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Prognostic Value of Risk Factors, Calcium Score, Coronary CTA, Myocardial Perfusion Imaging, and Invasive Coronary Angiography in Kidney Transplantation Candidates

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ABSTRACT

OBJECTIVES This study sought to perform a prospective head-to-head comparison of the predictive value of clinical risk factors and a variety of cardiac imaging modalities including coronary artery calcium score (CACS), coronary computed tomography angiography (CTA), single-photon emission computed tomography (SPECT), and invasive coronary angiography (ICA) on major adverse cardiac events (MACE) and all-cause mortality in kidney transplantation candidates.

BACKGROUND Current guidelines recommend screening for coronary artery disease in kidney transplantation candidates. Furthermore, noninvasive stress imaging is recommended in current guidelines, despite its low diagnostic accuracy and uncertain prognostic value.

METHODS The study prospectively evaluated 154 patients referred for kidney transplantation. All patients underwent CACS, coronary CTA, SPECT, and ICA testing. The clinical endpoints were extracted from patients' interviews, patients' records, and registries.

RESULTS The mean follow-up time was 3.7 years. In total, 27 (17.5%) patients experienced MACE, and 31 (20.1%) patients died during follow-up. In a time-to-event analysis, both risk factors and CACS significantly predicted death, but only CACS predicted MACE. Combining risk factors with CACS identified a very-low-risk cohort with a MACE event rate of 2.1%, and a 1.0% mortality rate per year. Of the diagnostic modalities, coronary CTA and ICA significantly predicted MACE, but only coronary CTA predicted death. In contrast, SPECT predicted neither MACE nor death.

CONCLUSIONS Compared with traditional risk factors and other cardiac imaging modalities, CACS and coronary CTA seem superior for risk stratification in kidney transplant candidates. Applying a combination of risk factors and CACS and subsequently coronary CTA seems to be the most appropriate strategy. (Angiographic CT of Renal Transplantation Candidate Study [ACToR]; NCT01344434) (J Am Coll Cardiol Img 2018;11:842–54)

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Coronary artery disease (CAD) is the leading cause of death in waiting-listed kidney transplant candidates, and the prevalence of CAD remains high after kidney transplantation. Currently, more than 100,000 patients are on a kidney transplant waiting list in the United States alone, and the past decades have seen an increase in the age and comorbidity of these patients. Thus, cardiac evaluation of kidney transplant candidates is a common challenge for nephrologists and cardiologists (1,2).

Screening for CAD in asymptomatic kidney transplant candidates is common, even though no current screening strategy has been shown to improve the outcome in these patients (1). Evidence is conflicting on the prognostic value of risk factors and the use of imaging modalities, including myocardial perfusion stress test and invasive coronary angiography (ICA).

In 2012 the American College of Cardiology/American Heart Association (ACC/AHA) published the scientific statement "Cardiac Disease Evaluation and Management Among Kidney and Liver Transplantation Candidates" in which they defined cardiovascular risk factors for chronic kidney disease (CKD) patients as follows: "Age more than 60 years, diabetes mellitus, smoking, dyslipidemia, hypertension, left ventricular hypertrophy, prior cardiovascular disease and more than 1 year on dialysis." In addition: "The specific number of risk factors that should be used to prompt testing remains to be determined, but the committee considers 3 or more as reasonable." After primary risk stratification with cardiovascular risk factors, the AHA/ACC statement recommends that "noninvasive cardiac stress testing may be considered in kidney transplantation candidates with no active cardiac conditions on the basis of the presence of multiple coronary artery disease risk factors regardless of functional status" (1).

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We demonstrated that coronary artery calcium score (CACS) and coronary computed tomography angiography (CTA) may have a role in identifying coronary stenosis in kidney transplantation candidates when compared with risk factors and single-photon emission computed tomography (SPECT) (3,4). However, the prognostic value of CACS and coronary CTA remains uncertain in these patients (1).

The aim of this prospective head-to-head comparison study was to evaluate the predictive value of clinical risk factors and a variety of cardiac imaging modalities including CACS, coronary CTA, SPECT, and ICA on major adverse cardiac events (MACE) and all-cause mortality in kidney transplantation candidates.

METHODS

STUDY DESIGN. In ACToR (Angiographic CT of Renal Transplantation Candidate Study), we conducted a prospective, observational cohort study enrolling patients referred for cardiac evaluation before kidney transplantation. The inclusion period was from February 2011 to February 2014. The inclusion criteria were advanced CKD and the presence of at least 1 of the following characteristics: age older than 40 years, diabetes, symptoms of cardiovascular disease, dialysis treatment for more than 5 years, or registration on a kidney transplant waiting list for more than 3 years without cardiac screening. The exclusion criteria were age younger than 18 years and unstable angina pectoris. Written informed consent was obtained from all patients. The study was approved by the Regional Ethics Committee and the Danish Data Protection Agency, and it was conducted in line with the principles of the Declaration of Helsinki.

All patients were scheduled for the following: 1) a medical interview to appraise clinical risk factors; 2) CACS; 3) coronary CTA; 4) stress SPECT; and 5) ICA. When clinically indicated, a rest SPECT was also performed (**Figure 1**). Before coronary CTA, clinical echocardiography was performed to assess left ventricular hypertrophy and ejection fraction, and valve disease. After the baseline diagnostic work-up, patients were followed, and MACE and death were registered. Diagnostic accuracy of the cardiac imaging tests with ICA as reference was described in a previous publication in which the imaging acquisition and interpretation are described in detail (3).

Analysis of the diagnostic tests was performed on a patient-level basis by 2 independent, blinded cardiologists or nuclear medicine physicians. In case of disagreement between the 2 readers, a consensus decision was obtained.

CARDIOVASCULAR RISK FACTORS. Clinical information was obtained by patient interviews and medical record reviews. Cardiovascular risk factors were evaluated as proposed by the AHA/ACC. These factors included the following: smoking, defined as active smoking; dyslipidemia, defined as ongoing statin treatment or total serum cholesterol exceeding 6.2 mmol/l (240 mg/dl); and hypertension, defined as current antihypertensive medical treatment. Left ventricular hypertrophy was diagnosed by echocardiography (moderately or severely abnormal myocardial wall thickness). Established

ABBREVIATIONS AND ACRONYMS

ACC/AHA = American College of Cardiology/American Heart Association

CACS = coronary artery calcium score

CAD = coronary artery disease

CKD = chronic kidney disease, (stages: 1 to 5, D: dialysis)

