Review

Statin Use in Patients with Diabetes and Kidney Disease: The Japanese Experience

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Diabetes is a leading cause of chronic kidney disease (CKD) and end-stage renal disease (ESRD) in developed nations, including Japan and the United States. Japan has the unenviable distinction of having one of the world’s highest rates of dialysis: in 2011, there were over 300,000 dialysis patients (2,383 per million people), with diabetic patients accounting for almost half of all incident cases. Concomitance of CKD and diabetes predicts a greater risk of cardiovascular disease (CVD) than either condition in isolation. Hence, appropriate management of modifiable cardiovascular (CV) risk factors, including dyslipidemia, is paramount in this high-risk group. The United States and Japan have distinct approaches to cholesterol management, with more stringent therapeutic targets for lipid control advocated in US guidelines. However, upward trends in cholesterol levels and coronary heart disease incidence in Japan may provide justification for more intensive CV risk factor management strategies by Japanese physicians to achieve maximum benefit. Attainment of recommended lipid goals in Japan is poor, particularly in patients with diabetes and/or CKD in whom CV risk factors are often undertreated. Statin therapy has been shown to be safe and effective in reducing CV risk in patients with diabetes and/or CKD stages 1-5. Moreover, statins may impart a renoprotective effect by preventing or delaying progressive loss of kidney function. This review summarizes evidence from studies in Western and Japanese populations to highlight the CV and renal benefits of lipid-lowering agents in CKD patients, including those with diabetes.


Key words; Chronic kidney disease (CKD), Diabetes, Cardiovascular (CV) risk, Statins

Introduction

Chronic kidney disease (CKD) is defined as the presence of kidney damage (e.g., albuminuria) or a decrease in the glomerular filtration rate (GFR) that persists for ≥3 months. Diabetes is a leading cause of CKD and end-stage renal disease (ESRD) in developed nations such as the United States and Japan, fueled by an epidemic of obesity and type 2 diabetes in these countries, particularly among children.

Compared with non-diabetic individuals, those with diabetes are at increased risk of CKD. In 14,836 US adults participating in the third National Health and Nutrition Examination Survey (NHANES III; 1988-1994), the prevalence of microalbuminuria was 43% among diabetic participants ≥70 years of age compared with 24% in those without diabetes. The prevalence of overt proteinuria was 8% in those with diabetes and 3% among non-diabetic participants. In a more recent NHANES survey from 1999 to 2006, the prevalence of CKD was 33% in those with diagnosed diabetes and 12% in those without diabetes.

Data from a number of large US cohort studies have indicated that the presence of diabetes confers a 2.5-13-fold increase in the risk of ESRD versus no diabetes. Similar observations of an increased risk of renal impairment in patients with diabetes have also been made in Japanese populations. An analysis of 2,321...
adults aged >40 years from Takahata found that diabetes was independently associated with the presence of microalbuminuria in both men (hazard ratio [HR], 2.20; 95% confidence interval [CI], 1.35-3.58; \( p = 0.0015 \)) and women (HR, 3.66; 95% CI, 2.19-6.12; \( p < 0.001 \))\(^{11}\). Similarly, diabetes and treated diabetes were baseline-adjusted predictors of developing proteinuria over 10 years of follow-up in a large \((n = 123,764)\) community-based population aged ≥40 years resident in the Ibaraki prefecture\(^{12}\). This study also found that individuals who were receiving treatment for diabetes had an increased relative risk of developing CKD (defined as an estimated glomerular filtration rate [eGFR] < 60 mL/min/1.73 m\(^2\)) of 20% in men and 12% in women\(^{12}\). Finally, diabetes was a significant predictor of ESRD in the general population of Okinawa \((n = 78,529);\) HR, 3.098; 95% CI, 1.738-5.525; \( p = 0.0001 \))\(^{13}\). In addition to the increased risk of CKD in patients with diabetes, evidence suggests that the rate of progression of CKD is usually faster among diabetic than non-diabetic individuals\(^{1} \). Despite these observations, CKD—particularly in diabetic patients—is often underdiagnosed and undertreated\(^{8, 14-18} \). For example, in the interim analysis of the Atorvastatin Lipid Lowering Assessment Survey in Patients with Hypercholesterolemia (ALWAYS) trial\(^{18} \), a post-marketing surveillance study of atorvastatin in Japan, the primary physician diagnosed 8% of the cases as having CKD. In contrast, among the cases whose eGFR had been confirmed before registration, 22.8% of patients had CKD at baseline (eGFR < 60 mL/min/1.73 m\(^2\))\(^{18} \). Physicians should be cognizant of the likelihood that their diabetic patients may also have or be at risk of CKD and therefore consider the potential renoprotective effects of a drug when evaluating treatment options for these patients\(^{19, 20} \).

