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Coronary computed tomography angiography in dialysis patients undergoing pre-renal transplantation cardiac risk stratification

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Abstract

Background: *This study addresses the safety, feasibility, and interpretability of coronary computed tomography angiography (CCTA) in excluding significant coronary artery disease in end-stage renal disease patients on dialysis undergoing pre-renal transplant cardiac risk evaluation.*

Methods: *Twenty nine patients (55.5 ± 10.2 years) undergoing cardiac risk assessment prior to renal transplantation, underwent research CCTA with calcium scoring and formed the study group. All CCTAs were performed using retrospective acquisition, with beta-blockade provided one hour prior to scanning.*

Results: *No major complications occurred in this group up to 30 days after CCTA. Of the total of 374 segments interpreted by both readers, only 36 (10%) were uninterpretable by both readers. Of these, 31 (86%) were from distal segments or branches. On a segmental level, there was 95% concordance between both readers for < 50% stenosis detection. Only three out of 28 (11%) CCTAs were deemed uninterpretable. Ten patients (36%) had zero calcium score, despite being on dialysis with no evidence of obstructive coronary artery disease by CCTA.*

Conclusions: *CCTA is feasible and safe in end-stage renal disease dialysis patients with the advent of 64-slice CCTA. Despite significant calcium burden, there was excellent inter-observer agreement at segment level for the left main and all three proximal-mid coronary arteries in excluding obstructive coronary artery disease (> 50% stenosis).* (Cardiol J 2010; 17, 4: 349–361)

Key words: coronary computed tomography angiography, end stage renal disease, coronary artery disease, renal transplantation, risk stratification, dobutamine echocardiography, stress myocardial perfusion imaging

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Introduction

Cardiovascular disease is the leading cause of mortality in end-stage renal disease (ESRD) patients on dialysis, accounting for 40–45% of all deaths [1]. The annual all-cause mortality rate for all US dialysis patients in 2002 was 210 per 1,000 patient years [2]. Therefore, renal transplantation (RT) is the treatment of choice for patients with ESRD and has been shown to improve survival. Cardiac screening of RT candidates is recommended in the hope of preventing cardiovascular death after transplantation [3]. Given a limited organ donor pool, adequate cardiac risk stratification is crucial.

Conflicting evidence exists regarding the best way to predict cardiac risk in ESRD patients prior to RT [4, 5]. Although we and others have shown that stress echocardiography (SE) and stress myocardial perfusion imaging (SMPI) are widely used in the initial risk stratification of RT candidates [6, 7], there are limitations with these techniques in ESRD patients. False positive SMPI from underlying co-morbidities such as hypertension and diabetes and endothelial dysfunction can occur in ESRD patients, who have a high prevalence of these conditions [8–10].

Dobutamine stress echocardiography (DSE) may be inconclusive or non-diagnostic due to the inability to achieve ≥ 85% maximal predicted heart rate which is a significant problem in this population [6]. Finally, coronary angiography, still considered the 'gold standard', is invasive and may expose patients to unnecessary risk considering that only a small fraction of non-diabetic ESRD patients have significant obstructive coronary artery disease (CAD) and very few revascularizations are performed in the subgroup of ESRD patients who undergo angiography [6, 11]. In a recent comprehensive review of coronary risk assessment in ESRD patients awaiting RT, we looked at all existing diagnostic modalities, and their limitations, and outlined possible strategies for approaching the ESRD population who represent a big challenge to the diagnostic armamentarium [12].

Rapid technological advances and new clinical applications in cardiovascular imaging technology have made coronary computed tomography angiography (CCTA) more widely available and increasingly popular. The value of CCTA lies mainly in its negative predictive value or its ability to exclude significant obstructive CAD [13]. ESRD patients on dialysis have largely been excluded from CCTA trials due to the high coronary artery calcium burden which may interfere with CCTA evaluation, as well as the high contrast volume load which raises safety concerns in ESRD patients with residual renal function. Thus, the exact role, if any, of CCTA in ESRD dialysis patients is unknown which forms the basis of this pilot study focusing on the pre-RT population.

The main aims of this study were firstly to assess the feasibility and interpretability of CCTA to exclude major proximal-mid epicardial vessel CAD which may affect revascularization decisions prior to RT; secondly, to determine the immediate and short term safety of CCTA procedure in ESRD dialysis patients undergoing pre-RT risk stratification; and thirdly to compare CCTA to dobutamine echocardiography in a subset of patients undergoing the latter for pre-transplant risk stratification.

Methods

Study population

Twenty-nine consecutive ESRD patients on dialysis referred for RT evaluation at Henry Ford Hospital were prospectively studied. All patients signed a written informed consent and the study was approved by the institutional review board at Henry Ford Hospital. One patient could not complete the CCTA due to IV infiltration and therefore was excluded from analysis, resulting in a final sample size of 28 patients. All were required to undergo a standard CCTA examination, as per the study protocol. Cardiac CTA findings were blinded to the referring physician as well as to the patient. Any significant non-cardiac findings noted were communicated to the patient's primary physician. Patients underwent routine clinical risk assessment as per our institution's RT work-up protocol and 23 patients also underwent a DSE (n = 20) or single-photon emission computed tomography (SPECT) (n = 3) examination as part of their risk stratification. The clinical assessment and stress test results were the only information used to make decisions for RT candidacy.

Exclusion criteria included age < 18 years, inability or refusal to sign consent, pregnancy, allergy or hypersensitivity to iodine, atrial fibrillation or significant ectopy precluding gating, ejection fraction < 40% or fluid overload status, contraindications to beta-blockers, and inability to obtain IV access. ESRD patients not on dialysis, or with reasonable residual renal function despite dialysis as determined by the nephrologist, were also excluded from the study to avoid any worsening of renal function secondary to contrast exposure.

Coronary computed tomography angiography

CCTA examinations were performed using a Siemens or GE 64-slice computed tomography scanner. In all patients, a non-contrast enhanced scan was performed prior to the 64-slice computed tomography angiography to assess the total coronary artery calcium burden by Agatston method.

All patients were asked to continue their existing anti-hypertensive medications, particularly beta-blockers prior to the test. The CCTA was performed on non-dialysis days. In patients with a HR ≥ 60 bpm, 50–150 mg of metoprolol was given prior to the CCTA if there was no contraindication to beta-blocker use. In addition, 2.5 mg of isosorbide dinitrate was used to facilitate coronary vasodilatation during the examination. Retrospective gating was employed with reconstructions performed at 65%, 70%, and 75% of the RR interval. The CCTA reconstructions were evaluated by standard methodology using maximum intensity projections followed by multi-planar reformatted images. The contrast agent used was 80cc of Optiray or Isovue. The patients were evaluated after the CCTA examination by a cardiology fellow or staff radiologist and were discharged from the facility when deemed stable clinically 30–45 minutes after the CCTA. The CCTAs were interpreted by two qualified CCTA Level 3-equivalent physicians blinded to all patient data. A third qualified reader settled any significant discrepancies. An 18-segment coronary vessel tree was used for grading. We used a six point scale for interpretation of stenosis (0 = normal, 1 = 1–25%, 2 = 26–50%, 3 = 51–70%, 4 > 70%, 5 = 100% stenosis). This grading was used for all segments and for overall study quality. In addition, assessment also included description of plaque as calcified, non-calcified, or mixed plaque. Quality of the study was rated as high, adequate, poor, or uninterpretable (based on motion and heart rate related issues). Standardized reporting format for CCTA coronary anatomy/plaque interpretation was used in our institution, similar to published guidelines [14], and was used by all readers.

