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Review Article

Prognostic utility of coronary computed tomographic angiography

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ABSTRACT

Coronary computed tomographic angiography (CCTA) employing CT scanners of 64-detector rows or greater represents a noninvasive method that enables accurate detection and exclusion of anatomically obstructive coronary artery disease (CAD), providing excellent diagnostic information when compared to invasive angiography. There are numerous potential advantages of CCTA beyond simply luminal stenosis assessment including quantification of atherosclerotic plaque volume as well as assessment of plaque composition, extent, location and distribution. In recent years, an array of studies has evaluated the prognostic utility of CCTA findings of CAD for the prediction of major adverse cardiac events, all-cause death and plaque instability. This prognostic information enhances risk stratification and, if properly acted upon, may improve medical therapy and/or behavioral changes that may enhance event-free survival. The goal of the present article is to summarize the current status of the prognostic utility of CCTA findings of CAD.

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1. Introduction

Current professional societal guidelines endorse the use of noninvasive imaging tests for the diagnostic evaluation of symptomatic patients with at least intermediate pre-test likelihood of anatomically obstructive coronary artery disease (CAD). These tests have historically comprised physiologic stress testing by electrocardiography, echocardiography, cardiac magnetic resonance and myocardial perfusion imaging (MPI). More recently, coronary computed tomographic angiography (CCTA) has emerged as a noninvasive anatomic alternative that has gained increasing utilization and importance for the diagnosis of CAD, with generally high diagnostic performance compared to invasive coronary angiography (ICA).

In particular, CCTA demonstrates a very high negative predictive value for the exclusion of anatomically obstructive CAD, which may prove useful for preventing unnecessary ICA. Recent data from the National Cardiovascular Death Registry revealed that, amongst 398,978 patients who underwent elective ICA at 663 hospitals between January 2004 through April 2008, 39.2% of patients had no evidence of significant CAD, defined as <20% stenosis in any vessels.¹ Notably, noninvasive examinations, including stress testing, were performed in 83.9% of the patients in this study population prior to ICA. These findings suggest the need for improved noninvasive measures to curb unnecessary ICA, and proponents of CCTA have posited this anatomic test as a means to achieve this goal.

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Over the last decade, significant technological advances have been introduced to improve multi-detector computed tomography (CT) technology, including the introduction of 64-detector row CT scanners in 2005, which enabled the reliable acquisition of generally motion-free images of the coronary arteries and allowing for assessment of coronary stenosis and atherosclerotic plaque. Since the introduction of 64-detector row scanners, an array of newer generation scanners have been introduced to improve upon the spatial and temporal resolution as well as the volume coverage. These have included high-definition scanners capable of 230 micron in-plane resolution; dual source and fast pitch helical scanners that achieve temporal resolution of 83 ms; and wide area detector CT which allow for 16 cm coverage within a single gantry revolution, therein allowing whole heart coverage during a single heart beat.

In a recent meta-analysis of 27 studies using 16 to 64-slice scanner, CCTA was reported to have a diagnostic sensitivity, specificity, negative predictive value (NPV), and positive predictive values (PPV) of 99%, 89%, 93% and 100%, respectively.² These meta-analytic findings mirror those of prospective multicenter trials. One such trial, the ACCURACY (Assessment by Coronary Computed Tomographic Angiography of Individuals Undergoing Invasive Coronary Angiography) study—represented the first prospective multicenter study evaluating 230 stable patients without known coronary artery disease undergoing CCTA before ICA³—demonstrated a diagnostic sensitivity, specificity, PPV, and NPV of 95%, 83%, 64%, and 99%, respectively, compared to a quantitative coronary angiographic reference standard. Subsequent to the ACCURACY study, two additional prospective multicenter studies also demonstrated high sensitivity, negative predictive value, and high diagnostic accuracy of 64-slice CCTA compared to invasive coronary angiogram—in particular for patients without known CAD—with study results similar to the ACCURACY trial.^{4,5}

One additional potential benefit of CCTA is its ability to characterize and quantify coronary atherosclerotic plaque and arterial wall features in addition to providing accurate evaluation of degree of coronary stenosis. Numerous prior studies have compared the ability of CCTA to characterize and quantify coronary plaque to a gold standard, typically employing gray scale intravascular ultrasound (IVUS).⁶ In a recent meta-analysis of 33 studies that comprised 946 patients, CCTA was noted to demonstrate excellent correlation to IVUS for numerous additional atherosclerotic measures beyond stenosis severity, including cross sectional area, plaque area, area stenosis, plaque volume and arterial remodeling.⁷

In addition to its high diagnostic performance against invasive angiography and IVUS, CCTA findings of CAD have been evaluated for its ability to predict future adverse CAD events. We herein describe the most current findings from CCTA studies evaluating its prognostic utility for future adverse events.