CTA = computed tomography angiography

HR = hazard ratio

ICA = invasive coronary angiography

IQR = interquartile range

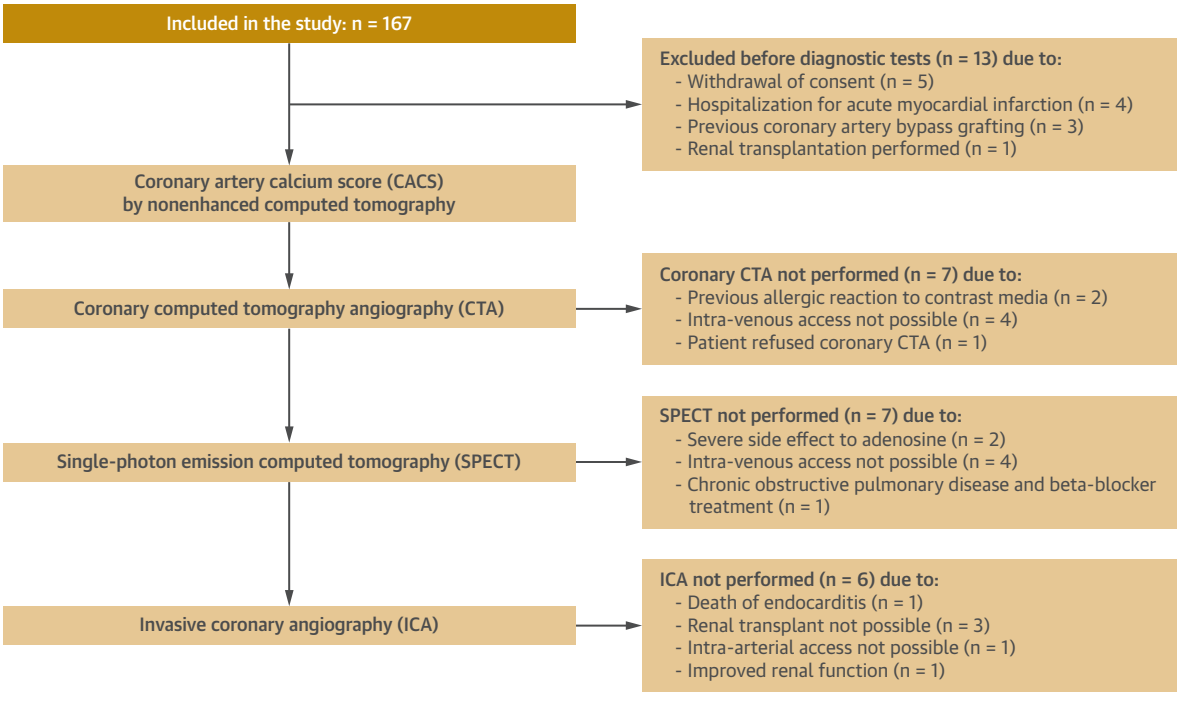
MACE = major adverse cardiac event(s)

QCA = quantitative coronary angiography

SPECT = single-photon emission computed tomography

STEMI = ST-segment elevation myocardial infarction

FIGURE 1 Flow Chart of Patients in the Study



The final study cohort (N = 154) represented patients who completed at least 1 of the imaging investigations.

cardiovascular disease was defined as previous myocardial infarction, stroke, transitory cerebral ischemia, peripheral artery disease, or intermittent claudication. A cutoff of 3 or more risk factors as defined by the AHA/ACC was considered high risk.

COMPUTED TOMOGRAPHY ACQUISITION AND INTERPRETATION. Computed tomography scans were performed on a dual-source scanner (SOMATOM Definition Flash, Siemens Healthcare, Erlangen, Germany). A nonenhanced scan was performed to obtain the Agatston CACS. Contrast-enhanced coronary CTA and aortography were acquired using a fixed intravenous contrast dose of Ioversol (95 ml, Optiray 350 mg/ml, Mallinckrodt, Germany).

A semiquantitative scale was used to grade the extent of luminal diameter stenosis, and obstructive CAD was defined as a segment with a diameter exceeding 2 mm and a minimum 50% reduction in luminal diameter (≈70% area reduction). Non-evaluable segments with a diameter exceeding 2 mm were defined as obstructive CAD. Coronary CTA results were defined as abnormal if obstructive CAD was not ruled out in all coronary segments.

SINGLE-PHOTON EMISSION COMPUTED TOMOGRAPHY ACQUISITION AND INTERPRETATION. SPECT was acquired using a dedicated gamma camera (Cardio-MD, Philips Healthcare, Best, the Netherlands) and analyzed on commercially available software (Auto-QUANT QGS/QPS, Cedars-Sinai, Los Angeles, California). Studies were performed using a 1-day stress study protocol with technetium-99m sestamibi. If needed for image interpretation, a rest study was performed on a separate day. Myocardial stress was induced by adenosine (140 μg/kg/min for 4 to 6 min) during light bicycle ergometer exercise or, in patients with severe chronic obstructive pulmonary disease, by bicycle ergometer alone or dobutamine stress.

SPECT images were assessed using a 17-segment model. An abnormal SPECT result caused by a reversible myocardial perfusion defect was defined as a summed difference score ≥4. In addition, a reduction of left ventricular ejection fraction of >10% during stress or a transient ischemic dilation value of >1.22 was defined as abnormal. For patients with no previous coronary revascularization, an irreversible perfusion defect or left ventricular ejection fraction <45% was considered abnormal.

INVASIVE CORONARY ANGIOGRAPHY ACQUISITION AND INTERPRETATION. ICA was performed using the contrast media iodixanol (350 mg/ml) and intracoronary glyceryl nitrate (200 μg). When a coronary stenosis was visually estimated to exceed a 30% luminal diameter stenosis in a segment with a vessel diameter exceeding 2 mm, quantitative coronary angiography (QCA) analysis was performed. QCA software (QAngioXA-7.3, Medis, Leiden, the Netherlands) was used for the analysis. Image frames of the coronary stenosis were selected in the end-diastolic phase with minimal vessel overlapping. Obstructive CAD was defined as a minimum 50% reduction in luminal diameter (≈70% area reduction) by QCA.

FOLLOW-UP. All patients were invited to attend a follow-up visit, approximately 2.5 years after inclusion, where a standardized patient interview was conducted. Clinical follow-up was otherwise performed according to routine practice at the participating centers. Clinical endpoint data were extracted from the standardized patient interviews, patient records, and the Western Denmark Heart Registry. The primary endpoint was defined as MACE (cardiac death, cardiac arrest with successful resuscitation; ST-segment elevation myocardial infarction [STEMI], non-STEMI, and/or revascularization). The secondary endpoint was all-cause mortality. Patients who had revascularization procedures in relation to the baseline cardiac evaluation were not excluded from the follow-up.

An endpoint committee, consisting of 1 nephrologist and 2 cardiologists, adjudicated all outcomes by consensus. The endpoint committee was blinded to all previous study results.

STATISTICAL ANALYSIS. Continuous variables were expressed as mean ± SD or median with total or interquartile range (IQR). Dichotomous or categorical variables were reported as frequencies (%). Time-to-event analysis was performed with Cox regression of hazard ratios (HRs). The models were examined for the proportional hazards assumption. Mortality was graphed according to the Kaplan-Maier failure method and MACE according to the Nelson-Aalen estimators for the cumulative cause-specific hazards. Cox multiple regression analysis was performed including number of risk factors ≥3 and kidney transplants during follow-up as a time-dependent variable for each of the cardiac imaging modalities because we estimated that these covariates affected the outcome most. The prognostic model was compared with Harrell's C-statistic. For all statistical analyses, 95% confidence intervals (CIs) were reported when appropriate, and a 2-tailed p value <0.05 was considered statistically significant. The statistical analyses were performed using STATA-13 (StataCorp, College Station, Texas).

