Coronary Calcium Score as Predictor of Stenosis and Events in Pretransplant Renal Chronic Failure

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Abstract

Background: Coronary artery disease (CAD) is the major cause of death among chronic renal failure (CRF) patients. Traditional, non-invasive exams to detect CAD and to predict events have shown insufficient results in this group. CT Scan evaluation of Coronary Calcium Score (CCS) has proven to be of prognostic value for the population reporting no renal condition.

Objective: To investigate CCS accuracy in detecting obstructive CAD and in predicting cardiovascular events in candidates to renal transplant as compared to quantitative invasive coronary angiography (ICA).

Methods: Ninety-seven (97) CRF patients aged ≥ 35 were evaluated. Obstructive CAD was considered as ≥50% or ≥70% stenosis on ICA. Descriptive data, concordance, diagnostic tests, Kaplan-Meier, and multivariate analysis were used.

Results: Agatston mean score was 580.6 ± 1102.2. Minimum and maximum values were 0 and 7994, with median at 176. Only 14 patients had zero calcium score. No differences were reported in regard to ethnicity. Highest regional calcium was associated to the highest probability of coronary stenosis in the same segment. Agatston calcium score showed high accuracy for the diagnosis of ≥50% and ≥70% stenosis, with area under ROC curve (AUC) of 0.75 and 0.70, respectively. At the threshold of 400, calcium score identified a subgroup with a higher rate of cardiovascular events at an average follow-up time of 29±11.0 months.

Conclusion: CCS proved to have good diagnostic and prognostic performance for cardiovascular events evaluation in CRF patients. (Arq Bras Cardiol 2010;94(2): 236-243)

Key Words: Tomography, emission-computed; calcio score; coronary artery disease; renal insufficiency, chronic; determination; prognostic.

Introduction

Coronary Artery Disease (CAD) is the major cause of death among chronic renal failure (CRF) patients[1]. The risk of death from CAD in this group of patients is higher than in the general population. Depending on CRF stage[2], cardiovascular risk may be significantly increased. Depending on the population under study, patients on dialysis – CRF stage 5 – cardiovascular risk is reported to be from 20 to 1,000 times higher than for the general population with no renal condition[2]. Among patients on hemodialysis or peritoneal dialysis coronary disease prevalence is approximately 40%[1]. In the United States, 10% of all patients on dialysis die from heart diseases every year. It has been consensual that CRF patients must be considered as high risk for the development of cardiovascular events. Therefore, they are to be submitted to frequent cardiovascular evaluation[3]. In the same group, diabetes mellitus poses a mortality risk level similar to that posed by CAD[4].

Non-invasive tests used for CAD evaluation in CRF patients have the purpose of identifying CAD condition and evaluating the risk of cardiovascular events and death[5].

In patients with CRF and high risk for CAD, the prevalence of CAD and the incidence of major adverse cardiovascular events (MACE) are high. Therefore, the best diagnostic methods available are to be used in order to reach improved prognostics for CAD. At InCor (Instituto do Coração - Heart Institute, São Paulo, Brazil) the specialized CRF service found that significant CAD as well as cardiovascular complications are not associated to most classic risk factors in this specific group of CRF patients. The authors conclude that patients presenting diabetes, peripheral artery disease, and previous infarction are under high risk of CAD, MACE, or both. Therefore, they must be submitted to invasive diagnostic procedure[6]. As for CAD evaluation strategies for those patients and their association to prognosis, De Lima et al[7] have published conclusive data

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showing that invasive coronary angiography (ICA) proved to be of higher prognostic value for CAD evaluation when compared to non-invasive tests (nuclear medicine and stress ECG)[7]. That paved the way for the investigation of new non-invasive diagnostic methods not yet under use for this group of CRF patients and which had been showing good performance in CAD patients in the general population. Among those new methods are the following: cardiovascular MRI and multi-detector CT (MDCT), to evaluate coronary calcium score and to detect coronary stenosis (CT coronary angiogram).

One of the key reasons to evaluate the presence of CAD is to use that information as prognostic data, since the information provides an estimate of individual risks to cardiovascular events and the adjustment of proper therapeutic and preventive actions against the risks posed to a specific patient. While ICA has proven to be a very effective prognostic exam[7], the new MDCT techniques have not been extensively tested in pretransplant CRF patients.