2. Prognostic value of CCTA for all-cause death from initial studies

The first large single center prognostic study evaluated the association of all-cause mortality with CCTA defined extent and severity of CAD in 1127 patients with suspected disease.⁸ In this study, the per-patient, per-vessel and per-segment stenosis severity by 16-detector row CCTA was scored as minimal (<30%), mild (30%–49%), moderate (50%–69%), or severe (\geq 70%). Atherosclerotic plaque was assessed by 3 distinct methods: 1) presence or absence of moderate or severe plaque; 2) coronary artery plaque burden as categorized by a modified Duke CAD index; and 3) simple clinical scores grading plaque extent and distribution. During a 15 month follow-up period, CCTA predictors of death included proximal left anterior descending artery (LAD) stenosis and number of vessels with \geq 50% and \geq 70% stenosis (all $p < 0.0001$). Furthermore, survival worsened with higher-risk Duke scores, ranging from 96% survival for 1 stenosis \geq 70% or 2 stenoses 50% ($p < 0.013$) to 85% survival for \geq 50% left main (LM) artery stenosis ($p < 0.0001$). In addition, clinical scores measuring plaque burden and distribution predicted 5–6% higher absolute death rate (6.6% vs. 1.6% and 8.4% vs. 2.5%; $p < 0.05$ for both). Importantly, a negative CCTA was noted to provide an extremely low risk for death. Subsequent to this initial investigation, multiple studies to date examined the prognostic value of 64-detector row CCTA have done so, but were generally limited to single centers and/or relatively small sample sizes^{9,10} (Table 1). One large-scale 2-center study examined 5330 consecutive patients without known CAD undergoing CCTA.¹¹ At 2.3 ± 0.6 year follow-up for an endpoint of all-cause mortality, obstructive CAD \geq 70% correlated with higher incident death [hazards ratio (HR) 2.44, 95% confidence interval (CI) 1.61–3.72, $p < 0.001$]. Compared to those without obstructive CAD, individuals with increasing numbers of vessels with obstructive CAD experienced increased risk of death: 1-vessel (HR 2.23, 95% CI 1.34–3.72), 2-vessel (HR 3.29, 95% CI 1.62–6.71), or 3-vessel (HR 7.35, 95% CI 3.79–14.29) ($p < 0.001$ for all). Further, by measures of left ventricular ejection fraction (LVEF) made possible by retrospective electrocardiographic gating,

Table 1 – Prognostic CCTA studies for mortality.

No	Author	Year	Study type	No of patients	Time of follow-up	Population	Slice of CCTA
1	Min ⁸	2007	Retrospective	1127	15 \pm 4 mo	Patients \geq 45 years old, chest symptoms	16
2	Ostrom ⁹	2008	Retrospective	2538	78 \pm 12 mo	Symptomatic	64
3	Min ¹¹	2010	Retrospective	5330	2 \pm 1 years	Without known CAD	64
4	Lin ¹⁰	2011	Prospective	2583	3 \pm 1 years	non-obstructive CAD	64

CCTA = coronary CT angiography; mo = months; CAD = coronary artery disease.

individuals with LVEF >50% – when compared to those with LVEF ≤ 50% – exhibited higher rates of death (HR 1.56, 95% CI 1.04–2.36, $p = 0.03$). When combined, annualized mortality rates in those with non-obstructive CAD and LVEF > 50% were low (0.51%) and increased accordingly for non-obstructive CAD and LVEF ≤ 50% (0.74%), obstructive CAD and LVEF > 50% (1.76%), and obstructive CAD and LVEF ≤ 50% (3.97%) (log-rank test $p < 0.001$).

3. Prognostic value of CCTA for major adverse cardiovascular event (MACE)

Although prior numerous studies have assessed the prognostic value of CCTA findings for mortality, relatively few studies have examined risk stratification of CAD findings by CCTA for prediction of major adverse cardiovascular events (MACE). These studies, similar to the initial mortality investigations, were limited by small samples at single centers with short to intermediate follow-up periods^{12–21} (Table 2). Of these, one of the larger scale studies with relatively longer follow-up was performed by Hadamitzky et al.²² At 18 months of follow-up, they prospectively identified among 1256 patients with suspected CAD the occurrence of MACE, inclusive of cardiac death, myocardial infarction (MI), or unstable angina requiring hospitalization; these were defined as “severe” CAD events. Further, they investigated the prognostic utility of CCTA when including target vessel revascularization >90 days after CCTA. In this study in 802 patients without obstructive CAD, there were 4 cardiac events, of which 1 was severe, whereas in 348 patients with obstructive CAD, there were 17 cardiac events, of which 5 were severe. The difference between the 2 groups was highly significant both for severe events [OR: 17.3, 95% CI: 3.6 to 82.5 and for all cardiac events (OR: 16.1, 95% CI: 7.2 to 36.0; both $p < 0.001$). A recent meta-analysis of 10 studies with 64-slice CCTA showed that the cumulative MACE rate over 21 months were 0.5% in patients with normal CTA, 3.5% in non-obstructive CAD and 16% in obstructive CAD.²³ Compared to normal CTA, non-obstructive CAD was associated with significant increased risk of MACE with OR = 6.68 (3.01–14.82 95% CI), $p = 0.0001$. Obstructive CAD was associated with further significant increased risk of MACE with OR = 41.19 (22.56–75.18, 95% CI), $p = 0.0001$.

4. Prognostic utility of atherosclerotic plaque features by CCTA

One potential advantage of CCTA is its ability to identify non-obstructive CAD stenoses while assessing overall coronary artery plaque burden. Indeed, prior reports have observed that approximately 60% of rupture-prone “vulnerable” plaques do not exhibit an anatomically significant stenosis.^{24,25} In this regard, several recent investigations have focused on additional atherosclerotic plaque feature by CCTA, and whether these findings can predict future acute coronary syndromes. Motoyama et al interrogated culprit lesions in acute coronary syndrome (ACS) by CCTA, and compared them with atherosclerotic plaques in patients presenting with stable angina pectoris (SAP).²⁶ The coronary plaques in ACS and SAP were evaluated for the CT plaque characteristics, including vessel remodeling, consistency of non-calcified plaque (NCP < 30 HU or 30 HU < NCP < 150 HU), and spotty or large calcification.

CT profiling of culprit ACS and SAP lesions demonstrated that positive remodeling (87% vs. 12%, $p < 0.0001$), NCP < 30 HU (79% vs. 9%, $p < 0.0001$), and spotty calcification (63% vs. 21%, $p = 0.0005$) were significantly more frequent in the ACS lesions. In a subsequent prospective study of 1059 patients who underwent CCTA, two atherosclerotic plaque features—namely positive arterial remodeling (PR) and low-attenuation plaque (LAP)—independently predicted incident ACS during a follow-up of 27 ± 10 months ACS (hazard ratio: 22.8, 95% confidence interval: 6.9 to 75.2, $p < 0.001$). There was a significantly higher likelihood of ACS in patients with 2- or 1-feature positive plaques compared to patients with 2- feature negative plaques or no plaques (22.2% vs. 3.7% vs. 0.49%, log-rank test $p < 0.001$) (Fig. 1). This study suggests the potential of CCTA to expand its prognostic utility beyond stenosis severity to include atherosclerotic plaque features not identifiable by conventional stress testing and ICA.²⁷

5. The CONFIRM registry

Although numerous studies have examined the potential for prognostication using CCTA results, most have been limited to small sample sizes in single-center studies. The Coronary CT

Table 2 – Prognostic CCTA studies for major adverse cardiovascular event.