Follow-up

Although not a primary aim of the study, in order to ensure that the CCTA procedure did not result in short term adverse consequences, the 28 patients were all followed up to identify any 30-day events following the CCTA examination. These 30-day events included death, myocardial infarction, congestive heart failure, and any reactions which could be directly attributable to the CCTA procedure. These events were mainly identified through electronic chart review focusing on emergency room visits, hospital admissions, and dialysis notes in the 30 days following CCTA.

Statistical analysis

All two-group comparisons of numeric data were performed using t-tests when the data is normally distributed, otherwise using the Wilcoxon rank sum test. All two-group comparisons of categorical data were performed using the χ^2 test for proportions when none of the expected cell counts are less than five, otherwise using the Fisher exact test. Segment independence has been assumed when comparing the interpretable segments to the uninterpretable segments. Spearman correlation coefficients and corresponding p-values have been used to evaluate the correlation between stenosis level and calcium score. The Kappa statistic has been used to measure the reader agreement of the segment stenosis levels. P-values less than 0.05 have been considered statistically significant throughout.

Results

A CCTA including calcium score estimation was performed in 28 patients. Table 1 displays their baseline demographics and characteristics. The notable findings were a rather young population (mean age of 55.2 ± 10.0 years) with a predominance of males (75%) and African American race (89%). All had hypertension and 93% were on hemodialysis. The etiologies of ESRD were hypertension in 39%, diabetes in 14% and a combination of hypertension and diabetes in 25%. Primary renal etiologies accounted for 22% of causes for ESRD. The mean duration of dialysis was 3.1 ± 3.5 years with an excellent average calcium-phosphorus product of 45.4 ± 8.2. There were 18 patients (64.3%) on beta-blockers and 16 patients (57.1%) on calcium channel blockers. A dose of 50–150 mg of oral metoprolol was administered to 22 patients (78.5%) to lower the heart rate, resulting in an average heart rate at acquisition of 64.9 beats/min.

The various CCTA characteristics are displayed in Table 2. Three out of the 28 CCTAs were considered uninterpretable and were excluded from analysis. A total of 123 coronary arteries were analyzed in this study. Using an 18-segment model, only 374 out of 504 (75%) coronary segments were analyzed by both readers, due mainly to inability to adequately visualize the most distal segments for analysis. The overall mean calcium scores in the CCTAs were 648.1 ± 1632.0. In addition, the ma-

Table 1. Baseline characteristics.

Characteristics	Total
Age (years)	55.2 ± 10.0
Gender:	
Male (%)	75.0
Female (%)	25.0
African American (%)	89
History of hypertension (%)	100.0
History of diabetes mellitus (%)	50.0
Type of dialysis:	
Hemodialysis (%)	92.9
Peritoneal dialysis (%)	7.1
Dialysis years	3.1 ± 3.5
Body mass index	31.3 ± 8.0
Calcium × phosphorous product	45.4 ± 8.2
Heart rate	76.3 ± 12.6
Heart rate acquisition	64.9 ± 5.4
Systolic blood pressure	137.0 ± 19.4
Diastolic blood pressure	77.1 ± 14.0
Prior beta-blocker usage (%)	64.3
Prior calcium channel blocker usage (%)	57.1
IV metoprolol dose used:	
0 (%)	96.4
5 (%)	3.6
PO metoprolol dose used:	
0 (%)	21.4
50 (%)	10.7
100 (%)	46.4
150 (%)	21.4

jority of the 25 interpretable CCTAs were considered adequate or high quality studies (61% for Reader 1 and 64% for Reader 2). Table 3 shows the comparison of variables for the 374 segments, breaking them down into interpretable (277) and uninterpretable (36) segments. Surprisingly, a higher heart rate was the only significant predictor of interpretability. Of the 36 uninterpretable segments, 86% were in the distal branch vessels of the coronary arteries.

Figure 1 shows the distribution of overall calcium scores across the range of stenosis reported. As can be seen, there is a significant correlation between higher calcium scores and more severe stenosis, although the number of patients with severe stenosis is very small. Figure 2 shows the distribution of the calcium scores in individual arteries analyzed at varying levels of stenosis severity. Despite very high calcium scores, many patients (particularly noted in the left artery descending and left circumflex distribution) had non-significant (< 50%) stenosis, highlighting the fact that a high calcium score does not automatically translate to a tight stenosis in this high-risk patient subset. Figure 3 displays the distribution of stenosis in different arteries. As illustrated, a majority of the stenosis in all three major vessels as well as the left main were less than 50%.

There was overall good correlation for adequacy of interpretability of segments between Reader 1 and Reader 2. Of the 374 segments examined,

Table 2. Coronary computed tomography angiography characteristics.

Characteristics	Reader 1 (28 patients)	Reader 2 (28 patients)	Reader 3 (two patients)
Overall calcium score	648.1 ± 1632.0	648.1 ± 1632.0	
RCA calcium score	202.4 ± 621.6	202.4 ± 621.6	
LM calcium score	26.3 ± 66.2	26.3 ± 66.2	
LAD calcium score	285.1 ± 748.9	285.1 ± 748.9	
LCX calcium score	134.2 ± 293.5	134.2 ± 293.5	
Study quality:			
Adequate–high	17/28 (61%)	18/28 (64%)	0/2 (0%)
Poor	11/28 (39%)	10/28 (36%)	2/2 (100%)
Overall study uninterpretable (fraction and %)	1/28 (3.6%)	3/28 (10.7%)	0/2 (0%)
LM stenosis uninterpretable (fraction and %)	1/28 (3.6%)	2/28 (7.1%)	0/2 (0%)
LAD stenosis uninterpretable (fraction and %)	0/28 (0.0%)	2/28 (7.1%)	0/2 (0%)
LCX stenosis uninterpretable (fraction and %)	2/28 (7.1%)	3/28 (10.7%)	0/2 (0%)
RCA stenosis uninterpretable (fraction and %)	3/28 (10.7%)	3/28 (10.7%)	0/2 (0%)

RCA — right coronary artery; LM — left main; LAD — left arterior descending; LCX — left circumflex

Table 3. Factors influencing segment interpretability.