Therefore, our assumption was that MDCT may be useful for the diagnosis of significant CAD as well as for prognostic estimate in CRF patients who are candidates for renal transplant. Our objective was to investigate whether coronary calcification detected by MDCT can be a predictor for coronary stenosis and cardiovascular events in CRF patients.

Methods

Ninety-seven (97) CRF patients already in a hemodialysis program and referred to to be submitted to renal transplant, and with clinical indication for ICA were included. The clinical indication for ICA was based on the fact that the patients belonged to the group under high risk for CAD either due to symptoms and/or previous invasive exams that would lead to a suspicion of CAD. Patients considered high risk were those who presented at least one of the following criteria:

1) Age ≥50;

2) *Diabetes mellitus*;

3) history or clinical evidence of cardiovascular disease[8]. Screening was done by the CRF specialized outpatient unit at the Hypertension Service, Heart Institute, University of São Paulo at São Paulo. In that service, the management of high risk patients or patients with suspicion of CAD includes ICA for its better prognostic performance[7]. Nonionic iodinated contrast was performed after the exclusion of contra-indication to the study and after the informed consent was signed. The project was approved by the Ethics and Research Committee at InCor and HCFMUSP (Medical School Clinics Hospital, University of São Paulo - CAPEPesq, 0195/04) and was sponsored by the State of São Paulo (FAPESP, 2004-08363-6). Inclusion criteria included: males or females who were 35 years old or older and with CRF and on a dialysis program, candidates for renal transplant, and with clinical indication for ICA, with a 1-year maximum MDCT interval (performed 1 year at maximum before the inclusion, or with ICA planned for the following months). Exclusion criteria included: known allergy to iodinated contrast media; atrial fibrillation, tachyarrhythmia or advanced atrioventricular block; evidence of symptomatic, severe heart failure (NYHA class III/IV); known aortic stenosis; previous heart surgery; coronary stent; known intolerance or contra-indication to beta-blockers, such as bronchospastic pulmonary disease.

For the purpose of the present study, ≥50% stenosis stood for significant CAD in major coronary branch, with luminal diameter larger than 1.5 mm as identified on ICA. Secondary analysis also focused ≥70% stenosis, as well as segmental analysis in those 2 threshold levels.

From the 97 patients available for the study, 63 (65.0%) were males and 34 (35.0%) were females. Mean age ± SD was 56.7±7.4 (Table 1). Minimum age was 35 and maximum, 76.

Table 1 - Continuous variables for anthropometry basic exams

Variable	Mean	Standard deviation	Min.	Max
Age (years)	56.7	7.4	35	76
Weight (kg)	68.7	14.5	40	107
Height (m)	1.62	0.08	1.37	1.85
BMI	26.1	5.6	17.1	44.2
SBP (mmHg)	175.8	32.4	100	280
DBP (mmHg)	102.6	17.2	70	150
Time on dialysis (months)	40.2	42.1	2	240
Creatinine (mg/dL)	8.9	2.8	4.3	18
Cholesterol (mg/dL)	181.2	45.7	85	304
Triglycerides (mg/dL)	157.2	114.6	32	602
Hematocrit (%)	35.8	5.8	21	48
Blood glucose level (mg/dL)	117.3	64.7	59	364
HR (bpm)	61.1	6.9	40	77

BMI - body mass index, SBP - systolic blood pressure, DBP - diastolic blood pressure, HR - heart rate (beats per minute - bpm).

Prevalence of traditional risk factors for CAD was the following: Systemic arterial hypertension - 87 (89.6%), diabetes mellitus - 37 (38.1%), dyslipidemia - 33 (34.0%), arteriopathy 33(34.0%), angina - 28 (28.9%), current smoking habits - 20 (20.6%), family history of CAD - 18 (18.6%), CVA - 12 (12.4%), CHF - 8 (8.2%), AMI - 7 (7.2%). It should be pointed out that patients who presented any symptom or angina were all stable, and the symptoms had occurred after to the indication for invasive coronariography. No patients with indication for coronariography to investigate recent onset chest pain (and potentially unstable) were included. Therefore, all patients included in the Protocol were asymptomatic at the time of inclusion.