No.	Study	Year	No. of patients	Follow-up	Population	Slice of CCTA
1	Pundziute ¹²	2007	100	16 mo	Known or suspected CAD	16 and 64
2	Gaempeli ¹³	2008	220	14 ± 4 mo	Known or suspected CAD	64
3	Aldrovandi ¹⁴	2009	187	24 mo	Suspected CAD	64
4	Carrigan ¹⁵	2009	227	2 ± 1 years	Suspected CAD with intermediate pre-test probability	64
5	Hadamitzky ²²	2009	1150	18 mo	Suspected CAD	64
6	Rubinshtein ¹⁶	2009	545	18 ± 6 mo	Suspected CAD	64
7	Gopal ¹⁷	2009	454	40 ± 9 mo	Suspected CAD	64
8	Abidov ¹⁸	2009	199	2 years	Sequential patients suspected for CAD with equivocal stress test	64
10	Motoyama ²⁷	2009	1059	27 ± 10 mo	Known or suspected CAD	64
11	Min ¹⁹	2010	172	22 ± 5 mo	Known or suspected CAD	64
12	Chow ²⁰	2010	2076	16 ± 8 mo	Known or suspected CAD	64
13	Kristensen ²¹	2011	312	16 mo	patients with NSTEMI	64

CCTA = coronary CT angiography; mo = months; CAD = coronary artery disease; NSTEMI = non ST elevation myocardial infarction.

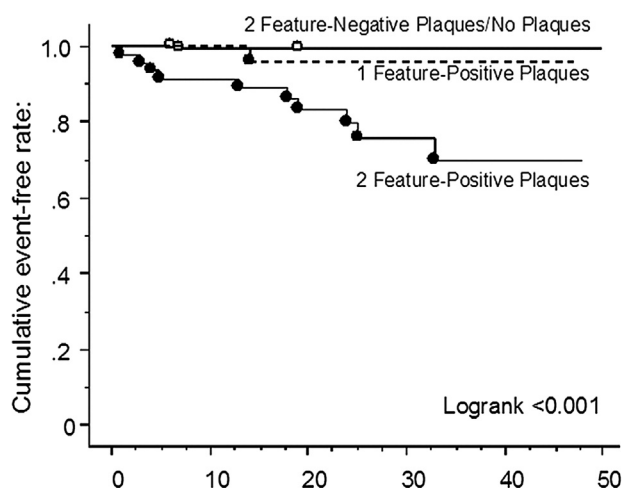


Fig. 1 – Kaplan–Meier curve for development of ACS on the basis of plaque characteristics patient stratification according to the presence of 2- and 1-feature positive, and 2-feature negative plaques/no plaques. The y-axis represents cumulative event-free rate (log-rank test, $p < 0.001$). ACS = acute coronary syndrome.

Angiography Evaluation For clinical Outcomes: An International Multicenter Registry, or CONFIRM, study was subsequently established as a large, prospective, multinational dynamic observational cohort study of patients undergoing 64-slice CCTA.²⁸ At present, the CONFIRM registry is comprised of 2 phases. Phase I CONFIRM is a derivation cohort that details demographic, clinical and CT findings for 27,125 consecutive patients (≥ 18 years of age), who were enrolled at 12 sites in 6 countries (United States, Canada, Germany, Switzerland, Italy, South Korea) between 2005 and 2009. These patients were followed for 2.3 ± 1.1 years for a primary endpoint of all-cause death. Phase II CONFIRM is a distinct non-overlapping validation cohort, detailing identical elements to Phase I and with event follow-up for 4682 patients at 6 sites in 4 countries (United States, Canada, Austria, South Korea). Patients enrolled in the CONFIRM study were followed up after CCTA to identify adverse CAD events including all-cause death, myocardial infarction, unstable angina, target vessel revascularization, and CAD-related hospitalization. This registry has provided numerous prognostic evidences by CCTA.

6. Prognostic value of CCTA in patients without known CAD (CONFIRM)

6.1. Symptomatic patients at intermediate pre-test risk with calcium 0

Prior studies have demonstrated that a non-negligible proportion of symptomatic patients presenting with chest pain and CAC scores of 0 do, in fact, possess obstructive CAD; with this findings especially noted among patients with a high pre-test risk of obstructive CAD.^{29–32} However, the prevalence of obstructive CAD among patients with CAC score of 0, who have a lower pre-test risk of CAD, had not been previously

examined. Additionally, the prognostic importance of obstructive CAD among patients with a CAC score of 0 and the incremental prognostic value of CAC scoring over CCTA had previously remained unclear. Villines and colleagues focused on the prognostic value of CCTA in symptomatic patients with CAC scores of 0.³³ They identified 10,037 symptomatic patients without known CAD, who underwent concomitant CCTA and CAC scoring from CONFIRM registry, and assessed the prevalence of obstructive CAD with CAC score of 0 (Fig. 2). Importantly, among patients with CAC score of 0, 84% had no CAD, but 13% had non-obstructive CAD and 3.5% had obstructive CAD, defined as $\geq 50\%$ stenosis. In addition, they noted that a CAC score > 0 had a high sensitivity and positive predictive value for identifying obstructive CAD, 89% and 96%, respectively at the cost of specificity and negative predictive value, which were 59% and 29%, respectively. In a multivariate analysis for prediction of obstructive CAD among symptomatic patients without CAC, family history of CAD and smoking were found to be the strongest predictors.

