Original Article

Declining Prevalence of Coronary Artery Disease in Incident Dialysis Patients Over the Past Two Decades

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***Aim*: The medical management of patients with chronic kidney disease (CKD) has changed within the past 20 years. We speculate that this change has resulted in a decrease in the prevalence of atherosclerotic cardiovascular disease in patients with CKD. The aim of the present study was to analyze changes in the prevalence of coronary artery disease (CAD) in patients newly started on hemodialysis, as well as trends in clinical factors and medications over the past two decades.**

***Methods*: This single-center cross-sectional study examined data for 315 consecutive patients starting hemodialysis (age, 64 ± 12 years; men, 73%; diabetic nephropathy, 57%) between January 1993 and December 2010. All patients were routinely screened for CAD within three months of starting hemodialysis, regardless of whether ischemic heart disease was suspected. The patients were categorized into six groups based on the date of the initial dialysis session in order to compare the historical prevalence of unidentified CAD (uCAD) in association with the clinical factors. In addition, we performed a subgroup analysis among 222 patients without known cardiac disease.**

***Results*: The prevalence of uCAD gradually declined from 69% to 25% over 18 years ($p<0.001$ for trend). The mean high-density lipoprotein cholesterol (HDL-C) concentration increased ($p<0.001$ for trend), while the median C-reactive protein (CRP) level decreased over time. In parallel with these trends, the proportion of statin users significantly increased over time ($p<0.001$ for trend). The use of erythropoiesis-stimulating agents (ESAs) and renin angiotensin aldosterone system inhibitors (RAS-Is) also increased during the same period (both $p<0.001$ for trend). A univariate logistic regression analysis identified a significant association between the prevalence of uCAD and the use of ESAs (OR: 0.565, $p=0.016$) or RAS-Is (OR: 0.501, $p=0.004$). In addition, a lower BMI, lower HDL-C level and higher CRP level were found to be closely associated with uCAD, independent of confounding variables. The findings for the new dialysis patients without cardiac disease were similar.**

***Conclusions*: The prevalence of uCAD in patients with end-stage kidney disease has remarkably decreased over the past two decades. Major improvements in the medical management of CKD may modify the prevalence of coronary atherosclerosis.**

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Key words: Chronic kidney disease, Cardiovascular atherosclerosis, Statin, Erythropoietin-stimulating agents, Renin angiotensin aldosterone system inhibitors

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Introduction

Although the mechanism underlying the development of cardiorenal syndrome has been determined in considerable detail over the past decade[1)], athero-

sclerotic cardiovascular disease (CVD) remains a leading cause of death among patients with chronic kidney disease (CKD)[2, 3]. The prevalence of atherosclerotic vascular disease at the start of renal replacement therapy is high. For instance, angiographic assessments have demonstrated that 40% to 50% of patients with new end-stage kidney disease (ESKD) in Japan exhibit significant coronary artery disease (CAD)[4, 5].

Clinical practice has substantially changed since the recognition of CKD as a risk factor for atherosclerotic CVD, and CKD is becoming increasingly important to physicians and the general population. Obtaining strict blood pressure control using rennin angiotensin aldosterone system (RAS) inhibitors (RAS-I) combined with other antihypertensive drugs[2, 6], maintaining an optimal hemoglobin concentration using erythropoiesis-stimulating agents (ESAs) and managing dyslipidemia via lifestyle interventions and/or the use of statins[7] are recommended in order to slow declines in the kidney function. Both statins and RAS-Is play important roles in preventing the progression of coronary atherosclerosis in the general population[8, 9]. A recent large cohort study in Japan[10] demonstrated a prevalence of CAD of approximately 30% among asymptomatic hemodialysis patients, which is lower than the 42% reported in a previous study[11]. These findings imply that changes in the medical management of CKD have favorably modified risk factors for atherosclerosis and may conceivably reduce the prevalence of CAD in patients with CKD. However, how changes in comorbid diseases, such as CAD, and shifts in medication use over time affect patients with CKD is less well understood.

The present study aimed to determine both historical changes in the prevalence of CAD at the start of dialysis therapy and temporal trends in the incidence of clinical coronary atherosclerosis risk factors and use of medications over the past 18 years. The associations between the occurrence of CAD and clinical factors, including the use of various medications, were also investigated.

Study Population and Methods

Study Design and Patients

We conducted a cross-sectional comparative analysis of patients with ESKD among different eras. Between January 1993 and December 2010, 485 patients with ESKD began treatment with chronic hemodialysis (HD) at our hospital. Among them, 170 declined screening; therefore, 315 consecutive patients starting hemodialysis completed screening for unidentified CAD (uCAD). As shown in **Fig. 1**, the 315 patients with ESKD were categorized into groups according to one of six eras over the 18-year period based on the date of the initial dialysis session. Temporal trends in the prevalence of uCAD and clinical characteristics were compared between the six groups.

In order to precisely evaluate the prevalence of uCAD and minimize bias, a subgroup analysis was also conducted. We studied all screened patients as well as all those without cardiac disease before starting dialysis. The criteria for excluding patients with previous cardiac disease were as follows: a history of New York Heart Association (NYHA) level Ⅲ or Ⅳ heart failure, coronary heart disease, such as myocardial infarction and/or coronary revascularization, and left ventricular dysfunction defined as an ejection fraction (EF) of $<50\%$ on echocardiography. We excluded 93 patients based on the above criteria (history of NYHA Ⅲ or Ⅳ heart failure, $n=34$; coronary heart disease, $n=58$ and EF $<50\%$, $n=53$) and performed a subgroup analysis among the remaining 222 patients without known cardiac disease.

All patients provided their informed consent to participate in this study, and the Ethics Committee for Clinical Research at Toho University Ohashi Medical Center approved the study protocol [Permission no. 21-30].