The anthropometric data from our sample, as well as heart rate (HR) at the time of CT are detailed in Table 1. Dialysis mean time was 40.2±42.1 months, with 26.5 months as median, for a minimum time of 2 months and a maximum time of 240 months.

Image acquisition protocol by *MDCT.*

MDCT exams were performed in 16 and 64-column detector-row (*Aquilion16*™ and *Aquilion64*™ - *Toshiba*™ *Medical Systems Corporation*, Otawara, Japan) at InCor - HCFMUSP.

Patients were informed about exam details, and positioned at the MDCT table in dorsal decubitus, dislocated towards the right, keeping their heart at X-Ray central focus. All patients were monitored electrocardiographically for synchronization with image acquisition and heart rate (HR) follow-up during the exam. Patients' arms were positioned above their head, and ECG leads off scan field.

Patients' heart rate (HR) during the exam was 61.1±6.9 bpm. Patients with heart rate (HR) above 70bpm at the time they reached CT Scan location received IV beta-blocker, metoprolol at the proper dose to reach target HR (60bpm) or to the maximum dose (15mg), since their protocol included associated coronary angiotomography acquisition. Heart rate was always measured during respiratory pause.

MDCT protocol - image acquisition

At a first moment the so-called scout images were obtained. Based on the first image, a scanning window would be visually established, covering from tracheal bifurcation (carina) up to the inclusion of cardiac silhouette. This design was used to obtain calcium score.

Calcium score was then obtained through prospective acquisition, and synchronized to ECG tracing. Images acquired were 3.0 mm thick, and view field was from 200 to 220mm for chest axial images covering all cardiac area and allowing the visualization of coronary arteries and possible calcification on coronary artery topography. Images were acquired at a diastolic moment that was defined following patient's heart rate. Calcium score required an average 15s inspiratory pause as per validated Protocol[9] to be obtained Calcium score parameters were: 0.75s tube rotation speed, 4.0 x 3.0 mm detector collimation, 120 kV tube voltage, and 300 mA tube flow.

Invasive coronary angiography acquisition

Coronary angiographies were performed using renowned techniques that have been standardized at InCor, HC-FMUSP[10] hemodynamics service techniques and with clinical indication that is independent from the research Protocol.

Follow-up of cardiovascular events

Follow-up data were obtained from at least one of the three sources:

1) routine visit at specialized outpatient unit;

2) telephone call to patient or relative to check on patient's health status;

3) review of patient's medical record.

The Protocol considered the following as cardiovascular events: cardiac death (consensually declared by 2 cardiologists after reviewing available data); acute myocardial infarction (AMI) (threefold enzyme increase as compared to normal values, associated to acute chest pain and/or ECG changes that are compatible with myocardial ischemia), cerebrovascular accident (clinical or imaging diagnosis), severe peripheral vascular disease or gangrene (severe ischemia of limbs leading to associated surgical procedure), Unstable angina (typical chest pain, ECG changes that are compatible with myocardial ischemia in patients presenting the likelihood of moderate CAD at least), congestive heart failure (clinical diagnosis and echocardiogram showing reduction of LV ejection fraction), and acute lung edema (clinical diagnosis and chest X-Ray, with evidence of interstitial pulmonary edema).

Data analysis

Calcium score analysis

Total calcium score – as per method described by Agatston et al[9] - was obtained for each patient (Figure 1) through workstation *Vitrea*™2, version 3.5 - *Vital Images Inc*, Plymouth, MN, EUA. For calcium score images analysis, two measures

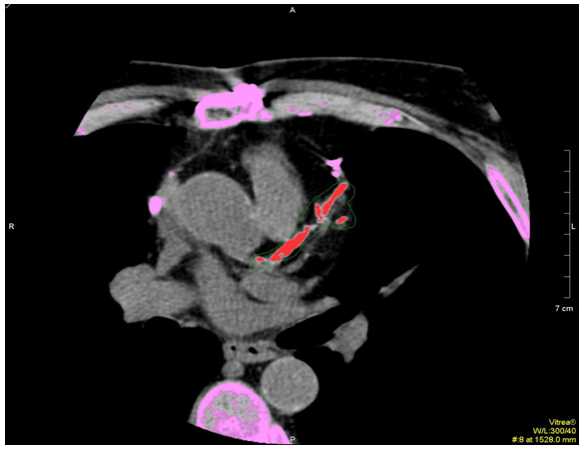

Figure 1 - *Example of Coronary Calcium Score to show significant calcification in anterior descending artery territory (in red).*

were used: Agatston[9] Score and calcium volume. Agatston Score has been most commonly found in the literature. It keeps an association with coronary disease and even with obstructive CAD if at very high levels (percentile above 75% or at 90%).