Interestingly, the results of this study demonstrated that there was no significant differences in all-cause mortality irrespective of obstructive CAD among patients with CAC score 0, a finding which may be related to sample size and reduced statistical power (Fig. 3). However, among those with CAC score of zero, patients with obstructive CAD experienced higher rates (3.9%) of MACE—inclusive of all-mortality, non-fatal MI, or coronary revascularization—compared to patients (0.8%) with no CAD or non-obstructive CAD ($p < 0.001$). The investigators explained these findings by pointing out that the majority of patients with CAC scores of 0 and obstructive CAD possessed single-vessel disease, with post-CCTA coronary revascularization comprising the majority of “adverse” cardiac events. Discriminatory power of a CAC > 0 by area under the receiver operating characteristics curve (ROC), CAC scores in symptomatic patients did not add incremental prognostic information for predicting MACE when compared with CAD

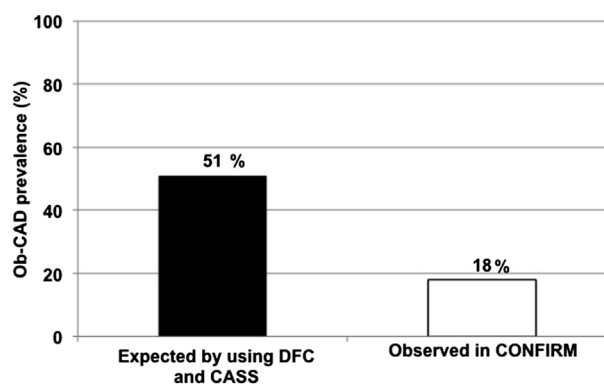


Fig. 2 – Overall obstructive CAD prevalence in patients with non angina, atypical angina, and typical angina. Observed prevalence (yellow bars) was lower than expected prevalence (red bars) for angiographically confirmed $\geq 50\%$ stenotic coronary artery disease. (18% vs. 51%; $p < 0.001$). Ob-CAD = obstructive coronary artery disease, NonAng = nonanginal chest pain, AtypAng = atypical chest pain, TypAng = typical angina, DFC = Diamond and Forrester classification, CASS = coronary artery surgery study.

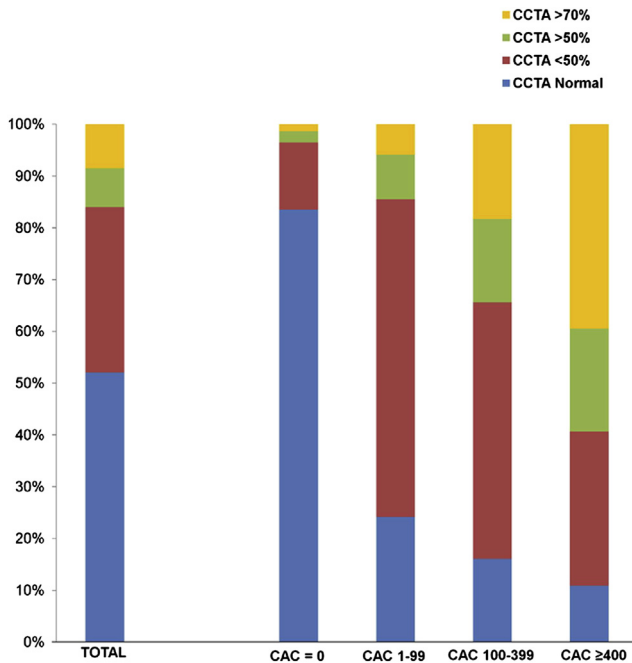


Fig. 3 – Coronary artery stenosis on CCTA. Increasing frequency of obstructive disease with increasing coronary artery calcification (CAC) (Agatston) scores is demonstrated. * $p < 0.001$ between groups. CCTA = coronary computed tomography angiography.

extent on CCTA (CCTA area under the curve = 0.825; CAC + CCTA area under the curve = 0.826; $p = 0.84$) (Fig. 4).

6.2. CAD severity for prediction of all-cause death in patients without known CAD: relation to age and gender (CONFIRM)

The high diagnostic performance of CCTA for CAD detection and exclusion has been previously examined.^{3–5} Min et al examined the all-cause mortality in relation to CAD severity in 24,775

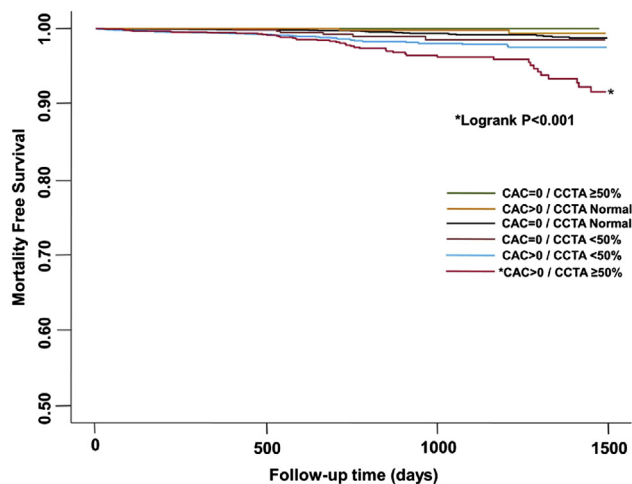


Fig. 4 – Survival according to CAC score and stenosis severity. All-cause mortality-free survival among patients according to CAC score and the severity of coronary artery disease on coronary CTA.

patients undergoing ≥ 64 -detector row CCTA without known CAD using the CONFIRM registry.³⁴ In risk-adjusted analysis, both per-patient obstructive ($>50\%$ stenosis) (HR: 2.60; 95% CI: 1.94–3.49; $p < 0.0001$) and non-obstructive (HR: 1.60; 95% CI: 1.18–2.16; $p = 0.002$) CAD conferred increased risk of mortality compared with patients without evidence of CAD. This data highlights the clinical importance of non-obstructive CAD—which comprises a significant number of patients for whom functional testing might be expected to be negative—and its strong relationship with all-cause mortality.

