



Diagnostic Performance of Coronary CT Angiography and Myocardial Perfusion Imaging in Kidney Transplantation Candidates

Simon Winther, MD,* My Svensson, MD, PhD,† Hanne Skou Jørgensen, MD,† Kirsten Bouchelouche, MD, DMSc,‡ Lars Christian Gormsen, MD, PhD,‡ Birgitte Bang Pedersen, MD, PhD,§ Niels Ramsing Holm, MD,* Hans Erik Bøtker, MD, DMSc,* Per Ivarsen, MD, PhD,† Morten Bøttcher, MD, PhD||

ABSTRACT

OBJECTIVES The goal of this study was to compare the diagnostic accuracy of the coronary artery calcium score (CACS), coronary computed tomography angiography (CTA), single-photon emission computed tomography (SPECT), and a combination of these tools in the diagnosis of obstructive coronary artery disease (CAD) in patients with chronic kidney disease referred for cardiac evaluation before kidney transplantation.

BACKGROUND The optimal method for the detection of obstructive CAD in potential kidney transplant patients has not yet been identified. Previous studies have found that established noninvasive stress tests have low diagnostic accuracy, while the diagnostic performance of coronary CTA remains unknown.

METHODS We prospectively studied 138 patients referred for pre-transplant cardiac evaluation (mean age 54 years; age range 22 to 72 years; 68% male; 43% treated with dialysis). All patients underwent CACS, coronary CTA, SPECT, and invasive coronary angiography. The results of the noninvasive tests were merged into integrated hybrid imaging results: Hybrid (CACS/SPECT) and Hybrid (coronary CTA/SPECT).

RESULTS The overall prevalence of obstructive CAD ($\geq 50\%$ reduction in luminal diameter) according to quantitative invasive coronary angiography was 22%. Two-thirds of the patients with obstructive CAD had a stenosis located in a proximal coronary segment. In a patient-level model, the sensitivity and specificity, respectively, for diagnosing obstructive CAD were as follows: CACS (threshold of 400), 67% and 77%; coronary CTA, 93% and 63%; SPECT, 53% and 82%; Hybrid (CACS/SPECT), 33% and 97%; and Hybrid (coronary CTA/SPECT), 67% and 86%. The sensitivity for diagnosing obstructive CAD in a proximal segment was 70% for CACS (threshold 400), 100% for coronary CTA, 60% for SPECT, 40% for Hybrid (CACS/SPECT), and 75% for Hybrid (coronary CTA/SPECT).

CONCLUSIONS Coronary CTA is a reliable test with high sensitivity and a high negative predictive value for diagnosing obstructive CAD before kidney transplantation. A noninvasive approach with use of either coronary CTA or a combination of coronary CTA and SPECT to rule out obstructive CAD seems recommendable in kidney transplant candidates. (ACToR-Study: Angiographic CT of Renal Transplantation Candidate-Study; [NCT01344434](https://clinicaltrials.gov/ct2/show/study/NCT01344434)) (J Am Coll Cardiol Img 2015;8:553-62) © 2015 by the American College of Cardiology Foundation.

From the *Department of Cardiology, Aarhus University Hospital, Aarhus, Denmark; †Department of Nephrology, Aarhus University Hospital, Aarhus, Denmark; ‡Department of Nuclear Medicine and PET Center, Aarhus University Hospital, Aarhus, Denmark; §Department of Nephrology, Aalborg University Hospital, Aalborg, Denmark; and the ||Department of Internal Medicine, Hospital Unit West, Herning, Denmark. This study was supported by the Karen Elise Jensen Foundation, the Bjørnøw's Foundation, the Danish Society of Nephrology Research Foundation, and the Health Research Fund of Central Denmark Region. Dr. Holm has received research grants from Terumo, St. Jude Medical, Boston Scientific, Medtronic, Tryton Medical, Alvimedica, and Biotronik; and speaker fees from Terumo, St. Jude Medical, and Biotronik. Dr. Bøtker has been a shareholder in CellAegis Devices Inc. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received September 15, 2014; revised manuscript received November 26, 2014, accepted December 4, 2014.

**ABBREVIATIONS
AND ACRONYMS****CACS** = coronary artery calcium score**CAD** = coronary artery disease**CI** = confidence interval**CKD** = chronic kidney disease**CKD-5** = stage 5 chronic kidney disease**CTA** = computed tomography angiography**ICA** = invasive coronary angiography**NLR** = negative likelihood ratio**NPV** = negative predictive value**PLR** = positive likelihood ratio**PPV** = positive predictive value**SPECT** = single-photon emission computed tomography

Patients with chronic kidney disease (CKD) have a high risk of cardiovascular events. In addition, symptoms of coronary artery disease (CAD) may be atypical due to neuropathy, overhydration, or low functional capacity. After kidney transplantation, cardiovascular risk is reduced but remains the most significant cause of morbidity and mortality (1,2). No prospective study has yet demonstrated the benefit of cardiac risk stratification before kidney transplantation. Optimizing medical treatment, pre-operative coronary revascularization, and individualized perioperative management might reduce the event rate after transplantation. Consequently, most institutions evaluate pre-operative cardiac state in accordance with the American Heart Association and the American College of Cardiology Foundation scientific statement (“Cardiac Disease Evaluation and Management Among

Kidney and Liver Transplantation Candidates-2012”) (2). This 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 CAD risk factors regardless of functional status” (2).

SEE PAGE 563

However, the diagnostic accuracy of noninvasive cardiac stress testing, such as single-photon emission computed tomography (SPECT), varies in patients with severe CKD (i.e., stage 5 [CKD-5]). A recent Cochrane review concluded that the pooled sensitivity of SPECT was 0.67 (95% confidence interval [CI]: 0.48 to 0.82), with a specificity of 0.77 (95% CI: 0.61 to 0.88), in kidney transplant candidates (3). Because the diagnostic accuracy of noninvasive stress testing is low, invasive coronary angiography (ICA) remains the gold standard for diagnosing obstructive CAD in kidney transplant candidates. ICA continues to be the preferred diagnostic tool in many institutions (4) despite the fact that the risk of complications is increased in patients with CKD.