Variable	Intrepretable by both readers (n = 277)	Uninterpretable by both readers (n = 36)	Comparison (p)
Overall calcium score	611.0 ± 1697.8	648.3 ± 1354.8	0.784
Overall calcium score ≥ 400	46 (16.6%)	9 (25.0%)	0.213
Overall moderate/severe calcium	124 (44.8%)	15 (41.7%)	0.725
Overall poor signal to noise ratio	169 (61.0%)	27 (75.0%)	0.103
Overall moderate/severe motion	151 (54.5%)	19 (52.8%)	0.844
Body mass index	31.3 ± 7.2	30.9 ± 9.7	0.762
Heart rate	77.4 ± 12.3	71.6 ± 9.6	0.006
Calcium × phosphorous product	45.1 ± 8.4	43.7 ± 4.6	0.360
Years on dialysis	3.3 ± 3.6	3.1 ± 2.9	0.970

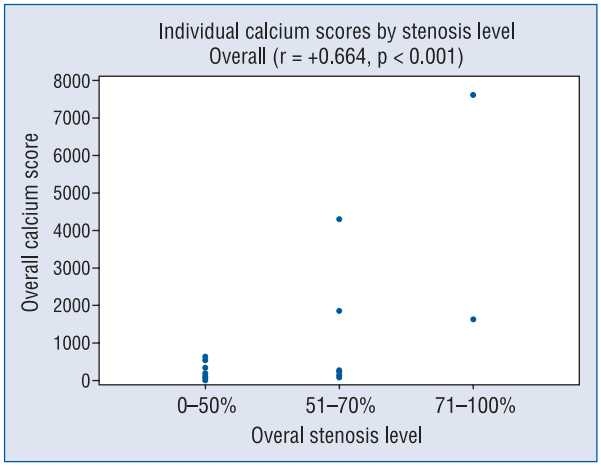

Figure 1. Individual calcium scores by stenosis levels.

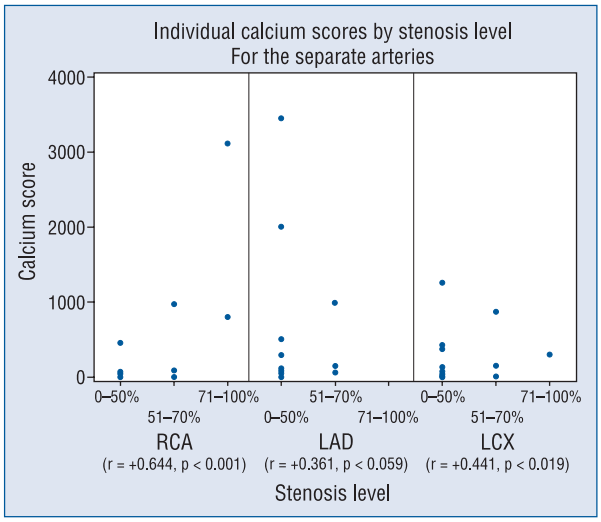

Figure 2. Distribution of calcium scores in individual coronary arteries; RCA — right coronary artery; LAD — left artery descending; LCX — left circumflex.

277 (74%) were deemed interpretable by both readers, whereas 36 (10%) were deemed uninterpretable by both readers (Table 4). Of the uninterpretable segments, most (86%) were located in distal segments or branches. Furthermore, the inter-reader agreement at the segment level for identifying less than 50% stenosis in 25 out of 28 patients was excellent, with a 96% concordance (both readers concordant for < 50% stenosis in 266 out of 277 segments). The overall Kappa statistic at segment level was fair at 0.46, which suggested a moderate level of correlation.

Ten out of the 28 (36%) patients actually had a total calcium score of 0. Six patients had a total coronary calcium score of 1–100, six patients had a total coronary calcium score of 101–400, and six patients had a total coronary calcium score of > 400. All ten of the patients with an overall coronary calcium score of 0 had normal coronary arteries by CCTA. Table 5 displays the relevant variables, comparing those with a calcium score of 0 to those with a calcium score higher than zero. No significant differences were noted between the two groups.

Twenty out of the 28 patients (71%) underwent a DSE as part of pre-transplant assessment in addition to a CCTA as deemed necessary by their physician. Table 6 displays the stress testing characteristics for the DSE studies that were performed. Table 7 shows the correlation between the DSE studies and CCTA in those 20 patients. Nine out of the 20 (45%) DSE studies were considered inconclusive or sub-maximal, mainly due to an inability to achieve ≥ 85% of the maximal predicted heart rate. The remaining DSE studies were all considered conclusive and negative for ischemia. In contrast, only three out of the 28 (11%) CCTAs performed were deemed uninterpretable. All nine patients with a sub-maximal dobutamine echocardiogram had an

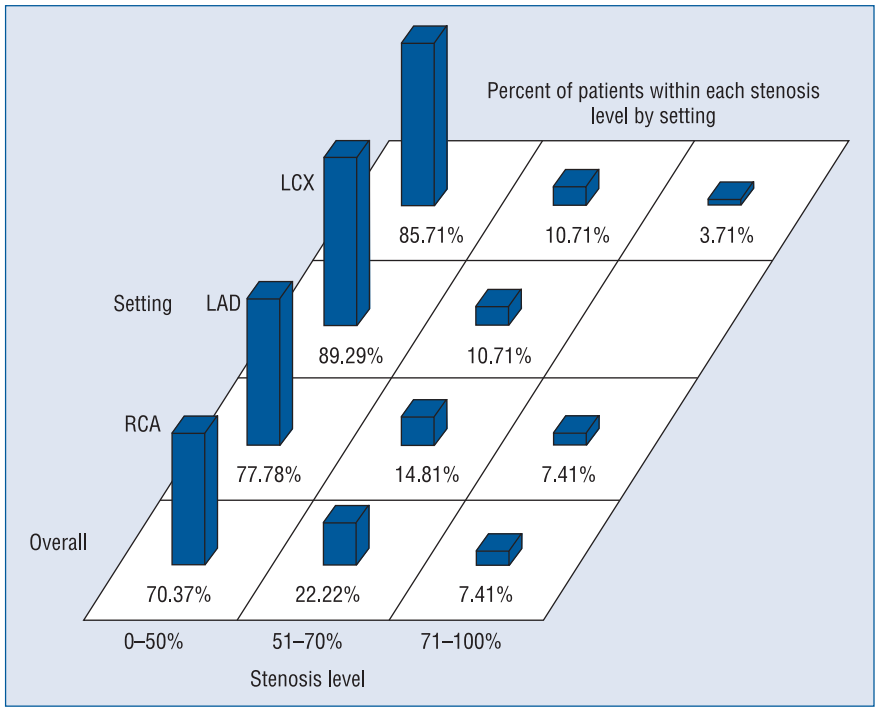

Figure 3. Distribution of stenosis by coronary artery; RCA — right coronary artery; LAD — left artery descending; LCX — left circumflex.

Table 4. Segment stenosis interpretability by readers.