The investigators also noted a dose–response relationship to the number of coronary vessels exhibiting obstructive CAD and all-cause mortality, with increasing risk observed for non-obstructive (HR: 1.62; 95% CI: 1.20 to 2.19; $p = 0.002$), obstructive 1-vessel (HR: 2.00; 95% CI: 1.43 to 2.82; $p < 0.0001$), 2-vessel (HR: 2.92; 95% CI: 2.00 to 4.25; $p < 0.0001$), or 3-vessel or left main (HR: 3.70; 95% CI: 2.58 to 5.29; $p < 0.0001$) CAD (Fig. 5). Importantly, the absence of CAD was associated with a very low annualized death rate of 0.28%.

Furthermore, due to the size of this study, the investigators were able to explore gender- and age-related differences in CAD-related outcomes. Adjusted hazard ratios for the prediction of all-cause mortality for non-obstructive CAD and 3-vessel/left main disease for females were higher than for males (HR: 4.21; 95% CI: 2.47–7.18; $p < 0.0001$ vs. HR: 3.27; 95% CI: 1.96–5.45; $p < 0.0001$). Moreover, when stratified by age into

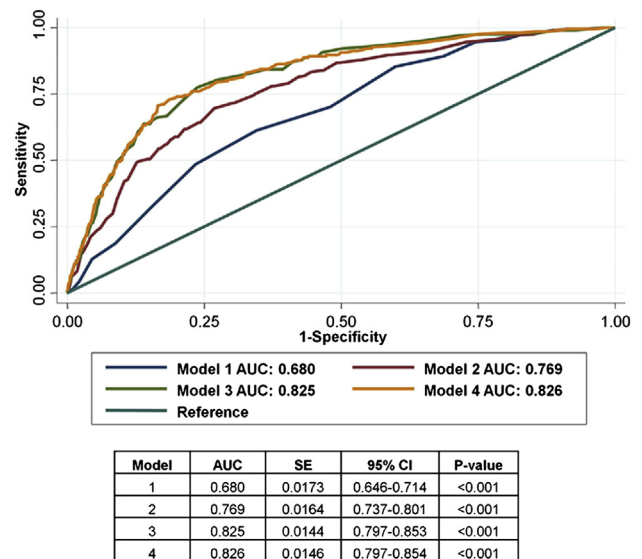


Fig. 5 – Receiver operator characteristic curves: Major adverse events. Receiver-operator characteristic curves of 4 models for predicting composite major adverse events in 8907 patients over a median of 2.1 years. CAC score categories were defined as: 0, ≤ 100 , 101–400, and > 400 . Model 2 (Morise score + CAC category) compared to Model 1 (Morise score only): $p < 0.001$. Model 3 (Morise score + number vessels $\geq 50\%$ stenosis) compared to Model 2 (Morise score + CAC category): $p < 0.001$. Model 4 (Morise score + CAC category + number vessels $\geq 50\%$ stenosis) compared to Model 2 (Morise score + CAC category): $p < 0.001$. Model 3 compared to Model 4: $p = 0.84$. AUC = area under the curve; CAC = coronary artery calcification; CI = confidence interval.

<65 years vs. ≥65 years, younger subjects experienced higher HR for death for 2-vessel (HR: 4.00; 95% CI: 2.16–7.40; $p < 0.001$, HR: 2.46; 95% CI: 1.51–4.02; $p = 0.0003$) or 3-vessel (HR: 6.19; 95% CI: 3.43–11.2; $p < 0.0001$, HR: 3.10; 95% CI: 1.954.92; $p < 0.0001$) obstructive CAD when compared to older patients. Furthermore, the investigators noted that although the pre-test likelihood of obstructive CAD as estimated by the Diamond Forrester tabular^{35,36} methods was highly predictive of obstructive CAD by CCTA, it was not predictive for all-cause mortality. These data suggest that a need for revision in the way we assess stable symptomatic patients with suspected CAD may be needed, and the CONFIRM investigators are currently attempting to improve these methods. Currently, the CONFIRM investigators are also investigating the prognostic value of CCTA findings for MACE including but not limited to all-cause death, such as non-fatal MI and late target vessel revascularization, in patients without known CAD.^{37,38}

7. Studies of prognostic value of CCTA findings in selected population

7.1. Diabetes mellitus

Current American Diabetes Association guidelines endorse cardiovascular disease primary prevention interventions for patients with diabetes mellitus (DM) based on an observational and population-based studies demonstrating excess cardiovascular risk and death attributable to diabetes.³⁹ However, prior data examining the incremental risk of DM for future adverse CAD events have generally lacked information regarding CAD prevalence and severity based on CCTA findings.^{39–43} Rana et al

