Low-dose coronary computed tomography angiography with prospective ECG triggering to predict cardiac events in the long term

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This article summarizes our recent study of the long-term prognostic performance of low-dose coronary computed tomography angiography (CCTA) with prospective ECG triggering [1]. Patient stratification using coronary lesion severity in CCTA with low radiation dose accurately predicted the risk of major adverse cardiac events in the long term. Thus, low-dose CCTA with prospective ECG triggering has excellent long-term prognostic performance and a "warranty" period >6 years for patients with normal coronary arteries.

INTRODUCTION

Coronary computed tomography angiography (CCTA) is increasingly being used for the non-invasive assessment of coronary artery disease (CAD). CCTA has an excellent diagnostic accuracy with outstanding sensitivity and negative predictive value [2, 3], as well as an excellent prognostic value for future cardiac events [4, 5, 6].

However, the average follow-up duration of previous studies of CCTA was only 2 years [4, 5], which seems short compared with the progressive development of coronary atherosclerosis. The few studies with longer follow-up periods were based on older CCTA techniques, such as electron-beam CT [7] or retrospective ECG gating [8], exposing patients to higher radiation doses. Prospective ECG triggering for 64-slice CCTA combines an excellent diagnostic accuracy [9] with low radiation dose [10], which may reduce the risk associated with CCTA. Moreover, its short-term prognostic performance is excellent [11].

Similarly, coronary artery calcium score (CACS) is a strong predictor of coronary events [12] with a high negative predictive value for cardiac events [13]. However, several experts warned about the risk of non-calcified coronary stenoses, which may cause cardiac events, but are not detected by CACS, in contrast to CCTA [14]. Thus, the comparative value of CACS versus CCTA remains a matter of debate. Few studies have compared the prognostic value of CCTA and CACS and those that did were again limited to follow-up periods of 2-3 years [15; 16].

Hence, the primary aim of the present study was to assess the long-term prognostic performance of low-dose CCTA with prospective ECG triggering on major adverse cardiac events (MACE). The secondary aim was to compare its prognostic performance versus CACS.

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METHODS

We included all consecutive patients undergoing low-dose 64-slice CCTA with prospective ECG triggering to evaluate CAD from September 2007 to December 2008 at our centre. At baseline, relevant clinical information was recorded. Follow-up was performed using telephone interviews with patients and referring physicians, and by searching electronic medical records. Primary endpoints were major adverse cardiac events (MACE), defined as cardiac death, non-fatal myocardial infarction or elective revascularization (percutaneous or surgical). Revascularization procedures within the first 6 weeks after CCTA were excluded to avoid an important confounder between the diagnostic and the prognostic value of the test [8,11].

CCTA was performed on a LightSpeed VCT XT scanner (GE Healthcare, Chicago, USA) using prospective ECG triggering with validated scanning protocols [10; 17]. Unenhanced CT was acquired in patients ≥45 years old using validated parameters to calculate the CACS with the Agatston method [18]. Two independent readers interpreted CCTA images and assessed coronary lesions. Patients were stratified according to coronary lesion severity: normal coronary arteries, non-obstructive lesions (luminal narrowing <50%), obstructive stenosis (luminal narrowing ≥50%), or previously revascularized patients. The segment severity score (SSS) was calculated (sum of segmental scores: 0 = no lesion, 1 = narrowing <50%, 2 = stenosis 50-69%, 3 = stenosis ≥70%).

To assess the prognostic value of CCTA according to lesion severity, we performed Kaplan-Meier survival analysis using

time to first MACE of each patient. We identified independent MACE predictors with multivariate Cox regression adjusted for demographics, cardiovascular risk factors, symptoms and previous cardiac events. We compared the prognostic value of CCTA and CACS using receiver operating characteristic (ROC) analysis and calculating the area under the curve (AUC). Finally, we assessed the reclassification rate after CCTA compared with the cardiovascular risk level according to the SCORE calculator of the European Society of Cardiology [19].

RESULTS

We enrolled 434 patients after low-dose CCTA with prospective ECG triggering. Twenty-nine patients (7%) were lost to follow-up. Thus, 405 patients were included in the study. Mean age was 59.4 ±11.4 years, with 64% of men. A total of 5,781 coronary segments were evaluated. Normal coronary arteries were observed in 153 patients (38%), non-obstructive lesions in 87 patients (21%) and obstructive stenosis in 131 patients (32%), whereas 34 patients (8%) were previously revascularized. Mean effective radiation dose was 1.72 ±0.59 mSv. Median CACS was 61 ±508 in 223 patients.

