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ORIGINAL ARTICLE
Ischemic Heart Disease

Comorbidities Associated With Residual Cardiovascular Risk in Patients With Chronic Coronary Syndrome Receiving Statin Therapy

— Subanalysis of the REAL-CAD Trial —

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Background: Even with high-dose statin therapy, residual cardiovascular event risks remain in patients with chronic coronary syndrome (CCS). Thus, future treatment targets need to be elucidated. This study determined the factors associated with residual cardiovascular risk in patients with CCS treated with high-dose statins.

Methods and Results: This study was a subanalysis of the REAL-CAD study. This study enrolled 5,540 patients with CCS receiving 4 mg/day pitavastatin and assessed the impacts of 3 representative risk factors (i.e., blood pressure, glucose level, and renal function), alone or in combination, on clinical outcomes. Each risk factor was classified according to its severity. The primary endpoint was a composite of cardiovascular death, non-fatal myocardial infarction, non-fatal ischemic stroke, and unstable angina requiring emergency hospitalization. After adjusting for the effects of confounders, a significantly worse prognosis was observed in the group with an estimated glomerular filtration rate (eGFR) ≤60 mL/min/1.73 m^2 (hazard ratio [HR] 1.36; 95% confidence interval 1.03–1.80; P=0.028). No other factors or combinations were associated with the primary endpoint. An eGFR ≤60 mL/min/1.73 m^2 was also associated with cardiac (HR 2.38; P=0.004) and all-cause (HR 1.51; P=0.032) death.

Conclusions: Insufficient renal function was associated with a worse prognosis in patients with CCS undergoing high-dose statin therapy, suggesting that renal function is the next target for reducing the risk of residual cardiovascular events.

Key Words: Chronic coronary syndrome; High-dose statin therapy; Renal function; Residual cardiovascular event

There is considerable evidence that statins reduce cardiovascular events, and the aggressive lowering of low-density lipoprotein cholesterol (LDL-C) levels by high-dose statins strongly decreases the risk of events in patients with atherosclerotic cardiovascular disease.[1,2] Recently, additional therapies, such as ezetimibe or a proprotein convertase subtilisin/kexin type 9-inhibiting monoclonal antibody, have made it possible to achieve appropriate LDL-C levels in almost all patients.[3,4] However, there is still residual cardiovascular risk, especially in patients with coronary artery disease (CAD).[5,6] To reduce residual cardiovascular risk, it is necessary to investigate the next targets for treatment and management. Hypertension, diabetes, and chronic kidney disease (CKD) are major risk factors for cardiovascular events.[7–10] However, previous studies have focused on further lowering LDL-C or other lipid

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markers.[5,6] Thus, the impact of blood pressure, glucose levels, or renal function on residual cardiovascular risk has been overlooked in the era of aggressive LDL-C-lowering therapy.

Recently, the REAL-CAD study (Randomized Evaluation of Aggressive or Moderate Lipid Lowering Therapy With Pitavastatin in Coronary Artery Disease) showed that over a median follow-up of 3.9 years, high-dose (4 mg/day) pitavastatin significantly reduced the risk of the primary endpoint (a composite of cardiovascular death, non-fatal myocardial infarction [MI], non-fatal ischemic stroke, and unstable angina requiring emergency hospitalization) in Japanese patients with chronic coronary syndrome (CCS) compared with low-dose (1 mg/day) pitavastatin (266 [4.3%] vs. 334 [5.4%] patients; hazard ratio [HR] 0.81; 95% confidence interval [CI] 0.69–0.95; P=0.01).[11] That study confirmed that high-dose pitavastatin significantly reduced cardiovascular events; however, there was still considerable residual cardiovascular risk, even with high-dose statin therapy. The present study focused on the impact of blood pressure, glucose levels, and renal function, alone or in combination, on residual cardiovascular risk in patients undergoing high-dose statin therapy. We stratified each factor and determined the factors or their combinations that were significantly associated with cardiovascular events only in the high-dose (4 mg/day) pitavastatin group from the REAL-CAD study.