**Epidemiology of Diabetic Nephropathy**

ESRD is more prevalent in Japan than in the United States. The Japanese Society for Dialysis Therapy reported that, as of 31st December 2010, over 298,000 patients (2,329 per million people) were undergoing dialysis in Japan\(^ {21} \). More than 300,000 patients were undergoing dialysis one year later, an increase of 2.1% \((\text{Fig. 1})\), indicating that Japan currently has one of the world’s highest rates of dialysis treatment at 2,383 per million people\(^{22} \), second only to Taiwan\(^ {23} \). For comparison, ~415,000 patients were receiving some form of dialysis in the United States at the end of 2010, corresponding to a rate of 1,218 per million people\(^ {23} \).

The relationship between dysglycemia and renal insufficiency is underscored by data showing that patients with diabetes represented 35.9% of all prevalent dialysis patients and 43.6% of all incident dialysis patients in Japan at the end of 2010\(^ {21} \). One year later, as of 31st December 2011, patients with diabetes represented 36.6% of all prevalent dialysis patients and 44.2% of all incident dialysis patients \((\text{Fig. 2})\)^\(^ {22} \). Similar trends have been reported for US dialysis patients: at the end of 2010, 44.1% of all prevalent dialysis patients and 44.8% of all incident dialysis patients had diabetes\(^ {23} \).

**Predictors of Cardiovascular Risk in CKD and Diabetes**

In both Western and Japanese populations, proteinuria and renal insufficiency each confer an increased risk of morbidity and mortality from cardiovascular disease (CVD)\(^ {24-30} \). Readers are referred to the recent review by Shoji et al. for a thorough discussion of the link between CKD and CVD risk\(^ {31} \). Similarly, glucose intolerance and diabetes present an excess risk of CVD events\(^ {30, 32-37} \). Although traditional risk factors (such as smoking, hypertension, and dyslipidemia) contribute to the association between CKD and adverse cardiovascular (CV) outcomes\(^ {38-40} \), they do not fully account for the increase in CV risk in patients with renal impairment, suggesting that non-conventional risk factors (such as endothelial dysfunction, oxidative stress, and inflammation) may also play an important role\(^ {41, 43} \). In addition to increased levels of triglycerides and hemoglobin A1c (HbA1c), low-density lipoprotein cholesterol (LDL-C) is a strong predictor of coronary heart disease (CHD) in patients with diabetes\(^ {44-46} \), however, as with CKD, nontraditional risk factors may also contribute to excess CV risk in diabetes\(^ {47-49} \).

**Lipid Targets and Treatment Options for Patients with CKD and Diabetes**

Given the associated increase in CV risk, CKD and diabetes are both considered CHD risk equivalents\(^ {1, 30, 50-52} \); therefore, appropriate management of CV risk factors including dyslipidemia should be a priority in these high-risk patients. However, it is unclear what the LDL-C target should be for patients with CKD. Current US guidelines for individuals with CKD or diabetes recommend an LDL-C goal of <100 mg/dL, and an optional target of <70 mg/dL for very high-risk patients, such as those with a prior history of CVD or with concomitant CKD and diabe-
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intensive lipid-lowering goals than guidelines in the United States. Previous Japan Atherosclerosis Society (JAS) guidelines from 2007 recommended an LDL-C goal of $<120$ mg/dL for high-risk patients (those with 3 or more CV risk factors other than LDL-C, or with concomitant diabetes, cerebral infarction or arteriosclerosis obliterans) and a more stringent goal of $<100$ mg/dL for patients with a prior history of CHD [57]. For primary prevention, the JAS suggests that both individual coronary risk and the effect of lifestyle modification should be evaluated thoroughly prior to initiation of drug therapy; for secondary prevention, drug therapy and lifestyle modification should be initi-

Historically in Japan, the prevalence of hypercholesterolemia and atherosclerotic CVD has been much lower than in Western countries, and more emphasis was traditionally placed on reducing hypertension and stroke mortality [53, 56]. This is reflected in Japanese clinical practice recommendations for the management of dyslipidemia, which advocate less-

Fig. 1. Number of patients undergoing dialysis in Japan, 1968-2011.

The data are redrawn and translated from the Japanese Society for Dialysis Therapy [22].

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Fig. 2. Percentage of incident dialysis patients according to primary diagnosis in Japan, 1983-2011.
Abbreviations: GN, glomerulonephritis; SLE, systemic lupus erythematosus.
The data are redrawn and translated from the Japanese Society for Dialysis Therapy.\textsuperscript{22}
tiated concomitantly. Similarly, current recommenda-
tions for those patients with CKD or diabetic CKD from the Japanese Society of Nephrology and the Japanese Diabetes Society suggest an LDL-C goal of <120 mg/dL or, where possible, stricter control to <100 mg/dL.\(^\text{58, 59}\).