Reader 1	Reader 2		
	Interpretable	Uninterpretable	Total
Interpretable	277 (74%)	22 (6%)	299 (80%)
Uninterpretable	39 (10%)	36 (10%)	75 (20%)
Total	316 (84%)	58 (16%)	374

interpretable CCTA and eight of them displayed a stenosis of < 70% in the proximal-mid coronary arteries. Figures 4A–D shows CCTA examples of four study patients. Patients 4A and 4B had inconclusive stress tests, but had CCTAs showing zero coronary calcium and no CAD. Patient 4C had a submaximal stress test, elevated calcium score, and no obstructive CAD. Finally, patient 4D had severe coronary calcification, no significant proximal obstructive disease despite this high calcium burden, and only mild-moderate distal right coronary artery disease by CCTA. A follow-up coronary angiogram revealed non-obstructive CAD, demonstrating that even markedly elevated calcium scores may not correlate with severe stenosis.

Follow-up

Although not a primary end-point in the study, a short 30-day follow-up period was obtained to evaluate the immediate post-CCTA outcomes. No serious adverse events were recorded. One patient was hospitalized for gastrointestinal bleeding felt to be secondary to oral anticoagulants. No significant change in patient symptomatology or dialysis frequency was noted, suggesting that CCTA had no adverse impact in this period.

Discussion

This study shows that CCTA is a feasible and safe modality in patients with pre-RT ESRD on dialysis. There were no immediate or short term

Table 5. Subgroup analysis based on calcium score (0 *vs* non-0).

Variable	Calcium score non-zero (n = 18)	Calcium score zero (n = 10)	P
Age (years)	56.2 ± 10.0	53.2 ± 10.2	0.455
Female gender	2 (11.1%)	5 (50.0%)	0.063
Diabetes mellitus	10 (55.6%)	4 (40.0%)	0.430
Dialysis mode:			0.276
HD	15 (83.3%)	7 (70.0%)	
PD	2 (11.1%)	0 (0.0%)	
Both	1 (5.6%)	3 (30.0%)	
Dialysis (years)	3.1 ± 3.9	3.2 ± 2.6	0.429
Prior TP	2 (11.1%)	1 (10.0%)	1.000
Phosphorous binder:			1.000
None	3 (16.7%)	1 (10.0%)	
Non calcium	10 (55.6%)	6 (60.0%)	
Calcium containing	4 (22.2%)	2 (20.0%)	
Both	1 (5.6%)	1 (10.0%)	
Average calcium	9.0 ± 0.5	8.5 ± 0.9	0.073
Average phosphorous	5.0 ± 0.7	5.4 ± 1.2	0.367
Average PTH	499.9 ± 201.6	726.1 ± 679.9	0.733
Average albumin	4.0 ± 0.3	4.0 ± 0.2	0.733
Calcium × phosphorous product	45.4 ± 7.0	45.4 ± 10.0	0.998
Ejection fraction (%)	55.1 ± 7.9	57.2 ± 5.1	0.447
Body mass index	32.8 ± 8.9	28.8 ± 5.5	0.209

HD — hemodialysis; PD — peritoneal dialysis; TP — transplantation

Table 6. Dobutamine stress test characteristics.

Characteristics	Total
Dobutamine stress echocardiography	20
Ejection fraction (%)	55.8 ± 7.0
Conclusive	11 (55%)
Submaximal	9 (45%)
Positive	0
Negative	11 (55%)

adverse reactions to pre-medications or radiocontrast dye used as part of CCTA. Secondly, our study shows that diagnostic images to exclude major vessel CAD, which could impact patient management prior to RT, was possible in the majority of the patients with current 64-slice CCTA technology. Although our study sample size is very small, thus precluding definitive conclusions, our study shows that a certain subset (10/28, 36%) ESRD dialysis patients actually have a low to zero calcium burden, which by itself makes major obstructive CAD very unlikely. If confirmed by

Table 7. Dobutamine stress echocardiography (DSE)/computed tomography angiography (CTA) correlation.

DSE results	CTA results			
	≤ 70% stenosis	≥ 70% stenosis	Uninterpretable	Total
Negative	10 (50%)	0	1 (5%)	11 (55%)
Inconclusive	8 (40%)	1 (5%)	0	9 (45%)
Total	18 (90%)	1 (5%)	1 (5%)	20