The coronary artery calcium score (CACS), as assessed by using nonenhanced computed tomography, provides an absolute measure of coronary calcification, adds prognostic information, and correlates moderately with obstructive CAD (5,6). Coronary computed tomography angiography (CTA) is established as a noninvasive diagnostic test for stenosis in patients without CKD. Coronary CTA has been shown in several multicenter studies to have a high sensitivity (5,7). However, its specificity is not

optimal due to false-positive results in patients with extensive coronary calcifications or high/irregular heart rates. These factors could be prevalent in kidney transplant candidates and affect the applicability of coronary CTA in this patient group. To our knowledge, no prospective studies have investigated the diagnostic accuracy of coronary CTA in patients with advanced CKD.

The combination of an anatomic test of stenosis (e.g., CACS or coronary CTA) and a functional stress evaluation of myocardial ischemia (e.g., SPECT) is known as cardiac hybrid imaging. This imaging has demonstrated improved sensitivity and specificity in patients with a high risk of CAD (8). It is unknown whether this would also apply in patients with CKD.

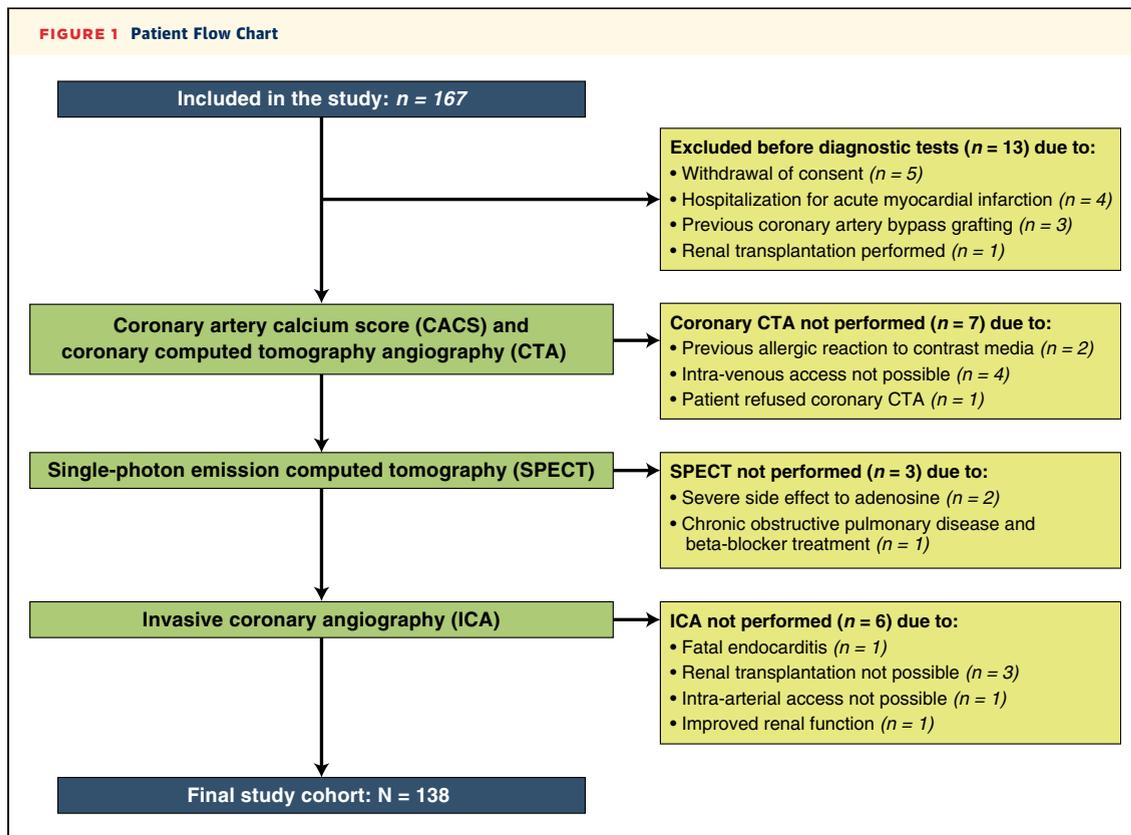
The aim of the present study was to compare the accuracy of diagnosing obstructive CAD by using CACS, coronary CTA, SPECT, and a combination of these techniques (with ICA as the reference) in a large cohort of kidney transplantation candidates.

METHODS

STUDY DESIGN. We conducted a prospective, observational, single-arm study enrolling patients with CKD referred for cardiac evaluation before kidney transplantation. Patients were recruited consecutively from 9 hospitals in the western part of Denmark from February 2011 to February 2014. Inclusion criteria were CKD and presence of at least 1 of the following characteristics: age >40 years, diabetes, dialysis treatment for >5 years, registered on kidney transplant waiting list for >3 years without cardiac screening, symptoms of cardiovascular disease, and the ability to provide informed written consent. Exclusion criteria were age <18 years and unstable angina pectoris. Written informed consent was obtained from all patients. The study was approved by the Danish Data Protection Agency and the Central Denmark Region Committees on Health Research Ethics, and it followed the principles in the Declaration of Helsinki.

All patients were scheduled for the following: 1) CACS and coronary CTA; 2) stress SPECT; and 3) ICA. When clinically required, a rest SPECT was performed (Figure 1). All diagnostic tests were performed at Aarhus University Hospital, Aarhus, Denmark. After study completion, patients were followed up for 30 days to register any complications, including acute kidney failure.

To prevent contrast-induced nephropathy, patients received oral acetylcysteine (600 mg) the day before and on the day of both the coronary CTA and the



ICA. In addition, the procedures with contrast media exposure were performed at least 4 weeks apart in all patients with CKD-5 and in those with CKD-5 undergoing dialysis who had preserved urine production.

Analysis of the diagnostic test results was performed on a patient-level basis. Proximal coronary segments were defined as left main coronary artery, proximal and middle segment of the left anterior descending artery, and proximal segment of the left circumflex artery and right coronary artery until the crux. Analyses of the diagnostic test results were performed by 2 experienced cardiologists or 2 nuclear medicine physicians. In case of disagreement between the 2 readers, a consensus decision was obtained. All readers were blinded to the results of the other diagnostic tests.