RESULTS

Of the 167 kidney transplant candidates, 13 patients were excluded from this study, thus leaving a final study cohort of 154 patients who completed at least 1 of the imaging investigations (Figure 1). Diagnostic investigation was completed in 154 (100%) of the CACS determinations, 147 (95%) of the coronary CTA studies, 147 (95%) of the SPECT studies, and 148 (96%) of the ICA studies. A total of 138 (90%) patients completed all diagnostic tests. Baseline and imaging study characteristics are listed in Tables 1 and 2.

The median follow-up time was 3.7 years (range 0.3 to 5.7 years). The minimum follow-up was 2.8 years or until death. In total, 107 patients (69%) participated in the follow-up visit, 20 patients (13%) died before the visit, 21 patients (14%) did not want to participate, and 6 patients (4%) did not participate for other reasons. No patients were lost to follow-up because we had access to all patients' records and all patients were registered in the Western Denmark Heart Registry.

During follow-up, 27 (17.5%) patients experienced MACE, representing an annual event rate of 4.8% (95% CI: 3.3% to 7.0%). All-cause mortality occurred in 31 (20.1%) patients, representing an annual event rate of 5.3% (95% CI: 3.7% to 7.5%) (Table 3). In total, 95 (61.7%) patients underwent transplant procedures during follow-up.

Seven patients (5%) underwent revascularization procedures in relation to the baseline cardiac evaluation; 1 patient underwent coronary artery bypass grafting, and 6 had percutaneous coronary interventions. All 7 patients had ≥3 risk factors, CACS >0, and abnormal coronary CTA findings. Furthermore, SPECT results were abnormal in 5 of 7 patients. During follow-up, 3 of 7 revascularized patients experienced MACE, and 1 patient died.

CARDIOVASCULAR RISK FACTORS. All patients in this cohort had between 1 and 6 of the risk factors defined by the ACC/AHA, with a median number of 3 (IQR: 2 to 4). Dot-plots of the sum of risk factors versus CACS and occurrence of MACE and mortality are shown in Figure 2. No single risk factor was associated with MACE, and only dyslipidemia was associated with mortality ($p < 0.05$) (Table 4).

In patients with <3 (n = 60) versus ≥3 (n = 94) risk factors, the event rates of MACE were 3.8% (95% CI: 2.0% to 7.3%) versus 5.5% (95% CI: 3.5% to 8.8%) per year and the mortality rates were 2.5% (95% CI: 1.1% to

TABLE 1 Patient Demographics (N = 154)

Characteristic	
Race, white	144 (93.5)
Male	105 (68.2)
Age, yrs	54 (22-72)
Body mass index, kg/m^2	25.7 ± 4.3
Symptoms of angina pectoris	4 (2.6)
Kidney diagnosis and status	
Etiology of kidney failure	
Diabetes	41 (26.6)
Hypertension or glomerulosclerosis	38 (24.7)
Glomerulonephritis or connective tissue disease	37 (24.0)
Polycystic kidney disease	20 (13.0)
Other diagnosis	18 (11.7)
Chronic kidney disease stage 5, nondialysis	86 (55.8)
Estimated glomerular filtration rate, ml/min/1.73 m^2	12.6 ± 5.6
Chronic kidney disease stage 5, dialysis	68 (44.2)
Peritoneal dialysis	19
Hemodialysis	49
Treatment with dialysis, months	18 (1-240)
Previous kidney transplantation	28 (18.2)
Cardiovascular risk factors	
Age >60 yrs	57 (37.0)
Diabetes	50 (32.5)
Hypertension	144 (93.5)
Dyslipidemia	74 (48.1)
Smoking, active	47 (30.5)
Dialysis treatment >1 yr	47 (30.5)
Left ventricular hypertrophy	20 (13.0)
Prior cardiovascular disease	24 (15.6)
Number of cardiovascular risk factors	3.0 (1-6)
Medication use	
Acetylsalicylic acid	48 (31.2)
Cholesterol-lowering drug	91 (59.1)
Number of antihypertensive agents	2.9 ± 1.4
Beta-blocker	94 (61.0)
Renin-angiotensin-aldosterone system inhibitors	112 (72.7)
Calcium-channel blocker	91 (59.1)
Diuretic	110 (71.4)
Laboratory findings	
Hemoglobin, mmol/l	7.3 ± 0.8
Albumin, g/l	38.1 ± 5.0
Calcium, mmol/l	1.2 ± 0.1
Phosphate, mmol/l	1.6 ± 0.4
C-reactive protein, mg/l	5.8 ± 9.4

Values are n (%), median (range), or mean ± SD.

TABLE 2 Imaging Study Characteristics

Coronary artery calcium score (n = 154)	
Coronary artery calcium score	137 (0-561)
0	40 (26.0)
>0 and ≤400	66 (42.9)
>400	48 (31.1)
Coronary computed tomography angiography (n = 147)	
Abnormal test result	73 (49.7)
1-vessel disease	21 (14.3)
2-vessel disease	25 (17.0)
3-vessel disease or left main	27 (18.4)
Single-photon emission computed tomography (n = 147)	
Abnormal test result	38 (25.8)
Sum difference score ≥4*	10 (6.8)
Irreversible defect and/or ejection fraction <45%*	27 (18.4)
Other*†	8 (5.4)
Invasive coronary angiography (n = 148)	
Obstructive coronary artery disease	33 (22.3)
1-vessel disease	22 (14.9)
2-vessel disease	8 (3.4)
3-vessel or left main artery disease	3 (2.0)

Values are median (interquartile range) or n (%). *More than 1 pathologic finding was present in 8 patients. †Other: transient ischemic dilation ratio ≥1.22 (n = 6), reduction of ejection fraction of >10% during stress (n = 1), inconclusive images (n = 1).

5.5%) versus 7.2% (95% CI: 4.8% to 10.7%) per year, respectively. In a time-to-event analysis, risk factors with a cutoff of ≥3 were associated with mortality, but not with MACE (Table 4, Figures 3A and 3B).

CORONARY ARTERY CALCIUM SCORE. When patients were grouped by CACS, 0 (n = 40), 1 to 399 (n = 66), and ≥400 (n = 48), MACE event rates were 2.0% (95% CI: 0.6% to 6.1%), 3.1% (95% CI: 1.6% to 6.2%), and 10.1% (95% CI: 6.2% to 16.5%) per year. Mortality rates were 3.3% (95% CI: 1.4% to 7.8%), 3.8% (95% CI: 2.0% to 7.1%), and 9.4% (95% CI: 5.7% to 15.3%) per year.