Methods

Study Design

This study was a subanalysis of the REAL-CAD study, in which 13,054 Japanese patients with stable CAD were randomized to low-dose (1 mg/day) or high-dose (4 mg/day) pitavastatin, and 12,413 patients were analyzed.[11] Briefly, patients eligible for the REAL-CAD study were aged 20–80 years, male or female, and with stable CAD, defined as a history of acute coronary syndrome or coronary revascularization >3 months previously or a clinical diagnosis of CAD with angiographically documented coronary artery stenosis with ≥75% diameter narrowing according to the American Heart Association classification.[12] The population of the present study had CCS.[7] The present subanalysis enrolled 5,540 patients in the high-dose (4 mg/day) pitavastatin group.

The REAL-CAD study was approved by the institutional review boards of each participating center, and all subjects provided written informed consent. This subanalysis was approved by the Ethics Committee of Showa University (21-229-A) and was conducted in accordance with the Declaration of Helsinki.

The REAL-CAD trial was funded by the Comprehensive Support Project for Clinical Research of Lifestyle-Related Disease of the Public Health Research Foundation. The company manufacturing the study drug (Kowa Pharmaceutical) provided financial support, but was not involved in study design, analysis, data interpretation, or manuscript preparation.

Table 1. Baseline Characteristics (n=5,540)

Age (years)	68.1±8.3
Sex (female/male)	937/4,603
BMI (kg/m²)	24.6±3.3
HR (beats/min)	69.5±11.7
SBP (mmHg)	
<120	1,587
120–129	1,476
130–139	1,303
>140	1,174
Pulse pressure (mmHg)	
<40	533
40–49	1,385
>50	3,622
HbA1c (%)	
<6.0	3,702
6.0–7.9	1,682
≥8.0	156
eGFR (mL/min/1.73 m²)	
<30	87
30–60	2,017
>60	3,436
Blood tests	
LDL-C (mg/dL)	87.6±19.0
HDL-C (mg/dL)	50.7±12.4
TG (mg/dL)	146.2±95.5
Comorbidities	
Brain infarction	379
Atrial fibrillation	343
Cancer	284
Chronic heart failure	283
PAD	378
Medication	
Antihypertensive drugs	4,559
Antidiabetic drugs	1,467

Unless indicated otherwise, data are presented as the number of patients in each group or as the mean ± SD. BMI, body mass index; CRP, C-reactive protein; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; HR, heart rate; LDL-C, low-density lipoprotein cholesterol; PAD, peripheral artery disease; SBP, systolic blood pressure; TG, triglycerides.

Classification of Comorbidities

Hypertension was classified as follows: first, use of antihypertensive drugs; second, systolic blood pressure (1) ≤120 mmHg, (2) 120–129 mmHg, (3) 130–139 mmHg, (4) ≥140 mmHg; and third, pulse pressure (1) ≤40 mmHg, (2) 40–49 mmHg, and (3) ≥50 mmHg. Diabetes mellitus was classified as follows: first, the use of antidiabetic drugs; and second, HbA1c (1) ≤6.0%; (2) 6.0–7.9%, and (3) ≥8.0%. CKD was classified as follows: eGFR (estimated glomerular filtration rate in mL/min/1.73 m²) (1) <30, (2) 30–60, and (3) >60.

Endpoints

Endpoints for risk stratification were determined as follows:

- Event 1: primary endpoint (a composite of cardiovascular death, non-fatal MI, non-fatal ischemic stroke, and unstable angina requiring emergency hospitalization)
- Event 2: a composite of Event 1 and/or coronary revascularization
- Event 3: death from any cause
- Event 4: cardiovascular death
- Event 5: cardiac death.