Data Collection

Clinical information for all patients was recorded before the first HD session. All patients were initially interviewed to determine their age, sex, smoking habits, type of primary renal disease, history of previous hospitalization and the presence of either hypertension or cardiac disease. We also collected information regarding the predialytic phase of CKD, including the use of medications, particularly erythropoietin. Blood pressure was recorded with the patient in the supine position, and blood samples were obtained immediately prior to the first HD session. The serum calcium (Ca) concentration was corrected according to the albumin level as follows: corrected Ca = measured Ca (mg/dL) + (4 - measured albumin level (g/dL)). The estimated glomerular filtration rate (eGFR) was calculated using the following equation for Japanese individuals[12]: eGFR (mL/min/1.73 m^2) = $194 \times Cr^{-1.094} \times Age^{-0.287}$ (for women $\times 0.739$). The body mass index (BMI) at the optimal weight was calculated as the weight (Kg) divided by the height (m) squared. All participants were assessed using echocardiography at a dry weight after a dialysis session or on an intermittent day of hemodialysis before discharge. Left ventricular (LV) dysfunction was defined as an ejection fraction of $<50\%$ on echocardiography.

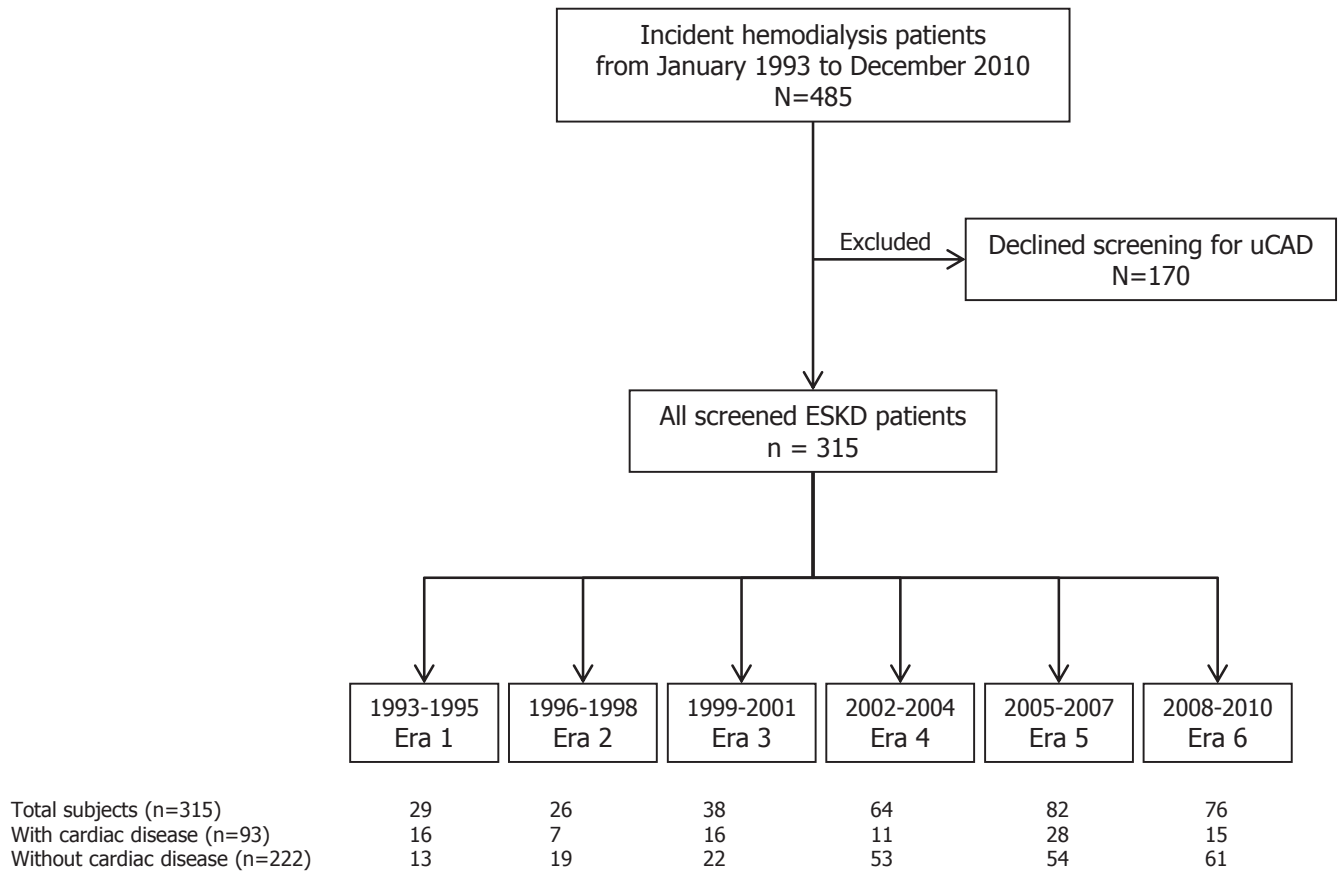

Fig. 1. Flow of the subjects.

Screening for CAD and Definition of Significant CAD

Since August 1992, patients with ESKD at our hospital have been routinely screened for CAD within three months of starting HD therapy, regardless of whether ischemic heart disease is suspected. The patients were primarily screened using coronary angiography (CAG) until the end of 1998. Between 1999 and 2001, the screening method changed from CAG to stress thallium-201 myocardial perfusion single photon emission computed tomography (MPS), then to primarily MPS thereafter. Clinically significant uCAD was defined as narrowing of the uninvolved reference segment diameter exceeding 75% in patients undergoing CAG or the presence of reversible myocardial perfusion defects in patients examined using pharmacological stress thallium-201 MPS. For the detection of multi-vessel CAD, we also employed the findings of transient ischemic dilation of the left ventricle under stress according to the article by Mazzanti *et al.*[13]. Pharmacological stress was induced via the intravenous infusion of adenosine triphosphate (ATP) or adenosine after a three-hour fast. The ATP or adenosine infusion was delivered at a rate of 0.16 mg/Kg/min or 0.12 mg/kg/min, respectively, over six minutes (using an automated pump), and thallium-201 (111 MBq) was injected into different veins in each arm five minutes after the start of the ATP or adenosine infusion. The patients were monitored electrocardiographically and hemodynamically, and symptoms related to the induction of pharmacological stress were recorded. Stress cardiac scintigraphic images were acquired five to 10 minutes after the end of the infusion and at four hours thereafter during the rest-redistribution phase. The images were acquired in 33 projections using a rotating three-headed gamma camera (Multispect 3; Siemens Medical Solutions, Chicago, IL, USA) equipped with low-energy cardiofocal collimators and interfaced with a computer (ICON; Siemens Medical Solutions). Oblique tomograms reoriented in the short, horizontal and long axes were acquired.

