Progression of coronary artery calcification and cardiac events in patients with chronic renal disease not receiving dialysis

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We tested for the presence of coronary calcifications in patients with chronic renal disease not on dialysis and studied its progression in 181 consecutive non-dialyzed patients who were followed for a median of 745 days. Coronary calcifications (calcium score) were tallied in Agatston units by computed tomography, and the patients were stratified into two groups by their baseline calcium score (100 U or less and over 100 U). Survival was measured by baseline calcium score and its progression. Cardiac death and myocardial infarction occurred in 29 patients and were significantly more frequent in those patients with calcium scores over 100 U (hazard ratio of 4.11). With a calcium score of 100 U or less, the hazard ratio for cardiac events was 0.41 and 3.26 in patients with absent and accelerated progression, respectively. Thus, in non-dialyzed patients, the extent of coronary calcifications was associated to cardiac events, and progression was an independent predictive factor of cardiac events mainly in less calcified patients. Hence, assessment of coronary calcifications and progression might be useful for earlier management of risk factors and guiding decisions for prevention of cardiac events in this patient population.

In incident and prevalent patients on dialysis, vascular calcifications are frequent. The results of the first seminal report showing that dialysis patients have remarkably higher incidence of coronary artery, mitral, and aortic valve calcification[1] have been repeatedly confirmed in recent years; hence, latest guidelines have included the detection of extra osseous calcification as a test for diagnosing mineral and bone disorders in chronic kidney disease (CKD).[2]

Vascular calcifications, namely, coronary artery calcifications (CACs), are regarded as markers of severe vasculopathy[1–5] and strong predictors of cardiovascular events.[2,4–6] Importantly, both in young[7] and adult dialysis patients,[1,6,8,9] calcifications progress more rapidly than in controls; the progression is an additional independent factor responsible for cardiovascular events.

CACs are present even in patients at early stages of CKD (CKD patients). Indeed, CACs were found in almost one half of non-diabetic predialysis patients (CKD stages 3–5);[10] higher prevalence of CAC in CKD patients compared with controls has been subsequently confirmed by larger studies that have included diabetic CKD patients.[11–14]

Faster progression of calcifications has been observed in CKD patients;[15–19] the underlying mechanisms are still not well determined. In fact, although in dialysis patients, the progression of calcification seems to be linked to deranged mineral metabolism,[7–9] in CKD patients, this link has not been confirmed[15–17,19] despite faster progression of CAC occurred in patients with high-normal serum phosphorus[15] and progression was reduced by binding the ion.[16]

Mild-to-moderate elevations in serum creatinine levels are associated with increased rates of all-cause[20,21] and cardiovascular mortality.[20,22,23] Thus, CKD patients are more exposed to risk of mortality than to start renal replacement therapy.[24,25] Multiple possible explanations exist for the association between CKD and increased mortality. Reduced kidney function is associated with independent and strong

risk factors, such as inflammation, abnormal apolipoprotein levels, elevated plasma homocysteine, enhanced coagulability, anemia, left ventricular hypertrophy, and endothelial dysfunction.[22,24–26]

The aim of the present study is to ascertain a potential association between the presence and progression of CAC with cardiac events in CKD-patients not on dialysis. This association has never been evaluated before.

RESULTS
Study population
The initial cohort consisted of 188 consecutive asymptomatic CKD patients who fulfilled the inclusion criteria. Seven patients (3.7%) were lost at the follow-up: three moved to another clinic and four withdrew the consent; thus, the final cohort was represented by 181 patients. No racial/ethnic-based differences were present. In the whole-cohort study, kidney diseases were: glomerulonephritis 27% (20.5–33.6, confidence interval, CI), ischemic nephropathy 11% (6.4–15.7, CI), biopsy-proven diabetic nephropathy 8.3% (4.2–12.3, CI), and other diseases 28.8% (19.5–32.4, CI); renal disease was unknown in the remaining cases. Median duration of diabetes was 174 months (48–228, interquartile range, IQR); hypertension was present in 95.6% (92.6–98.6, CI), with a median duration of 72 months (32–130, IQR). Patients were followed-up for a median time of 745 days (403–1078, IQR).