CACS AND CORONARY CTA 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 access the Agatston CACS. Pre-specified CACS thresholds of 0 and 400 were used to analyze accuracy. Contrast-enhanced coronary CTA was acquired with prospective electrocardiogram gating. A spiral acquisition protocol (0% to 100% of the heart cycle)

was applied in all patients, with dose modulation in the systolic or diastolic phase depending on heart rate. Tube settings were dependent on patient weight, and current modulation was applied. Coronary images were reconstructed for every 5% of the cardiac cycle by using raw data iterative reconstruction. In relation to the cardiac scan, a high-pitch, low-dose flash scan was performed for evaluation of the aorta and iliac arteries using the same contrast injection. The contrast medium used was ioversol (350 mg/ml), and all patients received glyceryl nitrate (0.8 mg) sublingually before the CTA. In addition, intravenous metoprolol was administered to obtain a heart rate of <65 beats/min to optimize coronary CTA images.

All coronary segments were visually analyzed according to standard clinical practice with the use of commercially available software (syngo.via, Siemens Healthcare) (5,6). The coronary CTA readers were permitted to use all the available post-processing image reconstruction algorithms, including axial images, multiplanar and curved reformation, maximal intensity projection, volume-rendered technique, and cross-sectional area analysis. A semi-quantitative scale was used to grade the extent of luminal diameter stenosis. The stenosis severity was obtained in

FIGURE 2 Hybrid Imaging

		SPECT	
		Normal	Abnormal
CACS	< 400	Hybrid (CACS/SPECT): Normal	Hybrid (CACS/SPECT): Normal
	≥ 400	Hybrid (CACS/SPECT): Normal	Hybrid (CACS/SPECT): Abnormal

		SPECT	
		Normal	Abnormal
Coronary CTA	Normal	Hybrid (coronary CTA/SPECT): Normal	Hybrid (coronary CTA/SPECT): Normal
	Abnormal	1-CVD or 2-CVD Hybrid (coronary CTA/SPECT): Normal	Hybrid (coronary CTA/SPECT): Abnormal
		3-CVD or LM Hybrid (coronary CTA/SPECT): Abnormal	

Combinations of **(A)** CACS, coronary CTA, and SPECT and the related Hybrid (CACS/SPECT) and **(B)** Hybrid (coronary CTA/SPECT). CVD = coronary vessel disease; other abbreviations as in [Figure 1](#).

the following manner: no stenosis: 0% diameter reduction (~0% area reduction); mild stenosis: 1% to 29% diameter reduction (~1% to 50% area reduction); moderate stenosis: 30% to 49% diameter reduction (~50% to 69% area reduction); and severe stenosis: 50% to 100% diameter reduction (~70% to 100% area reduction). Obstructive CAD was defined as a segment with a diameter >2 mm and a minimum 50% reduction in luminal diameter (~70% area reduction). Nonevaluable segments with a diameter >2 mm were defined as having obstructive CAD. Coronary CTA scan results were defined as abnormal if obstructive CAD was not ruled out in all coronary segments. No patients or segments were excluded from the analysis.

SPECT ACQUISITION AND INTERPRETATION. Gated SPECT was acquired by using a dedicated gamma camera (CardioMD, Philips Healthcare, Best, the Netherlands). Studies were performed by using a 1-day stress study protocol. If needed for image interpretation, a rest study was performed on a separate day. Myocardial stress was induced by adenosine (140 µg/kg) during low-level bicycle ergometer exercise or, in patients with chronic obstructive pulmonary disease, according to bicycle ergometer alone or by

using dobutamine. ^{99m}Tc-sestamibi was used in both stress (500 MBq) and rest (700 MBq) studies. All images were automatically analyzed without attenuation correction by using commercially available software (QGS/QPS, Cedars-Sinai, Los Angeles, California). Subsequent images were visually corrected and interpreted.

SPECT images were assessed by using a 17-segment model. All segments were scored for perfusion defects by using a 5-point scoring system (0: normal; 4: absence of tracer uptake). An abnormal SPECT due to 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.

HYBRID IMAGING INTERPRETATION. According to the pre-defined protocol, CACS, coronary CTA, and SPECT results were interpreted separately as normal or abnormal. Subsequently, the results were combined to give an integrated hybrid imaging result.

The Hybrid (CACS/SPECT) was categorized as normal when CACS was <400 or CACS was >400 and SPECT was normal. Hybrid (CACS/SPECT) was categorized as abnormal when CACS was >400 and SPECT was abnormal ([Figure 2A](#)). The Hybrid (coronary CTA/SPECT) result was categorized as normal when both coronary CTA and SPECT results were normal, coronary CTA was normal, and the SPECT was abnormal or coronary CTA was abnormal with 1-vessel or 2-vessel disease and the SPECT was normal. The Hybrid (coronary CTA/SPECT) result was categorized as abnormal when coronary CTA was abnormal with 3-vessel disease and the SPECT was normal or both coronary CTA and SPECT results were abnormal ([Figure 2B](#)).

ICA ACQUISITION AND INTERPRETATION. ICA was performed by using the contrast medium iodixanol (350 mg/ml) and standard techniques including intra-coronary glyceryl nitrate (200 µg). When a coronary stenosis was visually estimated to be greater than a 30% luminal diameter stenosis in a coronary segment with a luminal diameter >2 mm, a quantitative coronary angiography analysis was performed. Dedicated quantitative coronary angiography 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 a minimal overlapping of vessels. Obstructive CAD was defined as a minimum 50% reduction in luminal

diameter (~70% area reduction) according to quantitative coronary angiography.

SAMPLE SIZE CALCULATION. Derived from historical data, a coronary stenosis prevalence of 30%, a sensitivity of 0.88, and a specificity of 0.75 for both coronary CTA and SPECT were assumed. On the basis of these assumptions, a final study cohort of 135 patients was required for a minimum of 10% absolute precision on either side (one-half the width of the 95% CI) of the expected sensitivity and specificity. With an expected dropout rate of 10%, a minimum of 150 patients was needed to achieve sufficient power of the study.