However, recent upward trends in cholesterol levels\(^\text{60-62}\) and the incidence of CHD\(^\text{62, 63}\) in Japan, particularly in urban middle-aged men and likely due to the progressive westernization of the Japanese lifestyle, may provide justification for a more systematic, multi-factorial approach to CV risk assessment and management to avert a future epidemic of atherosclerotic CVD. In addition, large observational cohort studies of community-based populations in Japan have found CKD to be a risk factor for CVD\(^\text{27-29, 40}\). To this end, revised JAS guidelines\(^\text{64}\) that stratify patients according to absolute risk (based on the prediction of 10-year probability of CV death from NIPPON DATA\(^\text{80}\)\(^\text{65}\) and add CKD to the high-risk clinical group (Category III) alongside diabetes (which was already listed as a high-risk indicator) have been recently developed. As with the previous JAS guidelines of 2007, an LDL-C goal of <120 mg/dL has been set for high-risk primary prevention patients, with an LDL-C goal of <100 mg/dL recommended for secondary prevention patients. Whether more stringent, Western-style lipid targets are required in Japan, and whether intensive treatment to achieve these goals would provide a clear clinical benefit in Japanese patients, is the subject of much debate\(^\text{66, 67}\).

The proportion of secondary prevention patients who reach recommended lipid goals in Japan is traditionally very low (20%-40%)\(^\text{68, 69}\). Therefore, a renewed effort by physicians is needed to help secondary prevention patients in particular to achieve current LDL-C targets using standard lipid management strategies, followed by a more stringent treatment approach if appropriate.

The efficacy of statin therapy to achieve current lipid targets in Japanese patients stratified by CV risk has recently been demonstrated in an interim analysis of the ALWAYS study.\(^\text{18}\) This prospective, multicenter post-marketing surveillance study included >24,000 hypercholesterolemia patients in ordinary clinical practice who were not achieving LDL-C goals as recommended in the 2007 JAS guideline\(^\text{57}\). Patients initiated atorvastatin therapy at 10 mg/day and were followed for 24 weeks. As of the interim analysis (\(n=9,929\)), patients classified as being at high CV risk (as per the 2007 JAS guideline) experienced a 37.9% reduction in LDL-C levels to a mean ± standard deviation of 100.9 ± 28.7 mg/dL (from 164.2 ± 26.5 mg/dL); those with a prior history of CHD achieved a 36.0% reduction in LDL-C to 90.5 ± 26.5 mg/dL (from 143.9 ± 29.4 mg/dL) (both \(p<0.001\))\(^\text{18}\). In patients with CKD at baseline, defined as an eGFR <60 mL/min/1.73 m\(^2\), LDL-C levels were reduced by 38.7% to 97.6 ± 28.0 mg/dL (from 161.3 ± 28.6 mg/dL; \(p<0.001\))\(^\text{18}\).

### Statin Therapy in Diabetes and CKD: Non-Japanese Populations

#### Effects on Cardiovascular Disease in Patients with Diabetes and CKD

Statin therapy has been shown to reduce the risk of CV events in a variety of patient populations\(^\text{70-76}\), including those with diabetes\(^\text{77-81}\) or mild-to-moderate CKD\(^\text{82-87}\). The concomitance of diabetes and CKD portends a greater risk of coronary events than either condition in isolation\(^\text{89}\). Pooled data from 3 randomized trials of pravastatin 40 mg daily versus placebo demonstrated that the incidence of coronary events was lowest in those without CKD or diabetes (15.2%), intermediate in those with only CKD (18.6%) or diabetes (21.3%), and highest in patients with both CKD and diabetes (27.0%)\(^\text{88}\). Moreover, while pravastatin reduced the relative risk of a coronary event to a similar extent (~25%) in all patient subgroups, the absolute reduction in risk was highest in patients with concomitant CKD and diabetes (6.4%) and lowest in those with neither CKD nor diabetes (3.5%)\(^\text{88}\).