During the observation, time-measured creatinine clearance remained stable and no patient required dialysis treatment.

At baseline, CACs were found in 54.7% (47.4–61–9, CI) of the whole study population. Among males and females, there was no significant difference in incidence of calcification (56.8% (40.8–72.7, CI) and 55.5% (47.4–63.7, CI), respectively) and median CAC score (107 Agatston unit (AU; 36–145.5, IQR) and 168 AU (72.7–341.2, IQR), respectively). Median CAC score was 109 AU (55–220, IQR), 153 AU (37–257, IQR), 177 AU (87–454, IQR), and 168 AU (84–311, IQR) in patients at stages 2, 3, 4, and 5, respectively.

Patients were divided in two groups ($\leqslant 100$ and > 100 AU) according to baseline CAC score. The median interval between first multislice computed tomography (MSCT) and cardiac event or end of the study was 689 days (410–922, IQR) and 820 days (380–1178, IQR) in patients with CAC score $\leqslant 100$ and > 100 AU, respectively. Baseline characteristics of the two groups are reported in Table 1. Patients with CAC score $\leqslant 100$ AU (range: 0–98; mean: 14.6 ± 27.3 (s.d.); and median: 0 (0–17, IQR)) were 119; patients with CAC score > 100 AU (range: 105–2860; mean: 384.7 ± 453.8 (s.d.); and median: 234 (163–430, IQR)) were 62. CAC score was > 1000 AU in four patients of the latter group. Patients with CAC score > 100 AU were more likely to be older ($P = 0.0001$) and to have diabetes (28.8% (17.1–40.6, CI) versus 7.6% (2.8–12.4, CI; $P < 0.0002$)), hypertension (100 versus 93.3% (88.8–97.8, CI; $P = 0.0368$)), longer duration of hypertension (median duration: 120 months (48–170, IQR) versus 62 months (24–120, IQR); $P < 0.005$).

No significant differences were observed between other variables of the two groups. In particular, there was no difference in measured creatinine clearance, in variables of mineral metabolism (intact parathyroid hormone, serum calcium, and phosphorus), lipids (total cholesterol, triglycerides, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol), inflammation (homocysteine, fibrinogen, and high-sensitivity C-reactive protein), nutrition (total protein and serum albumin), and anemia (hematocrit). Furthermore, no significant difference was found in therapy with calcium channel blockers, statins, and phosphate binders.

During the observation time, 29 patients (16%) had a cardiac event (cardiac death or myocardial infarction). The events occurred more frequently in patients with CAC score > 100 AU (27.5% (16.2–38.7, CI)) than in those with CAC score $\leqslant 100$ AU (7.6% (2.7–12.4, CI); $P = 0.0003$); in the former group, the hazard risk (HR) for cardiac events was 4.11 (1.77–9.57, CI; $P < 0.0006$).

Association between baseline CAC score and survival is shown in Figure 1. After adjustment for age, diabetes, glomerular filtration rate (GFR) (as 24-h-measured creatinine clearance), and hypertension, baseline CAC score > 100 AU was a significant ($P = 0.0017$) predictor of cardiac events.

In the whole study population, survival was also analyzed on the basis of the annualized progression of CAC score (absent: 25th percentile; moderate: 25th–75th percentiles; and accelerated: > 75th percentile); the results are shown in Figure 2. After adjustment for age, diabetes, GFR (as 24-h-measured creatinine clearance), hypertension, and baseline CAC score, survival was significantly ($P < 0.0068$) worse in patients with accelerated progression; in patients with absent or moderate progression, survival curves overlapped.