Using a CACS of 0 as a reference, a time-to-event analysis showed that a CACS ≥400 was associated with MACE and mortality, whereas a CACS of 1 to 399 was not (Table 4, Figures 3C and 3D). In a multiple Cox regression analysis including CACS, risk factors with a cutoff of ≥3 and transplantation during follow-up, CACS remained associated with MACE, but not with mortality (Table 5). As a prognostic model compared using Harrell's C-statistic, CACS was significantly better than risk factors in predicting MACE (Harrell's C-statistic, 0.12; 95% CI: 0.00 to 0.25; $p < 0.05$) and equivalent in predicting mortality (Harrell's C-statistic, 0.01; 95% CI: −0.10 to 0.13; $p = 0.84$).

Combining risk factors and CACS: 1) <3 risk factors and CACS <400 (n = 48); 2) <3 risk factors and CACS ≥400 (n = 12); 3) ≥3 risk factors and CACS <400 (n = 58); and 4) ≥3 risk factors and CACS ≥400 (n = 36), the annual event rates of MACE were 2.1%, 11.4%, 3.3%, and 9.6%, respectively; the corresponding mortality rates were 1.0%, 8.8%, 5.9%, and 9.6%, respectively.

Patients with <3 risk factors and CACS ≥400 compared with CACS <400 had a MACE unadjusted HR of 5.8 (95% CI: 1.6 to 21.6; $p < 0.01$) and a mortality HR of 8.9 (95% CI: 1.6 to 48.9; $p < 0.05$). Similarly,

TABLE 3 Follow-Up (N = 154)

Major adverse cardiac events	27 (17.5)
Sudden cardiac death	12
Sudden cardiac arrest with successful resuscitation	1
Fetal myocardial infarction	0
ST-segment elevation myocardial infarction	4
Non-ST-segment elevation myocardial infarction	2
Revascularization	8
Mortality, all cause	31 (20.1)
Cardiac	12
Infection	5
Bleeding	3
Cancer	6
Other	5

Values are n (%) or n.

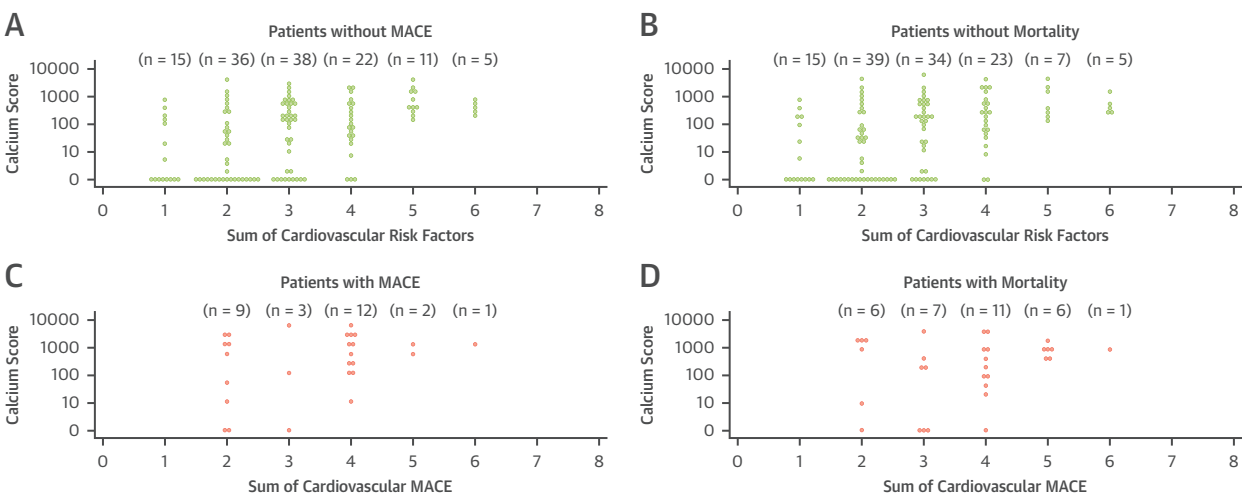
patients with ≥3 risk factors and CACS ≥400 compared with CACS <400 had a MACE unadjusted HR of 2.9 (95% CI: 1.1 to 7.6; p < 0.05) and a mortality HR of 1.6 (95% CI: 0.7 to 3.6; p = 0.22). Nonetheless, both groups had a significantly increased risk compared with patients who had <3 risk factors and CACS <400 (Table 4, Figures 3E and 3F).

As a prognostic model of MACE, combining risk factors with a cutoff of ≥3 and CACS with a cutoff ≥400 was significantly better than using risk factors alone (Harrell's C-statistic, 0.14; 95% CI: 0.04 to 0.24; p < 0.01), but similar to CACS alone (Harrell's C-statistic, 0.01; 95% CI: −0.04 to 0.06; p = 0.60). For prediction of mortality with combined risk factors and CACS, only a trend toward a better prediction was observed compared with risk factors (Harrell's C-statistic, 0.05; 95% CI: 0.00 to 0.10; p = 0.06) and CACS alone (Harrell's C-statistic, 0.06; 95% CI: −0.03 to 0.15; p = 0.16).

CORONARY COMPUTED TOMOGRAPHY ANGIOGRAPHY. Coronary CTA were classified as abnormal in 66 (45%) patients because they had 1 or more severe stenoses in a coronary segment and in 7 (5%) patients because they had solitary nonanalyzable segments. Patients with a normal (n = 74) versus abnormal (n = 73) coronary CTA results had an event rate of MACE of 1.4% (95% CI: 0.5% to 3.8%) versus 7.6% (95% CI: 4.9% to 11.8%) and a mortality rate of 3.1% (95% CI: 1.6% to 6.0%) versus 7.1% (95% CI: 4.1% to 11.1%).

In a time-to-event analysis, an abnormal coronary CTA result was associated with a worse prognosis in terms of both MACE and mortality than a normal coronary CTA result (Figures 4A and 4B). Coronary CTA remained associated with MACE after adjusting for risk factors with a cutoff of 3 and transplantation during follow-up. In addition, HR was increased in patients with multivessel disease (Tables 4 and 5). When analyzing patients with a high risk defined as ≥3 risk factors or CACS ≥400, coronary CTA still predicted MACE with an unadjusted HR of 4.8 (95% CI: 1.1 to 20.6; p < 0.05), but coronary CTA was no longer associated with mortality (Online Figures 1A and 1B).

FIGURE 2 Risk Factors and CACS Relation to MACE and Mortality



(A to D) Dot-plots of the individual sum of risk factors and coronary artery calcium score (CACS) illustrated for patients **(A)** without versus **(C)** with major adverse cardiac events (MACE) and who **(B)** did not or **(D)** did die.