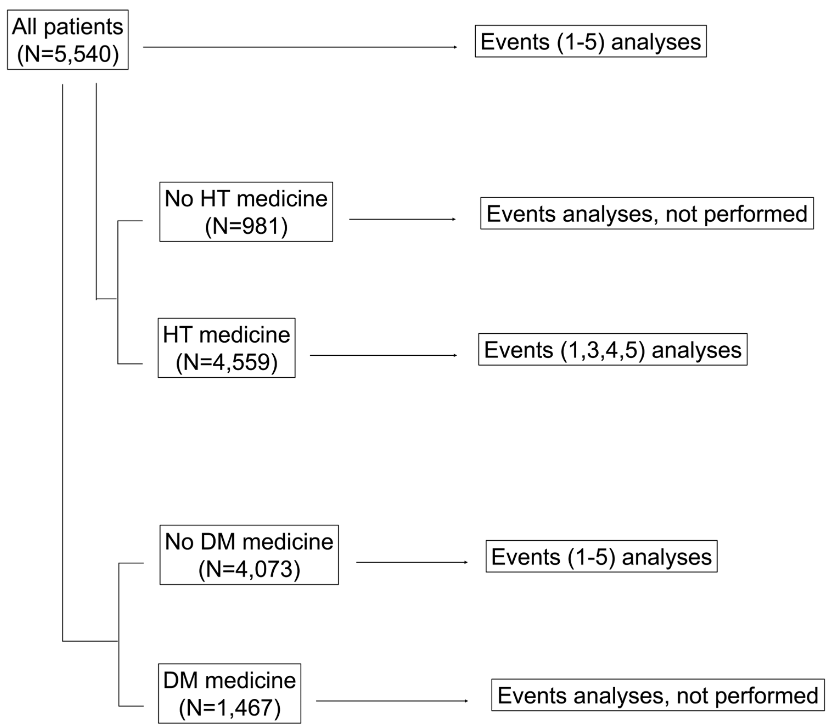

Figure 1. The study enrolled 5,540 patients; 4,559 of these patients were receiving antihypertensive drugs and 1,467 were receiving antidiabetic drugs. Statistical analyses were performed for each group to identify which combination of comorbidities predicted a worse prognosis. DM, diabetes; Event 1, primary endpoint (composite of cardiovascular death, non-fatal myocardial infarction, non-fatal ischemic stroke, and unstable angina requiring emergency hospitalization); Event 2, composite of Event 1 and/or coronary revascularization; Event 3, death from any cause; Event 4, cardiovascular death; Event 5, cardiac death; HT, hypertension.

Table 2. Predictors of Cardiovascular Events in All Patients (n=5,540)

	HR	SE	P value	95% CI
Event 1				
eGFR >60 mL/min/1.73 m²	Ref.			
eGFR ≤60 mL/min/1.73 m²	1.36	0.19	0.028	1.03–1.80
Event 2				
HbA1c <6.0%	Ref.			
HbA1c ≥6.0%	1.11	0.12	0.313	0.90–1.37
Event 3				
eGFR >60 mL/min/1.73 m² + HbA1c <6.0%	Ref.			
eGFR >60 mL/min/1.73 m² + HbA1c ≥6.0%	1.59	0.36	0.041	1.02–2.48
eGFR ≤60 mL/min/1.73 m²	1.51	0.29	0.032	1.04–2.19
Event 4				
eGFR >60 mL/min/1.73 m²	Ref.			
eGFR ≤60 mL/min/1.73 m²	1.44	0.36	0.145	0.88–2.34
Event 5				
eGFR >60 mL/min/1.73 m²	Ref.			
eGFR ≤60 mL/min/1.73 m²	2.38	0.72	0.004	1.32–4.29

CI, confidence interval; eGFR, estimated glomerular filtration rate; Event 1, primary endpoint (composite of cardiovascular death, non-fatal myocardial infarction, non-fatal ischemic stroke, and unstable angina requiring emergency hospitalization); Event 2, composite of Event 1 and/or coronary revascularization; Event 3, death from any cause; Event 4, cardiovascular death; Event 5, cardiac death; HR, hazard ratio; SE, standard error.

Statistical Analyses

The following statistical analyses were performed to investigate the proposed working hypothesis by examining the relationship between the incidence of the major events defined above (Events 1–5) and risk factors after adjusting for the effects of confounders. Blood pressure, glucose levels, and renal function were considered risk factors. As described above, each of the risk factors was further subdivided into categories for the sensitivity analyses. Pitavastatin dose (1 vs. 4 mg), age, sex, body mass index, LDL-C, high-density lipoprotein cholesterol (HDL-C), triglyceride, C-reactive protein, and heart rate were considered regulatory variables. Five major events were analyzed separately using exploratory statistical methods.