Finally, survival was assessed in two groups taking in account both baseline value of CAC score and progression. With CAC score $\leqslant 100$ AU, HR for cardiac events was 0.41 and 3.26 in patients with absent and accelerated progression, respectively; in contrast, with CAC score > 100 AU, HR was 4.72 and 2.97 in patients with absent and accelerated progression, respectively. Therefore, accelerated progression affected survival of patients with a low baseline CAC score by a greater extent compared with those with a high one. The final multiple Cox regression model is shown in Table 2. Among all potential confounders (listed in Table 1), only diabetes reached a P-value < 0.2 and entered into multiple Cox regression analysis. In this model, baseline CAC score and progression independently predicted cardiac events. In addition, stratification by both factors (baseline CAC score and progression) pointed out a possible effect modification. Baseline CAC score > 100 AU and accelerated progression (> 75th percentile) significantly interacted and reduced the risk of outcomes (HR < 1). Because of this interaction, HR was 4.2 (as a result of $8.4 \times 6.3 \times 0.08$) in patients with CAC score > 100 AU and accelerated progression; therefore, it was lower than that caused by each variable itself.

Table 1 | Baseline characteristics of patients stratified by CAC score

	CAC score ⩽100 AU (n=119)	CAC score >100 AU (n=62)	P
Demographics			
Age (years)[a]	54 (41–60)	62 (56–68)	0.0001
Female[b]	21.9 (14.3–29.3)	17.7 (8.1–27.4)	0.5156
Male[b]	78.1 (7.1–85.7)	82.3 (72.6–91.9)	0.5156
Clinical characteristics			
Diabetes[b]	7.6 (2.8–12.4)	28.8 (17.1–40.6)	0.0002
Hypertension[b]	93.3 (88.8–97.8)	100	0.0368
Duration of hypertension (months)[a]	63 (24–120)	120 (48–170)	0.005
Laboratory data[a]			
GFR (ml/s)	0.83 (0.40–1.30)	0.68 (0.40–1.16)	0.3983
Homocysteine (umol/l)	20 (15–29)	19 (14–30)	0.7500
Fibrinogen (μmol/l)	352.0 (300–414)	378.5 (307–406)	0.1767
hsCRP (mg/dl)	0.30 (0.30–0.39)	0.31 (0.30–0.42)	0.8079
Hematocrit (%)	40.9 (35.85–44.0)	39.95 (36.55–42.7)	0.7704
iPTH (pg/l)	6.2 (4.3–12.8)	6.2 (4.2–12.6)	0.7347
Calcium (mmol/l)	2.37 (2.27–2.45)	2.40 (2.30–2.50)	0.0586
Phosphorus (mmol/l)	1.2 (1.0–1.4)	1.1 (1.1–1.3)	0.3497
Total serum proteins (g/l)	74 (70–77)	74 (69–77)	0.7980
Serum albumin (g/l)	44 (41–46)	42 (40–46)	0.0755
UAE (mg/24 h)	625 (150–1780)	460 (90–2000)	0.5076
Serum bicarbonate (mmol/l)	25 (23–27)	25 (23–27)	0.8477
Total cholesterol (mmol/l)	4.9 (4.4–5.7)	4.8 (4.3–5.5)	0.5878
Triglycerides (mmol/l)	1.4 (1.0–1.9)	1.5 (1.2–2.0)	0.4624
HDL cholesterol (mmol/l)	1.2 (0.9–1.5)	1.2 (1.0–1.5)	0.9226
LDL cholesterol (mmol/l)	2.9 (2.4–3.6)	2.8 (2.3–3.4)	0.3067
Baseline therapy[b]			
Statins	37.1 (28.2–45.7)	46.8 (34.1–59.4)	0.2022
Calcium channel blockers	38.7 (29.8–47.5)	51.7 (38.7–64.8)	0.0992
Sevelamer	12.6 (6.6–18)	8.3 (1.2–15.4)	0.3918
Other binders	11.8 (5.9–17.6)	5.0 (−0.6–10.6)	0.0992