Quantitative coronary angiography (QCA)

An observer experienced in QCA technique and who did not participate in the MDCT analysis - also blind and independent - analyzed all ICA by using *QCA* (Coronary Analysis Angiographic System - CASS II, *Pie Medical Imaging BV* ™, Maastricht, The Netherlands)[11-14].

Stenosis diameter - visually considered at least as intermediate (≥ 50%) - was objectively, percentually assigned in relation to "reference diameter" (the diameter of the same vessel that was disease free, immediately proximal to stenosis). The diameter is determined orthogonally, with average determining final stenosis severity.

All injuries with reference diameter ≥ 1.5 mm were included in the comparative analysis for the present study. Should the same segment in main artery or first order branch present more than one significant stenosis, only the most severe stenosis would be compared to its correspondent through MDTC[10,15,16].

Statistical analysis

Descriptive variables were expressed as means, SD and medians, whenever appropriate. Having presented an asymmetric distribution curve, coronary artery calcification levels were expressed through medians, percentiles, and end points.

With the purpose of establishing MDCT diagnosis accuracy, the authors resorted to a classic 2x2 table.

Fisher exact test was used to calculate MDCT diagnosis accuracy as compared to *QCA* in regard to the identification of ≥ 50% and ≥ 70%.coronary stenosis. In order to compare the different coronary calcium scores obtained through MDCT at corresponding sites, Mann-Whitney test was used.

Kaplan-Meier curves were also used for time events analysis in the different subgroups. All analyses were performed using Stata™/SE 8 (StataCorp LP, College Station, TX).

Results

Agatston mean score for the sample of CRF patients was 580.6 ± 1,102.2. Minimum and maximum values ranged from 0 to 7,994. Out of the 97 patients analyzed for calcium score, only 14 patients failed to have detectable coronary calcification, which means to say, zero calcium score. Table 2 also shows score values and total volume for the whole coronary tree as well as specific coronary territories, with means, SD, medians, and minimum and maximum values for each category. Table 3 shows percentiles for age and gender. Mean percentile values for age, gender, and ethnicity based on the MESA (Multiethnic Study of Atherosclerosis) Study are referred to as MESA in Table 3.

CCS distribution is significantly asymmetric. Therefore, total Agatston score median as well as its percentile distribution have been reported (Table 3).

As for patients ethnicity, no significant CCS difference was reported in the different ethnic groups.

Table 2 - Global and regional calcium score

Agatston score	Median	Mean	Standard deviation	Min.	Máx.
Total	176.0	580.6	1,102.2	0	7,994
Cx	3.5	153.8	390.7	0	2,091
DA	74.0	229.7	331.4	0	1,559
L Main	0	24.2	52.3	0	245
RCA	7.0	181.1	519.5	0	4,358
Calcium volume					
Total	178.0	531.5	900.5	0	6,169
Cx	8.5	138.00	315.9	0	1,623
DA	92.0	201.5	268.9	0	1,249
L Main	0	21.4	42.5	0	195
RCA	19.0	171.9	421.9	0	3,350
Percentile (%)	90.0	67.0	37.4	0	100
MESA (%)	91.0	70.0	37.9	0	99
CAD < 50%*	36.5	221.4	463.5	0	2,687.0
CAD ≥ 50%*	439.0	854.9	1,349.0	0	7,994.0
CAD < 70%*	127.0	372.9	646.7	0	3,620.0
CAD ≥ 70%*	625.0	1,179.0	1,766.0	0	7,994.0

*MESA - multiethnic study of atherosclerosis. * P < 0.01 between presence and absence of significant CAD (≥ 50% or ≥ 70%).*

Calcium score *versus* coronary stenosis

Calcification level between patients with or without significant obstructive coronariopathy (stenosis ≥70%) was compared. It was demonstrated through Wilcoxon test (Table 2) that Agatston score is significantly higher in the group reporting significant CAD on catheterization. Time elapsed between MDCT ICA was in average 99.03 days, SD 87.65 days, and median 79 days. Minimum interval was 2 days, and maximum interval was 380 days. Only 2 cases exceeded 1 year, and 16 cases had an interval over 6 months.