Statistical Analysis

The data are expressed as the mean ± SD. Cate-

gorical data as well as the mean and median values were compared between the six groups using the χ^2 test, analysis of variance (ANOVA) and Kruskal-Wallis test, respectively. A p value of <0.05 was considered to be significant for the individual comparisons. Overall p values reflecting temporal trends between groups were also analyzed using the Jonckheere-Terpstra trend test, as appropriate. Factors associated with uCAD were assessed using simple and multiple logistic regression analyses, the latter of which included parameters with p values of <0.05 in the univariate analysis. The association between the rate of medication use and the prevalence of uCAD was assessed in each of the six eras using a linear regression analysis. All data were statistically analyzed using the SPSS software package for Windows, version 20 (IBM Corporation, NY).

Results

Analysis of the 315 Patients Screened for uCAD

Characteristics of the Patients

Table 1 shows the baseline characteristics of the 315 patients screened for uCAD. The mean age of these patients was 64±12 years. A total of 73% of the subjects were men and 57% had diabetic nephropathy. The proportion of patients with diabetic nephropathy was higher than that observed in the entire Japanese population of patients on dialysis[14]. The mean values of Cr and eGFR at the start of dialysis were 9.3±3.5 mg/dL and 5.5±2.2 mL/min/1.73 m^2, respectively, which were similar to those observed in the total Japanese population on dialysis[14]. The prevalence of heart failure, coronary heart disease and an EF of $<50\%$ was 11%, 15% and 17%, respectively. Fifty-three percent of the patients were prescribed ESAs or RAS-Is and 22% were prescribed statins.

Temporal Trend in the Prevalence of Coronary Artery Disease Over the Six Eras

The prevalence of uCAD over the two decades was 36%. The prevalence of uCAD gradually declined over the six eras from 69% to 25% ($p<0.001$ for trend). The CAG and MPS findings also revealed that the prevalence of uCAD tended to decline in both eras 1-3 and eras 3-6 (**Table 1**, **Fig. 2-A**).

Temporal Trends in the Clinical Characteristics Over the Six Eras

As shown in **Table 1**, the patient age increased from 59 to 67 years between eras 2 and 6 ($p=0.153$). The mean LDL-C ($p=0.002$ for trend) and HDL-C ($p<0.001$ for trend) levels significantly decreased and increased over time, respectively. The median level of CRP also declined over the past two decades ($p=0.008$ for trend). The rate (%) of ESA, RAS-I and statin use increased over time. The analysis of variance confirmed that the Ca levels significantly varied, although the Jonckheere-Terpstra test did not identify any significant temporal differences ($p=0.267$ for trend). The prevalence of heart failure ($p=0.002$ for trend) and an EF of $<50\%$ ($p=0.003$ for trend) notably declined over time. Although the prevalence of coronary heart disease declined from 38% to 12% over time, the difference did not reach statistical significance ($p=0.210$ for trend).

Parameters Associated with uCAD

The parameters associated with uCAD were initially analyzed using a simple logistic regression analysis. As shown in **Table 2**, significant negative associations were observed between the occurrence of uCAD and BMI, the levels of creatinine, HDL-C and phosphate, the use of ESAs and RAS-Is and the calendar year. Cigarette smoking, eGFR and the levels of hemoglobin, calcium and CRP were positively associated with uCAD. We then developed two models of multiple logistic regression analyses to identify independent factors contributing to the development of uCAD. Consequently, a multivariate logistic regression analysis of BMI, smoking, eGFR, HDL-C and CRP selected BMI, HDL-C and CRP as independent risk factors associated with uCAD (Model 1 in **Table 2**). Because the hemoglobin, calcium and phosphate levels at the start of dialysis are closely linked to the eGFR, only eGFR was entered into the multivariate analysis in Model 1. In order to identify medications modifying the prevalence of uCAD, a Model 2 analysis was performed, which included three medications: ESAs, RSA-Is and statins. Of these medications, only the use of RAS-Is was found to be negatively associated with the incidence of uCAD.

Association between the Use of ESAs, RASIs and Statins and the Incidence of uCAD

Fig. 3 presents on the associations between the prevalence of uCAD and the use of medications in each of the six eras. Clear negative associations were noted between the prevalence of uCAD and the use of ESAs or RAS-Is, but not statins, over the six eras.

Subgroup Analysis of the 222 Patients on Dialysis without Cardiac Disease

Table 3 shows the baseline characteristics of the 222 patients. The mean age of the patients was 63±12 years, 69% of whom were men and 56% of whom had diabetic nephropathy. The prevalence of uCAD gradually declined from 54% to 15% over the six eras

Table 1. Characteristics of the 315 screened patients and the temporal trends in the six era groups