Abbreviations: AU, Agatston unit; CAC, coronary artery calcification; CI, confidence interval; GFR, glomerular filtration rate, as 24-h-measured creatinine clearance; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; iPTH, intact parathyroid hormone; IQR, interquartile range; LDL, low-density lipoprotein; UAE, 24-h urinary protein excretion.
[a]Data are expressed as median (IQR).
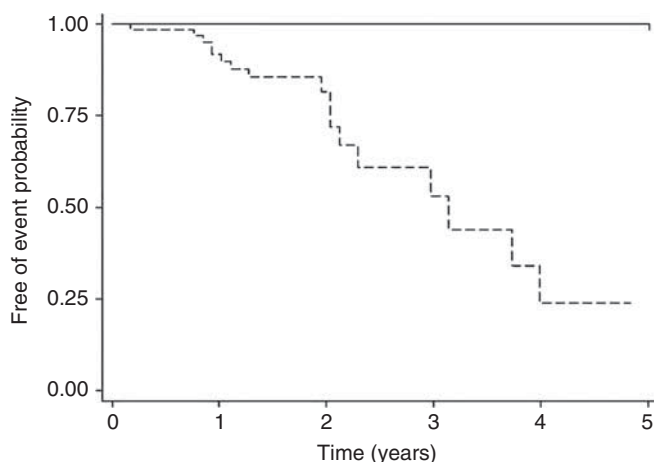[b]Data are expressed as percentage (95% CI).

Figure 1 | Adjusted survival according to baseline coronary artery calcification (CAC) score. Multivariable-adjusted (age, diabetes, GFR, and hypertension) association between baseline CAC score ⩽100 AU (continuous line) and CAC score >100 AU (dashed line) and survival. Survival was significantly (P = 0.0017) worse in presence of CAC score >100 AU. AU, Agatston unit (for scoring CAC); GFR, glomerular filtration rate.

DISCUSSION

Large epidemiological studies have reported that CKD patients are more likely to die than to start renal replacement therapy.[24,25] CACs are regarded as markers of severe vasculopathy and strong predictor of cardiovascular mortality in patients on dialysis.[3–5,26–28] As CACs are present even at early stages of CKD,[10,11,15–17] it is reasonable to hypothesize that CAC may be involved in the high mortality occurring in CKD-patients not on dialysis yet. On this regard, an associations between severity of CAC and all-cause mortality and between presence of CAC and combined outcomes have been evidenced in proteinuric diabetic[29] and non-diabetic[30] CKD patients, respectively. All-cause mortality and combined outcomes may mask the incidence of cardiac events that are more strictly dependent on CAC. Therefore, in the present study, cardiac events such as cardiac death or myocardial infarction were recorded, and a potential association with the presence and the progression of CAC was evaluated. The impact of CAC progression on mortality has never been evaluated in CKD patients.
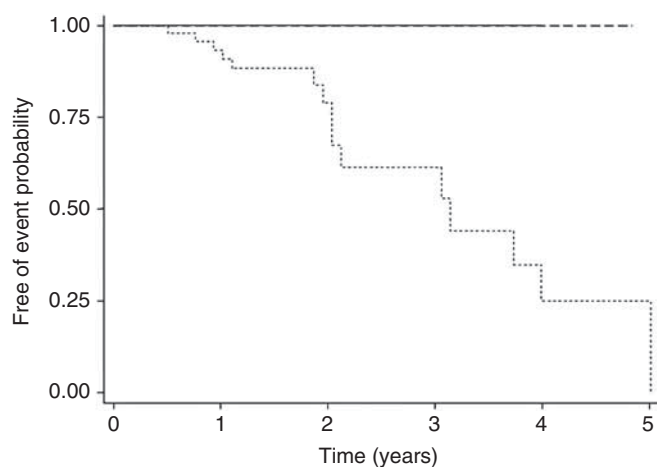
Figure 2 | Adjusted survival according to progression of baseline coronary artery calcification (CAC) score. Multivariable-adjusted (age, diabetes, GFR, and hypertension) association between progressions of baseline CAC score (absent: ⩽25th percentile, continuous line; moderate: 25th–75th percentiles, dashed line; and accelerated: >75th percentile, dotted line). Survival was significantly (P<0.0068) worse in patients with accelerated progression. In patients with absent or moderate progression, survival curves overlapped. *P*-value represents significance across all three groups. AU, Agatston unit (for scoring CAC); GFR, glomerular filtration rate.