TABLE 4 Unadjusted Cox Regression Analysis

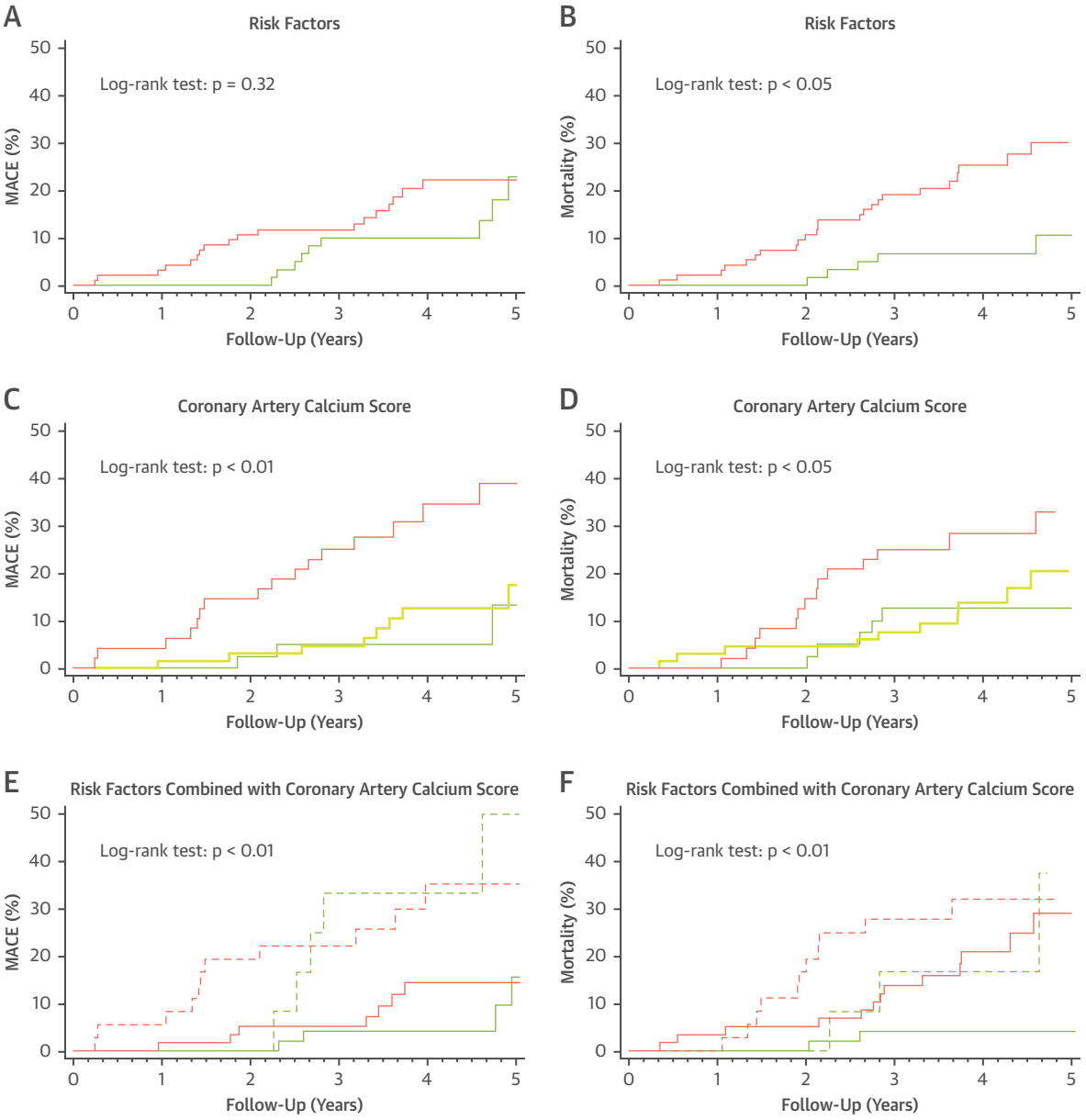
	MACE		Mortality	
	HR (95% CI)	p Value	HR (95% CI)	p Value
Clinical variables				
Male	0.9 (0.4–1.9)	0.69	1.5 (0.7–3.4)	0.32
Age (per 10 yrs)	1.0 (0.7–1.5)	0.82	1.4 (1.0–2.0)	<0.05
Kidney transplant before inclusion	0.6 (0.2–1.8)	0.33	0.7 (0.2–1.9)	0.46
Kidney transplant during follow-up	0.3 (0.1–0.7)	<0.01	0.3 (0.1–0.7)	<0.01
Cardiovascular risk factors				
Age more than 60 yrs	0.9 (0.4–2.0)	0.80	1.7 (0.8–3.4)	0.16
Diabetes	1.5 (0.7–3.3)	0.28	1.8 (0. –3.7)	0.10
Hypertension	1.5 (0.2–11.2)	0.69	0.5 (0.2–1.7)	0.25
Dyslipidemia	1.7 (0.8–3.6)	0.20	2.8 (1.3–6.0)	<0.05
Smoking, active	1.7 (0.8–3.7)	0.18	1.3 (0.6–2.8)	0.45
Dialysis treatment	1.6 (0.7–3.5)	0.23	1.3 (0.6–2.6)	0.22
Left ventricular hypertrophy	0.8 (0.3–2.8)	0.77	0.9 (0.3–2.7)	0.90
Established cardiovascular disease	0.9 (0.3–2.6)	0.85	1.6 (0.7–3.7)	0.30
Number of risk factors ≥3	1.5 (0.7–3.4)	0.32	3.0 (1.2–7.4)	<0.05
Coronary artery calcium score				
0	Ref		Ref	
>0 and <400	1.5 (0.4–5.7)	0.54	1.2 (0.4–3.4)	0.76
≥400*	5.1 (1.5–17.5)	<0.05	3.0 (1.1–8.1)	<0.05
Cardiovascular risk factors and coronary artery calcium score				
Number of risk factors <3 and CACS <400	Ref		Ref	
Number of risk factors <3 and CACS ≥400	5.8 (1.6–21.6)	<0.01	8.9 (1.6–48.8)	<0.05
Number of risk factors ≥3 and CACS <400	1.7 (0.5–5.7)	0.42	6.0 (1.4–26.7)	<0.05
Number of risk factors ≥3 and CACS ≥400	4.9 (1.6–15.4)	<0.01	9.9 (2.2–44.2)	<0.01
Coronary computed tomography angiography				
Abnormal test result	5.3 (1.8–15.6)	<0.01	2.3 (1.0–5.0)	<0.05
No-vessel disease	Ref		Ref	
1-vessel disease	3.3 (0.8–13.4)	0.09	1.5 (0.5–4.9)	0.50
2-vessel disease	4.1 (1.1–15.4)	<0.05	2.9 (1.1–7.5)	<0.05
3-vessel disease or left main artery disease	8.2 (2.6–25.9)	<0.001	2.4 (0.9–6.2)	0.07
Single-photon emission computed tomography				
Abnormal test result	1.6 (0.7–3.6)	0.30	1.0 (0.5–2.4)	0.93
Normal	Ref		Ref	
Sum difference score ≥4	4.2 (1.5–11.7)	<0.01	1.2 (0.3–5.0)	0.85
Irreversible defect and/or ejection fraction <45%	0.8 (0.3–2.8)	0.72	1.1 (0.4–2.9)	0.91
Other	0.8 (0.1–5.9)	0.80	1.4 (0.3–6.0)	0.65
Invasive coronary angiography				
Obstructive coronary artery disease	3.0 (1.4–6.5)	<0.01	1.5 (0.7–3.3)	0.31
No vessel disease	Ref		Ref	
1-vessel disease	1.8 (0.6–4.9)	0.27	1.5 (0.6–3.8)	0.37
2- or 3-vessel disease or left main artery disease	6.2 (2.5–15.3)	<0.001	1.5 (0.4–5.1)	0.51

*p values for hazard ratio differences between CACS >0 and <400 vs. CACS >400 for MACE were $p < 0.01$, and p values for mortality were $p < 0.05$.
CACS = coronary artery calcium score; CI = confidence interval; HR = hazard ratio; MACE = major adverse cardiac event(s); Ref = reference value.