Similarly, a post-hoc analysis of the Treating to New Targets (TNT) study investigated the effect of intensive (80 mg/day) versus moderate (10 mg/day) atorvastatin therapy in 1,431 patients with stable CHD and diabetes, with or without mild-to-moderate CKD\(^\text{89}\). Patients with concomitant diabetes and CKD were at increased risk of a major CV event compared with diabetic patients without CKD (HR, 1.32; 95% CI, 1.00-1.72; \(p<0.05\))\(^\text{89}\). Compared with low-dose atorvastatin, intensive atorvastatin treatment was associated with a 35% reduction in the relative risk of a major CV event for patients with diabetes and CKD (HR, 0.65; 95% CI, 0.43-0.98; \(p=0.04\))\(^\text{89}\). Interestingly, achieving an LDL-C level of ~75-80 mg/dL almost completely abolished the increased CV risk attributed to CKD status in TNT patients overall (Fig. 3A) and in the subset of TNT patients with diabetes (Fig. 3B)\(^\text{88, 89}\). A subanalysis of the Collaborative Atorvastatin Diabetes Study (CARDS), investigating the effect of statin therapy in the primary prevention of CVD in patients with diabetes, found that treatment with low-dose atorvastatin (10 mg/day) was...
Fig. 3. Time to first major CV event in (A) all patients and (B) diabetic patients by atorvastatin treatment and baseline CKD status in the TNT trial. The data are redrawn from Shepherd et al.83, 89.
associated with a 42% decrease in the relative risk of a primary outcome (major CVD event) in diabetic patients with an eGFR < 60 mL/min/1.73 m² (HR, 0.58; 95% CI, 0.36-0.96; \( p=0.03 \))\(^{90} \). The effect of atorvastatin in reducing the relative risk of the primary endpoint and its components in patients with diabetes was consistent irrespective of baseline eGFR status (< or \( \geq 60 \) mL/min/1.73 m²; \( p > 0.25 \) for all eGFR-by-treatment interactions)\(^{90} \).

For patients with more advanced CKD, the Study of Heart and Renal Protection (SHARP) trial in 9,270 pre-dialysis and dialysis patients—nearly one-quarter of whom had diabetes—demonstrated that lipid lowering with ezetimibe plus simvastatin reduced the relative risk of major atherosclerotic events by 17% versus placebo (HR, 0.83; 95% CI, 0.74-0.94; \( p=0.0021 \))\(^{91} \). However, as a result of the design of the SHARP trial and the lack of CV outcome trials in other populations, it remains unclear whether ezetimibe therapy—despite lowering LDL-C levels—provides any incremental CV event reduction over that provided by simvastatin alone\(^{92} \).

In contrast to the reduction of CV events following statin therapy in CKD patients, it is still uncertain whether ESRD patients on dialysis or renal transplant recipients derive a comparable CV benefit. In the SHARP trial, there was no significant heterogeneity in treatment effect on risk between pre-dialysis patients and dialysis patients \( ( \chi^2=1.34; p=0.25 ) \), although the reduction in relative risk was smaller and non-statistically significant in dialysis versus non-dialysis patients: 10% and 22%, respectively\(^{91} \). The German Diabetes and Dialysis (Die Deutsche Diabetes Dialyse; 4D) study\(^{90} \) assigned 1,255 patients with type 2 diabetes on maintenance hemodialysis to atorvastatin 20 mg/day or placebo, but failed to demonstrate a significant reduction in CV events (cardiac death, nonfatal myocardial infarction [MI], or fatal or nonfatal stroke) with statin therapy (HR, 0.92; 95% CI, 0.77-1.10; \( p=0.37 \)). However, a recent post-hoc analysis of the 4D study showed that atorvastatin did reduce the risk of CV events (HR, 0.69; 95% CI, 0.48-1.00; \( p=0.05 \)) in the quartile of patients with the highest pretreatment LDL-C levels (\( \geq 145 \) mg/dL; 3.76 mmol/L)\(^{94} \).

The AURORA (A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events) trial, which investigated the effect of rosvastatin therapy on time to major CV event in 2,776 ESRD patients receiving chronic dialysis treatment (~20% due to diabetic nephropathy), also failed to demonstrate a significant CV benefit with statin therapy\(^{95} \).

Similarly, the ALERT (Assessment of Lescol in Renal Transplantation) trial\(^{90} \), in 2,102 renal transplant patients (19% with diabetes) with total cholesterol levels of 155-348 mg/dL (4.0-9.0 mmol/L) who were randomized to fluvastatin 40-80 mg daily or placebo and followed for up to 6 years, demonstrated a trend towards reduction in the risk of a major cardiac event (cardiac death, nonfatal MI or coronary intervention), although the difference compared to placebo was not statistically significant (HR, 0.83; 95% CI, 0.64-1.06; \( p=0.139 \)). However, treatment with fluvastatin did result in significant reductions in the relative risk of cardiac death (38%; \( p=0.031 \)), nonfatal MI (32%; \( p=0.050 \)), and the combined endpoint of cardiac death or nonfatal MI (35%; \( p=0.005 \))\(^{90} \). A recent meta-analysis assessing the effect of statin therapy in patients with CKD reviewed data from 80 clinical trials comprising > 50,000 patients, and found that while statins reduced the risk of CV events in pre-dialysis patients (HR, 0.76; 95% CI, 0.73-0.80), there was little or no apparent effect in patients receiving dialysis treatment (HR, 0.95; 95% CI, 0.87-1.03)\(^{86} \). The differential effects of statin therapy in patients with mild-to-moderate CKD versus those with ESRD in reducing CV events underscore the need to identify CKD at an early stage so that lifestyle changes and risk factor modification strategies may be initiated as warranted.