Patients with ≥ 50% and ≥ 70% coronary stenosis on ICA were assessed for the different CCS extracts. A significant, progressive, linear increase in the number of CAD patients and coronary calcification level (Figure 2) could be observed. A total of 55/97 (57%) patients presented stenosis from ≥50% ICA; and 25/97 (26%) from ≥70%.

When coronary calcification was evaluated against ICA it could be observed that for ≥ 50% and ≥ 70% stenosis Agatston's score of 400 threshold was statistically associated to a higher number of significant stenosis ($p < 0.001$, by Chi-square, Figure 2).

Regional analysis of calcium score also showed the same differences as observed for global score, except on left main coronary artery. Therefore, regional scores were significantly higher in segments with ≥ 50% and 70% when compared to segments with no stenosis.

Calcium score accuracy in coronary stenosis diagnosis was also evaluated using the MESA Study (75th percentile). Data can be found in Table 4.

From the 14 zero calcium score patients, 4 (28%) presented ≥50% stenosis on ICA and only 2 (14%) ≥ 70% stenosis. While using binary calcium score - zero or higher than zero - as a predictor for coronary stenosis, our sample showed a negative predictive value: 71% for ≥50% stenosis and 86% for ≥70% stenosis.

Calcium score as a predictor for coronary stenosis

The authors also investigated - by logistic regression and ROC curves - whether calcium score is successful in predicting coronary stenosis on ICA.

They investigated the accuracy of calcium score through ROC curve analysis both for the 50% stenosis threshold (AUC = 0.75) and the 70% threshold (AUC = 0.70), as defined on ICA (Figure 3 - A for 50% and B for 70% threshold).

Based on logistic regression and on ROC curves, the authors could say that calcium score does predict ≥50% coronary stenosis on ICA, at 186.53 as the best threshold, 66% accuracy, 65% sensitivity, 66% specificity, 72% positive predictive value and 60% negative predictive value (p=0.01).

Likewise, calcium score does predict ≥70% coronary stenosis on ICA, at 1330.72 as the best threshold, 65% accuracy, 64% sensitivity, 65% specificity, 39% positive predictive value and 84% negative predictive value (p=0.01).

Table 3 - Calcium Score Distribution (Calcium Score – Agatston Score) and Confidence Interval

Percentil	Sample values	[95% conf. interval	MESA study values*
5	0	0 – 0	0
10	0	0 – 1	0
25	10.5	1 – 55.1	0
50	176	78.9 – 360.7	13
75	626	446.6 – 856.8	97
90	1757.4	859.3 – 2712.8	303
95	2699	1743.9 – 6114.9	555

Percentiles estimated for white, 57-year-old asymptomatic males, with previous coronary or vascular disease, in the MESA study (The Multi-Ethnic Study of Atherosclerosis).