STATISTICAL ANALYSIS. Continuous variables were expressed as mean or median ± SD, total or interquartile range, or percentiles. Categorical variables were reported as frequencies (percentages). Sensitivity, specificity, positive and negative predictive values (PPV and NPV, respectively), and positive and negative likelihood ratios (PLR and NLR) were calculated for the noninvasive diagnostic tests, with quantitative ICA as reference. McNemar's test was used to compare sensitivity and specificity. The kappa coefficient was calculated to measure the degree of nonrandom agreement between readers' diagnostic conclusions. For all statistical analysis, a 2-tailed p value <0.05 was considered statistically significant, and 95% CIs were reported when appropriate. Statistical analysis was performed using Stata version 13 (Stata Corp., College Station, Texas).

RESULTS

A total of 167 patients were studied. Twenty-nine patients were excluded because they did not complete the coronary CTA, SPECT, or ICA, leaving a final cohort of 138 patients (Figure 1). Baseline characteristics are summarized in Table 1. Only 4 patients had typical symptoms of exercise-induced angina pectoris. The median intertest interval from first noninvasive test to the ICA was 34 days (10th and 90th percentiles: 24 and 48 days).

INVASIVE CORONARY ANGIOGRAPHY. Thirty patients (22%) had obstructive CAD on quantitative coronary angiography. One-vessel disease was present in 22 (16%) patients, 2-vessel disease in 5 (4%) patients, and 3-vessel or left main artery disease in 3 (2%) patients (Table 2). Twenty patients had stenosis in a proximal coronary segment.

CORONARY ARTERY CALCIUM SCORE. The median Agatston CACS was 137 (interquartile range: 0 to 570). The CACS was 0 in 35 (25%) patients and >400 in 45 (33%) patients (Table 2). The prevalence of obstructive CAD was 0% and 44% in patients with CACS of 0 and

TABLE 1 Patient Demographic Characteristics (N = 138)

White	128 (92.8)
Male	94 (68.1)
Age, yrs	54 (22-72)
Body mass index, kg/m ²	25.8 ± 4.3
Kidney diagnosis and status	
Etiology of kidney failure	
Diabetes	38 (27.5)
Hypertension or glomerulosclerosis	36 (26.1)
Glomerulonephritis or connective tissue disease	31 (22.5)
Polycystic kidney disease	17 (12.3)
Other diagnosis	16 (11.6)
Chronic kidney disease stage 5, nondialysis	79 (57.2)
Estimated glomerular filtration rate, ml/min/1.73 m ²	12.7 ± 5.9
Chronic kidney disease stage 5, dialysis	59 (42.8)
Peritoneal dialysis	18
Hemodialysis	41
Treatment with dialysis, months	36.9 (1-204)
Previous kidney transplantation	23 (16.7)
Cardiovascular risk factors and disease	
Diabetes	46 (33.3)
Hypertension	129 (93.5)
Dyslipidemia	69 (50.0)
Smoking, active	43 (31.2)
Established cardiovascular disease	19 (13.8)
Previous percutaneous coronary intervention	8 (5.8)

Values are n (%), mean (range), or mean ± SD. Hypertension was noted if the patient received antihypertensive medical treatment; dyslipidemia if the patient received statin treatment or total cholesterol was >6.2 mmol/l (240 mg/dl); established cardiovascular disease comprised previous myocardial infarction, stroke, transitory cerebral ischemia, peripheral artery disease, or verified intermittent claudication.

>400, respectively. With a CACS threshold of 400, the sensitivity, specificity, PPV, and NPV for the detection of obstructive CAD defined according to ICA were 67% (95% CI: 47% to 83%), 77% (95% CI: 68% to 84%), 44% (95% CI: 30% to 60%), and 89% (95% CI: 81% to 95%), respectively, in a patient-level model (Figures 3A and 4). The PLR and NLR were 2.9 (95% CI: 1.9 to 4.4) and 0.4 (95% CI: 0.3 to 0.7). The sensitivity for obstructive CAD in a proximal segment was 70% (95% CI: 46% to 88%).

CORONARY COMPUTED TOMOGRAPHY ANGIOGRAPHY.

The mean number of segments analysis at coronary CTA was per patient 11.5 ± 2.4. The mean number of segments <2 mm was 2.5 ± 1.4, and not anatomically present was 3.4 ± 1.3 segments. The mean number of nonanalyzable segments per patient due to reduced contrast was 0.1 ± 0.4, movement artifact was 0.3 ± 1.0, and other reason was 0.2 ± 0.9; a total of 25 patients were affected. During coronary CTA acquisition, the mean heart rate was 67 ± 11 beats/min.

Sixty-eight patients (49%) had an abnormal coronary CTA scan. Two patients were misclassified as normal according to coronary CTA despite obstructive CAD on ICA. Stenoses in these 2 patients were located

TABLE 2 Imaging Study Characteristics (N = 138)

Invasive coronary angiography	
Obstructive coronary artery disease	30 (21.7)
1-vessel disease	22 (15.9)
2-vessel disease	5 (3.6)
3-vessel or left main artery disease	3 (2.2)
CACS	137 (0-570)
0	35 (25.4)
>0 and ≤400	58 (42.0)
>400	45 (32.6)
Coronary CTA	
Abnormal test result	68 (49.3)
1-vessel disease	21 (15.2)
2-vessel disease	23 (16.7)
3-vessel disease or left main disease	24 (17.4)
SPECT	
Abnormal test result	36 (26.1)
Sum difference score ≥4*	8 (5.8)
Reduction of ejection fraction of >10% during stress*	1 (0.7)
Transient ischemic dilation ratio ≥1.22*	6 (4.3)
Irreversible defect and/or ejection fraction <45%*	27 (19.6)
Inconclusive images*	1 (0.7)
Hybrid (CACS/SPECT)	
Abnormal test result	13 (9.4)
Hybrid (coronary CTA/SPECT)	
Abnormal test result	35 (25.4)

Values are n (%), median (interquartile range), or mean ± SD. *More than 1 pathologic finding was present in 6 patients.
CACS = coronary artery calcium score; CTA = computed tomography angiography; SPECT = single-photon emission computed tomography.

in the distal right coronary artery and in the second diagonal branch (Figure 3B). The kappa value for the interobserver variability for coronary CTA was 0.71 (95% CI: 0.59 to 0.83).