**Effects on Proteinuria and Kidney Function in CKD Patients**

In addition to reducing CV risk in CKD patients, evidence suggests that statin therapy in patients with predialysis CKD may slow progressive loss of kidney function, measured as changes in urinary protein excretion or eGFR\(^{84, 97-101} \). For CKD in the context of diabetes, the CARDS trial found that atorvastatin therapy (10 mg/day) was associated with a small improvement in the annual change in eGFR (net improvement over placebo, 0.18 mL/min/1.73 m²/year; 95% CI, 0.04-0.32; \( p=0.01 \))\(^{90} \). However, there was an overall decrease in eGFR in patients with albuminuria at baseline, but an overall improvement in eGFR in those who were normoalbuminuric at baseline\(^{90} \). The effect of atorvastatin treatment was most notable in patients with baseline albuminuria (net improvement over placebo, 0.38 mL/min/1.73 m²/year; 95% CI, 0.04-0.72; \( p=0.03 \)); in patients who were normoalbuminuric at baseline, the effect of atorvastatin was a non-significant increase in annual improvement by 0.13 mL/min/1.73 m²/year (95% CI, -0.02-0.30; \( p=0.1 \))\(^{90} \).

Similarly, in post-hoc analyses of the TNT trial, a
progressive increase in eGFR was observed in patients with CKD and/or diabetes treated with atorvastatin; this renal benefit was greater with the higher (80 mg/day) dose than with the lower (10 mg/day) dose of the drug (Fig. 4)\(^9\). For example, in patients with diabetes with or without CKD, the mean ± standard error change eGFR from baseline to final visit showed an increase of 0.5 ± 0.43 mL/min/1.73 m\(^2\) in the 10-mg/day group and 2.6 ± 0.5 mL/min/1.73 m\(^2\) in the 80-mg/day group (\(p<0.001\)) (Fig. 4)\(^8\).

In a prospective, controlled, open-label study, Bianchi et al. found that atorvastatin 10-40 mg/day reduced proteinuria and the rate of progression of kidney disease in 56 patients with CKD, proteinuria and hypercholesterolemia who had been treated with angiotensin-converting enzyme (ACE) inhibitors and/or angiotensin II receptor blockers (ARBs), as well as other antihypertensive medications as required, to achieve blood pressure <140/90 mm Hg, before random assignment to supplemental atorvastatin or placebo\(^10\). However, in the SHARP study, while allocation to ezetimibe plus simvastatin produced a significant reduction in major atherosclerotic events in patients with baseline microalbuminuria (urinary albumin : creatinine ratio, \(\geq 30\)–\(\leq 300\) mg/g; HR, 0.75; 95% CI, 0.57-0.97) or baseline proteinuria (urinary albumin : creatinine ratio, >300 mg/g; HR, 0.72; 95% CI, 0.57-0.91), combination therapy did not produce significant reductions in progression to ESRD or doubling of baseline serum creatinine\(^9\).

**Effects on Kidney Function in Renal Transplant Recipients**

The clinical evidence to support the therapeutic efficacy of statins in transplantation settings is mixed\(^10\). A retrospective analysis of 77 renal transplant recipients found that creatinine clearance was significantly higher at 12-months post-surgery among patients given statins than among those who were not treated\(^10\). In another study, renal transplant recipients randomly assigned to pravastatin for 4 months had half the rate of acute rejection than those receiving placebo (25% versus 58%; \(p<0.01\)).

By contrast, no benefit on the rate of acute rejection was observed in a 90-day trial of initiating simvastatin therapy immediately after renal transplantation (starting at 2 weeks), even though the levels of total cholesterol and LDL-C were significantly lower in statin-treated patients than in those receiving a fibrate or placebo\(^10\). Also, no benefit on acute rejection rate was observed in the ALERT trial of fluvastatin 40-80 mg daily versus placebo\(^10\), which demonstrated a lack of improvement in the incidence of renal graft loss or reduction in the doubling of serum creatinine levels; active therapy was also not associated with a reduction in the deterioration of eGFR over time in comparison to placebo.
Statin Therapy in Diabetes and CKD: Japanese Populations

Effects on Cardiovascular Disease

Statin therapy has been shown to be effective in reducing the risk of CV events in Japanese populations, as in Western populations. The MEGA (Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese) study, where 7,832 patients with hypercholesterolemia and no prior history of CHD or stroke were randomly assigned diet or diet plus pravastatin 10-20 mg/day, revealed that the relative risk of CHD events was significantly lower in the group receiving pravastatin than the diet-only group (HR, 0.67; 95% CI, 0.49-0.91; p=0.01)\(^{109}\).