The main aim of the statistical analyses was to construct a risk stratification of patients with CCS. To this end, we

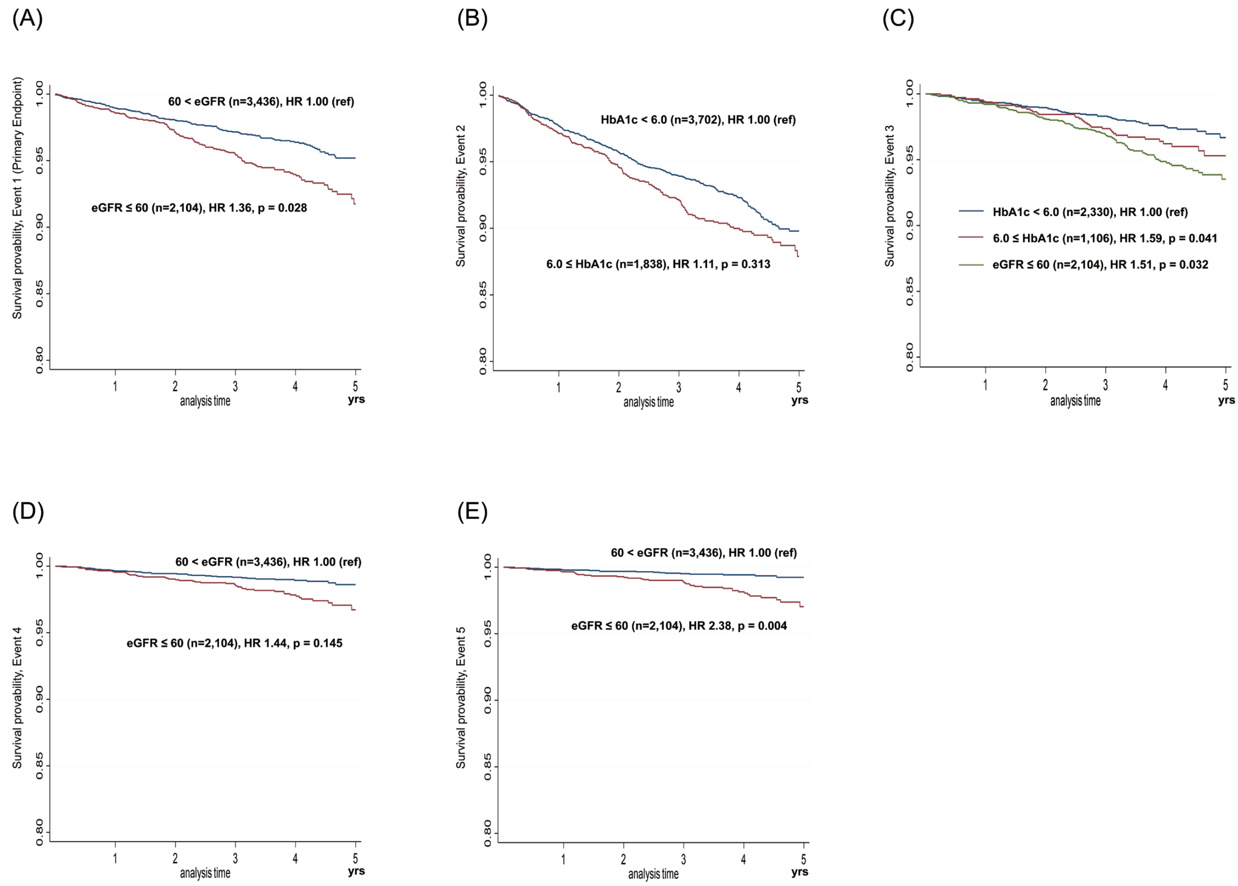

Figure 2. (**A**) A significantly worse prognosis for Event 1 (composite of cardiovascular death, non-fatal myocardial infarction, non-fatal ischemic stroke, and unstable angina requiring emergency hospitalization) was observed in the group with an estimated glomerular filtration rate (eGFR) ≤60 mL/min/1.73 m². (**B**) HbA1c ≥6.0% was the only predictor of Event 2 (composite of Event 1 and/or coronary revascularization), but its predictive ability was not significant. (**C**) For Event 3 (death from any cause), eGFR ≤60 mL/min/1.73 m² was the most important significant predictor. For patients with eGFR >60 mL/min/1.73 m², HbA1c ≥6.0 was a significant predictor of death from any cause. (**D**) For Event 4 (cardiovascular death), eGFR ≤60 mL/min/1.73 m² was the only predictor, but its predictive ability was not significant. (**E**) For Event 5 (cardiac death), eGFR ≤60 mL/min/1.73 m² significantly predicted a worse prognosis. HR, hazard ratio.

used a classification and regression tree (CART), which is a non-parametric decision tree learning technique that partitions future space with the set of all possible combinations of a set of risk factors. Partitioned future space consists of an asymmetrical combination of risk factors that provide interpretable patient clinical profiles as various degrees of risk for clinical outcome. This learning technique has been applied to data analyses in the field of clinical epidemiology as well as in prospective epidemiological studies.[13,14] The HR between each layer was examined after controlling for the effects of regulatory variables.

From a clinical point of view, sensitivity analyses were also performed in some extracted layers of the model constructed from each data analysis. From the parameter estimates obtained from these statistical analyses, we evaluated the appropriate blood pressure, glucose levels, and renal function and verified the working hypotheses related to the therapeutic strategy and improvement of poor prognosis.

Statistical analyses were performed using StataMP 16 Statistical Software (StataCorp, College Station, TX, USA).