The sensitivity, specificity, PPV, and NPV for diagnosing obstructive CAD were 93% (95% CI: 78% to 99%), 63% (95% CI: 53% to 72%), 41% (95% CI: 29 to 54), and 97% (95% CI: 90 to 100), respectively (Figure 4). The sensitivity of coronary CTA was higher ($p < 0.01$) and specificity was lower ($p < 0.001$) compared with CACS. The PLR and NLR were 2.5 (95% CI: 1.9 to 3.3) and 0.1 (95% CI: 0.0 to 0.4). The sensitivity for obstructive CAD in a proximal segment was 100% (95% CI: 83 to 100).

SINGLE-PHOTON EMISSION COMPUTED TOMOGRAPHY. Myocardial stress was induced by adenosine in 127 (92%) patients, dobutamine in 3 (2%), and bicycle ergometer testing in 8 (6%). A total of 36 (26%) patients had an abnormal SPECT (Table 2). The kappa value for interobserver variability according to SPECT was 0.72 (95% CI: 0.59 to 0.85).

The sensitivity, specificity, PPV, and NPV were 53% (95% CI: 34% to 72%), 82% (95% CI: 73% to 88%), 44% (95% CI: 28% to 62%), and 86% (95% CI: 78% to 92%), respectively. Comparing the diagnostic performance

of SPECT versus CACS revealed no significant differences. Compared with coronary CTA, the sensitivity was lower ($p < 0.01$) and specificity was higher ($p < 0.01$) (Figures 3C and 4). PLR and NLR for SPECT were 2.9 (95% CI: 1.7 to 4.8) and 0.6 (95% CI: 0.4 to 0.8). SPECT sensitivity for obstructive CAD in a proximal segment increased to 60% (95% CI: 36 to 81) compared with 53% (95% CI: 34 to 72) in the patient-level model. **HYBRID IMAGING.** With the Hybrid (CACS/SPECT) modality, only 13 (9.4%) patients were categorized as abnormal according to the CACS threshold of 400. The sensitivity, specificity, PPV, and NPV were 33% (95% CI: 17% to 53%), 97% (95% CI: 92% to 99%), 77% (95% CI: 46% to 95%), and 84% (95% CI: 76% to 90%), respectively (Figures 3D and 4). The PLR and NLR were 12.0 (95% CI: 3.5 to 40.8) and 0.7 (95% CI: 0.6 to 0.7). Sensitivity was significantly lower but specificity was significantly higher compared with CACS, coronary CTA, and SPECT. PPV was higher compared with any other modality. The sensitivity for obstructive CAD in a proximal segment was 40% (95% CI: 19% to 64%). If the CACS threshold for a hybrid imaging approach had been 0, the sensitivity was equal to SPECT ($p = 1.00$) alone, and the specificity increased from 82 for SPECT alone to 86% ($p = 0.06$).

The Hybrid (coronary CTA/SPECT) was categorized as normal in 70 patients because of a normal coronary CTA, and the Hybrid (coronary CTA/SPECT) was abnormal in 24 patients due to a coronary CTA displaying 3-vessel or left main disease. In the 44 patients with 1- or 2-vessel disease, the Hybrid (coronary CTA/SPECT) was categorized as normal in 33 patients because of a normal SPECT, and the Hybrid (coronary CTA/SPECT) was abnormal in 11 patients due to an abnormal SPECT. In total, 35 patients were classified as abnormal and 103 as normal on the basis of Hybrid (coronary CTA/SPECT) (Table 2, Figure 2).

The sensitivity, specificity, PPV, and NPV were 67% (95% CI: 47% to 83%), 86% (95% CI: 78% to 92%), 57% (95% CI: 39% to 74%), and 90% (95% CI: 83% to 95%), respectively, in a patient-level model (Figures 3E and 4). The PLR and NLR were 4.8 (95% CI: 2.8 to 8.2) and 0.4 (95% CI: 0.2 to 0.6).

Sensitivity was equal, but specificity was significantly higher with Hybrid (CACS/SPECT) compared with CACS. Compared with coronary CTA, the sensitivity was significantly lower, whereas specificity was significantly higher. Moreover, the sensitivity and specificity of Hybrid (coronary CTA/SPECT) were nonsignificantly higher than SPECT. PPV increased from 41% for coronary CTA and 44% for SPECT to 57% for the combined Hybrid (coronary CTA/SPECT).

For proximal segments, the sensitivity for Hybrid (coronary CTA/SPECT) was 75% (95% CI: 51% to 91%).

FIGURE 3 Cross-Tabulation of Noninvasive Test Results Versus the ICA

ICA		CACS	
		< 400	≥ 400
Normal		83 (60.1%)	25 (18.1%)
Abnormal		10 (7.2%)	20 (14.5%)

ICA		Coronary CTA	
		Normal	Abnormal
Normal		68 (49.3%)	40 (29.0%)
Abnormal		2 (1.4%)	28 (20.3%)

ICA		SPECT	
		Normal	Abnormal
Normal		88 (63.8%)	20 (14.5%)
Abnormal		14 (10.1%)	16 (11.6%)

ICA		Hybrid (CACS/SPECT)	
		Normal	Abnormal
Normal		105 (76.1%)	3 (2.2%)
Abnormal		20 (14.5%)	10 (7.2%)

ICA		Hybrid (Coronary CTA/SPECT)	
		Normal	Abnormal
Normal		93 (67.4%)	15 (10.9%)
Abnormal		10 (7.2%)	20 (14.5%)

Cross-tabulation of CACS (A), SPECT (B), coronary CTA (C), Hybrid (CACS/SPECT) (D), and Hybrid (coronary CTA/SPECT) (E) results versus the ICA. Values are n (%). N = 138. Abbreviations as in Figure 1.