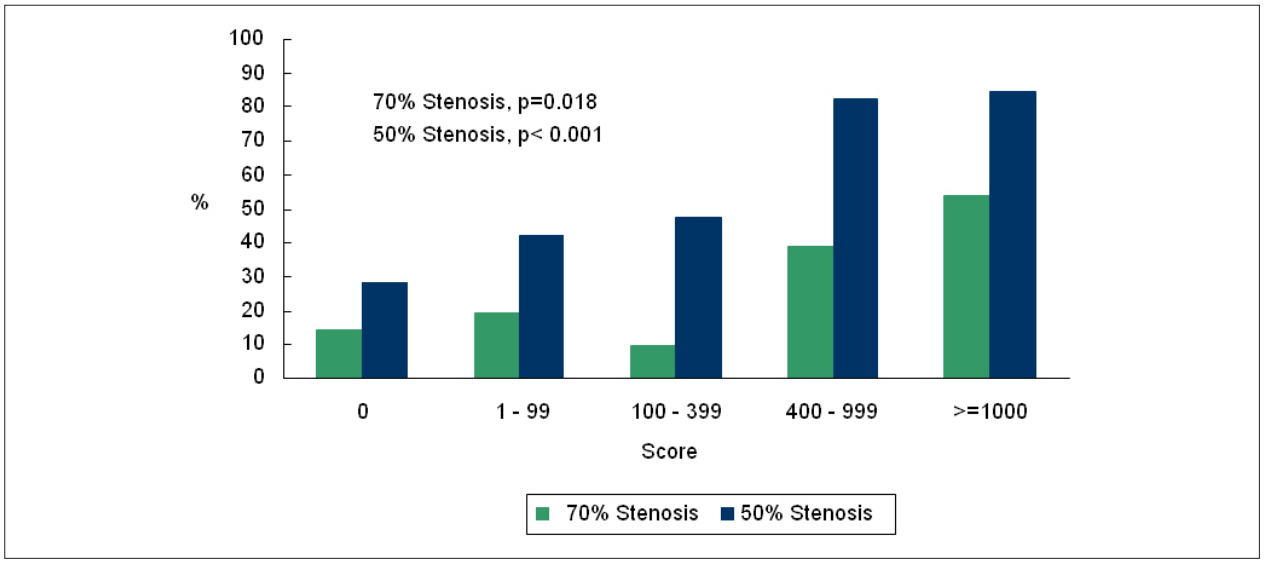

Figure 2 - Number of patients with significant CAD on ICA in the different calcium score extracts.

Table 4 - Diagnostic accuracy of calcium score 75th percentile on MESA study *vs* ICA (n=97 patients)

Stenosis	S	E	PPV	VPN	A	Kappa	p
≥ 50%	81,8%	55,8%	70,3%	70,6%	70,4%	0,39	<0,001
≥ 70%	84,0%	41,1%	32,8%	88,2%	52,0%	0,17	0,011

S - sensitivity, E - specificity, PPV - positive predictive value, VPN - negative predictive value, A - accuracy, Kappa - Kappa Test, p - Kappa statistic significance.

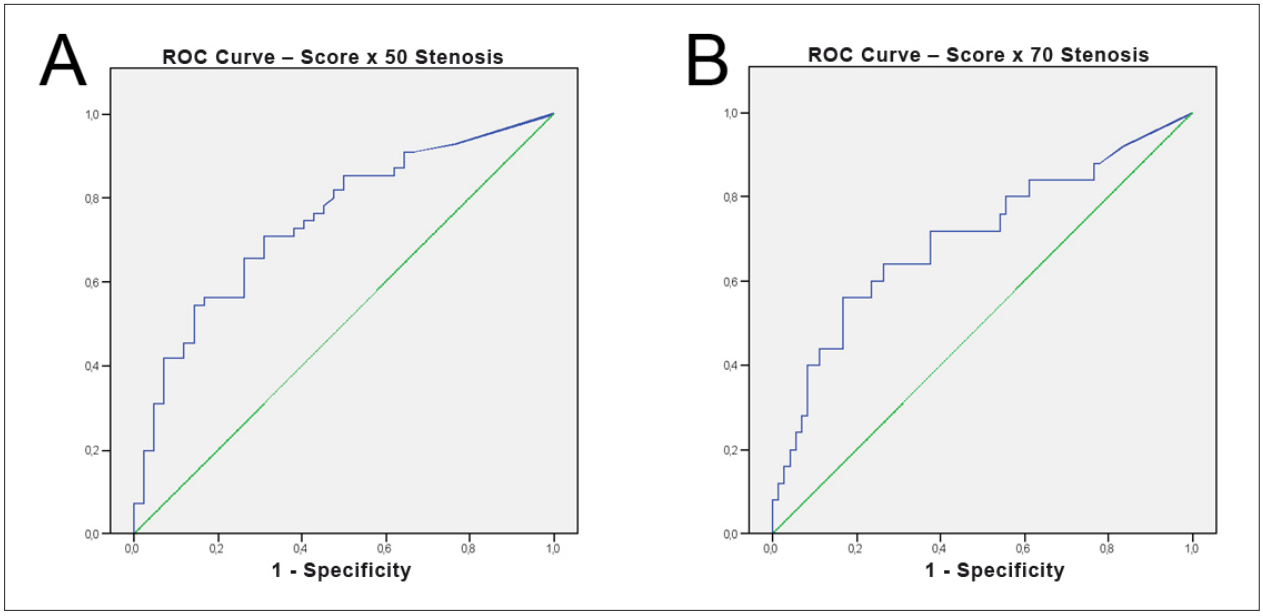

Figure 3 - ROC Curve of Calcium score (Agatston) for ≥ 50% and ≥70% stenosis on ICA (AUC = 0.75 ,75 and 0.70).