SINGLE-PHOTON EMISSION COMPUTED TOMOGRAPHY. A similar event rate was demonstrated for patients with a normal (n = 109) versus abnormal (n = 38) SPECT results for MACE: 3.8% (95% CI: 2.3% to 6.3%) versus 6.1% (95% CI: 3.1% to 11.8%); and for mortality: 4.8% (95% CI: 3.1% to 7.5%) versus 5.2% (95% CI: 2.6% to 10.3%). No association was detected in the time-to-event analysis in this cohort or in subgroups of high-risk patients with ≥3 risk factors or CACS ≥400 (**Figures 4C and 4D,** Online Figures 1C and 1D). However, a subgroup of patients with reversible ischemia at SPECT (summed difference score ≥4; n = 10) had an unfavorable prognosis regarding MACE, but not an unfavorable prognosis of mortality compared with patients with a normal SPECT result (**Tables 4 and 5**).

As a prognostic model, SPECT was inferior to coronary CTA in predicting MACE (Harrell's C-statistic, −0.17; 95% CI: −0.28 to 0.06; $p < 0.01$), and the same trend was observed when comparing

FIGURE 3 **Time-to-Event Analysis**



Number of risk factors by **(A)** major adverse cardiac events (MACE) and **(B)** mortality. The **green and pink lines** represent patients with <3 versus ≥3 risk factors, respectively. Coronary artery calcium score group by **(C)** major adverse cardiac events and **(D)** mortality. The **green, yellow, and pink lines** represent patients with coronary artery calcium scores of 0, 1 to 399 versus ≥400. Number of risk factors combined with coronary artery calcium scores by **(E)** major adverse cardiac events and **(F)** mortality. The **green solid and dashed lines** represent patients with <3 risk factors and coronary artery calcium scores <400 versus ≥400, respectively. The **pink solid and dashed lines** represent patients with ≥3 risk factors and coronary artery calcium scores <400 versus ≥400, respectively.

prediction of mortality (Harrell's C-statistic, −0.10; 95% CI: −0.21 to 0.02; p = 0.10).

INVASIVE CORONARY ANGIOGRAPHY. Patients without (n = 115) versus with (n = 33) obstructive coronary stenosis at ICA had an event rate of MACE of 3.5% (95% CI: 2.1% to 5.8%) versus 10.6% (95% CI: 6.0 to 18.7%) and a mortality rate of 4.6% (95% CI: 2.9% to 7.1%) versus 7.0% (95% CI: 3.7% to 13.5%). In a time-to-event analysis, obstructive coronary

TABLE 5 Adjusted Cox Regression Analysis

	MACE		Mortality	
	HR (95% CI)	p Value	HR (95% CI)	p Value
Coronary artery calcium score model				
Number of risk factors ≥3	0.9 (0.4–2.2)	0.86	2.3 (0.9–6.0)	0.09
Transplant during follow-up	0.4 (0.1–0.9)	<0.05	0.4 (0.2–0.9)	<0.05
Coronary artery calcium score				
>0 and ≤400	1.6 (0.4–6.5)	0.48	0.9 (0.3–2.8)	0.87
>400	4.6 (1.2–16.7)	<0.05	1.8 (0.6–5.3)	0.27
Coronary computed tomography angiography model				
Number of risk factors ≥3	1.0 (0.4–2.5)	0.98	2.4 (0.9–6.7)	0.08
Transplant during follow-up	0.4 (0.1–1.0)	0.06	0.3 (0.1–0.7)	<0.01
Coronary CTA abnormal	4.6 (1.5–14.0)	<0.01	1.5 (0.6–3.3)	0.38
Single-photon emission computed tomography model				
Number of risk factors ≥3	1.2 (0.5–2.9)	0.66	2.7 (1.0–7.2)	<0.05
Transplant during follow-up	0.3 (0.1–0.8)	<0.05	0.2 (0.1–0.6)	<0.01
SPECT abnormal	1.4 (0.6–3.3)	0.41	0.8 (0.4–1.9)	0.67
Invasive coronary angiography model				
Number of risk factors ≥3	1.0 (0.4–2.2)	0.95	2.9 (1.1–7.9)	<0.05
Transplant during follow-up	0.3 (0.1–0.7)	<0.01	0.3 (0.1–0.8)	<0.01
ICA abnormal	2.7 (1.2–6.1)	<0.05	1.1 (0.5–2.4)	0.90
Diagnostic imaging model				
Coronary CTA abnormal	4.4 (1.4–14.0)	<0.05	3.0 (1.2–7.7)	<0.05
SPECT abnormal	0.8 (0.3–2.1)	0.64	0.9 (0.4–2.2)	0.80
ICA abnormal	1.7 (0.7–4.5)	0.26	0.9 (0.4–2.4)	0.90

Variables entered in the model are presented in the table for each model.
CTA = computed tomography angiography; ICA = invasive coronary angiography; SPECT = single-photon emission computed tomography; other abbreviations as in Table 4.

stenosis at ICA was associated with MACE, but not with mortality (Figures 4E and 4F). These results were unchanged in high-risk patients (Online Figures 1E and 1F). After adjusting for risk factors with a cutoff of 3 and transplantation during follow-up, obstructive coronary stenosis at ICA remained associated with MACE (Tables 4 and 5). As a prognostic model of MACE, ICA was similar to coronary CTA (Harrell's C-statistic, −0.06; 95% CI: −0.17 to 0.04; p = 0.23) and superior to SPECT (Harrell's C-statistic, 0.11; 95% CI: 0.01 to 0.22; p < 0.05). In predicting mortality, no differences between ICA and coronary CTA (Harrell's C-statistic, 0.09; 95% CI: −0.01 to 0.19; p = 0.08) or SPECT (Harrell's C-statistic −0.02, 95% CI: −0.12 to 0.07; p = 0.65) were observed.

Finally, when including coronary CTA, SPECT, and ICA in a multiple time-to-event Cox regression analysis, only coronary CTA was associated with MACE and mortality (Table 5).

Time-to-event analyses of combined MACE and all-cause mortality endpoints are illustrated for all tests in Online Figures 2A to 2F.