Results

Study Flow

In all, 5,540 patients were enrolled in the present study, there were 937 female and 4,603 male patients aged 68.1±8.3 years. Of these patients, 4,559 were receiving antihypertensive drugs and 1,467 were receiving antidiabetic drugs (**Table 1**). Statistical analyses were performed in each group to identify which combination of comorbidities predicted a worse prognosis (**Figure 1**).

Entire High-Dose (4 mg/day) Pitavastatin Population

In the high-dose (4 mg/day) pitavastatin group, the mean LDL-C level at baseline (run-in period of ≥1 month with 1 mg/day pitavastatin) and 1 year was 87.7 and 75.5 mg/dL, respectively. As seen in **Table 2** and **Figure 2A**, a significantly worse prognosis was observed in terms of Event 1 in the group with eGFR ≤60 mL/min/1.73 m². HbA1c ≥6.0% was the only predictor for Event 2 (**Table 2**; **Figure 2B**), but its predictive ability was not significant. For Event 3 (death from any cause), eGFR ≤60 mL/min/1.73 m² was the most important predictor (**Table 2**; **Figure 2C**). For events in the eGFR >60 group, the combination of HbA1c ≥6.0% was also a significant predictor (**Table 2**; **Figure 2C**). The only predictor for Event 4 (cardiovascular death) was eGFR ≤60 mL/min/1.73 m^2, but its predictive ability was not significant (**Table 2**; **Figure 2D**). For Event 5 (cardiac death), eGFR ≤60 mL/min/1.73 m^2 significantly predicted a worse prognosis (**Table 2**; **Figure 2E**).

No-Antihypertensive-Drug Population

No significant predictors were detected in the no-antihypertensive-drug group. Therefore, event analyses were not performed.

Antihypertensive Drug Population

For Event 1, eGFR ≤60 mL/min/1.73 m^2 was the only significant predictor (**Supplementary Table A**; **Supplementary Figure 1A**). For Event 1 and/or coronary revascularisation (Event 2), no significant predictors were found. For Event 3 (death from any cause) and Event 4 (cardiovascular death), eGFR ≤60 mL/min/1.73 m^2 was the only predictor, but its predictive ability was not significant (**Supplementary Table A**; **Supplementary Figure 1B**,**C**). For Event 5 (cardiac death), eGFR ≤60 mL/min/1.73 m^2 was the only significant predictor (**Supplementary Table A**; **Supplementary Figure 1D**).