A subanalysis of the MEGA study in 2,210 patients with diabetes or impaired fasting glucose demonstrated that treatment with low-dose pravastatin significantly reduced the relative risk of CVD events by 32% (HR, 0.68; 95% CI, 0.48-0.96)\(^{110}\). Similarly, a post-hoc analysis of the MEGA study, in which 7,196 patients were stratified by CKD status at baseline, demonstrated that low-dose pravastatin significantly reduced the relative risk of CHD events by 48% (HR, 0.52; 95% CI, 0.31-0.89; p=0.02) and CVD events by 55% (HR, 0.45; 95% CI, 0.30-0.69; p<0.01) in those patients with moderate CKD\(^{111}\).

Owing to the limited availability of clinical data in Japanese patients with diabetes and/or CKD, information on the CV benefit of statin therapy in these high-risk groups may be inferred from studies of other Asian populations. In a prospective analysis of 4,521 Chinese diabetic patients from the Hong Kong Diabetes Registry, statin therapy was associated with a 34% reduction in the relative risk of CV events (HR, 0.66; 95% CI, 0.50-0.88; p=0.0038)\(^{112}\). A retrospective analysis of 12,865 patients from the Korea Acute Myocardial Infarction Registry (KAMIR), of which 3,256 patients had renal insufficiency (eGFR <60 mL/min/1.73 m\(^2\)), demonstrated that patients who received statin therapy had significant reductions in the rate of major cardiac events irrespective of baseline eGFR, even in those with severe renal impairment (eGFR <30-15 mL/min/1.73 m\(^2\) and <15 mL/min/1.73 m\(^2\))\(^{113}\).

Effects on Proteinuria and Kidney Function

Similarly, limited data on the effect of statins on proteinuria and kidney function improvement are available from Japanese populations. The post-hoc analysis of MEGA patients stratified by CKD status at baseline also demonstrated that improvement in eGFR during follow-up was significantly higher in those patients with moderate CKD assigned to receive diet plus pravastatin 10-20 mg/day (6.3% increase) than in those on diet alone (5.1% increase; p=0.03)\(^{111}\).

Several small studies have investigated the effects of statin therapy on kidney function. A prospective, open-label study of Japanese hyperlipidemic patients with CKD (including those on dialysis) (n=84) reported that atorvastatin treatment reduced LDL-C levels regardless of baseline renal status\(^{114}\). Although serum creatinine was not affected by atorvastatin, a significant reduction in proteinuria (from 2.59 g/day to 1.58 g/day) was reported in a subgroup of patients who had not taken antihyperlipidemic medications before the trial. A small study of rosuvastatin in 91 patients with CKD and LDL-C levels >120 mg/dL demonstrated that, while there was no significant effect on eGFR, albuminuria was significantly decreased\(^{115}\).

For those patients with diabetes, two small studies conducted by Tanaka demonstrated that treatment with atorvastatin improved, or at least preserved, renal function in patients with diabetes\(^{116}\). Similarly, a study in diabetic patients with mild-to-moderate renal impairment and hyperlipidemia (n=98), where patients were assigned to dietary therapy, pravastatin 10 mg/day or atorvastatin 10 mg/day, found that after 18 months of follow-up, eGFR improved from baseline in the atorvastatin group (p=0.058), whereas it remained stable in the pravastatin group and declined in the dietary group (p=0.07)\(^{117}\).

In a retrospective study of 128 patients with chronic heart failure (CHF) and diabetes, atorvastatin therapy was shown to significantly reduce the deterioration in eGFR from baseline over the 2-year follow-up period compared with no statin treatment\(^{118}\). Similarly, Kawasaki et al. found that, after a mean follow-up period of 5.9 years, the reduction in eGFR was significantly less in CHF patients (n=38) with versus without atorvastatin 10 mg/day (p=0.024); the annual reduction in eGFR was also significantly smaller in patients treated with atorvastatin versus those that did not receive statin therapy (p=0.02)\(^{119}\).

A study investigating the effect of combination therapy with an ARB and atorvastatin on renal outcomes in Japanese patients with diabetic nephropathy demonstrated significant reductions in both LDL-C and proteinuria (Fig. 5) in those patients receiving combination therapy\(^{120}\). The albumin excretion ratio (AER) was reduced by 10.4% in the combination therapy group with atorvastatin, whereas a 5.5% increase in AER was observed in the group receiving conventional therapy without atorvastatin (Fig. 5)\(^{120}\).

The lack of well-controlled studies investigating the renoprotective effect of statins in Japanese patients
randomized non-inferiority renal safety study of the effects of rosuvastatin 10 mg/day, rosuvastatin 40 mg/day, or atorvastatin 80 mg/day on proteinuria and eGFR in 353 patients with diabetes and CKD\textsuperscript{123}). The primary endpoint was the change in the urinary protein : creatinine ratio from baseline to week 52; secondary endpoints included changes in eGFR from baseline. The study showed that patients treated with atorvastatin had an average decrease in proteinuria of ~13% and no significant change in eGFR by 52 weeks. In contrast, patients treated with rosuvastatin exhibited no significant change in proteinuria and a significant, dose-related decrease in eGFR\textsuperscript{123}). It is important to note, however, that this study was not sufficiently powered to directly compare the effects of these two statins.