	Total	Era 1 93-95	Era 2 96-98	Era 3 99-01	Era 4 02-04	Era 5 05-07	Era 6 08-10	*p*
Total patients No.	485	58	53	87	86	105	96	
Screening patients No.	315	29	26	38	64	82	76	
Age, years	64 ± 12	65 ± 9	59 ± 12	63 ± 11	63 ± 13	63 ± 13	67 ± 12	0.153
Male, %	73	69	85	79	64	72	76	0.333
Diabetes, %	57	55	65	53	61	55	54	0.867
Significant CAD, %	36	69	46	50	30	29	25	<0.001
MPS, %	73	0	4	45	94	99	95	<0.001
Significant CAD by CAG, % (*n* = 75)		69	44	57				0.186
Significant CAD by MPS, % (*n* = 230)				41	27	28	22	0.453
BMI, kg/m^2	22 ± 3	21 ± 3	22 ± 4	22 ± 4	22 ± 4	22 ± 3	23 ± 3	0.305
Smoking, %	57	62	50	68	46	52	64	0.233
Systolic BP, mmHg	154 ± 26	162 ± 25	158 ± 27	150 ± 28	151 ± 24	153 ± 28	155 ± 24	0.366
Diastolic BP, mmHg	78 ± 17	77 ± 19	87 ± 19	77 ± 14	80 ± 14	77 ± 21	75 ± 13	0.114
Heart rate, beats/min	81 ± 16	79 ± 19	89 ± 13	83 ± 20	82 ± 15	79 ± 14	81 ± 16	0.377
Heart failure (%)	11	21	12	26	6	10	4	0.003
Coronary heart disease (%)	15	38	12	11	6	18	12	0.002
Ejection fraction (%)	62 ± 13	57 ± 12	61 ± 12	60 ± 16	63 ± 14	62 ± 13	65 ± 10	0.044
Ejection fraction < 50% (%)	17	28	23	26	14	18	7	0.038
Hemoglobin, g/dL	8.3 ± 1.6	8.5 ± 1.2	8.6 ± 1.6	8.0 ± 1.5	8.3 ± 1.7	8.1 ± 1.5	8.6 ± 1.6	0.295
Albumin, g/dL	3.3 ± 0.5	3.1 ± 0.6	3.3 ± 0.6	3.4 ± 0.4	3.3 ± 0.5	3.4 ± 0.5	3.3 ± 0.5	0.071
Creatinine, mg/dL	9.3 ± 3.5	7.9 ± 2.7	9.3 ± 3.4	9.0 ± 2.9	8.8 ± 3.0	9.9 ± 4.6	9.7 ± 2.8	0.081
eGFR, mL/min/1.73^2	5.5 ± 2.2	6.2 ± 2.2	5.8 ± 2.8	5.6 ± 1.9	5.5 ± 2.1	5.3 ± 2.2	5.1 ± 2.0	0.199
LDL-C, mg/dL	102 ± 38	117 ± 35	91 ± 29	114 ± 39	107 ± 41	101 ± 42	93 ± 33	0.013
HDL-C, mg/dL	46 ± 16	38 ± 12	41 ± 16	43 ± 13	47 ± 15	48 ± 13	50 ± 19	0.002
Calcium, mg/dL	8.1 ± 1.0	8.5 ± 1.0	7.9 ± 1.2	8.3 ± 1.0	8.0 ± 0.9	7.9 ± 1.1	8.3 ± 0.9	0.007
Phosphate, mg/dL	6.0 ± 1.7	5.4 ± 1.6	6.2 ± 2.1	6.0 ± 1.5	6.2 ± 1.4	6.2 ± 1.9	6.0 ± 1.8	0.449
Ca x P product	48 ± 13	45 ± 9	47 ± 13	49 ± 13	48 ± 10	48 ± 16	49 ± 13	0.803
C-reactive protein, mg/dL	0.20 (0.10 0.60)	0.50 (0.15 0.85)	0.50 (0.18 0.75)	0.30 (0.10 0.73)	0.20 (0.10 0.40)	0.10 (0.10 0.70)	0.10 (0.00 0.50)	0.030
HbA1C, %	5.7 ± 2.1	6.8 ± 1.5	6.0 ± 1.7	5.4 ± 1.2	6.4 ± 4.0	5.3 ± 0.7	5.3 ± 0.7	0.116
ESA, %	53	0	12	37	50	71	80	<0.001
RAS-I, %	53	14	23	19	56	63	79	<0.001
Statin, %	22	10	8	24	14	21	39	0.001
Aspirin, %	24	21	27	22	16	30	25	0.442
Beta blocker, %	19	10	15	22	23	13	24	0.373

BMI, body mass index; CAD, coronary artery disease; CAG, coronary angiography; MPS, myocardial perfusion single photon emission computed tomography; DM, diabetes mellitus; BP, blood pressure; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Ca, calcium; P, phosphate; ESA, erythropoiesis-stimulating agent; RAS-I, rennin angiotensin system inhibitor.