No-Antidiabetic-Drug Population

In the no-antidiabetic-drug population, eGFR ≤60 mL/min/1.73 m^2 was the only significant predictor of Events 1 and 5 (**Supplementary Table B**; **Supplementary Figure 2A**,**E**) and a non-significant predictor of Events 2–4 (**Supplementary Table B**; **Supplementary Figure 2B–D**).

Antidiabetic Drug Population

No significant predictors were detected in the antidiabetic drug group. Therefore, event analyses were not performed.

Discussion

Using exploratory statistical methods, the present study determined the impact of major risk factors, namely blood pressure, glucose level, and renal function, on the residual cardiovascular risk in 5,540 patients receiving high-dose statins in the REAL-CAD study. The major findings of the present study are that: (1) renal insufficiency, defined as eGFR ≤60 mL/min/1.73 m^2, was significantly associated with a composite endpoint of cardiovascular death, non-fatal MI, non-fatal ischemic stroke, and unstable angina requiring emergency hospitalization; (2) blood pressure or glucose levels were not associated with cardiovascular events; (3) the impact of renal insufficiency on cardiovascular events was consistent with specific populations, such as patients receiving antihypertensive drugs or patients without antidiabetic drugs; and (4) renal insufficiency was associated with cardiac mortality and all-cause mortality.

Residual cardiovascular risk has been a topic of interest since the era of statin therapy. However, most studies have focused on further lowering LDL-C or other lipid markers, such as oxidized low-density lipoprotein (LDL), small-dense LDL, triglycerides, or lipopolysaccharide (a).[5,6] Thus, information regarding the effects of blood pressure, glucose, and renal function on residual cardiovascular risk with statin therapy is scarce. To the best of our knowledge, this is the first report to assess the effect of representative risk factors, namely blood pressure, glucose level, and renal function, on clinical outcomes in patients with atherosclerotic cardiovascular disease receiving high-dose statin therapy.

Identifying the Next Target to Reduce the Residual Risk of Cardiovascular Events

It is important to determine the effect of further reductions in LDL-C on residual cardiovascular risk in patients with low baseline LDL-C levels. We previously reported that the efficacy of LDL-lowering therapy with statins for decreasing coronary plaque was lower in patients with low than moderate or high baseline non-HDL-C levels.[15] Recently, meta-analyses and meta-regressions have demonstrated that more intensive, compared with less intensive, LDL-C lowering was associated with a greater reduction in the risk of all-cause and cardiovascular mortality in trials of patients with higher baseline LDL-C levels.[16] This association was not present when baseline LDL-C was <100 mg/dL, suggesting that the greatest benefit from further LDL-C-lowering therapy may occur only in patients with higher baseline LDL-C levels. Thus, the next target for reducing the residual risk of cardiovascular events beyond LDL-C-lowering therapy should be determined. In the present study, the mean LDL-C level at baseline (run-in period of ≥1 month with 1 mg/day pitavastatin) and at 1 year in patients with CCS under high-dose statin (4 mg/day pitavastatin) was 87.7 and 75.5 mg/dL, respectively. The results suggest that renal function, rather than the other major factors (blood pressure and glucose level), may be a key predictor of the residual risk of cardiovascular events.

Comorbidities in CCS

Hypertension is the most prevalent comorbidity in patients with CCS.[7] Blood pressure lowering reduces the risk of cardiovascular events in the general population;[17] however, previous studies showed that strict lowering of blood pressure, such as systolic blood pressure <120 mmHg or diastolic blood pressure <70 mmHg, increased cardiovascular events.[18,19] Thus, there may be a J-curve phenomenon in patients with CCS, as suggested previously,[7] and this may play a role because blood pressure was not associated with cardiovascular event risk in the present study. Although blood pressure is not important in patients with CCS receiving high-dose statin therapy, the optimal lowering of blood pressure prevents the progression of CKD[20,21] and is still necessary.