DISCUSSION

In this prospective study of kidney transplant candidates, we demonstrate that CACS is a better prognostic marker of MACE than traditionally used risk factors. Combining risk factors and CACS in a prognostic model seems to improve risk prediction compared with using both risk factors or CACS alone. This approach allowed for identification of 31% of the cohort as very-low-risk patients (<3 risk factors and CACS <400 with an event rate of MACE at 2.1% and mortality 1.0% per year) and the rest of the patients as high-risk patients (event rate of MACE at 6.2% and mortality 7.4% per year).

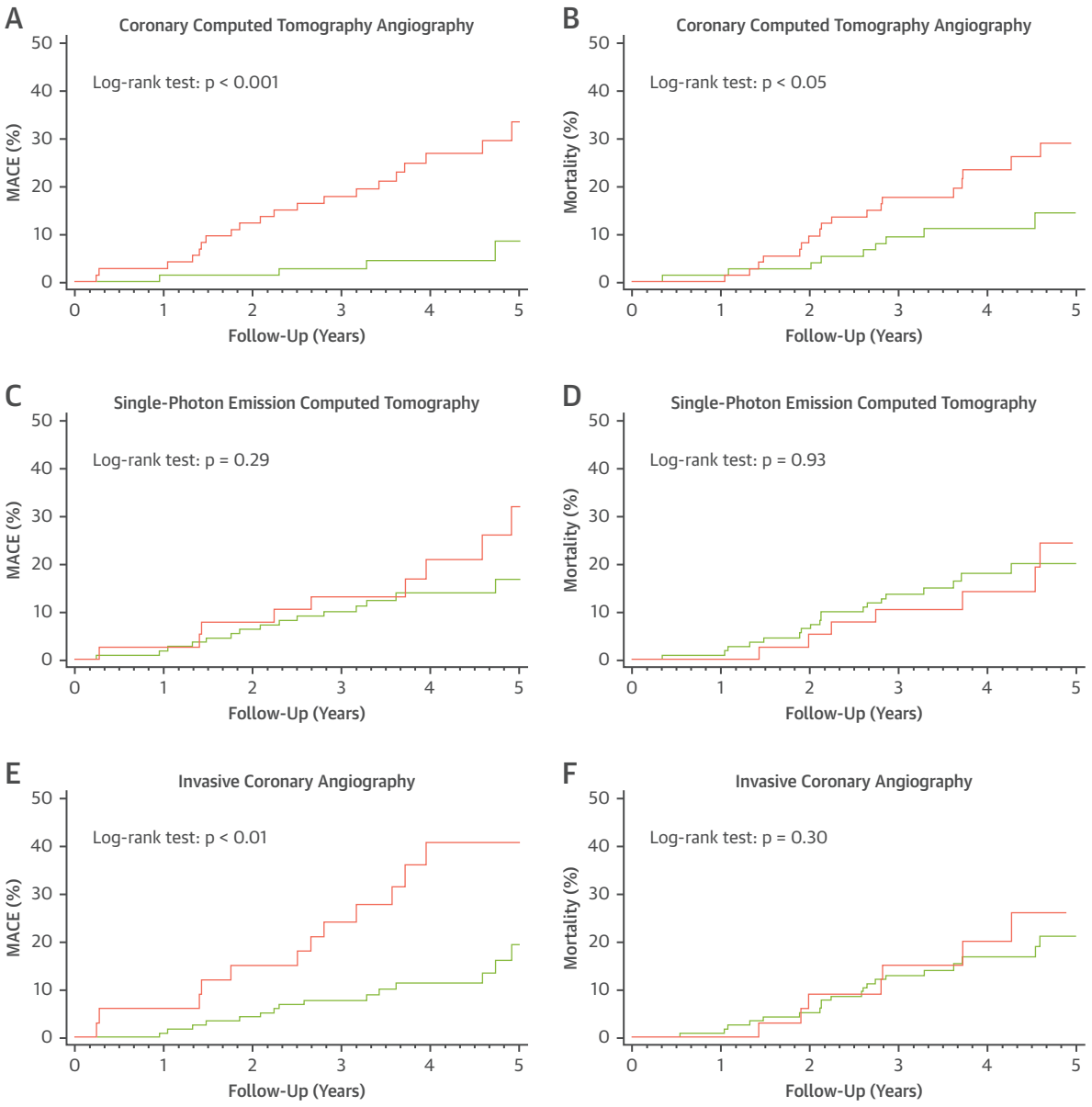
Among the diagnostic modalities, coronary CTA, SPECT, and ICA, only coronary CTA significantly predicted both MACE and mortality. Additionally, coronary CTA identified approximately 50% of the patients as low-risk patients (event rate of MACE 1.4% and mortality 3.1% per year) and 50% of the patients as high-risk patients (event rate of MACE 7.6% and mortality 7.1% per year). Interestingly, SPECT, which is currently recommended in guidelines, had no significant prognostic power regarding either MACE or mortality.

CARDIOVASCULAR RISK FACTORS. To date, no study has investigated the predictive value of cardiovascular risk factors as proposed in the ACC/AHA guidelines (1). In the present study, neither a single risk factor nor the presence of ≥3 risk factors predicted MACE, but the presence of ≥3 risk factors was associated with an unadjusted HR of 3.0 of mortality. Retrospective studies have demonstrated an HR for single risk factors of approximately 1.2 to 2.5 for MACE (5). The lack of power of risk factors to predict MACE may reflect the low correlation with coronary disease severity (6).

CORONARY ARTERY CALCIUM SCORE. The CACS significantly improves long-term risk stratification of MACE and mortality compared with risk factors in asymptomatic patients in the general population (7,8). The prognostic value of CACS has also been demonstrated in smaller studies of patients with advanced CKD (2).

Only 2 studies have investigated the predictive value of CACS on cardiac events in asymptomatic kidney transplant candidates. One study followed patients treated with hemodialysis for a median period of 31 months. At baseline, 14% had a CACS of 0, and the median was 176 (IQR: 11 to 626). The event rate was 24% (23 cardiac events in 97 patients). The investigators showed significantly different event rates for CACS with a threshold of 400 (9). A larger study by Moody et al. (10) evaluated 194 candidates. CACS and technetium-99m SPECT imaging were performed at baseline, and patients were followed for a median duration of 18 months, with a total of 15

FIGURE 4 **Time-to-Event Analysis**



Coronary computed tomography angiography results by **(A)** major adverse cardiac events and **(B)** mortality. Single-photon emission computed tomography results by **(C)** major adverse cardiac events and **(D)** mortality. Invasive coronary angiography results by **(E)** major adverse cardiac events and **(F)** mortality. The **green and pink lines** represent patients with a normal versus an abnormal result, respectively. Hazard ratios are listed in Table 4.

primary events (8 deaths and 7 myocardial infarctions). In contrast to our study, this study cohort was multiethnic, and 25% had chest pain suggestive of CAD. The CACS distribution in that study was similar to that reported in the present study. With a CACS threshold of 100, Moody et al. (10) found an annual event rate of 12.8% compared with 7.6% in patients with low CACS (HR: 3.6). However, a CACS >100 did not increase the prognostic value of risk stratification with risk factors such as age, sex, and diabetes. In addition, risk stratification with CACS was inferior to clinical risk factors combined with SPECT. The lower CACS threshold and the larger proportion of patients with clinical symptoms may explain the discrepancy with our study. We demonstrated an increased prognostic value of MACE by

CACS ≥400 compared with both CACS of 0, CACS of 1 to 399, and risk factors and SPECT. Interestingly, we found no difference in MACE or mortality for patients with CACS of 0 versus CACS of 1 to 399, a finding indicating that only high CACS values change the prognosis in CKD patient substantially.