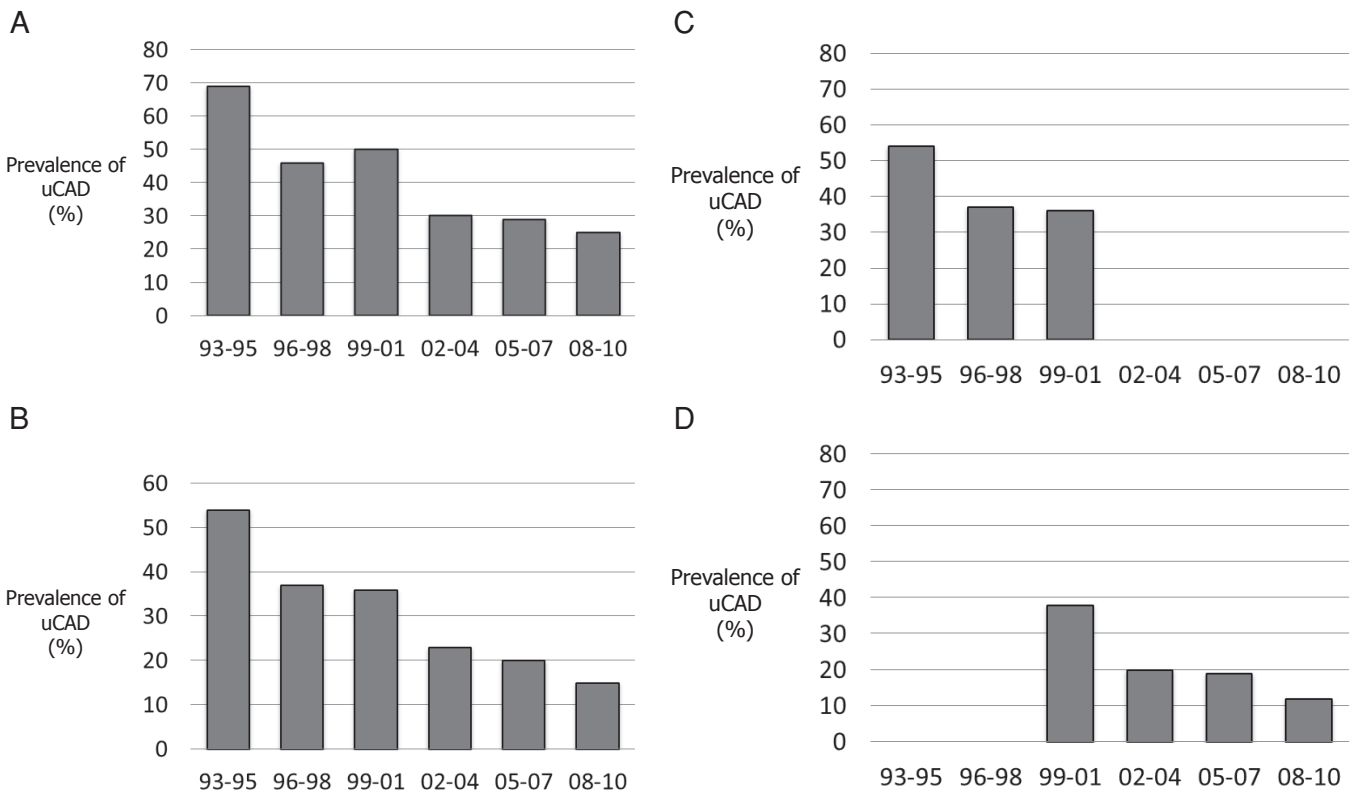

Fig. 2. Annual trend in the prevalence of uCAD over the six eras.

The annual trends in the prevalence of uCAD are shown as a chart for the three separate groups of patients. The prevalence of uCAD gradually and significantly declined from 69% to 25% in the total 315 patients (A, $p<0.001$ for trend; Jonckheere-Terpstra test) and from 54% to 15% in the 222 subgroup patients (B, $p=0.001$ for trend; Jonckheere-Terpstra test) over 18 years. A declining tendency in the prevalence of uCAD was observed in both screening modality groups, CAG (C) and MPS (D), among the 222 patients.

($p=0.001$ for trend), as shown in **Table 3** and **Fig. 2-B**. The analysis of the CAG and MPS findings showed that the prevalence of uCAD over time decreased among these patients, as observed in the 315 patients with cardiac disease (**Fig. 2, C** and **D**). The mean diastolic pressure and HDL-C level significantly decreased over time ($p=0.007$ and <0.001 for trend, respectively). In addition, the median CRP level declined over the past two decades ($p=0.064$ for trend). The proportion of patients prescribed ESAs, RAS-Is and statins increased over time ($p<0.001$ for all three trends). Meanwhile, a univariate logistic regression analysis identified BMI, the HDL-C level and the use of ESAs or RAS-Is to be negatively associated with the incidence of uCAD and smoking and the CRP level to be positively associated with the incidence of uCAD (**Table 4**). Furthermore, a multivariate logistic regression analysis including BMI, smoking and the HDL-C and CRP levels selected BMI and the HDL-C level as independent factors associated with the incidence of uCAD (Model 3 in **Table 4**). In Model 4, only the use of RAS-Is was found to be negatively associated with the incidence of uCAD among the three medications (RSA-Is, ESAs and statins); however, the difference did not reach a statistically significant level ($p=0.053$).

Discussion

The medical management of patients with CKD has remarkably changed over the past 20 years[15]. The current results confirmed that the prevalence of uCAD at the start of dialysis therapy has remarkably declined over a period of 18 years. In parallel with this phenomenon, a favorable change was observed in the HDL-C and CRP levels from the viewpoint of coronary atherosclerosis and the use of medications, including ESAs, ARBs/ACE-Is and statins, all of which are potentially protective against CAD. Although the cross-sectional study design cannot be used to support the argument that these comprehensive changes resulted in the inhibition of the progression of CAD,

Table 2. Logistic regression analysis of factors associated with the incidence of uCAD in the 315 patients with ESKD

	Univariate analysis			Model 1*			Model 2†		
	Odds ratio	95% CI	*p*	Odds ratio	95% CI	*p*	Odds ratio	95% CI	*p*
Age, per year	1.015	0.995-1.035	0.143						
Male, vs. female	1.381	0.810-2.352	0.235						
Diabetes	0.953	0.599-1.515	0.840						
BMI, per kg/m^2	0.894	0.827-0.967	0.005	0.911	0.833-0.996	0.04			
Smoker, vs. non-smoker	1.873	1.153-3.042	0.011	1.192	0.666-2.133	0.555			
Systolic BP, per mmHg	0.994	0.985-1.004	0.226						
Diastolic BP, per mmHg	0.999	0.984-1.013	0.876						
Heart rate, per beats/min	1.012	0.994-1.031	0.200						
Hemoglobin, per g/dL	1.273	1.088-1.489	0.003						
Albumin, per g/dL	0.92	0.568-1.489	0.734						
Creatinine, per mg/dL	0.922	0.854-0.995	0.036						
eGFR, per mL/min/1.73^2	1.156	1.035-1.291	0.010	1.045	0.889-1.230	0.593			
LDL-C, per mg/dL	1.006	1.000-1.012	0.069						
HDL-C, per mg/dL	0.968	0.951-0.987	0.001	0.976	0.955-0.997	0.029			
Calcium, per mg/dL	1.299	1.017-1.659	0.036						
Phosphate, per mg/dL	0.834	0.716-0.970	0.019						
Ca x P product, per 1 increment	0.981	0.962-1.000	0.054						
C-reactive protein, per mg/dL	1.434	1.073-1.915	0.015	1.921	1.045-3.532	0.036			
HbA1c, per %	1.195	0.959-1.490	0.113						
ESA, users vs. nonusers	0.565	0.355-0.899	0.016				0.675	0.412-1.106	0.119
ARB/ACE-I, users vs. nonusers	0.501	0.314-0.800	0.004				0.536	0.325-0.882	0.014
Statin, users vs. nonusers	1.455	0.846-2.503	0.176				1.644	0.939-2.877	0.082
Calendar year, per year	0.889	0.845-0.935	<0.001						

BMI, body mass index; BP, blood pressure; Ca, calcium; DM, diabetes mellitus; ESA, erythropoietin-stimulating agent; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; P, phosphate; RAS-I, rennin angiotensin system inhibitor; *A multiple logistic regression analysis was performed including BMI, smoking, eGFR, HDL-C and C-reactive protein to identify independent risk factors for uCAD †A multiple logistic regression analysis was performed including three medications (ESAs, RSA-Is and statins) to identify medications modifying the prevalence of uCAD.

such interactions may, at least in part, favorably affect the decline in the prevalence of uCAD over time.