FOLLOW-UP AND SAFETY. Acute renal failure. A total of 95 ml of contrast medium was used for the CTA of the coronary arteries, aorta, and iliac arteries. For ICA, the mean contrast dose of medium was 52 ± 22 ml. Seven (9%) of the 79 patients included were not on dialysis at inclusion but began dialysis treatment in the time interval between the coronary CTA and the ICA. In addition, 4 (6%) patients began dialysis treatment within 30 days after the ICA. In all cases, dialysis treatment was planned and was not considered to be due to contrast-induced nephropathy.

Complications. During the 30-day follow-up, 8 patients needed additional hospital observation for groin hematomas after the femoral access ICA. No major vascular or other complications were registered.

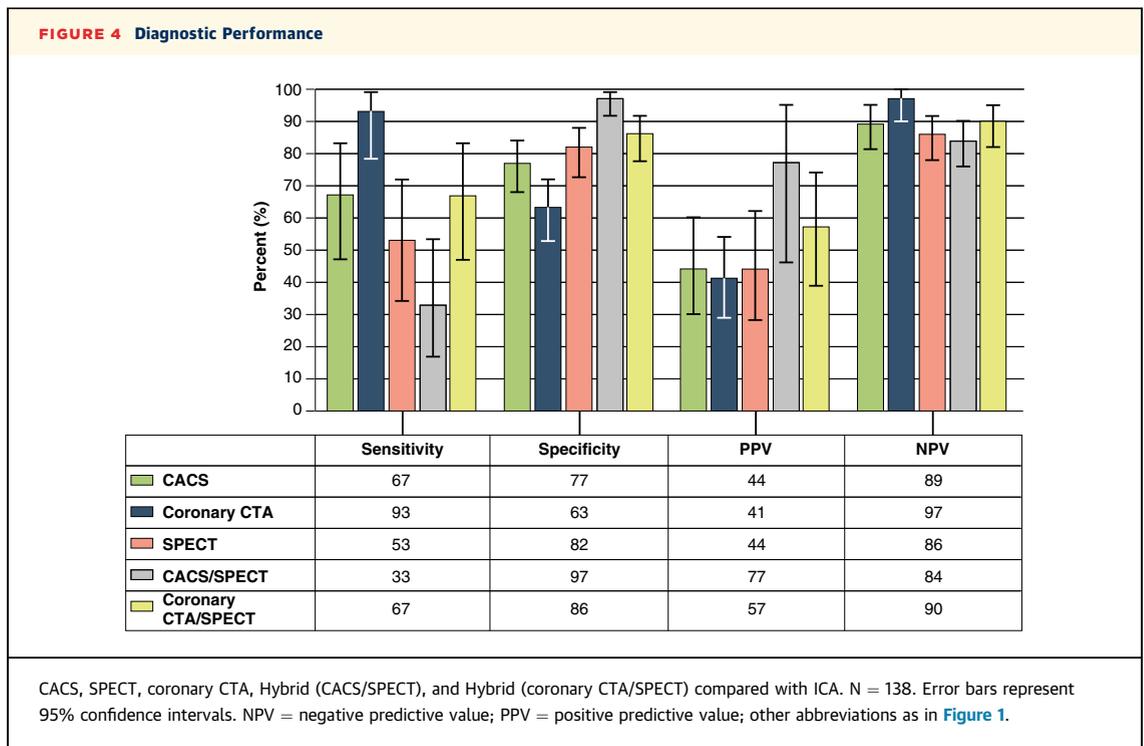
DISCUSSION

The main finding in this study was that coronary CTA had a significantly higher sensitivity and NPV for diagnosing obstructive CAD but a lower specificity

than CACS and SPECT. Hybrid imaging with coronary CTA and SPECT had a moderate sensitivity and a high specificity compared with SPECT or coronary CTA alone.

CACS AND CORONARY CTA. The pre-defined CACS threshold of 400 in this study had moderate diagnostic accuracy, equal to SPECT. This result is similar to that of Rosario et al. (9), who investigated the best CACS threshold for predicting obstructive CAD in 97 kidney transplantation candidates. The optimal CACS cutoff in this study was 187, yielding a sensitivity and specificity of 65% and 66%.

The applicability of coronary CTA before kidney transplantation was studied by Mao et al. (10). Of the 29 study patients with CKD-5 undergoing dialysis, 36% had normal coronary arteries with a CACS of zero. The authors excluded obstructive CAD in 70% of the cohort by using coronary CTA. The accuracy of coronary CTA was not compared with ICA in their study but was in 2 subsequent studies. Jug et al. (11) examined 31



patients with advanced CKD referred for coronary CTA and ICA as part of a pre-transplantation clinical evaluation or as part of the ACCURACY (Assessment by Coronary Computed Tomographic Angiography of Individuals Undergoing Invasive Coronary Angiography) trial (5). The median CACS was 519, and the prevalence of ICA-verified obstructive CAD was high (61%). Coronary CTA had a sensitivity and specificity of 100% and 91%, respectively. Park et al. (12) evaluated 87 patients with CKD-5 undergoing dialysis by using coronary CTA as part of the clinical evaluation or the evaluation before kidney transplantation. The median CACS was 138. ICA was performed in 29 (33%) patients, and 14 (48%) had obstructive CAD. Sensitivity and specificity were of the same order of magnitude as in the study by Jug et al. (11).

Our study is the first to prospectively compare the diagnostic performance of coronary CTA in a large cohort with advanced CKD without selection bias and partial verification bias. The high sensitivity of coronary CTA in our study is in line with the 2 previous studies of patients with advanced CKD and in studies in the general population. The reduced specificity compared with previous studies of patients with CKD is related to a high rate of false-positive coronary CTA results, most likely due to a high calcium burden in coronary vessels without obstructive CAD. This type of patient might have been more frequent in our cohort of predominantly asymptomatic CKD patients.

The high prognostic value of coronary CTA in the general population has been confirmed in patients with advanced CKD (13-15). De Bie et al. (14) showed that in patients with CKD-5 undergoing dialysis and obstructive CAD at coronary CTA, the incidence of cardiovascular events after 2 years of follow-up was 36% versus 0% in patients without stenosis.