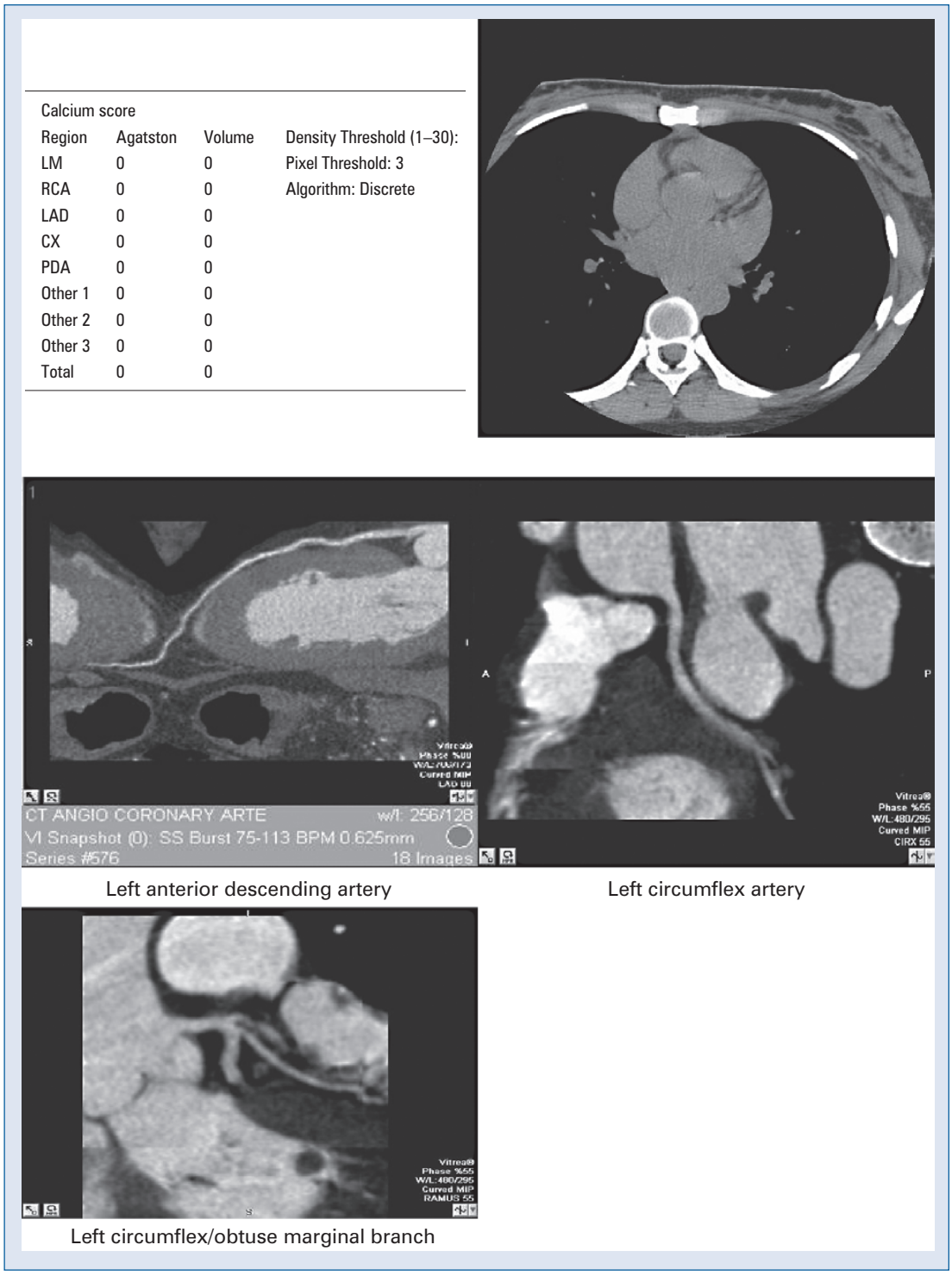

Figure 4. A. A 55 year-old patient on hemodialysis; submaximal dobutamine stress echocardiography requiring additional testing with stress myocardial perfusion scan. His research coronary computed tomography angiography (CCTA) is shown. As can be seen, there was no coronary calcium detected and no obstructive coronary artery disease documented and the CCTA was of diagnostic quality.

larger studies, this makes CCTA a diagnostic option in this subset where further testing could be avoided if patients are asymptomatic during their pre-RT evaluation process.

The main modalities used for RT cardiovascular risk assessment include exercise electrocardiography (ECG) testing, myocardial perfusion imaging, or echocardiography using exercise or dobu-

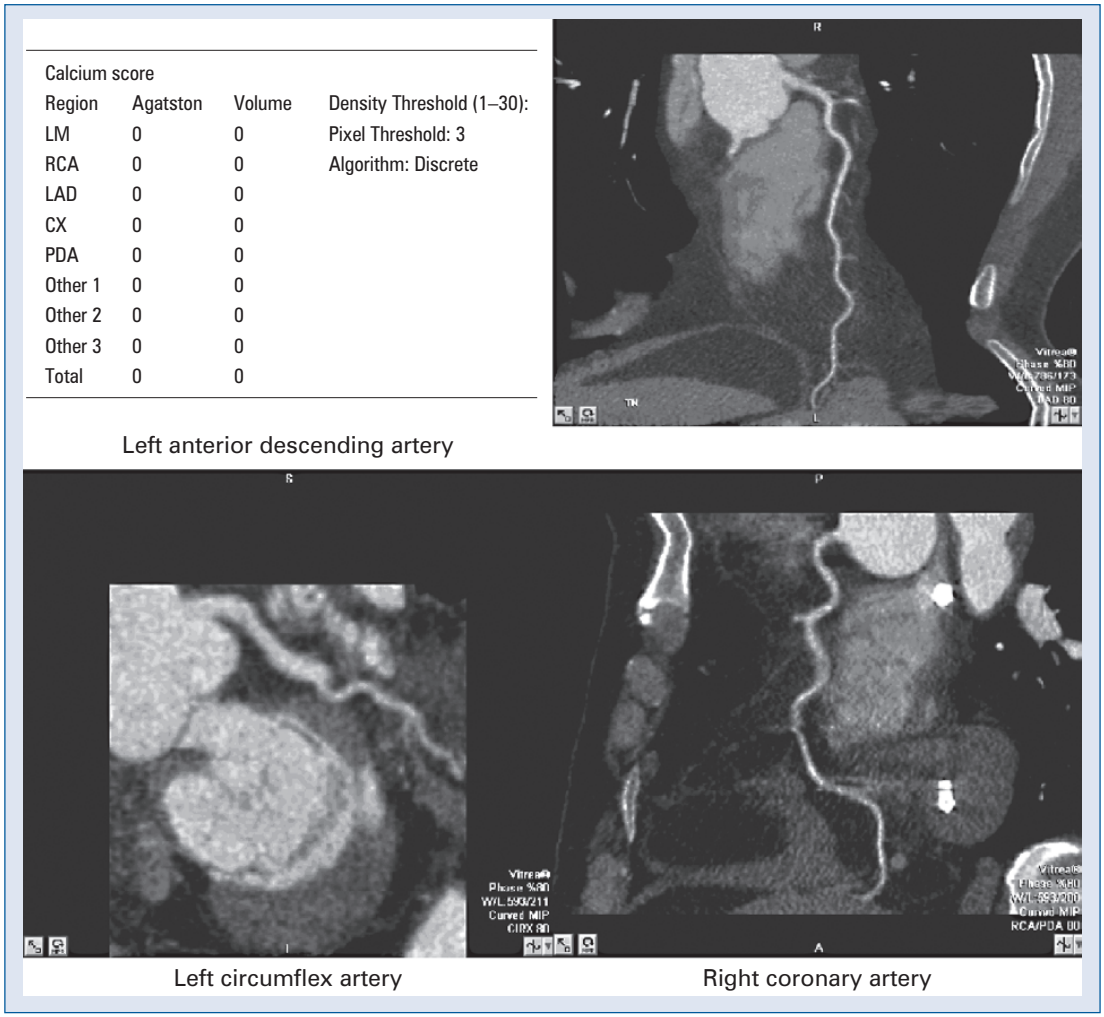

Figure 4. B. A 57 year-old patient with diabetes on hemodialysis; equivocal stress echocardiography referred for coronary angiography. Research CCTA shows zero calcium score and no significant coronary disease and interpretable scan.

tamine. While exercise ECG testing has been shown to identify patients at increased surgical risk in the non-ESRD population, there are few studies examining this screening modality in patients with renal failure, mainly due to the markedly reduced exercise capacity of these patients and abnormal baseline ECG. In a recent study of RT candidates, exercise ECG only had a sensitivity of 32% for predicting coronary artery disease [11].

Debate still exists regarding the accuracy and predictive value of DSE in the evaluation of ESRD patients who are being considered for renal transplant. The study by Herzog et al. [15] showed that 20% of RT candidates with a negative DSE experienced cardiac death, myocardial infarction, or coronary revascularization. In support of non-invasive risk stratification, studies from the authors' institution showed very good negative predictive value, with a negative SE and much worse outcomes for those with positive SE regardless of extent of angiographic disease [6].

De Lima et al. [4] demonstrated that both DSE and SPECT have very low sensitivities (< 60%) for predicting obstructive CAD. In this study, only risk stratification and coronary angiography (CA) were able to reliably predict the probability of event-free survival. However, there is no convincing evidence that routine CA is needed in all RT candidates, as only a minority of these diagnostic catheterizations lead to any revascularization in the pre-RT ESRD patient [6, 11].

