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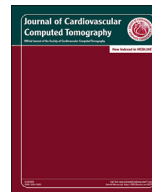
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Research paper

Long term prognostic utility of coronary CT angiography in patients with no modifiable coronary artery disease risk factors: Results from the 5 year follow-up of the CONFIRM International Multicenter Registry

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ABSTRACT

Background: Coronary computed tomography angiography (coronary CTA) can prognosticate outcomes in patients without modifiable risk factors over medium term follow-up. This ability was driven by major adverse cardiovascular events (MACE).

Objective: Determine if coronary CTA could discriminate risk of mortality with longer term follow-up. In addition we sought to determine the long-term relationship to MACE.

Methods: From 12 centers, 1884 patients undergoing coronary CTA without prior coronary artery disease (CAD) or any modifiable CAD risk factors were identified. The presence of CAD was classified as none (0% stenosis), mild (1% to 49% stenosis) and obstructive ($\geq 50\%$ stenosis severity). The primary endpoint was all-cause mortality and the secondary endpoint was MACE. MACE was defined as the combination of death, nonfatal myocardial infarction, unstable angina, and late target vessel revascularization (>90 days).

Results: Mean age was 55.6 ± 14.5 years. At mean 5.6 ± 1.3 years follow-up, 145(7.7%) deaths occurred. All-cause mortality demonstrated a dose-response relationship to the severity and number of coronary vessels exhibiting CAD. Increased mortality was observed for >1 segment non-obstructive CAD (hazard ratio [HR]:1.73; 95% confidence interval [CI]: 1.07–2.79; $p = 0.025$), obstructive 1&2 vessel CAD (HR: 1.70; 95% CI: 1.08–2.71; $p = 0.023$) and 3-vessel or left main CAD (HR: 2.87; 95% CI: 1.57–5.23; $p = 0.001$). Both obstructive CAD (HR: 6.63; 95% CI: 3.91–11.26; $p < 0.001$) and non-obstructive CAD (HR: 2.20; 95% CI: 1.31–3.67; $p = 0.003$) predicted MACE with increased hazard associated with increasing CAD severity; 5.60% in no CAD, 13.24% in non-obstructive and 36.28% in obstructive CAD, $p < 0.001$ for trend.

Conclusions: In individuals being assessed for CAD with no modifiable risk factors, all-cause mortality in the long term (>5 years) was predicted by the presence of more than 1 segment of non-obstructive plaque, obstructive 1- or 2-vessel CAD and 3 vessel/left main CAD. Any CAD, whether non-obstructive or obstructive, predicted MACE over the same time period.

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1. Introduction

Clinicians are frequently confronted with patients requiring assessment for chest pain or equivalent symptoms.¹ While cardiovascular risk factors provide some guidance,^{2,3} there is no close association between traditional risk factors and the presence of atherosclerosis identified by coronary computed tomography angiography (coronary CTA).⁴ The prognostic utility of coronary artery disease (CAD) detected by coronary CTA in those with no medically modifiable risk factors has been described for the medium term only. Over this time period (2.3 ± 1.2 years) the ability of coronary CTA to discriminate risk was largely driven by the combined endpoint of major adverse cardiovascular events (MACE) defined as death, nonfatal myocardial infarction, unstable angina, and late target vessel revascularization (>90 days).⁴ However, CAD identified on coronary CTA did not confer an increased risk of mortality in the medium term. The primary purpose of this study was therefore to determine the long term (>5 year) prognostic utility of CAD detected in coronary CTA with regards to all-cause mortality in patients with no modifiable risk factors. To do so, we conducted a sub-analysis of the long-term Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter (CONFIRM) registry.

2. Method**2.1. Patient population**

The rationale and methods of the CONFIRM registry have been described previously.⁵ In the long term cohort of the CONFIRM registry, in which patients have a mean follow-up of 5.6 years, 12086 patients were prospectively enrolled between February 2003 and December 2009 across 12 sites in 6 countries within North America, Europe, and Asia. Enrolled sites collected clinical information on risk factors, clinical presentation and follow-up for

all-cause mortality and MACE in addition to coronary CTA data(5). Institutional review board approval was obtained at each center.

2.2. Inclusion criteria

Inclusion criteria¹ age ≥ 18 years²; CAD evaluation by coronary CTA using a CT system with ≥ 64 detector rows³; clinically indication for CAD evaluation⁴; interpretable coronary CTA; and⁵ prospective data collection for CAD risk factors. Clinical indications were defined as angina-equivalent symptoms including pain, tightness, and pressure, shortness of breath, pre-surgical evaluation, and structural indications (e.g., pulmonary vein mapping). In addition, individuals without chest pain syndrome could be assessed for CAD in the context of congenital heart disease, risk assessment of CAD in individuals who were considered to have severe vascular disease or had a concerning family history of vascular disease.