During a median follow-up of 6.1 ±0.6 years, 116 MACE occurred in 101 patients (25%). After exclusion of 50 early revascularizations, we studied 66 MACE occurring in 55 patients (14%). No MACE occurred in patients with normal coronary arteries, but event-free survival decreased according to increasing lesion severity [Figure 1]. Annual event rates were 0% with normal coronary arteries, 1% with non-obstructive lesions, 14% with obstructive stenosis and 7% in previously revascularized patients (all P ≤0.003 for pairwise comparisons, except non-significant for obstructive vs. revascularized). Similarly, event-free survival decreased with increasing CACS (P for trend <0.001). [Figure 2]. However, 4% of patients with a CACS of 0 nevertheless experienced MACE.

In multivariate Cox regression analysis, obstructive stenosis in CCTA, SSS and CACS were independent MACE predictors (all P ≤0.001). Obstructive stenosis and SSS remained independent MACE predictors even after adding CACS to the regression model (all P ≤0.01). Head-to-head comparison of CCTA and CACS in ROC analysis showed a slightly better MACE prediction with CCTA findings versus CACS, but without significant difference (AUC CCTA-SSS 0.79 [0.73-0.86] vs. CACS 0.75 [0.65-0.84]).

Reclassification analysis showed that 50% of the patients were reclassified by CCTA compared with SCORE, particularly patients at intermediate risk (72%). ROC curve analysis demonstrated a significantly better MACE prediction with CCTA versus SCORE (AUC CCTA-SSS 0.83 [0.76-0.90] vs. SCORE 0.65 [0.54-0.76]; P =0.005,) [Figure 3].

DISCUSSION

Our results highlight the excellent long-term prognostic performance of low-dose CCTA with prospective ECG triggering regarding cardiac events. All patients with normal coronary arteries remained free of cardiac events during the median follow-up of 6.1 years. Patients with non-significant lesions experienced a significantly higher 1% annual event rate. Those with obstructive stenosis were exposed to a much higher risk, with a 14% annual event rate.

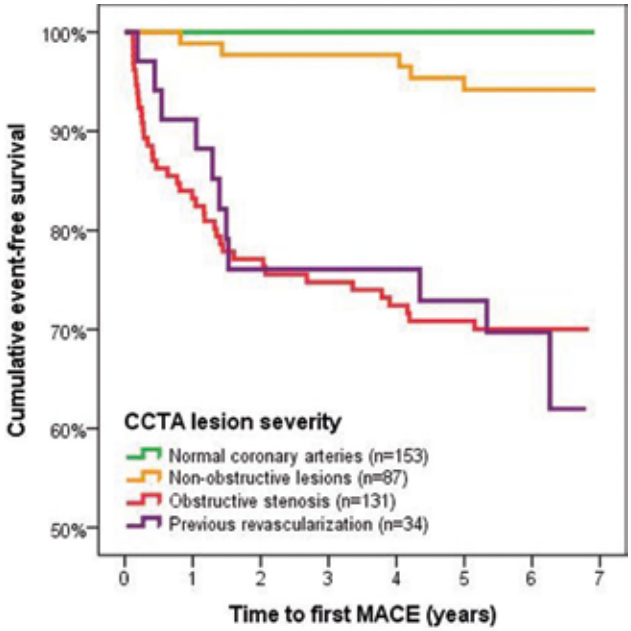

Figure 1. Kaplan-Meier cumulative event-free survival according to lesion severity in CCTA. Log-rank test showed significant differences in cardiac events for all pairwise comparisons between groups (all P ≤0.003), except for obstructive stenosis versus previous revascularization (P =0.82). CCTA: coronary CT angiography

CACS allowed for similar risk stratification. CCTA and CACS were both strong and independent predictors of MACE. Reclassification analysis showed a 50% risk reclassification by CCTA compared with SCORE, and even 72% in patients at intermediate risk, with a significant improvement of MACE prediction.

Our findings are in line with previous short-term results on the prognostic value of low-dose CCTA with prospective ECG triggering [11] or of other CCTA methods [4, 5, 6], which showed an accurate stratification of patients into risk categories after mean follow-up periods of 1-3 years. A few studies have assessed a longer follow-up after CCTA than the present study, and gave similar results However the early studies used older CCTA techniques with higher radiation doses, such as electron-beam CT [7] and retrospective ECG gating [8]. Hence, the present study extends previous knowledge on long-term prognosis after low-dose CCTA with prospective ECG triggering. The mean radiation dose of 1.7 mSv highlights an improved risk-to-benefit ratio of this technique.

Of note, we found that low-dose CCTA with prospective ECG triggering can identify patients at very low cardiac risk, without any cardiac event in the follow-up. Thus, the "warranty period" of a normal CCTA, seems to be very long, rendering repeat testing unnecessary for at least 6 years. This differs from other non-invasive imaging tests based on myocardial perfusion, only detecting obstructive, flow-limiting stenoses. Thus, patients with normal perfusion tests may have several non-obstructive lesions, which may explain the shorter "warranty periods" of 2–4 years after stress echocardiography, SPECT, PET and MRI.