identified 23,643 consecutive individuals undergoing ≥64-detector row CCTA without known CAD from CONFIRM registry (Diabetes Care 2012 in press). In this study, 3370 individuals with DM who were propensity-matched in 1:2 fashion to 6740 unique non-DM individuals. The presence of CAD on CCTA was graded as none, non-obstructive (1–49% stenosis), or obstructive (≥50% stenosis). DM individuals possessed higher frequencies of obstructive CAD (37% vs. 27%, $p < 0.0001$) and lower frequencies of normal arteries (28% vs. 36%, $p < 0.0001$) compared to non-DM individuals. In addition, CAD extent was higher for DM vs. non-DM individuals for obstructive 1-vessel disease [VD] (19% vs. 14%, $p < 0.0001$), 2-VD (9% vs. 7%, $p < 0.0001$) and 3-VD (9% vs. 5%, $p < 0.0001$) with higher per-segment stenosis in the proximal and mid segments of every coronary artery ($p < 0.001$ for all). Furthermore, the risk of mortality for DM individuals was significantly higher than those non-DM individuals for those with no CAD, (HR: 3.64; 95% CI: 1.67–7.91; $p = 0.001$), non-obstructive CAD (HR: 5.25; 95% CI: 2.56–10.8; $p < 0.001$), 1-VD (HR: 6.39; 95% CI: 2.98–13.7; $p < 0.0001$), 2-VD (HR 12.33; 95% CI: 5.62–27.1; $p < 0.0001$) and 3-VD (HR: 13.25; 95% CI: 6.15–28.6; $p < 0.0001$) (Fig. 6). This data identified a heightened risk of mortality that was more than 5-fold higher for DM individuals with non-obstructive CAD, and almost 10-fold higher for those with obstructive CAD compared to non-DM individuals. When CAD extent and severity was stratified on a per-vessel analysis as no CAD, non-obstructive CAD, obstructive 1-VD, obstructive 2-VD or obstructive 3-VD, the risk of mortality associated with the presence of DM, resulted in a stepwise increase in risk, as compared to those with non-DM individuals. The CONFIRM investigators are also currently evaluating the mortality risk for DM and non-DM individuals enrolled into CONFIRM with a longer follow-up period.

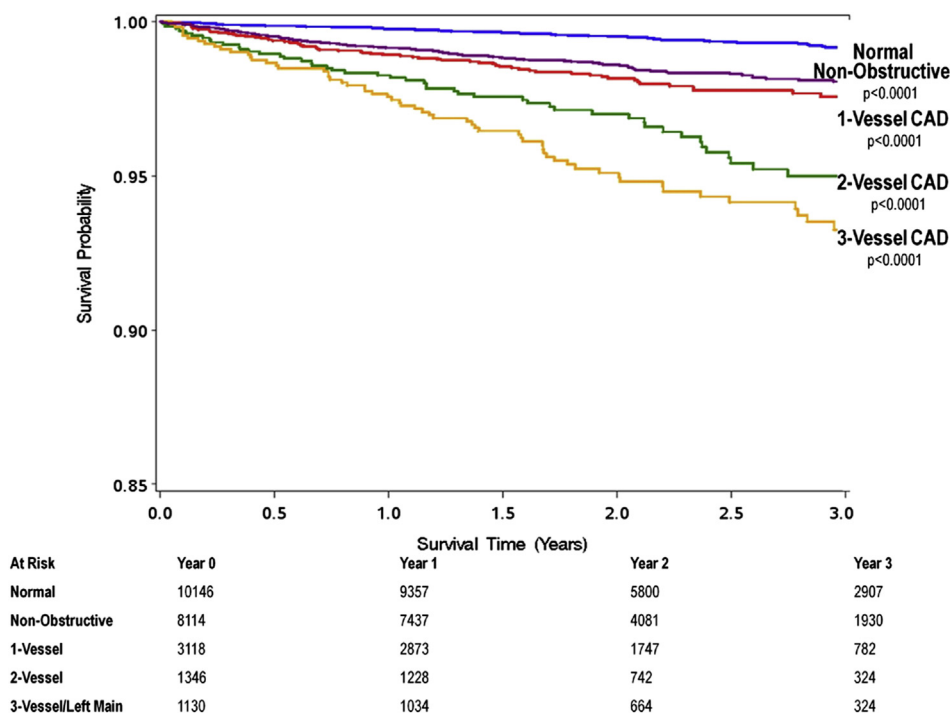


Fig. 6 – Unadjusted all-cause 3-year Kaplan–Meier survival by the presence, extent and severity of CAD by CCTA. There is a dose response relationship of mortality to increasing numbers of vessels with obstructive coronary artery disease. CAD = coronary artery disease, CCTA = coronary computed tomography angiography.

8. Ethnicity difference

Studies examining CCTA have demonstrated increased mortality related to CAD severity but have been limited to relatively non-diverse ethnic populations. Hulten et al studied the prognostic significance of CAD on CCTA according to ethnicity for 16451 patients (60.1% Caucasian, 34.4% East Asian, and 5.5% Africa) without previous CAD followed for a median of 2.0 years (interquartile range 1.4–3.2). The annualized incidence of death or MI comparing obstructive ($\geq 50\%$ stenosis) to no obstructive CAD among Caucasians was 2.2% vs. 0.7% (adjusted hazard ratio [aHR] 2.77, 95% confidence interval [CI] 1.73 to 4.43, $p < 0.001$), 4.8% vs. 1.1% (aHR 6.25, 95% CI 1.12 to 34.97, $p = 0.037$) among Africans, and 0.8% vs. 0.1% (aHR 4.84, 95% CI 2.24 to 10.9, $p < 0.001$) among East Asians. Compared to other ethnicities, East Asians had a lower risk of events (aHR 0.25, 95% CI 0.16–0.38, $p < 0.001$).⁴⁴

9. Prognostic value of CAD severity for prediction of mortality risk: relation to left ventricular ejection fraction

Previously, the examination of the prognostic value of CAD severity and LVEF by CCTA has been limited to single center studies.²⁰ Chow et al examined the prognostic value of CAD severity, LVEF, and clinical variables for predicting all-cause mortality in 14,064 patients without known CAD who underwent ≥ 64 -slice CCTA.⁴⁵ The National Cholesterol Education Program-Adult Treatment Panel III risk was calculated as a summary measure of clinical characteristics denoting risk. A multivariate Cox model for predicting all-cause mortality revealed that abnormal LVEF (HR: 2.74; 95% CI: 2.12–3.51)—defined as $< 50\%$ and CAD severity (HR: 1.58; 95% CI: 1.42–1.76) were independent predictors after adjusting for clinical characteristics. Furthermore, Chow also assessed the improvement of reclassification based on CAD severity and LVEF using net reclassification improvement (NRI) method.⁴⁶ Patient reclassification was significantly improved when LVEF was added to clinical variables alone (NRI: 22.5%; $p < 0.001$) and when CAD severity was added to the model of clinical variable and LVEF (NRI: 17.8%; $p < 0.001$). At present, the CONFIRM investigators are examining whether not only abnormal vs. normal LVEF is useful for enhancing risk stratification, but also whether the degree of left ventricular dysfunction by CCTA improves risk stratification for all-cause mortality.⁴⁷