2.3. Chest pain categorization

Categorization of chest pain was based on the Diamond-Forrester criteria for angina pectoris.⁶ At each site, symptom category was prospectively determined through either written survey or interview by a doctor or allied health professional.

2.4. Exclusion criteria

Exclusion criteria for our analysis were all patients with modifiable risk factors for coronary artery disease ($n = 8501$) and patients with known CAD ($n = 1593$) and those with missing data relating to modifiable risk factors ($n = 73$), stenosis assessment ($n = 33$) and age ($n = 2$). Modifiable coronary risk factors included diabetes mellitus, hypertension, dyslipidemia, and smoking. Standardized definitions for modifiable risk factors were used. Diabetes mellitus was defined as a fasting glucose level of 126 mg/dL

(6.99 mmol/L) or higher and/or use of diabetic mediations. Hypertension was defined by a systolic blood pressure of 140 mm Hg or higher or diastolic blood pressure of 90 mm Hg or higher and/or use of antihypertensive therapy. Dyslipidemia was defined as a total cholesterol level of 200 mg/dL (5.18 mmol/L) or above or the use of lipid lowering therapy. Patients were considered smokers if they currently smoke or quit smoking within 3 months prior to coronary CTA. Patients with prior known CAD defined by previous myocardial infarction, percutaneous coronary intervention, or coronary artery bypass surgery were excluded from analysis. Importantly, family history of CAD was not an exclusion criteria, it is not modifiable and affected patients were therefore included in the analysis.

2.5. Outcomes

The primary endpoint was all cause mortality. The secondary endpoint was major adverse cardiovascular events (MACE), defined as the combination of death, nonfatal myocardial infarction, unstable angina, and late target vessel revascularization (>90 days). At each individual institution a physician and/or research nurse, who was blinded to coronary CTA results, conducted follow-up for mortality and MACE. At United States sites death was determined by query of the Social Security Death Index. At all other sites direct interview and/or telephone contact and/or review of medical records was used to determine mortality and MACE.

2.6. Scan protocol and image reconstruction, analysis and interpretation

Coronary CTA image acquisition at each site was performed according to Society of Cardiovascular Computed Tomography guidelines. CT system of various types and vendors, either single or dual source were included, the only restriction being that all scanners were required to be 64–detector rows or greater. Coronary segments were scored for stenosis severity using a 16-segment coronary artery model with the intention-to-diagnose. The definition of coronary atherosclerosis as visualised on CT was any lesion ≥ 1 mm² that existed either within the lumen of the coronary vessel or adjacent to the lumen that could be differentiated from surrounding pericardial tissue, epicardial fat, or the vessel lumen itself.⁵ Stenosis severity was graded on a per-patient, per-vessel, and per-segment basis. In epicardial coronary arteries of at least 2 mm in diameter, atherosclerotic lesions were graded as normal (no atherosclerosis), mild (1%–49% stenosis), or obstructive ($\geq 50\%$ stenosis). Each lesion was interrogated via numerous methods including maximum intensity projection and multiplanar reconstruction along the transverse plane and several longitudinal axes.

2.7. Statistical analysis

Statistical calculations were performed using STATA, version 13 (StataCorp LP, College Station, Texas). Absolute counts and percentages were used for categorical variables and means \pm standard deviations were used to express continuous variables. Categorical variables were compared with the χ^2 test or Fisher Exact test for cell counts <6 and continuous variables were analyzed with the student t test or Mann–Whitney two-sample test, as appropriate. The χ^2 test for trend was used to compare categorical variables across ordered groups. Time to death or MACE were analyzed using Kaplan–Meier survival curves and compared using the log-rank test. Predictors of death and MACE were assessed using univariable and multivariable Cox proportional hazards models and the resulting hazard ratios (HR) and 95% confidence intervals were

reported. Multivariate models were adjusted for age, sex \pm family history. Statistically significant difference was defined as those with a two tailed p-value of <0.05.

3. Results

3.1. Study population

The CONFIRM long term cohort comprises 12086 patients of which 1593 individuals with a history of myocardial infarction, target vessel revascularization, cardiac transplant and loss to MACE follow-up were excluded. An additional 8574 individuals had medically modifiable CAD risk factors and were excluded from the analysis (hypertension, 1514; dyslipidemia, 3429; diabetes mellitus, 3333; smoking, 225). The final study cohort consisted of 1919 individuals. Complete follow-up was available in 1884 (98%), with 35 individuals lost to follow-up. A smaller cohort of 885 individuals had MACE follow-up data available for analysis.

The overall study cohort was middle-aged (mean age, 56 \pm 15 years; 60% male patients), with a 24% prevalence of obstructive CAD. The mean follow-up period was 5.6 \pm 1.3 years. The majority of study individuals presented with low (33.8%) or intermediate (58.5%) pretest likelihood of obstructive CAD. Only a minority (7.7%) had a high pretest likelihood of CAD (Table 1).