CCTA is an excellent non-invasive tool for exclusion of CAD, as reconfirmed by the publication of the multicenter ACCURACY trial [16]. However,

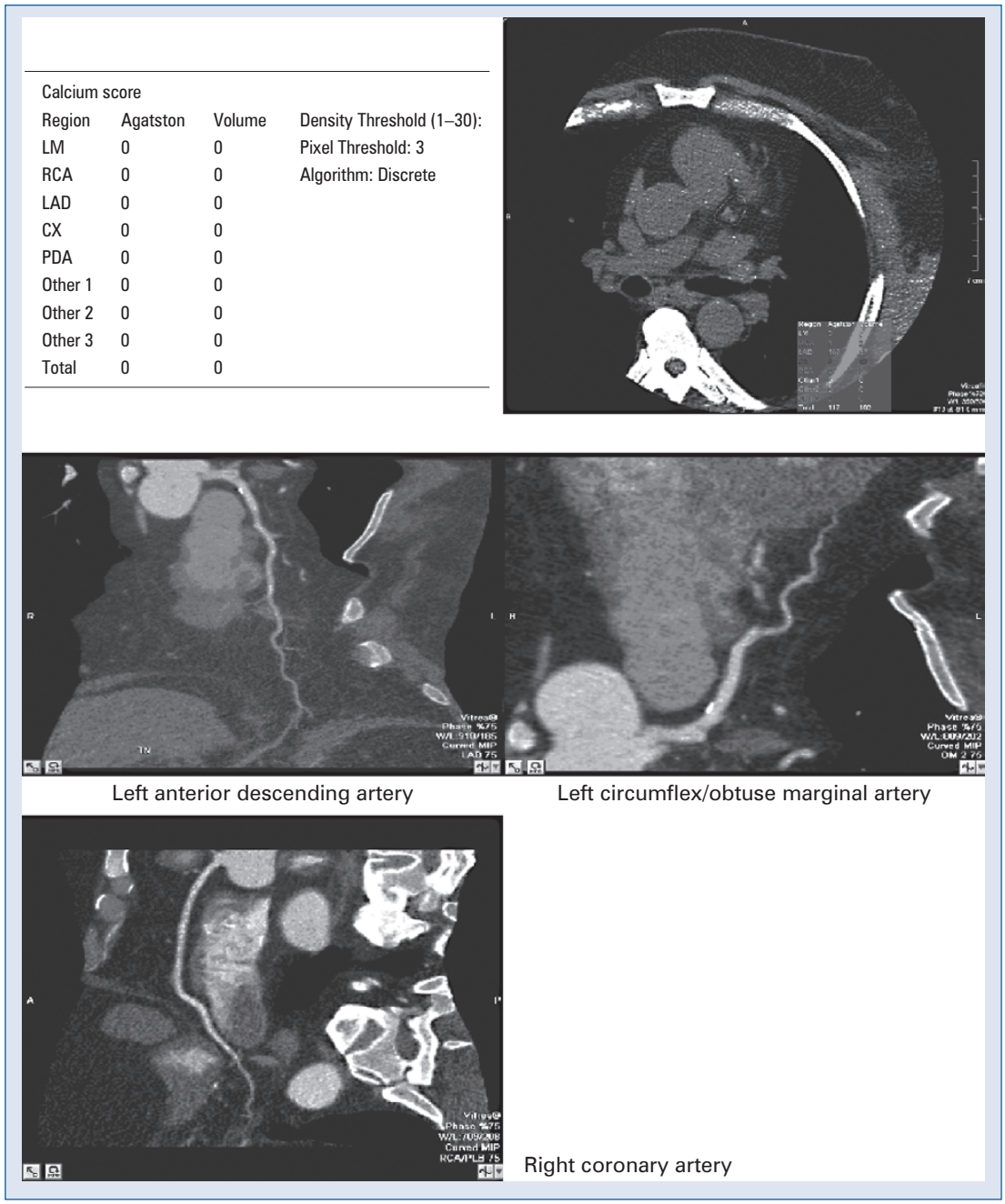

Figure 4. C. A 56 year-old female submaximal exercise echocardiography referred for additional stress myocardial perfusion imaging. Research CCTA shows no obstructive coronary disease.

its use in ESRD patients is not studied due to concerns about potential kidney function deterioration in non-dialysis situations. The high calcium burden in ESRD patients has served as the other major barrier to use of CCTA. In diabetic patients with chronic kidney disease, coronary calcification starts early and progresses rapidly after initiation of hemodialysis [17]. These and other electron beam computed tomography (EBCT) studies have shown accelerated coronary calcification in hemodialysis patients [18, 19]. However, prior data comparing EBCT calcium burden with CA has shown that calcific burden in ESRD patients correlates poorly with obstructive CAD [20]. These discrepancies could likely be coexistent medial vascular calcification (Monckeberg's sclerosis or more appropriately cur-