A previous meta-analysis demonstrated that patients with diabetes generally have a 2-fold greater risk of CAD.[22] Pivotal trials demonstrated the absence of significant effects of intensive glucose control on cardiovascular events, such as cardiovascular and all-cause deaths.[23–25] The results of the present study confirm that glucose levels are not associated with cardiovascular event risks, even in patients with CCS receiving high-dose statin therapy. Previous studies have demonstrated that intensive glucose control reduces nephropathy in patients with type 2 diabetes.[23–25] Glucose levels seem not to be the next target for residual cardiovascular risk; however, optimal glucose control is important to prevent decreased renal function, which could result in worse outcomes.

Previous studies investigated the relationship between renal function and tissue characterization of coronary plaque composition using imaging modalities such as integrated backscatter or virtual histology intravascular ultrasound and pathology.[26–28] These studies demonstrated an increase in the relative volumes of both lipid plaque and dense calcium with decreasing renal function. More high-risk plaque in the coronary artery may play a role in the increased risk of cardiovascular events in patients with CKD. Renal insufficiency is considered a major risk factor in patients with CCS. However, little information is available regarding its effect on clinical outcomes in patients receiving high-dose statin therapy. It is unclear whether treatment for renal dysfunction improves clinical outcomes in patients with CCS based on the results of the present study. However, CART analyses suggest that the prevention of worsening renal function by maintaining eGFR >60 mL/min/1.73 m^2 is associated with better outcomes. Thus, preventing a worsening renal function needs to be discussed.

Management to Prevent Worsening of Renal Function

As mentioned above, optimal lowering of blood pressure and glucose levels is vital to prevent worsening of renal function. Guidelines recommend treatments such as renin-angiotensin system blockade, restrictions of dietary sodium or protein, and regular exercise to manage early-stage CKD with or without diabetes.[29,30] Recently, sodium-glucose cotransporter 2 (SGLT2) inhibitors have been recommended for patients with type 2 and CKD.[29] Trials are underway to evaluate the effects of SGLT2 inhibitors on renal and cardiovascular outcomes in non-diabetic kidney disease.[31,32] Early initiation of these treatments may prevent the worsening of renal function in patients with CCS.

A recent study demonstrated that interleukin-1β inhibition with canakinumab reduced rates of major adverse cardiovascular events among patients with high-risk atherosclerosis and CKD undergoing statin therapy.[33] Thus, anti-inflammatory therapy may be useful in improving clinical outcomes in CKD patients with high levels of inflammation, even under high-dose statin therapy.

Study Limitations

This study had several limitations. First, it was a subanalysis of the REAL-CAD study. Even after adjusting for the effects of regulators, including age, sex, or other lipid markers, we could not exclude the possibility of residual contributing factors as a result of the presence of unmeasured confounders. Second, the REAL-CAD study was not conducted to address the topic investigated in the present study; thus, some important data, such as the presence of proteinuria or microalbuminuria, were not available. Blood pressure or HbA1c levels sometimes notably change during follow-up; however, serial data at 6 months or 1 year were not assessed. Third, patients undergoing hemodialysis were excluded from the REAL-CAD study because of safety concerns related to the potential toxic effects of high-intensity statins. Finally, pitavastatin (4 mg/day) is regarded as a high-dose statin in Japan; however, the mean serum LDL-C concentration was 75.5 mg/dL at 1 year in the 4-mg pitavastatin population, and did not reach the goal of <70 mg/dL for secondary prevention in current clinical practice. Furthermore, 4 mg/day pitavastatin may be treated as a moderate dose in other countries. Data regarding the use of ezetimibe or proprotein convertase subtilisin/kexin type 9-inhibiting monoclonal antibody were not available in the present study.

Conclusions

Insufficient renal function was associated with a worse prognosis in patients with CCS undergoing high-dose statin therapy, suggesting that renal function is the next target for reducing the residual risk cardiovascular events.

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IRB Information

This study was approved by the Showa University Institutional Review Board for Clinical Research (Reference no. 21-229-A).

Data Availability

The deidentified participant data will not be shared.

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Supplementary Files

Please find supplementary file(s);
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