Table 2 | Predictors of cardiac events by Cox regression analysis

Independent variables	HR (95% CI)	*P*
CAC score >100 AU	8.4 (2.3–30.1)	0.001
Accelerated progression (>75th percentile)	6.3 (1.5–26.2)	0.011
Diabetes	2.0 (0.8–4.9)	0.115
Interaction: CAC score >100 AU and accelerated progression	0.08 (0.01–0.5)	0.006

Abbreviations: AU, Agatston unit; CAC, coronary artery calcification; CI, confidence interval; HR, hazard risk.
Among all potential confounders (see 'Materials and Methods' and 'Results'), only diabetes reached a *P*-value<0.20 and entered into multiple Cox regression analysis.
Baseline CAC score >100 AU and accelerated CAC score progression (>75th percentile) independently predicted cardiac death or myocardial infarction.
Baseline CAC score >100 AU and accelerated progression (>75th percentile) significantly interacted and reduced the HR for cardiac events (0.08 (0.01–0.5)). In patients with CAC score >100 AU and accelerated progression, HR was 4.2 (as a result of 8.4 × 6.3 × 0.08); this HR was lower than that of each variable.

The attained data seem to support this association. Presence of CAC and accelerated progression were, in fact, associated to and predictive of cardiac death or myocardial infarction. These findings confirm that the process leading to CAC formation and progression is already acting at early stages of CKD. In addition, it is worth noticing that cardiac events occurred even in patients with CAC score consistent with a low mortality risk,[31] indicating that CKD patients are very vulnerable to the presence of CAC. The distinctive location of calcification on coronary tree may explain the high vulnerability of CKD patients. In this population, calcification process develops both in intimal and medial layer. Intimal calcification is more rupture- and erosion-prone,

causing distal emboli, with consequent acute coronary syndromes. Medial calcification induces stiffness of coronary wall, leading to reduction of myocardial perfusion. In addition, medial calcification is present in peripheral arterial tree; stiffness of these arteries reduces elastic recoil of the wall and ultimately increases myocardial afterload with left ventricular hypertrophy and cardiac failure.

Electron beam-computed tomography and magnetic resonance have shown that CAC can be several millimeters thick, occupying the full thickness of the arterial wall of patients with renal failure; unfortunately, both procedures are unable to distinguish the location of calcification. This limitation also applies to MSCT employed for CAC scoring in the present study. Therefore, no available non-invasive-imaging procedure is able to distinguish intimal from medial calcification.

Fast progression of CAC has been documented in patients on dialysis.[7–9] However, assessment of CAC progression is regarded as not adequately powerful when follow-up is shorter than 1 year.[32,33] In the present study, progression of CAC score was an independent predictive factor of cardiac events. For the first time, therefore, an association between CAC progression and survival has been found in CKD-patients not on dialysis who have been followed-up for long time.

Accelerated progression reduced survival of our patients with a low baseline CAC score by a greater extent compared with those with a high one. In the latter group, a worse survival should have been expected considering that high CAC score indicates the presence of heavily calcified plaque on coronary artery.