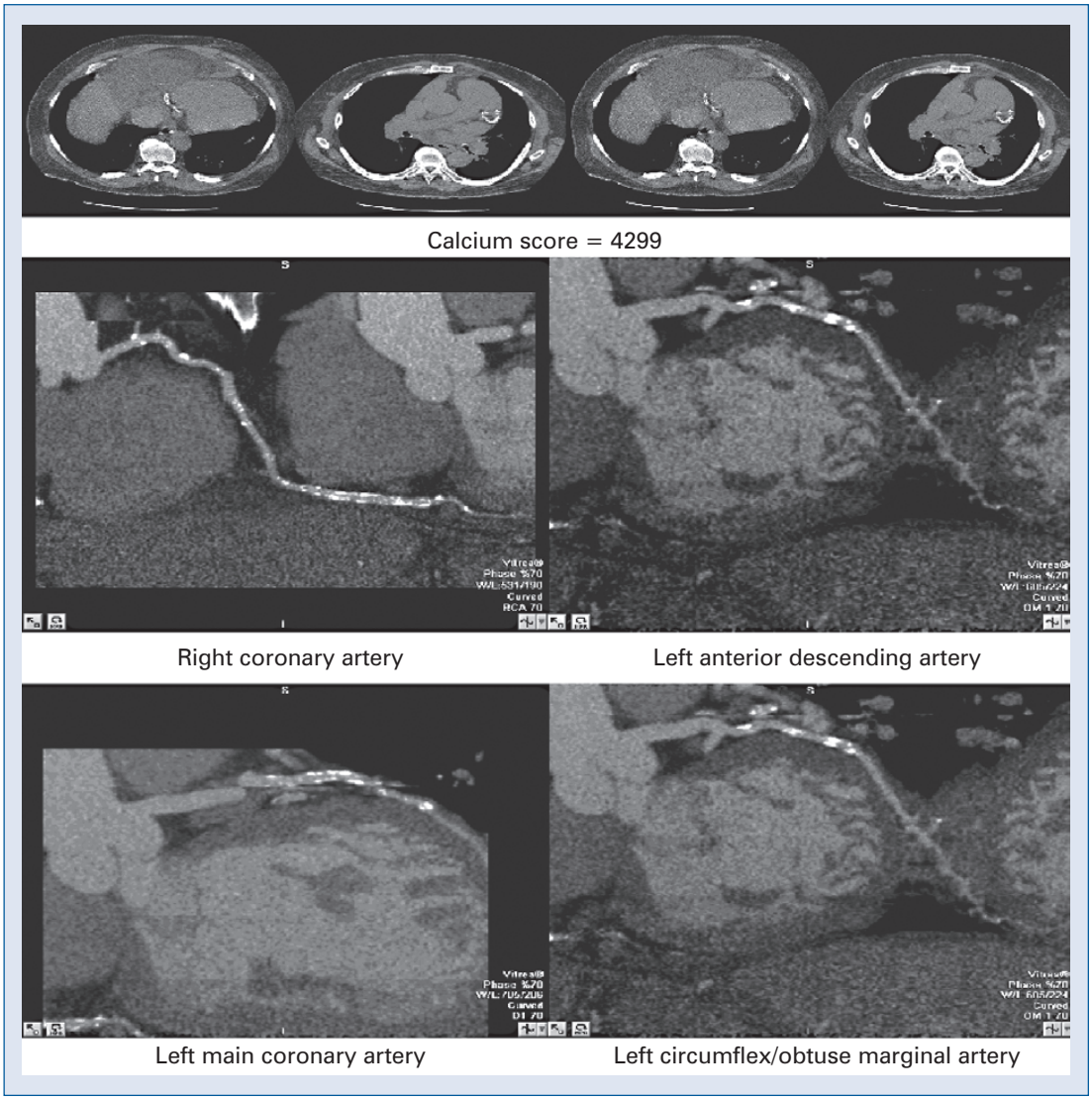

Figure 4. D. A 58 year-old male with ejection fraction of 40%, moderate-severe mitral regurgitation on dobutamine echocardiography which was negative for ischemia referred for catheterization given significant mitral regurgitation. Research CCTA in this patient shows markedly elevated calcium but no obvious obstructive coronary angiography on CCTA confirmed by cardiac catheterization which showed minimal coronary luminal irregularities despite substantial coronary calcification.

rently considered as American Heart Association Stage Va and V11 lesions) that is measured as part of the EBCT calcium assessment which cannot differentiate intimal from medial calcification. Although medial calcification contributes to overall cardiovascular mortality in the ESRD population [21], it is not associated with coronary atherosclerosis which is more closely linked to intimal calcification and adverse prognosis in both ESRD and normal population [21]. Medial calcification can occur in younger patients who have been on dialysis and multiple mechanisms have been proposed [22–24].

Our study confirms prior results in ESRD patients but shows this for the first time using CCTA as a reference rather than angiography. Although the overall correlation between high calcific burden and obstructive disease was good, a significant number of patients with calcium scores between 400 and 2,000 had less than 70% disease, with many having < 50% disease by CCTA in the major coronary arteries (Fig. 2). Furthermore, as shown in prior trials [20, 25, 26], our study also highlights the important fact that the traditional cut-off used in the general population for predicting higher likelihood of obstructive CAD may not apply to the ESRD

population. There was no significant overall difference between the Agatston calcium scores between interpretable and uninterpretable segments (611.0 ± ± 1697.8 *vs* 648.3 ± 1354.8, p = 0.784). Furthermore, despite high mean calcium values (> 600–2,200), only two patients in our study population had a major epicardial stenosis interpreted as ≥ 70%. This is consistent with the dissociation between calcium burden and obstructive CAD in ESRD patients shown in other studies [20, 25]. Thus, widely used traditional coronary calcium cut-off values of ≥ 400 for predicting obstructive CAD in the general population [27] may not apply to ESRD dialysis patients. The cut-off may be much higher and needs to be individualized given a substantial intermix of medial and intimal calcification contributing to higher calcium scores [13].

Although a systematic comparison between stress testing and CCTA was not an objective of the study, we compared the two modalities in patients who had had a DSE as part of their RT evaluation and the research CCTA. Almost half of DSE studies were sub-maximal, mainly due to the inability to achieve ≥ 85% of predicted maximal heart rate. We have previously shown that sub-maximal DSE is a significant problem in ESRD patients [6] and when being evaluated for RT this poses a dilemma for clinicians who have to consider whether an alternative test, like nuclear perfusion stress or coronary angiography, would be needed to conclusively rule out CAD. In the present study, 64-slice CCTA was diagnostic in the majority of patients with sub-maximal DSE, thus raising the possibility that it could serve as a second line modality when further testing is contemplated.

A substantial minority (36%) of our patients had zero calcium score. It is unclear from our study as to why calcium was absent in this subset as no significant differences were noted in the two groups with and without calcium (Table 5). One factor could be that 89% of our study population were African Americans, where coronary calcium burden is found to be the lowest as noted in the Multiethnic Study of Atherosclerosis [28]. This factor, in addition to the relatively young age in our study population, the short duration of dialysis, and excellent control of calcium phosphorous product, could have played a role apart from unknown individual patient characteristics involving calcium metabolism. This aspect needs further research, as our study was not designed to address this issue.

Despite the high calcium scores, only a minority of studies were considered to be of poor quality and only a very few were considered uninterpretable. Segments that were deemed uninterpretable were mainly distal (accounting for 86% of uninterpretable segments) and related to a calcium score ≥ 400, poor signal-to-noise ratio, or an elevated heart rate. Furthermore, there was excellent correlation between the two readers for the proximal-mid individual coronary arteries. However, there was poor correlation between the readers in seven of the 25 patients at the segment level, which likely reflects the limitations of interpreting scans with very high calcium scores.

Safety of CCTA

CCTA was very well tolerated in this high-risk subset of patients. One patient developed a vasovagal reaction during IV access prior to the exam. However, symptoms responded to intravenous fluids and the patient was able to complete the examination. Furthermore, there were no 30 day event rates including death, myocardial infarction, congestive heart failure, or any other reactions related to the CCTA procedure. One patient did develop a lower GI bleed related to coumadin within 30 days of the CCTA examination.

Limitations of the study

This is a pilot study, and therefore the results should be verified in a larger subset of patients. The small sample size of this study prevents definitive conclusions. No catheterization correlation was readily available, making true assessment of the accuracy of the CCTA difficult as coronary catheterization is still considered the gold standard technique for identifying and planning management of CAD. About 10% of segments were deemed uninterpretable by both readers, although 86% of these were in the distal vessels where revascularization strategies likely would not be applied. However, 95% concordance was achieved at a segmental level in excluding > 50% stenosis between two readers. As shown in the literature, our study suggests that CCTA's main strength lies in its ability to exclude significant major vessel epicardial disease which was well assessed at the patient level in which 89% (25 of 28) of studies were deemed interpretable and only 11% (3 of 28) were uninterpretable between both readers. Therefore, it is very likely that once proximal to mid major epicardial CAD is excluded, further anatomic delineation will likely not have much impact on therapeutic strategies in asymptomatic patients.