10. Prognostic value of CCTA in patients with known CAD (CONFIRM)

The utility of CCTA for risk stratification in coronary artery bypass graft (CABG) patients has not been fully examined. Small et al identified 657 CABG patients who had undergone CCTA and assessed the prognostic value of unprotected coronary territory (UCT) or a summary of native vessel disease and graft patency: the coronary artery protection score (CAPS).⁴⁸ The investigators demonstrated that LVEF, creatinine, age, severity of native vessels disease were all univariate

independent predictors for all-cause mortality ($p < 0.001$). In multivariate analysis, adjusted for the EuroSCORE, both UCT ($p = 0.004$) and CAPS ($p < 0.001$) were found to be predictors for all-cause mortality.

11. Patients with acute chest pain syndrome

Particularly, the low negative likelihood ratio of CCTA suggests its utility for efficient ACS. In addition to evaluating the coronary artery anatomy of patients suspected of ACS in the emergency department (ED), CCTA may also allow timely diagnosis or exclusion of ACS and has the potential to be cost-effective.^{49,50} Recently, several studies have also evaluated the long-term outcome of patients discharged from the ED with negative CCTA.⁵¹

Hollander et al prospectively evaluated 481 consecutive low-to-intermediate risk patients who underwent CCTA in the ED for evaluation of a potential ACS.⁵² At one year of follow-up, there were 53 patients (11%) rehospitalized and 51 patients (11%) who received further diagnostic testing (stress or catheterization). There was one death (0.2%; 95% CI = 0.01–1.15%) with unclear etiology, no MIs (0%; 95% CI = 0–0.76%), and no revascularization procedures (0%; 95% CI = 0–0.76%) during this time period. This study concluded that for the low to intermediate risk chest pain population presenting to the ED for evaluation with negative initial biomarkers, ECG findings and TIMI risk score < 2 , CCTA is highly predictive in excluding ACS.

ROMICAT trial was a similar prospective, double-blind observational study that included 368 ED patients with acute chest pain and a low to intermediate risk of ACS.⁵³ From this study, 368 patients who presented to the ED with acute chest pain, negative initial troponin, and a non-ischemic electrocardiogram were followed for 2 years.⁵⁴ Investigators found that the cumulative probability of 2-year MACE increased across CCTA strata for CAD (no CAD 0%; non-obstructive CAD 4.6%; obstructive CAD 30.3%; log-rank $p < 0.0001$) and across combined CCTA strata for CAD and regional wall motion abnormalities (RWMA) [no stenosis or RWMA 0.9%; 1-feature—either RWMA [15.0%] or stenosis [10.1%], both stenosis and RWMA 62.4%; log-rank $p < 0.0001$]. The C statistic for predicting MACE was 0.61 for clinical thrombolysis in myocardial infarction risk score and improved to 0.84 by adding CT CAD data and improved further to 0.91 by adding RWMA (both $p < 0.0001$).

12. Comparison of the prognostic utility of CCTA to myocardial perfusion imaging (MPI)

CCTA has been compared as a prognostic tool with other noninvasive testing, such as nuclear MPI. Shaw et al performed a matched cohort comparison of patients with suspected CAD referred for evaluation of new onset chest pain with 693 and 3067 patients undergoing CTA and MPI. They found that annual mortality rates were similar with CCTA-detected Duke CAD index and nuclear MPI-identified percentage of ischemic myocardium ($p = 0.53$).⁵⁵ Furthermore, van Werkhoven observed an incremental prognostic

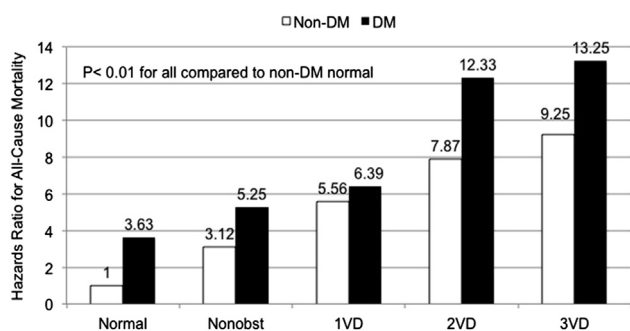


Fig. 7 – Multivariable risk-adjusted hazards ratio for coronary artery disease and severity on a per-vessel basis for matched individuals with and without diabetes. Non-DM = non-diabetes mellitus; DM = diabetes mellitus; Non obst = non-obstructive CAD < 50% maximal per-patient stenosis; 1-VD = 1-vessel obstructive CAD > 50% stenosis; 2-VD = 2-vessel obstructive CAD > 50% stenosis; 3-VD = 3-vessel obstructive CAD > 50% stenosis.

value was seen when CCTA-detected CAD was combined with MPI-identified ischemia looking at 541 patients who had both multislice CT (MSCT) Fig. 8 and single photon emission tomography (SPECT).⁵⁶ Global chi-square tests demonstrated that the addition of non-calcified plaque on CCTA (≥ 2 segments with non-calcified plaque) resulted in further incremental prognostic potential over baseline clinical variables, MPI, and significant CAD ($\geq 50\%$ stenosis) on MSCT (Fig. 7).