The data of the present study cannot provide plausible explanations for the unexpected effect of accelerated progression on survival in less calcified CKD patients. Only hypotheses may be advanced. Consensus exists that calcification is a regulated process prompted by inflammation. Inflammation precedes the osteogenic conversion of vascular smooth muscle cells.[34] This initial process generates micro-calcifications in the arterial wall.[34] Calcification within the plaque increases over time concomitantly with inflammation via cytokines released by macrophages and increased expression of alkaline phosphatase in vascular smooth muscle cells.[35–37] In contrast to early plaque with spotty calcification, in more advanced plaques, the progression of calcification seems less or not at all dependent on inflammation; areas of inflammation, in fact, decrease in advanced calcified plaques.[34,38] This finding arises the possibility that more extended calcifications are potentially less malignant because inflammation is dampened.[38] Furthermore, in more calcified plaques, the prevalent role for further progression of calcification process may be played by physiochemical processes and absence of mineralization inhibitors.[38] Clinical studies have shown that spotty calcification is commonly present in soft lipid-rich plaque that is more rupture prone and thrombogenic, and predictive of cardiovascular events than heavy calcification.[39–43] On the basis of above points,

we can speculate that low baseline CAC score in our patients was a sign of prevailing soft lipid-rich plaque with more active inflammatory processes; progression occurring in a still inflamed and unstable plaque might have reduced survival. In contrast, high baseline CAC score was likely a sign of stable plaque with less active or absent inflammatory lesions, and the progression in this plaque might have occurred by factors other than inflammation with minor impact on survival.

It is important to underline that higher baseline CAC score and accelerated progression interacted significantly despite they were independently associated to cardiac events; because of this interaction, the risk of events was lower than that predicted by each variable. This interaction is, in our opinion, relevant and should be taken into account for reliable evaluation of data from trials assessing the association between extent, progression of CAC and events.

Despite major societies recommend CAC assessment for stratification of cardiovascular risk,[44] the usefulness of screening asymptomatic patients for CAC has been recently disputed because data on potential association between CAC score and outcomes are regarded as not adequately robust, especially in low-risk patients.[32,33,45] Likely, this opinion is not appropriate for CKD patients. CKD itself increases the likelihood of cardiac event; therefore, CKD patients are already at intermediate risk. Screening for presence of CAC may be appropriate in CKD patients who are reallocated in high risk of coronary event by any degree of CAC. The data of the present study may support this view.

In conclusion, in CKD patients, an association is present between extent of CAC and cardiac events; progression of calcification process is an independent predictive factor of cardiac events with prevailing negative impact on survival of less calcified patients; the assessment of both baseline CAC score and its progression might be useful for cardiovascular risk stratification and guiding decisions for the prevention of cardiac outcomes. Larger trials focusing on combined effects of baseline CAC score and its progression on cardiac events are mandatory.

MATERIALS AND METHODS

The protocol was approved by the local institutional review board. Consecutive male and not pregnant female outpatients receiving care at the Department of Nephrology of University 'Federico II', Naples (Italy), screened for CAC from January 2003 to December 2006, entered the study after they had signed informed consent. Inclusion criteria were: age $\geqslant 18$ years, CKD stages 2–5 (GFR: 1.48 to >0.25 ml/s) not requiring dialysis treatment, no less than 6-month follow-up before the enrollment, and at least two CAC-score assessments before the occurrence of cardiac event or closing of study. Exclusion criteria were: symptoms of heart failure and/or coronary artery disease, previous history of myocardial infarction, coronary bypass surgery, angioplasty, stroke, arrhythmia (that would impede assessment of CAC score with MSCT), and rapidly progressive renal disease. Diabetic patients were those on regular use of insulin or oral hypoglycemic drugs.

Routine blood chemistry and serum concentrations of calcium, phosphorus, intact parathyroid hormone, homocysteine, C-reactive protein, triglycerides, total cholesterol, and high-density lipoprotein cholesterol were serially measured. These variables were assessed at the enrollment and every 6 and 3 months in patients with CKD stages 2–3 (GFR: 1.48–0.5 ml/s) and CKD stages 4–5 (GFR: 0.48–<0.25 ml/s), respectively. Results were averaged for statistical analysis. Low-density lipoprotein cholesterol was calculated using the Friedewald equation. GFR was given by 24-h-measured creatinine clearance. Intact parathyroid hormone was assayed by chemiluminescent immunometric method (Diagnostic Products, Los Angeles, CA) and high-sensitivity C-reactive protein by immunoturbidimetric method.