Atorvastatin and rosuvastatin were similarly tested in a proteinuric, non-diabetic CKD population ($n=237$) under a very similar protocol (PLANET II); primary and secondary endpoints were the same as in PLANET I\textsuperscript{123}). At 52 weeks, a ~24% decrease in urinary protein/creatinine excretion and micro-hematuria, whereas this effect was not apparent with other statins\textsuperscript{122}).

**Are All Statins Equally Effective in Reducing Proteinuria and CKD Progression?**

Current evidence leads many to believe that the renoprotective benefit of statin therapy is not a class effect and particular caution must be used with high doses of rosuvastatin in patients with proteinuria and pre-existing CKD. For example, a review of clinical trial data suggested that rosuvastatin use was associated with a dose-dependent increase in urine protein excretion and micro-hematuria, whereas this effect was not apparent with other statins\textsuperscript{122}).

The Prospective Evaluation of Proteinuria and Renal Function in Diabetic Patients With Progressive Renal Disease (PLANET I) trial was a prospective, randomized non-inferiority renal safety study of the effects of rosuvastatin 10 mg/day, rosuvastatin 40 mg/day, or atorvastatin 80 mg/day on proteinuria and eGFR in 353 patients with diabetes and CKD\textsuperscript{123}). The primary endpoint was the change in the urinary protein : creatinine ratio from baseline to week 52; secondary endpoints included changes in eGFR from baseline. The study showed that patients treated with atorvastatin had an average decrease in proteinuria of ~13% and no significant change in eGFR by 52 weeks. In contrast, patients treated with rosuvastatin exhibited no significant change in proteinuria and a significant, dose-related decrease in eGFR\textsuperscript{123}). It is important to note, however, that this study was not sufficiently powered to directly compare the effects of these two statins.

**Fig. 5.** Effect of combination therapy with an ARB plus atorvastatin on change in log-transformed albumin excretion ratio. The data are redrawn and translated from Inukai et al.\textsuperscript{120}).
Mechanism of Renal Function Improvement

The mechanism by which statins provide renal benefit is not fully understood: one of the main uncertainties is whether the effect of statins on kidney function is directly derived from LDL-C lowering, or pleiotropic effects such as reducing oxidative stress and inflammation.

A post-hoc analysis of the TNT study showed that on-treatment (3-month) LDL-C levels were a significant predictor of change in eGFR in CHD patients, showing a greater improvement in eGFR for a lower on-treatment LDL-C, suggesting that the renal benefit derived from statin therapy could be primarily related to changes in LDL-C levels in this population.

However, a similar analysis of diabetic CHD patients, with or without mild-to-moderate CKD, from the TNT study found that the level of LDL-C during treatment was not a significant predictor of change in eGFR, indicating that other cholesterol-independent mechanisms may play a more prominent role in this cohort. Such pleiotropic actions of statin therapy may include a positive effect on nitric oxide production in a variety of vascular beds, and amelioration of vascular inflammation.

The gradual improvement in eGFR observed during the follow-up period of the TNT study may indicate such a delayed effect on the vasculature that improves over time.

Safety of Statin Therapy in Patients with CKD and Diabetes

Statins, as a class, are generally well tolerated. The most frequently reported adverse events include myalgia (discussed below), gastrointestinal intolerance (dyspepsia, nausea, constipation, diarrhea and abdominal pain), headache, and sleep disturbance; however, hepatic and muscle toxicity are the two most notable adverse events associated with statin use. The most common hepatic adverse effect is a transient increase in liver transaminase levels. Clinically significant increases in liver enzyme levels >3× the upper limit of normal have been reported in <1% of patients on low or intermediate statin doses, and 2-3% of patients on high-dose statin therapy. The most common muscle side effect is myalgia (muscle pain or weakness without elevation of creatinine phosphokinase [CPK] levels). The incidence of serious muscle toxicity (muscle symptoms with accompanying CPK elevations), namely myositis/myopathy and rhabdomyolysis, in clinical trial patients receiving statin therapy is relatively rare.

Factors that increase plasma levels of statins, such as impaired liver or renal function, concomitant therapy with fibrate or cyclosporine, and advanced age, may increase the risk of statin-related muscle injury. Statin dosing in patients with mild or moderate CKD is similar to the general population; however, depending on the statin, dose reductions may be necessary in patients with severe CKD, in part due to differences in renal excretion.