Those thresholds were also the ones to present the best possible negative predictive values, therefore answering the question as to the calcium score level that can be predictive of the absence of significant stenosis.

Calcium score *versus* cardiovascular events

Average follow-up time for the evaluation of events in our population was 29.1±11.0 months, with median at 31 months, and minimum follow-up time of 3 months, and maximum of 43 months. Events observed and their absolute frequency were: acute myocardial infarction (AMI) (8), cerebrovascular accident (5), severe peripheral vascular disease or gangrene (4), unstable angina (2), sudden death (2), congestive heart failure (1), and acute lung edema (1). The total number of events was 23. Out of the 97 patients, 23 presented events (23.7% in the sample). No events were reported by 71 patients; and 3 were lost to follow-up.

As for CCS as a predictor in this population, the authors observed that MESA study percentile for the same population did not prove to be a significant predictor, either for percentile 75th and 90% threshold.

Also while analyzing events, the authors investigated calcium score as predictive of events at different cut-off thresholds: 0 (presence or absence), 10, 100 and 400. The 400 calcium score threshold showed Kaplan-Meier curves with rate of significantly different events (Figure 4).

Discussion

The present research work was the first to show that MDCT does provide prognostic information about CRF patients who are candidates for renal transplant.

CCS proved to have a correlation with the presence of stenosis, as well as good diagnostic performance in regard to ICA in detecting stenosis. It also showed prognostic performance of Agatston score of 400 as cut-off point in our population.

Average scores showed to be quite high. Scores above 300 or 400 have been reported in the literature for non-CRF patients as associated to a high probability of obstructive CAD and high risk of cardiovascular events[17,18].

CRF patients on dialysis have reported a 2.5 fold magnitude for coronary calcification[19-22]. However, such high level has mostly been related to traditional CAD risk factors in this population rather than factors associated to renal function of dialysis[23]. Vascular calcification is described as related to dialysis. It is called uremic arteriopathy, and is characterized by diffuse calcification of artery middle layer, and thrombosis that may result in ulcer and skin necrosis. It is not yet clear to what extent that mechanism may influence coronary artery calcification in this group of patients[24].

Although only a partial correlation could be observed between calcification and coronary obstruction in the general

population[18], good diagnostic correlation and accuracy could be seen between calcium score and coronary stenosis through MDCT and ICA in the CRD group of patients. Percentile 75th in the MESA study showed 82% sensitivity and 84% detection for CAD with ≥ 50% and 70% obstructive stenosis respectively. The outcome seems to be highly encouraging for the use of such simple technique, with low radiation level and no need for contrast agents. Those sensitivity levels are not typically reached, not even by pharmacological stress tests such as scintigraphy and echocardiogram. In a study conducted by our group using a cardiac MRI dipyridamole stress test and scintigraphy, 84% and 66% sensitivity levels were respectively obtained for this population of patients[25]. However, both MRI and other stress tests are complex, time-consuming, and quite expensive tests, posing higher risk to patients when compared to calcium score.

The use of absolute calcium score provided sensitivity levels lower than those reached by 75th percentile. Therefore, the authors have concluded that MESA study 75th percentile was the most accurate to detect CAD when compared to absolute calcium score. Absolute calcium score best accuracy to detect stenosis was ≥50%, while ICA was 186. Those threshold values have reported the best possible negative predictive value in the sample. Therefore, our data indicate that <186 calcium score - or under 75th percentile – may rule out significant coronary stenosis at a level close to 90% in this group of patients. So, calcium score seems to be even more significant in the CRF group of patients. That correlation showed to be true both for global and regional Agatston score. It should also be pointed out that coronary angiotomography may be of limited effectiveness for patients reporting high calcification level for luminal reduction evaluation, although special techniques and experienced observers may turn such assessment clinically useful[26].