We compared the prevalence of uCAD in incident dialysis patients treated in six eras, among both the total subject population ($n=315$) and a subgroup of subjects without known cardiac disease ($n=222$). We found that the prevalence of uCAD significantly declined over the past two decades, regardless of the presence or absence of cardiac disease. Moreover, the findings of separate CAG and MPS evaluations also indicated that the prevalence of uCAD tended to decrease over time. Such findings provide an answer to the question of whether the progression of coronary atherosclerosis has improved over time in patients with ESKD. The prevalence of patients with ESKD and previous cardiac disease, such as heart failure or an EF of $<50\%$, has also declined over time, which further supports our main findings. A recent community study of a general Japanese population also found that the incidence of sudden cardiac death due to myocardial infarction declined between 1981 and 2005[16].

Both HDL-C and CRP play key roles in the decline of the prevalence of uCAD. Among atherogenic factors, these two parameters met the conditions of favorable changes over time and exhibited a remarkable association with the incidence of uCAD in this study, independent of other contributing parameters, according to a logistic regression analysis. A low serum HDL-C concentration is closely associated with the presence of coronary atherosclerosis on coronary CT[17] and MRI[18] in Japanese populations. Moreover, the increase in the HDL-C level brought about by statin therapy is also associated with the regression of coronary atherosclerosis[19, 20]. Based on dialysis registry data (in Japan), Shoji *et al.* demonstrated that the risk of incident myocardial infarction is inversely associ-

ated with the HDL-C level, even in patients on dialysis[21]. Therefore, the improvements in the prevalence of uCAD over the past two decades may be due, at least in part, to the increase in the HDL-C levels.

The reduction in the mean CRP level over time may be associated with the improved prevalence of uCAD. Chronic inflammation is thought to comprise one of the central reasons for the high incidence and prevalence of atherosclerotic cardiovascular disease in patients with CKD[22]. Moreover, the level of CRP, a marker of inflammation, is closely associated with the severity of atherosclerosis and cardiovascular events in patients with CKD[11, 23]. Therefore, the decrease in the CRP levels over time may be another causal contributor to the improvement in the uCAD prevalence.

It is notable that BMI was found to be inversely associated with the incidence of uCAD, independent of other confounding variables. As a surrogate marker of the nutritional status and malnutrition, this parameter represents a powerful risk factor for atherosclerotic disease combined with chronic inflammation in patients with CKD[24]. We previously identified a significant inverse relationship between the angiographic severity of coronary atherosclerosis and the BMI values among patients newly treated with hemodialysis[25]. Based on these findings, dyslipidemia, malnutrition and inflammation are potential modifiable factors for retarding the progression of coronary atherosclerosis in patients with conservative CKD. However, the BMI values did not remarkably change over time in the present study. Therefore, we consider BMI to be minimally associated with the improvement in the prevalence of uCAD observed in the present study.

As the eras progressed, a significant negative correlation was observed between the prevalence of uCAD and the rate of ESA and RAS-I use. It has been reported that treatment with ESAs and RAS-Is plays a favorable role in preventing coronary atherosclerosis in the general population. For instance, erythropoietin receptors have been identified on endothelial cells and cardiomyocytes[26]. Preclinical studies have also shown that erythropoietin plays a cardioprotective role in various experimental models of myocardial ischemia and ischemia reperfusion[27-29]. Angiotensin II stimulates intracellular pathways that promote atherosclerosis via inflammation, endothelial dysfunction, proliferation, fibrosis and thrombosis[30-32]. Clinical studies have also demonstrated that inhibition of the renin-angiotensin system suppresses or retards the progression of coronary atheroma on intravascular ultrasound, independent of blood pressure control[9, 33]. On the other hand, the use of statins, which are expected to beneficially affect coronary atherosclerosis, did not