Fewer data are available that speak to the safety and tolerability of statins in patients with CKD. In a sub-analysis of the TNT study, the safety profile of atorvastatin 80 mg/day was found to be similar between CKD patients and the overall TNT population. The SHARP trial, where CKD patients were randomized to ezetimibe plus simvastatin, or placebo, revealed no evidence of excess risk of persistent increases in liver enzyme levels, hepatitis, or cancer with combination therapy; the excess incidence of myopathy was only ~2 per 10,000 patients per year of treatment. A Cochrane review found no significant difference in the incidence of elevated liver enzymes, rhabdomyolysis, and treatment withdrawal due to adverse events in CKD patients treated with placebo or statin. Similarly, two recent meta-analyses of data from patients with CKD participating in lipid-lowering therapy trials have also reported that rates of key adverse events (e.g., myalgia, rhabdomyolysis, abnormal liver function, treatment withdrawal, cancer) were similar between treatment and control groups. For patients with diabetes, an analysis of the CARDS trial assessing safety and tolerability found atorvastatin 10 mg/day was well tolerated during long-term treatment; however, statin therapy in non-diabetics has been associated with a slight increase in the risk of new-onset diabetes (NOD). Two meta-analyses of statin-treated patients without diabetes at baseline reported a 9-12% increase in the relative risk of incident diabetes among patients assigned to statin therapy versus control, or intensive-dose statin versus moderate-dose statin therapy; however, the risk was low both in absolute terms and in comparison to
the benefit of CV event reduction. The pathophysiological mechanism underlying the apparent increased risk of NOD in patients receiving statin therapy is presently unknown. A post-hoc analysis of three large randomized atorvastatin trials indicated that baseline fasting plasma glucose and certain features of metabolic syndrome (triglycerides, body mass index, and hypertension) were the main predictors of NOD in statin-treated patients, but that these patients derived a similar CV benefit from statin therapy to those who remained normoglycemic. A recent post-hoc analysis of the JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) cohort reached similar conclusions, and also indicated that statin-treated patients who contracted NOD did so only ~5 weeks ahead of those receiving placebo. It is conceivable that the increased risk of NOD may be specific to those patients already at high risk of developing diabetes. Fewer data are available on the incidence of NOD in Japanese statin users, but a recent study in a Taiwanese population suggested a similarly small risk of NOD offset by the CV benefits of statin therapy, as has been reported previously in predominantly Western populations.

The availability of statin safety data among Asian patients from large-scale clinical trials is limited. The MEGA trial of Japanese patients with hypercholesterolemia (n=7,832) found no differences in the rates of myopathy or liver enzyme elevations between those assigned to diet or diet plus pravastatin 10-20 mg/day. In the Japan Lipid Intervention Trial (J-LIT), where 51,321 patients received low-dose, open-label simvastatin therapy over a 6-year period, hepatic and musculoskeletal disorders occurred at an incidence of <1% (0.97% and 0.68%, respectively). Post-marketing surveillance data from 4,805 Japanese patients with hyperlipidemia or familial hypercholesterolemia who received atorvastatin therapy have shown the statin to be well tolerated; importantly, no difference was observed in overall adverse event rates between patients with and without renal insufficiency (12.68% versus 11.95%, respectively; p=0.754). Additional information on the tolerability of atorvastatin in Japanese patients will be available once the final analysis of the ALWAYS study is completed.

Conclusions

Data from clinical studies in predominantly Western populations have highlighted the CV and potential renal benefits of statin therapy in patients with CKD and/or diabetes, and it is reasonable to expect similar benefits in comparable Japanese populations. In the TNT trial, the CV benefit of statins appeared to be more pronounced in patients with CKD than in patients with normal kidney function, particularly when an LDL-C of 75-80 mg/dL was achieved with high-dose atorvastatin treatment. Hence, revised JAS guidelines that stratify patients according to absolute risk and incorporate CHD risk equivalents such as CKD and diabetes will provide a framework for future risk factor management strategies to achieve the maximum benefit in this population—particularly important in light of recent trends toward an increase in cholesterol levels and CHD incidence in urban areas of Japan. Further studies are needed to demonstrate that high-risk Japanese populations, such as those with concomitant CKD and/or diabetes, may derive incremental benefit from a more intensive therapeutic approach that focuses on treating to an LDL-C goal <100 mg/dL, and perhaps even optimally to <75 mg/dL.

The potential for incremental benefit through greater LDL-C reduction with higher- versus lower-dose statin therapy highlights the dose-dependent lowering of LDL-C levels by statins as an important consideration in determining the underlying mechanism of renoprotection. Additional prospective, randomized trials in Japanese patients are needed to determine whether and how statins may reduce the rate of CKD progression. We look forward to the results of the ASUCA trial, a prospective, randomized study designed to assess the effect of statin therapy on eGFR as the primary endpoint, to provide further guidance on the clinical management of patients with CKD, including those with diabetes.

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Conflicts of Interest

Daisuke Koya: Dr Koya has nothing to disclose.
Vito M. Campese: Dr Campese is a member of the Speaker’s Bureau for Pfizer, Inc. and Merck & Co., Inc.

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