart disease and chronic kidney disease. J Am Coll Cardiol 2008; 51: 1448-1454.

53) 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. J Am Coll Cardiol 2010; 55: 1266-1273.

54) Rutter MK, Prais HR, Charlton-Menys V, Gittins M, Roberts C, Davies RR, Moorhouse A, Jinadev P, France M, Wiles PG, Gibson JM, Dean J, Kalra PA, Cruickshank JK, Durrington PN. Protection Against Nephropathy in Diabetes with Atorvastatin (PANDA): a randomized double-blind placebo-controlled trial of high- vs. low-dose atorvastatin1. Diabet Med 2010; 28: 100-108.

55) Zhang Z, Wu P, Zhang J, Wang S, Zhang G. The effect of statins on microalbuminuria, proteinuria, progression of kidney function, and all-cause mortality in patients with non-end stage chronic kidney disease: a meta-analysis. Pharmacol Res 2016; 105: 74-83.

56) Douglas K, O'Malley PG, Jackson JL. Meta-analysis: the effect of statins on albuminuria. Ann Intern Med 2006; 145: 117-124.

57) Ohsawa M, Tamura K, Wakui H, Kanaoka T, Azushima K, Uneda K, Haku S, Kobayashi R, Ohki K, Haruhara K, Kinguchi S, Toya Y, Umemura S. Effects of pitavastatin add-on therapy on chronic kidney disease with albuminuria and dyslipidemia. Lipids Health Dis 2015; 14: 161.

58) Shen X, Zhang Z, Zhang X, Zhao J, Zhou X, Xu Q, Shang H, Dong J, Liao L. Efficacy of statins in patients with diabetic nephropathy: a meta-analysis of randomized controlled trials. Lipids Health Dis 2016; 15: 179-179.

59) Zhao L, Li S, Gao Y. Efficacy of statins on renal function in patients with chronic kidney disease: a systematic review and meta-analysis. Ren Fail 2021; 43: 718-728.

60) Zhao R, Lu Z, Yang J, Zhang L, Li Y, Zhang X. Drug delivery system in the treatment of diabetes mellitus. Front Bioeng Biotechnol 2020; 8: 880.

61) Lv J, Ren C, Hu Q. Effect of statins on the treatment of early diabetic nephropathy: a systematic review and meta-analysis of nine randomized controlled trials. Ann Palliat Med 2021; 10: 11548-11557.

62) Nasri H, Hasanpour Z, Nematbakhsh M, Ahmadi A, Rafieian-Kopaei M. The effect of the various doses of atorvastatin on renal tubular cells; an experimental study. J Nephropathol 2016; 5: 111-115.

63) Koren MJ, Davidson MH, Wilson DJ, Fayyad RS, Zuckerman A, Reed DP, ALLIANCE Investigators. Focused atorvastatin therapy in managed-care patients with coronary heart disease and CKD. Am J Kidney Dis 2009; 53: 741-750.

64) Pinal-Fernandez I, Casal-Dominguez M, Mammen AL. Statins: pros and cons. Med Clin (Barc) 2018; 150: 398-402.

65) Verdoodt A, Honore PM, Jacobs R, De Waele E, Van Gorp V, De Regt J, Spapen HD. Do statins induce or protect from acute kidney injury and chronic kidney disease: an update review in 2018. J Transl Int Med 2018; 6: 21-25.

66) Harky A, Joshi M, Gupta S, Teoh WY, Gatta F, Snosi M. Acute kidney injury associated with cardiac surgery: a comprehensive literature review. Braz J Cardiovasc Surg 2020; 35: 211-224.

67) Romagnoli S, Ricci Z. Statins and acute kidney injury following cardiac surgery: has the last word been told? J Thorac Dis 2016; 8: E451-E454.

68) Billings FTt, Hendricks PA, Schildcrout JS, Shi Y, Petracek MR, Byrne JG, Brown NJ. High-dose perioperative atorvastatin and acute kidney injury following cardiac surgery: a randomized clinical trial. JAMA 2016; 315: 877-888.

69) Mohammed NMA, Mahfouz A, Achkar K, Rafie IM, Hajar R. Contrast-induced nephropathy. Heart Views 2013; 14: 106-116.

70) Lekawanvijit S, Krum H. Cardiorenal syndrome: acute kidney injury secondary to cardiovascular disease and role of protein-bound uraemic toxins. J Physiol 2014; 592: 3969-3983.

71) Kumar S, Bogle R, Banerjee D. Why do young people with chronic kidney disease die early? World J Nephrol 2014; 3: 143-155.

72) Ozbek E, Cekmen M, Ilbey YO, Simsek A, Polat EC, Somay A. Atorvastatin prevents gentamicin-induced renal damage in rats through the inhibition of p38-MAPK and NF-kB pathways. Ren Fail 2009; 31: 382-392.

73) Acharya T, Huang J, Tringali S, Frei CR, Mortensen EM, Mansi IA. Statin use and the risk of kidney disease with long-term follow-up (8.4-year study). Am J Cardiol 2016; 117: 647-655.

74) Su X, Zhang L, Lv J, Wang J, Hou W, Xie X, Zhang H. Effect of statins on kidney disease outcomes: a systematic review and meta-analysis. Am J Kidney Dis 2016; 67: 881-892.

75) Chung YH, Lee YC, Chang CH, Lin MS, Lin JW, Lai MS. Statins of high versus low cholesterol-lowering efficacy and the development of severe renal failure. Pharmacoepidemiol Drug Saf 2013; 22: 583-592.

76) Thompson PD. Statin-associated myopathy. JAMA 2003; 289: 1681-1690.

77) van Zyl-Smit R, Firth JC, Duffield M, Marais AD. Renal tubular toxicity of HMG-CoA reductase inhibitors. Nephrol Dial Transplant 2004; 19: 3176-3179.

78) National Kidney Foundation. KDOQI clinical practice guideline for diabetes and CKD: 2012 update. Am J Kidney Dis 2012; 60: 850-886.

79) Levey AS, Coresh J, Balk E, Kausz AT, Levin A, Steffes MW, Hogg RJ, Perrone RD, Lau J, Eknoyan G. National kidney foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Ann Intern Med 2003; 139: 137-147.