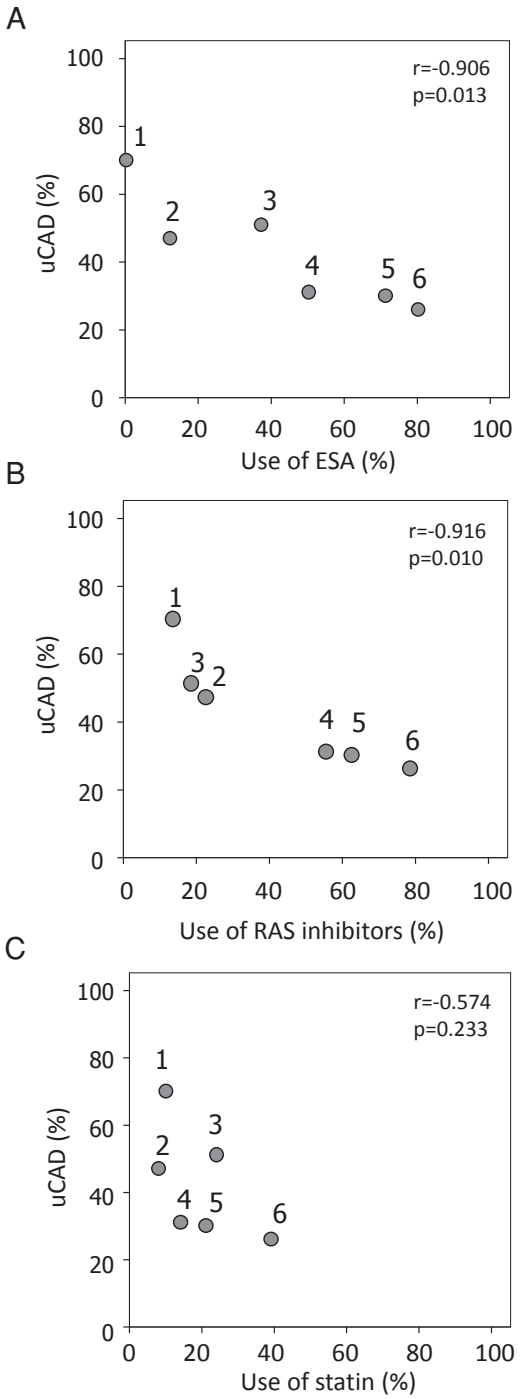

Fig. 3. Correlations between the prevalence of uCAD and the rate of medication use in each of the six eras.

Correlation between the prevalence of uCAD and the rate of medication use in each era was assessed according to a linear regression analysis. The number over each dot indicates the era number. As the eras progressed, a significant negative association was noted between the prevalence of uCAD and the rate of ESA ($r=-0.906$, $p=0.013$) and RASI ($r=-0.916$, $p=0.010$) use (A and B). No associations were found between the incidence of uCAD and the rate of statin use (C).

Table 3. Characteristics of the 222 screened patients without cardiac disease and the temporal trends in the six era groups

	Total	Era 1 93-95	Era 2 96-98	Era 3 99-01	Era 4 02-04	Era 5 05-07	Era 6 08-10	*p*
Patients No.	222	13	19	22	53	54	61	
Age, years	63 ± 12	64 ± 11	59 ± 12	61 ± 9	62 ± 13	63 ± 13	67 ± 11	0.147
Male, %	69	62	79	77	62	67	74	0.579
Diabetes, %	56	38	63	68	55	56	54	0.635
Significant CAD, %	24	54	37	36	23	20	15	0.022
MPS, %	78	0	0	59	94	98	95	<0.001
Significant CAD by CAG, % (n=41)		54	37	33				0.560
Significant CAD by MPS, % (n=174)				38	20	19	12	0.165
BMI, kg/m^2	22 ± 4	21 ± 3	23 ± 4	23 ± 4	22 ± 4	22 ± 3	23 ± 3	0.343
Smoking, %	52	62	42	64	43	49	58	0.497
Systolic BP, mmHg	156 ± 25	157 ± 27	164 ± 22	163 ± 25	153 ± 23	152 ± 29	158 ± 23	0.349
Diastolic BP, mmHg	79 ± 17	76 ± 21	91 ± 17	79 ± 12	80 ± 14	76 ± 22	75 ± 13	0.034
Heart rate, beats/min	79 ± 13	78 ± 21	84 ± 12	76 ± 12	81 ± 13	77 ± 12	81 ± 14	0.458
Ejection fraction, %	66 ± 9	64 ± 8	64 ± 9	69 ± 9	67 ± 11	66 ± 9	67 ± 9	0.519
Hemoglobin, g/dL	8.2 ± 1.5	8.7 ± 1.3	8.4 ± 1.7	7.6 ± 1.5	8.1 ± 1.5	8.0 ± 1.3	8.4 ± 1.6	0.170
Albumin, g/dL	3.3 ± 0.5	3.1 ± 0.7	3.4 ± 0.6	3.3 ± 0.4	3.3 ± 0.5	3.4 ± 0.5	3.4 ± 0.5	0.355
Creatinine, mg/dL	9.7 ± 3.4	9.2 ± 3.1	9.9 ± 3.6	10.0 ± 3.6	9.0 ± 3.0	10.0 ± 4.4	9.9 ± 2.9	0.618
eGFR, mL/min/1.73^2	5.1 ± 1.7	5.0 ± 1.2	5.1 ± 1.4	4.8 ± 1.4	5.4 ± 1.8	5.1 ± 1.9	4.9 ± 1.7	0.669
LDL-C, mg/dL	100 ± 37	120 ± 39	88 ± 28	110 ± 47	104 ± 41	98 ± 33	95 ± 33	0.158
HDL-C, mg/dL	47 ± 17	36 ± 9	37 ± 12	42 ± 15	47 ± 16	49 ± 14	51 ± 20	0.003
Calcium, mg/dL	8.0 ± 1.0	8.2 ± 1.3	8.0 ± 1.1	8.2 ± 0.9	7.9 ± 0.9	7.7 ± 1.1	8.4 ± 0.9	0.021
Phosphate, mg/dL	6.2 ± 1.8	5.8 ± 2.1	6.2 ± 2.2	6.4 ± 1.8	6.2 ± 1.4	6.3 ± 1.8	6.1 ± 1.9	0.904
Ca x P product	49 ± 13	46 ± 10	48 ± 13	52 ± 14	49 ± 10	48 ± 14	50 ± 14	0.730
C-reactive protein, mg/dL	0.20 (0.02-0.50)	0.35 (0.13 0.78)	0.50 (0.20 0.85)	0.12 (0.06 0.55)	0.20 (0.00 0.40)	0.10 (0.08 0.55)	0.10 (0.00 0.50)	0.080
HbA1C, %	5.7 ± 2.3	6.9 ± 2.3	6.1 ± 1.9	5.3 ± 1.1	6.3 ± 4.1	5.3 ± 0.7	5.2 ± 0.8	0.390
ESA, %	55	0	16	36	45	69	82	<0.001
RAS-I, %	55	8	26	27	55	61	79	<0.001
Statin, %	20	0	11	14	11	19	38	0.002
Aspirin, %	14	8	26	9	11	17	15	0.585
beta blocker, %	18	15	21	23	21	15	18	0.956

BMI, body mass index; CAD, coronary artery disease; CAG, coronary angiography; MPS, myocardial perfusion single photon emission computed tomography; DM, diabetes mellitus; BP, blood pressure; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Ca, calcium; P, phosphate; ESA, erythropoiesis-stimulating agent; RAS-I, rennin angiotensin system inhibitor.