Data in the literature have shown calcium score as a more effective predictor of cardiovascular events when compared to coronary stenosis for patients in the general population[17]. MESA study has recently confirmed such data in the different ethnic groups[27], thus emphasizing the prognostic role played by calcium score. The present study has shown that the correlation between calcium and events among CRF patients was significant for Agatston score of 400, thus suggesting that it may be used as predictive prognostic threshold. Therefore, out data suggest that in the CRF group of patients calcium score does hold predictive value not only for events but also for the detection of coronary stenosis, differently from what was observed in the general population. In that respect, the 7 patients with previous myocardial infarction were a limiting component faced by the present study, since that may have increased the diagnostic power of the test in this specific population. However, when those patients were excluded in a sensitivity analysis, no significant change was observed in the diagnostic performance of calcium score in our group.

On the other hand, our study has resorted to recently described, advanced methodology for coronary tree segmentation and for statistical analysis[28], which stands for some evolution in the scientific method in this field. Our groups has used it in a highly impacting multicenter study[29].

Some relevant implications from the results in the present study, associated to data collected by the authors as well as available in the literature, may be found to be of clinical use.

Considering the high number of ICA reporting absence of CAD or non-obstructive CAD (approximately 40%)[30], associated to characteristics of the excellent safety profile shown by calcium score, as well as the low cost and good sensitivity level shown by the present study results for CRF patients, it seems it is a good, cost-effective tool for the detection of CAD. Cost-effectiveness was not an objective in the present study. That should be done in future projects that focus this kind of analysis in a direct fashion.

Conclusion

The authors state that calcium score through CT Scan

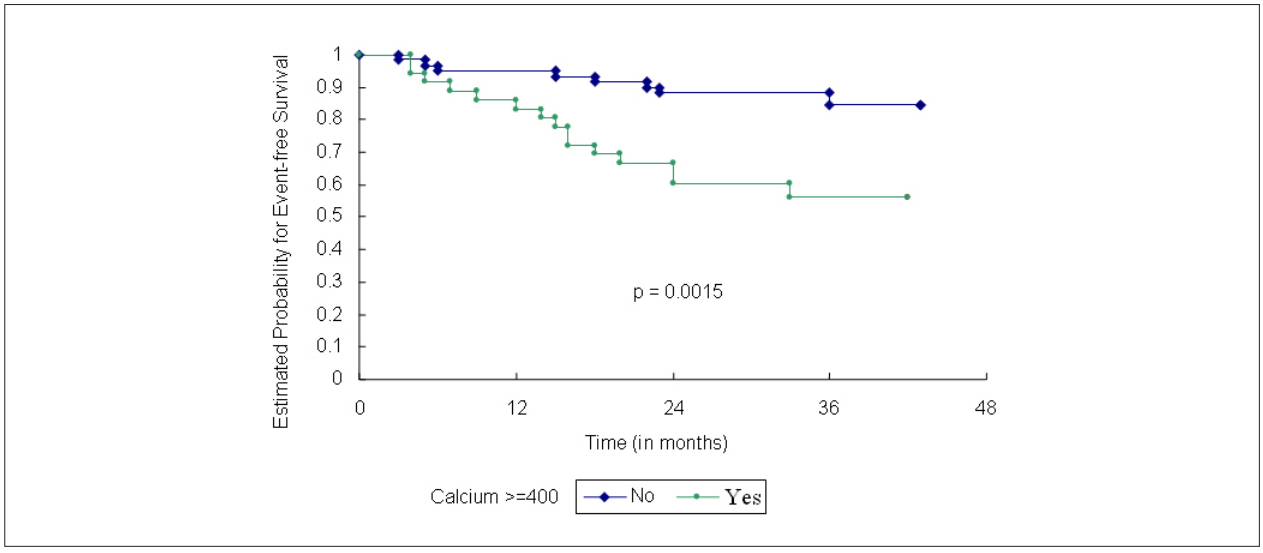

Figure 4 - Kaplan-Meier Curve for calcium score ≥ 400 and cardiovascular events.

has shown to be a good diagnostic predictor of coronary stenosis (75 percentil and 186 absolute value), and a good prognostic predictor of cardiovascular events (400 absolute value) among renal failure patients.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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