SINGLE-PHOTON EMISSION COMPUTED TOMOGRAPHY. In a recent Cochrane review of kidney transplantation candidates, results from 7 small SPECT studies were merged and a reference threshold of $\geq 70\%$ luminal cross-sectional area stenosis by ICA was applied as a cutoff value for obstructive CAD (3). The pooled sensitivity was 0.67 (95% CI: 0.48 to 0.82) and the specificity was 0.77 (95% CI: 0.61 to 0.88), consistent with the diagnostic performance of SPECT in the present study.

The reduced diagnostic performance of SPECT in patients with advanced CKD compared with the general population may be due to an impaired response to myocardial stress agents (16,17). In addition, false-negative results may be obtained in patients with severe CAD and balanced ischemia. Finally, SPECT requires a substantial area of ischemia (10% of the myocardium) to be determined as positive, and it might not identify coronary stenosis in vessels supplying smaller territories. However, in our study, the sensitivity of SPECT was not substantially increased when only proximal stenosis was

considered. Nonetheless, SPECT may still provide additional prognostic information in kidney transplantation candidates (2).

HYBRID IMAGING. Although anatomic detection of atherosclerosis and functional detection of ischemia might provide better diagnostic accuracy and short- and long-term risk assessment (8,18), no previous study has quantified the diagnostic accuracy or prognostic value of a noninvasive hybrid imaging approach in patients with CKD.

Hybrid (CACS/SPECT) with a CACS threshold of 400 had reduced sensitivity compared with the other modalities. However, a high PPV was achieved in the 13 patients with an abnormal test result. There was a minimal benefit of a hybrid imaging approach, with a CACS threshold of 0 compared with SPECT alone.

Previous studies in the general population used different methods to merge coronary CTA and SPECT into a Hybrid (coronary CTA/SPECT) result. A consensus regarding the methods has not been achieved. Schaap et al. (8) conducted a hybrid imaging study in which coronary CTA and SPECT were separately categorized as normal, nonconclusive, or abnormal and subsequently merged into a hybrid result. Compared with ICA and fractional flow reserve, the diagnostic accuracy of hybrid imaging demonstrated sensitivity, specificity, PPV, and NPV as high as 96%, 95%, 96%, and 95%, respectively.

In the present study, a simple and clinically applicable method was used to merge coronary CTA and SPECT into a Hybrid (coronary CTA/SPECT) result. The rationale was that the Hybrid (coronary CTA/SPECT) was classified as normal regardless of the SPECT result when the coronary CTA results were normal because of the very high NPV of coronary CTA. In addition, it was classified as abnormal regardless of the SPECT result when the coronary CTA displayed 3-vessel or left main disease because of the risk of “balance ischemic” vessel disease, a situation in which the SPECT result is false negative due to the flow reserve of each of the coronary arteries being equally impaired. The Hybrid (coronary CTA/SPECT) reduced the sensitivity and increased the specificity compared with coronary CTA alone, and the PPV increased from 41% for coronary CTA to 57% for the Hybrid (coronary CTA/SPECT). Hybrid (coronary CTA/SPECT) outperformed SPECT on all diagnostic variables.

CLINICAL IMPLICATIONS. To date, only 1 randomized study has evaluated the benefit of coronary revascularization compared with medical treatment before kidney transplantation (19). The study included patients with diabetes and was terminated prematurely due to a high number of events in the nonrevascularized study arm. However, data justifying a benefit

of general cardiac evaluation before kidney transplantation are not available and might be difficult to achieve with the low sensitivity of the myocardial perfusion imaging techniques used in previous strategies. With a more exact diagnosis of CAD, it may be possible to optimize individualized medical treatment (e.g., statin, aspirin, beta-blockade therapy). In addition, careful perioperative management and coronary revascularization might also reduce morbidity and mortality.

We demonstrated that coronary CTA can be used with high sensitivity and NPV to diagnose coronary stenosis during cardiac evaluation of kidney transplantation candidates. However, the high number of false-positive results indicates that additional downstream testing is necessary in some patients. The low sensitivity of SPECT means that this method must be removed from the first-choice modality for diagnosing obstructive CAD in potential kidney transplant patients. Cardiac magnetic resonance imaging is not feasible due to the contraindication of gadolinium in patients with advanced CKD. The hybrid imaging approach with SPECT as a secondary stress test after coronary CTA may be used to reduce the need for ICA but at the cost of lower sensitivity.

Our study may provide an alternative to current guidelines that recommend stress testing as the initial approach to rule out coronary stenosis in kidney transplant candidates. Initial coronary CTA can identify these patients without further diagnostic testing and reduce the need for subsequent stress imaging testing or ICA.

STUDY LIMITATIONS. We used the clinical standard for addressing obstructive CAD on coronary CTA, 50% diameter stenosis visual assessment, and compared this with a 50% diameter stenosis assessment using quantitative analysis of ICA. A visual assessment of stenosis at coronary CTA was used, which may overestimate stenosis compared with quantitative assessment (20-22). We also compared a coronary anatomic test (coronary CTA) and a myocardial ischemia test (SPECT) with ICA as reference. ICA is a coronary anatomic test, and angiographically obstructive CAD may not always cause myocardial ischemia. This method may have limited the diagnostic accuracy of SPECT and hybrid imaging and favored coronary CTA.

CONCLUSIONS

Coronary CTA is a safe, feasible, and reliable test for ruling out obstructive CAD in kidney transplantation candidates. Compared with SPECT, coronary CTA had higher sensitivity but lower specificity. Coronary CTA seems to be a valid alternative to an initial diagnostic

strategy using a stress imaging test and invasive angiography. A hybrid imaging approach with coronary CTA and SPECT did not improve overall diagnostic accuracy compared with coronary CTA alone. However, the PPV was increased by using hybrid imaging that advocated personalized downstream testing including either SPECT or ICA after an initial diagnostic strategy with coronary CTA in patients undergoing cardiac evaluation before kidney transplantation.