13. CCTA for predicting complications of percutaneous coronary intervention (PCI) complication

Nakazawa and his colleagues⁵⁷ reported that lower CT plaque density was significantly related to the “no-reflow” pheno-

menon during percutaneous coronary intervention [PCI] (67.0 ± 10.1 vs. 97.8 ± 37.2 Hounsfield units, $p = 0.018$). In addition, a signet ring-like appearance—the so-called “napkin ring” sign—was observed more frequently in patients with transient no-reflow (55.6% vs 16.7% , $p = 0.013$). Similarly, Kodama et al⁵⁸ compared pre-PCI CCTA plaque characteristics for age-, sex-, and culprit CAD-matched patients who underwent PCI during the same period and did not develop slow flow. Calcium deposition in the perimeter of a plaque, or circumferential plaque calcification (CPC), was significantly more frequent in the slow flow (SF) group (25 of 40, 63%) than the no-SF group (2 of 40, 5.0%) ($p < 0.001$). The positive remodeling index was significantly higher ($1.5 [1.3–1.8]$ vs. $1.2 [1.0–1.5]$; $p < 0.001$) and plaque density significantly lower ($23.5 [9.5–40]$ HU vs. $45 [29–86]$ HU; $p = 0.001$) in the SF group. The conditional logistic regression analysis revealed that CPC, plaque density, and dyslipidemia were the predictors of slow flow, with CPC being the strongest (odds ratio: 79; 95% CI: 8–783, $p < 0.0001$). They concluded that CCTA-verified CPC with low-attenuation plaque and positive remodeling were determinants of slow flow during PCI.

Uetani et al⁵⁹ quantified coronary plaque in 189 consecutive patients undergoing planned coronary intervention by CCTA. The volume and fraction of low-attenuation plaque (< 50 Hounsfield units [HU]) in target lesions was found to be independently associated with peri-procedural MI after adjustment for multiple confounders. The fraction of moderate attenuation (50–150 HU) or fibrous plaque inversely correlated with post-procedural levels of cardiac biomarkers.

Similarly, Watanabe et al assessed coronary plaque feature of culprit lesions in stable angina patients ($n = 107$) with normal pre-PCI cTnT levels underwent 64-slice MDCT before PCI.⁶⁰ Patients were divided into 2 groups according to presence (group I, $n = 36$) or absence (group II, $n = 71$) of post-PCI cTnT elevation ≥ 3 times the upper limit of normal (0.010 ng/ml) at 24 h after PCI. CCTA attenuation values were significantly lower in group I than in group II ($43.0 [26.5–75.7]$ HU vs. $94.0 [65.0–109.0]$ HU, $p < 0.001$). A positive remodeling index was also significantly greater in group I than

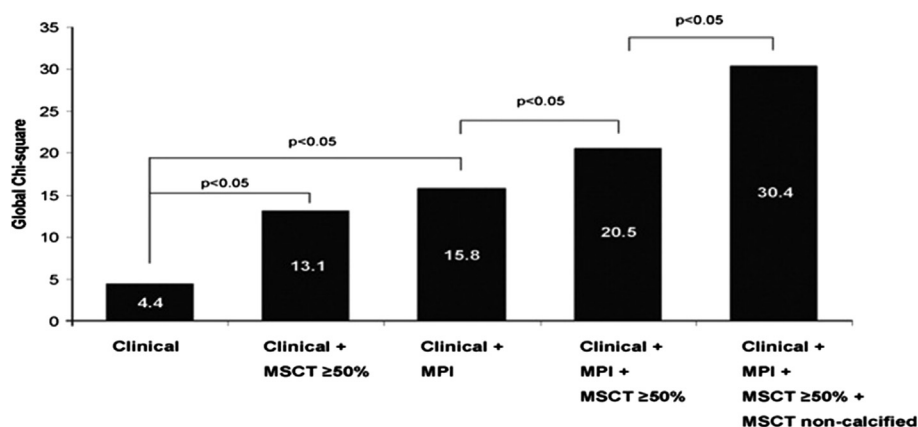


Fig. 8 – Incremental prognostic value of MSCT bar graph illustrating the incremental prognostic value (depicted by chi-square value on the y axis) of MSCT. The addition of MSCT provides incremental prognostic information to baseline clinical variables and MPI. Furthermore, the addition of non-calcified plaque on MSCT (≥ 2 segments with non-calcified plaque) results in further incremental prognostic information over baseline clinical variables, MPI, and significant CAD ($\geq 50\%$ stenosis) on MSCT. MSCT = multislice computed tomography coronary angiography; MPI = myocardial perfusion imaging; CAD = coronary artery disease.

in group II (1.20 ± 0.18 vs. 1.04 ± 0.15 , $p < 0.001$). Spotty calcification was also observed significantly more frequently in group I than in group II (50% vs. 11%, $p < 0.001$). Multivariate analysis demonstrated the presence of positive remodeling (remodeling index > 1.05 ; odds ratio: 4.54; 95% confidence interval: 1.36–15.9; $p = 0.014$) and spotty calcification (odds ratio: 4.27; 95% confidence interval: 1.30–14.8; $p = 0.016$) to be significant independent predictors for cTnT elevation. For prediction of cTnT elevation, the presence of all 3 variables (CCTA attenuation value < 55 HU; remodeling index > 1.05 , and spotty calcification) showed a high positive predictive value of 94%, with their absence notable conferring a high negative predictive value of 90%. These investigators suggested that, based upon these study findings, CCTA might be useful for detecting which lesions are at high risk for myocardial necrosis after PCI. Although these prior studies demonstrated the potential of CCTA to predict PCI complication, future large sized prospective study must be performed to generalize these findings.

14. Conclusion

In addition to high diagnostic performance for anatomically obstructive CAD, coronary CCTA findings of CAD convey important prognostic information. Large international cohorts such as the CONFIRM study have expanded the generalizability of prior small studies. CCTA measures, including the presence, extent and severity of CAD—as determined by the number of vessels with obstructive stenosis, segment involvement and stenosis scores, and stenosis location—have been well validated by the CONFIRM registry. Future studies are still needed in this relatively nascent field, with newer CT technologies—including rest-stress myocardial perfusion and noninvasive calculation of fractional flow reserve—may further expand the diagnostic and prognostic abilities of CCTA.

Conflicts of interest

All authors have none to declare.

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