COMBINED RISK FACTORS AND CORONARY ARTERY CALCIUM SCORE. In patients traditionally classified as being at low risk because they have <3 risk factors, 20% (12 of 60 patients) had a CACS ≥400, thus causing an unadjusted HR of 5.8 for MACE and 8.9 for mortality. In addition, coronary stenosis noted on ICA at baseline was seen in only 2% of patients with <3 risk factors and CACS <400, compared with 42% of patients with <3 risk factors and CACS ≥400 (6). This finding indicates that a true low-risk kidney transplant candidate is identifiable by combining risk factors and CACS and that in such patients, further pre-transplant evaluation may safely be terminated.

This study demonstrates that CACS predicts all-cause mortality in transplant candidates. The reason for the increased predictive power of CACS compared with ICA may be that CACS correlates better with arteriosclerotic risk factors, inflammation, and duration and severity of CKD, which are also risk factors for mortality. Furthermore, nonstenotic coronary plaques detected by CACS may cause plaque rupture.

CORONARY COMPUTED TOMOGRAPHY ANGIOGRAPHY. Coronary CTA has a prognostic value in predicting MACE and mortality beyond the prognostic value of risk factors and CACS in asymptomatic patients with and without diabetes (11). In patients with advanced CKD, the prognostic value was investigated in a previous study. De Bie et al. (12) studied 70 dialysis-treated patients with a mean age of 66 ± 8 years and with a median CACS of 623 (IQR: 79 to 1,619). During a 2-year follow-up period, the incidence of myocardial infarction and revascularization was 36% in patients with stenosis noted on coronary CTA (n = 30) compared with 0% in patients without stenosis (n = 40). Our study cohort included both patients who did not require dialysis (56%) and patients who did require dialysis (44%) who were younger and had a lower CACS than did patients in the study by de Bie et al. (12). At the 2-year follow-up, only 1 of our 74 patients (1.4%) without stenosis at coronary CTA had a STEMI, and 2 patients (2.7%) had died of infection and bleeding, respectively. Our results confirm that the 2-year prognosis in patients with advanced CKD without stenosis at coronary CTA, who represented 50% of our cohort, is excellent. Our study also demonstrates that these results are sustained consistently during long-term follow-up and that they are also representative for patients selected for kidney transplant work-up.

SINGLE-PHOTON EMISSION COMPUTED TOMOGRAPHY. A previous review demonstrated that kidney transplantation candidates with reversible ischemia on SPECT or dobutamine stress echocardiography have an approximately 6-fold increased risk of myocardial infarction and a 4-fold increased risk of cardiac death. Even so, the presence of scar or fixed defects predicted only cardiac death (relative risk: 4.7), and not myocardial infarction (13). However, a recent review by Wang et al. (14) found no evidence that reversible defects compared with both fixed and reversible abnormalities in SPECT were better predictors of MACE.

We failed to demonstrate a prognostic impact of SPECT in our cohort according to our definition of abnormal SPECT and MACE. Nonetheless, a small subgroup of patients with reversible ischemia, defined by a sum difference score ≥4 (n = 10; 7%), had a 4.2 HR of MACE. Our predefined definition of an abnormal SPECT also included other abnormalities in an attempt to increase the low sensitivity of SPECT to diagnose coronary stenosis previously published, but we did not succeed in doing so (3,4).

INVASIVE CORONARY ANGIOGRAPHY. Our results demonstrate that obstructive coronary stenosis on ICA is a valid predictor of MACE, but not of mortality. This finding may clarify the variable results previously reported for the prognostic value of ICA in patients undergoing transplant evaluation, results that may reflect different study endpoints (1). In contrast to our results, a recently published meta-analysis demonstrated that ICA did predict all-cause mortality (14). Referral bias may have affected these results; for example, many studies included patients who had an abnormal noninvasive cardiac stress test result before undergoing ICA.

CLINICAL IMPLICATIONS. This study raises 2 clinically important points. First, the combination of risk factors and CACS may identify a group of patients (31% of this cohort) with an excellent prognosis who may not need further cardiac evaluation. In the present study, we used a threshold for risk factors of <3 combined with a CACS threshold of <400. However, a more conservative CACS threshold (e.g., 0 or 100) may also be appropriate because 12 of 31 (39%) patients with a CACS of 100 to 399 had significant coronary stenosis at ICA (6). Second, coronary CTA is a strong predictor of MACE and mortality and is superior to SPECT.

STUDY LIMITATIONS. This study is limited by the ethnically uniform study population. According to clinical practice, all patients were pre-screened for severe comorbidity by a nephrologist, and echocardiography was performed before patients were referred for coronary artery evaluation. In this study, we used SPECT as a noninvasive myocardial perfusion imaging modality. However, other modalities, such as stress echocardiography and positron emission tomography, which potentially have a better diagnostic accuracy, may also have a higher prognostic value than SPECT.

Finally, in patients with advanced CKD, the use of iodinated contrast media for CTA and ICA is a concern because of the risk of post-contrast acute kidney injury. This was a pre-defined safety endpoint in the subgroup of pre-dialysis patients in our study; and we have previously published these results showing a low rate of transient post-contrast acute kidney injury after CTA (13%) and ICA (3%) (15). However, post-contrast acute kidney injury did not increase the risk of accelerated CKD progression or the time to initiation of dialysis or death. These results are in line with those reported by Kumar et al. (16).

CONCLUSIONS

Compared with traditional risk factors and other cardiac imaging modalities, CACS and coronary CTA seem superior for risk stratification in kidney transplant candidates. The use of a combination of risk factors and CACS and subsequent coronary CTA seems to be the most appropriate strategy for cardiac evaluation of renal transplant candidates.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Screening for CAD in asymptomatic kidney transplant candidates by using clinical risk factors and noninvasive stress imaging is recommended in guidelines, with a level of evidence C. Previously, we demonstrated a high sensitivity and negative predictive value of the CACS and of coronary CTA. In this cohort, we report superior risk stratification.

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Pre-transplant work-up evaluating both the coronary artery and the aortic/pelvic vessel is possible, accurate, and safe using a CTA protocol with only 1 contrast dose.

TRANSLATIONAL OUTLOOK: Future large randomized studies are needed to compare diagnostic strategies and document the improved patient outcome by screening for CAD in asymptomatic kidney transplant candidates.

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KEY WORDS coronary angiography, coronary artery calcium score, coronary computed tomography angiography, renal transplantation, single-photon emission computed tomography

APPENDIX For supplemental figures, please see the online version of this paper.