Table 4. Logistic regression analysis of factors associated with the incidence of uCAD among the 222 patients with ESKD

	Univariate analysis			Model 3 ¶			Model 4 #		
	Odds ratio	95% CI	*p*	Odds ratio	95% CI	*p*	Odds ratio	95% CI	*p*
Age, per year	1.006	0.981-1.033	0.625						
Male, vs. female	1.75	0.854-3.585	0.126						
Diabetes	1.016	0.548-1.884	0.959						
BMI, per kg/m^2	0.864	0.776-0.961	0.007	0.861	0.760-0.975	0.018			
Smoker, vs. non-smoker	2.03	1.077-3.853	0.029	1.453	0.706-2.989	0.31			
Systolic BP, per mmHg	0.999	0.986-1.012	0.866						
Diastolic BP, per mmHg	1.001	0.982-1.020	0.903						
Heart rate, per beats/min	1.013	0.986-1.041	0.345						
Hemoglobin, per g/dL	1.16	0.946-1.422	0.153						
Albumin, per g/dL	1.101	0.589-2.058	0.764						
Creatinine, per mg/dL	1.000	0.914-1.094	1.000						
eGFR, per mL/min/1.73^2	1.026	0.858-1.228	0.777						
LDL-C, per mg/dL	1.005	0.997-1.013	0.246						
HDL-C, per mg/dL	0.96	0.935-0.986	0.002	0.96	0.932-0.988	0.006			
Calcium, per mg/dL	1.276	0.96-1.758	0.137						
Phosphate, per mg/dL	0.974	0.814-1.167	0.777						
Ca x P product, per 1 increment	1.003	0.979-1.027	0.826						
C-reactive protein, per mg/dL	2.45	1.189-5.049	0.015	1.614	0.702-3.711	0.26			
HbA1c, per %	1.315	0.944-1.831	0.105						
ESA, users vs. nonusers	0.517	0.278-0.962	0.037				0.59	0.312-1.118	0.106
ARB/ACE-I, users vs. nonusers	0.468	0.250-0.873	0.017				0.529	0.277-1.009	0.053
Statin, users vs. nonusers	0.76	0.339-1.703	0.505				0.861	0.377-1.967	0.722
Calendar year, per year	0.881	0.822-0.945	<0.001						

BMI, body mass index; DM, diabetes mellitus; BP, blood pressure; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Ca, calcium; P, phosphate; ESA, erythropoietin-stimulating agent; RAS-I, rennin angiotensin system inhibitor; ¶A multiple logistic regression analysis was performed including BMI, smoking, HDL-C and C-reactive protein to identify independent risk factors for uCAD #A multiple logistic regression analysis was performed including three medications (ESAs, RSA-Is and statins) to identify medications modifying the prevalence of uCAD.

exhibit a significant negative correlation with the prevalence of uCAD in this study. The reduced rate of statin use compared to that of RAS-Is and ESAs over time is a possible explanation for this unexpected result. However, the cross sectional design of the present study does not allow for a discussion of the causal beneficial effects of these medications on the incidence of coronary atherosclerosis among patients with CKD.

The present study is associated with some limitations. The means of diagnosing CAD differed between the first and second halves of the study period. Coronary angiography can be used to identify morphological narrowing of the coronary artery, while MPS can be used to detect myocardial ischemia during stress. Boudreau *et al.* reported a sensitivity and specificity of pharmacological stress testing on thallium-201 MPS for diagnosing significant angiographic coronary artery disease of 86% and 79%, respectively, in ESKD patients[34]. Therefore, we believe that, even among dialysis patients, the diagnostic accuracy of MPS for detecting CAD is adequately reliable. Moreover, the separate CAG and MPS evaluations both showed the same tendency of a decline in the prevalence of uCAD over time. Hence, we do not believe that the change in diagnostic method significantly affected our main findings. Regarding the 35% of patients who declined screening, the characteristics of the two patient groups (with screening and without screening) in each era were compared in order to confirm selection bias (data not shown). Except for the percentage of patients with a previous history of coronary heart disease, we were unable to find any significant differences between the two groups that may have affected our results. Therefore, we conducted a subgroup analysis among the 222 patients without known cardiac disease. However, we did not have any longitudinal data regarding indi-

vidual atherogenic factors during the predialysis phase. Hence, we are unable to explain the causal effects of such factors on the prevalence of uCAD. Nevertheless, a comparison of historical changes may minimize the bias conferred by the cross sectional design. Another limitation is that a small sample of patients was studied at a single center. Our findings and theories may not be globally applicable to all dialysis units.

In conclusion, the prevalence of uCAD among patients with ESKD has remarkably decreased over the past two decades. We believe that changes in the medical management of patients with CKD over a period of 18 years have modified the prevalence of coronary atherosclerosis by favorably affecting the incidence of dyslipidemia, malnutrition and inflammation. However, a large-scale longitudinal study is required to confirm this notion.

Abbreviations

ANOVA, analysis of variance; BMI, body mass index; BP, blood pressure; Ca, calcium; CAD, coronary artery disease; CAG, coronary angiography; CHD, coronary heart disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; ESA, erythropoietin-stimulating agent; ESKD, end-stage kidney disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; P, phosphate; RAS-I, rennin angiotensin system inhibitor; SPECT, single-photon emission computed tomography.

Competing Interests

None of the authors have any conflicts of interest or financial disclosures associated with this study.

Authors' Contributions

H.H. and N.J. had full access to all the data in the study and take responsibility for the integrity of the data and the analytical accuracy.

Study concept and design: H.H., N.J. and Y.T.

Data acquisition: Y.T., M.I., S.K., T.H., T.A., Y.T., Y.I., A.M. and K.H.

Data analysis and interpretation: M.I. and N.J.

Drafting of the manuscript: M.I. and N.J.

Statistical analysis: M.I. and N.J.

Administrative, technical and material support: K.H.

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Conflicts of Interest

None of the authors have any conflicts of interest associated with this study.

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