Both CCTA and CACS offer a robust prognostic performance [6; 12]. An additional value of CCTA over CACS is a matter of debate [14], based on short-term studies [15; 16). Our long-term results suggest a tendency towards a higher predictive value with

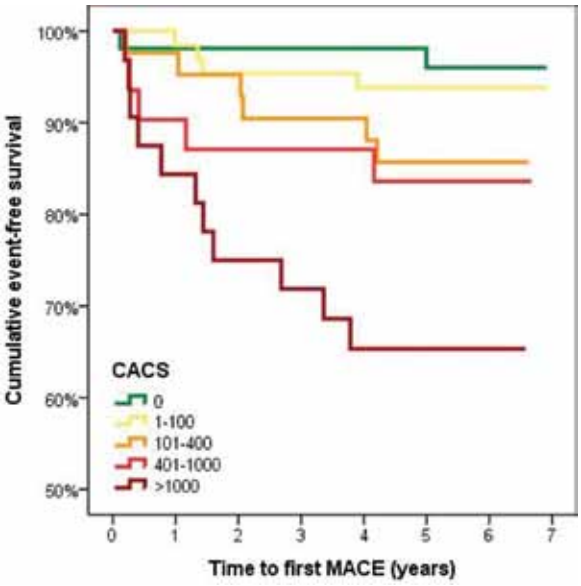

Figure 2. Kaplan-Meier cumulative event-free survival according to CACS. Test for trend was significant for a shorter event-free survival with increasing CACS (P <0.001). CACS: coronary artery calcium score

CCTA than CACS, but without asignificant difference in direct comparison. It should be noted however that our patient sample was not primarily powered for this analysis. However, CCTA findings remained independent MACE predictors even after adjustment for CACS. As previously reported [14], a CACS of 0 could not predict complete freedom from MACE during follow-up, unlike normal CCTA. Thus, non-calcified coronary lesions seem to be associated with a cardiovascular risk not assessed by CACS. Moreover, although CACS is a strong predictor of cardiac events at the cohort level, it does not provide a clear decisional cut-off on an individual basis. By contrast, CCTA provides a

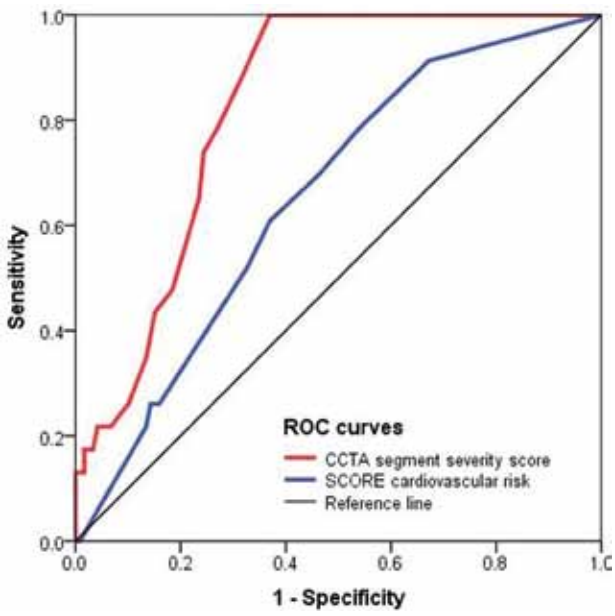

Figure 3. Receiver operating characteristic analysis of MACE prediction by CCTA versus SCORE. Area under the curves with 95% confidence intervals: CCTA segment severity score 0.83 [0.76-0.90] vs. SCORE 0.65 [0.54-0.76]; P =0.005. N =142 because of the required data for SCORE calculation.
CCTA: coronary CT angiography. ROC: receiver operating characteristic. SCORE: cardiovascular risk calculator of the European Society of Cardiology

cut-off value of ≥50% stenosis to trigger further investigations for the individual patient in clinical practice.
In the present study, the inclusion of elective coronary revascularizations in the composite end-point may be perceived as a potential limitation. This, however, ensures comparability with previous studies [8, 11]. Moreover, the exclusion of early revascularizations from the analyses, but not of the patients undergoing them, avoided an important confounder between diagnostic and prognostic value, without hampering our ability to study high-risk patients. Furthermore, CACS was only performed in a subgroup of patients, limiting the comparison with CCTA. Finally, our low radiation dose does not reach the newest ultra-low dose CCTA protocols [20], for which no long-term data exist yet. However, our study has important strengths, such as the long follow-up, the extensive data collected allowing multivariate modelling, and the high generalisability of the results.

CONCLUSION

Low-dose CCTA with prospective ECG triggering has an excellent prognostic performance with a warranty period of at least 6 years for patients with normal coronary arteries.

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