Cardiac death and myocardial infarction were regarded as outcome and assigned by a blinded cardiologist. Screening of CAC was performed by MSCT and CAC score measured as AU. CAC score was obtained at the entry into the study (baseline CAC score) and every 12 months. To calculate the annual progression of CAC score that accounts for the time between scans, the following formula was used: last CAC score−baseline CAC score/days of follow-up × 365 (ref. 46). In patients who experienced a cardiac event, the CAC score assessed before the event was assumed as the last; in other patients, the last CAC score was performed at the closing of the study. The annual progression of CAC score was categorized as follows: absent ($\leqslant$25th percentile), moderate (25th–75th percentiles), and accelerated ($>$75th percentile). Scans were analyzed by two radiologists (MS and ML) who were unaware of the patient's clinical characteristics and previous MSCT scoring.

Patients were classified in two groups according to baseline CAC score ($\leqslant$100 and $>$100 AU). The CAC score of 100 AU was chosen as cutoff because it predicted coronary heart disease-related events[47] and provided evidence of obstructive coronary artery disease[48] in symptomatic patients undergoing angiography; in asymptomatic subjects, it was the threshold that was able to identify definite to extensive plaque burden and patients with moderately high to very high cardiovascular risk.[31]

During the follow-up, clinicians did not take into account the result of CT scan; changes in lifestyle or medication use were based on clinical condition and blood chemistry.

Scans were performed using an Aqualon 64-slice MSCT scanner (Toshiba Medical Systems; Tokyo, Japan). Unenhanced calcium scoring scan was obtained with the following protocol: retrospective ECG gating; tube voltage 120 kV; tube current 180 mAs; rotation time 330 ms; detector collimation 24 × 1.2 mm; reconstructed slice thickness 3.0 mm; and pitch 0.2. The scan range extended from the level of the carina to just below the diaphragm. The field of view was adjusted according to the size of the heart. CT data sets were subsequently transferred to a workstation: 3-D line Vitrea work-station (Vital Images; Plymouth, MN). Calcium score was performed using a semi automated threshold-dependent algorithm. Calcifications within the coronary artery tree above a threshold of 130 HU were included. Calcifications present in each coronary artery (left main, left anterior descending, diagonal branches, circumflex, obtuse marginal branches, right coronary, acute marginal branches, posterior descending artery, and posterior lateral segmental branches) were scored and summed to obtain the CAC score.

Data are shown as percentage (95% CIs) for categorical variables and as median (IQR) for continuous or discrete variables.

The Kaplan–Meier survival analysis was performed to compare survival curves of patients divided according to baseline CAC score

($\leqslant 100$ and $>100\,$AU); the log-rank test was used to compare survival curves. For group comparisons, multinomial logistic regression was performed for comparison of proportions and its 95% CIs were computed by a bootstrap resampling procedure (50 times). The Mann–Whitney *U*-test was used as non-parametric test for comparison of medians. The Cox regression analysis was performed to find the model that best predicted the combined outcome (cardiac death and myocardial infarction) using fractional polynomial regression to study the relationship between continuous and discrete variables and outcome. All the variables reported in Table 1 were considered, and only those that reached a *P*-value level <0.20 at univariate analysis were included and reported in the multivariate Cox regression model.

Interaction between baseline CAC score and its progression was also analyzed because stratification by both factors pointed out a possible effect modification with statistically significant Cox regression-based test for equality of survival curves. Afterward, annualized progression was dichotomized using the 75th percentile value (below and above or equal) because only accelerated progression was strongly informative in the final model. Finally, Jackknife procedure was used to validate the best-fit regression model and compute standard errors. STATA/SE, version 9.2 for Windows (Stata Corp, College Station, TX), was used to analyze the data.

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