ACKNOWLEDGMENTS The authors acknowledge the following as important contributors to this paper: J.N. Bech, Department of Internal Medicine, Holstebro, Denmark, and E. Randers, Department of Internal Medicine, Viborg, Denmark.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Simon Winther, Department of Cardiology, Aarhus University Hospital, Brendstrupgaardsvej 100, DK-8200 Aarhus, Denmark. E-mail: sw@dadlnet.dk.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE:

Cardiac risk stratification of kidney transplantation candidates is important due to a high incidence of cardiovascular disease in patients with end-stage renal disease. Due to the relatively low accuracy of noninvasive stress testing in this population, alternative methods should be considered. Coronary CTA has emerged as a noninvasive alternative to stress testing for the diagnosis of CAD.

TRANSLATIONAL OUTLOOK: Future large-scale prospective comparative effectiveness studies are required to determine the most clinically and cost-efficient approach to evaluation of patients considered for renal transplantation.

REFERENCES

- Pilmore H, Dent H, Chang S, McDonald SP, Chadban SJ. Reduction in cardiovascular death after kidney transplantation. *Transplantation* 2010;89:851-7.
- Lentine KL, Costa SP, Weir MR, et al. Cardiac disease evaluation and management among kidney and liver transplantation candidates: a scientific statement from the American Heart Association and the American College of Cardiology Foundation. *J Am Coll Cardiol* 2012;60:434-80.
- Wang LW, Fahim MA, Hayden A, et al. Cardiac testing for coronary artery disease in potential kidney transplant recipients. *Cochrane Database Syst Rev* 2011;(12):CD008691.
- De Lima JJ, Sabbaga E, Vieira ML, et al. Coronary angiography is the best predictor of events in renal transplant candidates compared with noninvasive testing. *Hypertension* 2003;42:263-8.
- Budoff MJ, Dowe D, Jollis JG, et al. Diagnostic performance of 64-multidetector row coronary computed tomographic angiography for evaluation of coronary artery stenosis in individuals without known coronary artery disease: results from the prospective multicenter ACCURACY (Assessment by Coronary Computed Tomographic Angiography of Individuals Undergoing Invasive Coronary Angiography) trial. *J Am Coll Cardiol* 2008;52:1724-32.
- Raff GL, Abidov A, Achenbach S, et al. SCCT guidelines for the interpretation and reporting of coronary computed tomographic angiography. *J Cardiovasc Comput Tomogr* 2009;3:122-36.
- Miller JM, Rochitte CE, Dewey M, et al. Diagnostic performance of coronary angiography by 64-row CT. *N Engl J Med* 2008;359:2324-36.
- Schaap J, Kauling RM, Boekholdt SM, et al. Incremental diagnostic accuracy of hybrid SPECT/CT coronary angiography in a population with an intermediate to high pre-test likelihood of coronary artery disease. *Eur Heart J Cardiovasc Imaging* 2013;14:642-9.
- Rosario MA, Lima JJ, Parga JR, et al. Coronary calcium score as predictor of stenosis and events in pretransplant renal chronic failure. *Arq Bras Cardiol* 2010;94:236-43, 252-60, 239-47.
- Mao J, Karthikeyan V, Poopat C, et al. Coronary computed tomography angiography in dialysis patients undergoing pre-renal transplantation cardiac risk stratification. *Cardiol J* 2010;17:349-61.
- Jug B, Kadakia J, Gupta M, et al. Coronary calcifications and plaque characteristics in patients with end-stage renal disease: a computed tomographic study. *Coron Artery Dis* 2013;24:501-8.
- Park MY, Choi SJ, Kim JK, et al. Use of multi-detector computed tomography for evaluating coronary artery disease in patients undergoing dialysis. *Nephrology (Carlton)* 2011;16:285-9.
- Lee JE, Lee YK, Choi EJ, Nam JS, Choi BW, Kim BS. Usefulness of multidetector row computed tomography for predicting cardiac events in asymptomatic chronic kidney disease patients at the initiation of renal replacement therapy. *Sci World J* 2013;2013:916354.
- de Bie MK, Buiten MS, Gaasbeek A, et al. CT coronary angiography is feasible for the assessment of coronary artery disease in chronic dialysis patients, despite high average calcium scores. *PLoS One* 2013;8:e67936.
- Hulten EA, Carbonaro S, Petrillo SP, Mitchell JD, Villines TC. Prognostic value of cardiac computed tomography angiography: a systematic review and meta-analysis. *J Am Coll Cardiol* 2011;57:1237-47.
- Ragosta M, Samady H, Isaacs RB, Gimple LW, Sarembock IJ, Powers ER. Coronary flow reserve abnormalities in patients with diabetes mellitus who have end-stage renal disease and normal epicardial coronary arteries. *Am Heart J* 2004;147:1017-23.
- Murthy VL, Naya M, Foster CR, et al. Coronary vascular dysfunction and prognosis in patients with chronic kidney disease. *J Am Coll Cardiol Img* 2012;5:1025-34.
- Pazhenkottil AP, Nkoulou RN, Ghadir JR, et al. Prognostic value of cardiac hybrid imaging integrating single-photon emission computed tomography with coronary computed tomography angiography. *Eur Heart J* 2011;32:1465-71.
- Manske CL, Wang Y, Rector T, Wilson RF, White CW. Coronary revascularisation in insulin-dependent diabetic patients with chronic renal failure. *Lancet* 1992;340:998-1002.
- Boogers MJ, Schuijf JD, Kitslaar PH, et al. Automated quantification of stenosis severity on 64-slice CT: a comparison with quantitative coronary angiography. *J Am Coll Cardiol Img* 2010;3:699-709.
- Kang DK, Im NJ, Park SM, Lim HS. CT comparison of visual and computerized quantification of coronary stenosis according to plaque composition. *Eur Radiol* 2011;21:712-21.
- Rossi A, Papadopoulou SL, Pugliese F, et al. Quantitative computed tomographic coronary angiography: does it predict functionally significant coronary stenoses? *Circ Cardiovasc Imaging* 2014;7:43-51.

KEY WORDS coronary angiography, coronary computed tomography angiography, renal transplantation, sensitivity and specificity, single-photon emission computed tomography