Conclusions

CCTA seems feasible and safe as a diagnostic screening tool to exclude major epicardial CAD in the asymptomatic ESRD population on dialysis being evaluated for transplant. Despite high calcium scores, current 64-slice CCTA in ESRD patients helps to exclude major CAD, thus avoiding cardiac catheterization. Given that more than a third of ESRD patients may have low to zero calcium scores, further studies are needed to correctly identify this population so that any testing could be avoided if the patient is asymptomatic. CCTA could also be used as the initial diagnostic strategy to exclude significant CAD in this subset and avoid further downstream testing in the next few years. Our study also demonstrates that CCTA may be a useful tool to exclude major epicardial CAD in asymptomatic ESRD dialysis patients who have non-diagnostic pre-operative stress tests. Further studies in ESRD dialysis patients using CA as a reference standard is needed to see if CCTA can be useful in pre-RT ESRD patients.

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References

1. Incidence and Prevalence of ESRD. United States Renal Data System. Am J Kidney Dis, 1998; 32 (2 suppl. 1): S38–S49.
2. National Institute of Diabetes and Digestive and Kidney Diseases. U.S. Renal Data System, USRDS 2008 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States 2004.
3. Kasiske BL, Cangro CB, Hariharan S et al. The evaluation of renal transplant candidates: Clinical practice guidelines. Am J Transplant, 2001; 1: 5–95.
4. 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: 263–268.
5. Rabbat CG, Treleaven DJ, Russell JD, Ludwin D, Cook DJ. Prognostic value of myocardial perfusion studies in patients with end--stage renal disease assessed for kidney or kidney-pancreas transplantation: A meta-analysis. J Am Soc Nephrol, 2003; 14: 431–439.
6. Tita C, Karthikeyan V, Stroe A, Jacobsen G, Ananthasubramaniam K. Stress echocardiography for risk stratification in patients with end-stage renal disease undergoing renal transplantation. J Am Soc Echocardiogr, 2008; 21: 321–326.
7. Patel AD, Abo-Auda WS, Davis JM et al. Prognostic value of myocardial perfusion imaging in predicting outcome after renal transplantation. Am J Cardiol, 2003; 92:146–151.
8. De Lorenzo A, Lima RS, Siqueira-Filho AG, Pantoja MR. Prevalence and prognostic value of perfusion defects detected by stress technetium-99m sestamibi myocardial perfusion single--photon emission computed tomography in asymptomatic patients with diabetes mellitus and no known coronary artery disease. Am J Cardiol, 2002; 90: 827–832.
9. Joannides R, Bakkali EH, Le Roy F et al. Altered flow-dependent vasodilatation of conduit arteries in maintenance haemodialysis. Nephrol Dial Transplant, 1997; 12: 2623–2628.
10. Soman P, Dave DM, Undelson JE et al. Vascular endothelial dysfunction is associated with reversible myocardial perfusion defects in the absence of obstructive coronary artery disease. J Nucl Cardiol, 2006; 13: 756–760.
11. Sharma R, Pellerin D, Gaze DC et al. Dobutamine stress echocardiography and the resting but not exercise electrocardiograph predict severe coronary artery disease in renal transplant candidates. Nephrol Dial Transplant, 2005; 20: 2207–2214.
12. Karthikeyan V, Ananthasubramaniam K. Coronary risk assessment and management options in chronic kidney disease patients prior to kidney transplantation. Curr Cardiol Revi, 2009; 5: 177–186.
13. Escolar E, Weigold G, Fuisz A, Weissman NJ. New imaging techniques for diagnosing coronary artery disease. CMAJ, 2006; 174:487–495.
14. 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: 122–126.
15. Herzog CA, Marwick TH, Pheley AM, White CW, Rao VK, Dick CD. Dobutamine stress echocardiography for the detection of significant coronary artery disease in renal transplant candidates. Am J Kidney Dis, 1999; 33:1080–1090.
16. 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: 1724–1732.
17. Mehrotra R, Budoff M, Hokanson JE, Ipp E, Takasu J, Adler S. Progression of coronary artery calcification in diabetics with and without chronic kidney disease. Kidney Int, 2005; 68: 1258––1266.
18. Braun J, Oldendorf M, Moshage W, Heidler R, Zeitler E, Luft FC. Electron beam computed tomography in the evaluation of cardiac calcifications in chronic dialysis patients. Am J Kid Dis, 1996; 7: 394–401.
19. Raggi P, Boulay A, Chasan-Taber S et al. Cardiac calcification in adult hemodialysis patients: A link between end-stage renal disease and cardiovascular disease? J Am Coll Cardiol, 2002; 39: 695–701.
20. Sharples EJ, Pereira D, Summers S et al. Coronary artery calcification measured with electron-beam computerized tomography correlates poorly with coronary artery angiography in dialysis patients. Am J Kid Dis, 2004; 43: 313–319.
21. Blacher J, Guerin AP, Pannier B, Marchais SJ, London GM. Arterial calcifications, arterial stiffness, and cardiovascular risk in end-stage renal disease. Hypertension, 2001; 38: 938–942.
22. London G, Guérin A, Marchais S, Métivier F, Pannier B, Adda H. Arterial media calcification in end-stage renal disease: Impact on all-cause and cardiovascular mortality. Nephrol Dial Transplant, 2003; 18: 1731–1740.
23. El-Abbadi M, Giachelli C. Arteriosclerosis, calcium phosphate deposition and cardiovascular disease in uremia: Current concepts at the bench. Curr Opin Nephrol Hypertens, 2005; 14: 519–524.
24. Gallucci M, Tomassini M, Simonetti G et al. Cardiac calcifications: Fetuin-A and other risk factors in hemodialysis patients. ASAIO J, 2006; 52: 150–156.
25. Fujimoto N, Iseki K, Tokuyama K, Tamashiro M, Takishita S. Significance of coronary artery calcification score (CACS) for the detection of coronary artery disease (CAD) in chronic dialysis patients. Clinica Chimica Acta, 2006; 367: 98–102.
26. Haydar AA, Hujairi N, Covic AA, Pereira D, Rubens M, Goldsmith D. Coronary artery calcification is related to coronary atherosclerosis in chronic renal disease patients: A study comparing EBCT-generated coronary artery calcium scores and coronary angiography. Nephrol Dial Transplant, 2004; 19: 2307–2312.
27. O'Rourke RA, Brundage BH, Froelicher VF et al. American College of Cardiology/American Heart Association Expert Consensus Document on Electron-Beam Computed Tomography for the Diagnosis and Prognosis of Coronary Artery Disease. Circulation, 2000; 102: 126–140.
28. Bild DE, Detrano R, Peterson D et al. Ethnic differences in coronary calcification: The Multi-Ethnic Study of Atherosclerosis (MESA). Circulation, 2005; 111: 1313–1320.