3.2. Clinical characteristics associated with CAD and all-cause mortality

There were 145 deaths in the entire cohort. Chest pain typicality information was available in 1518 patients. All-cause mortality was associated with higher age (HR 1.07, $p < 0.001$) but not male sex (HR 0.91, $p = 0.58$). There was a paradoxical relationship between chest pain typicality and mortality with atypical chest pain patients having a reduced mortality (HR 0.58, $p = 0.04$), while non-anginal chest pain (HR 1.28, $p = 0.36$) and typical angina (HR 0.96, $p = 0.88$) had no relationship to mortality when compared to asymptomatic patients (Table 2).

3.3. Effect of per-patient and per-vessel CAD in coronary CTA on mortality

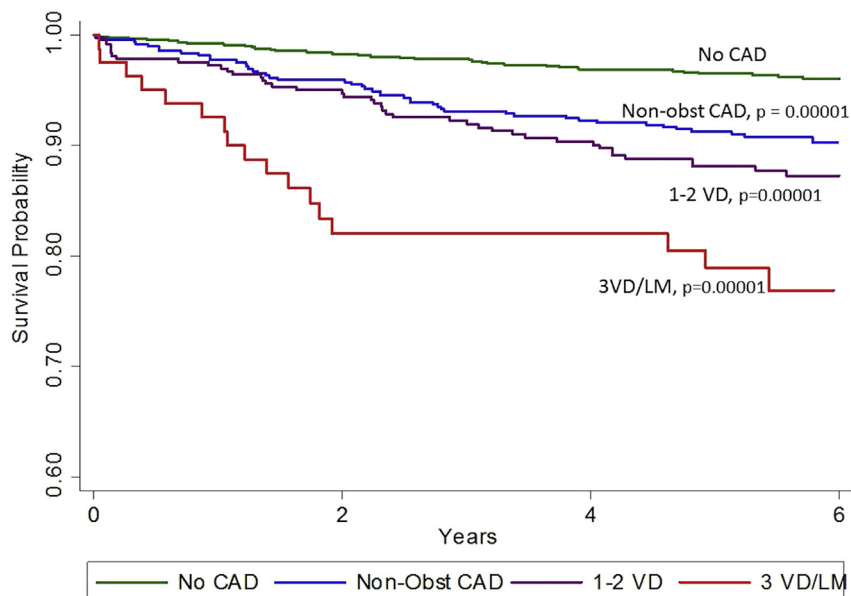
A dose-response relationship was observed for increased hazards of death for non-obstructive, 1- or 2-vessel obstructive CAD and 3 vessel/left main obstructive CAD (Fig. 1). Importantly, the

Table 1
Baseline clinical and CAD characteristics study population N = 1884.

Characteristic	Datum n (%)
Age (years)	55.6 \pm 14.5
Male patients	1122 (59.6)
Chest pain typicality:	
Typical	241 (15.9)
Atypical	492 (32.4)
Non-anginal	218 (14.4)
Asymptomatic	567 (37.4)
Family history status	
Family history of CAD	589 (31.3)
No family history of CAD	1295 (68.7)
Pretest likelihood of CAD	
Low ≤ 0.10	513 (33.8)
Intermediate 0.11–0.89	887 (58.5)
High ≥ 0.90	116 (7.7)
CCTA identified CAD	
Normal	936 (49.7)
Non-obstructive	496 (26.3)
Obstructive ($\geq 50\%$)	452 (24.0)

Table 2
Chest Pain Typicality and All Cause Death (n = 1518).

Chest pain typicality n = 1518	No death (n = 1418) n (%)	Death (n = 100) n (%)	Hazard ratio	P-value
Typical	224 (15.8)	17 (17.0)	0.96	0.88
Atypical	471 (33.2)	21 (21.0)	0.58	0.04
Non-anginal	197 (13.9)	21 (21.0)	1.28	0.36
Asymptomatic	526 (37.1)	41 (41.0)	1	0.44

**Figure 1.** Unadjusted Kaplan–Meier curve for mortality-free survival on the basis of the presence of no CAD, non-obstructive CAD, 1&2 vessel obstructive CAD and 3 vessel obstructive & left main CAD for individuals without modifiable CAD risk factors (p values based on log-rank tests).**Table 3**
Hazard Ratio Of All Cause Mortality Stratified By Presence And Extent Of CAD On A Per-Patient And Per-Vessel Basis.

CCTA result	Risk-adjusted ^a hazard ratio HR (95% CI)	P-value
Per-patient CAD		
Non obstructive	1.49 (0.96–2.32)	0.078
Obstructive 1 & 2 Vx Dx	1.7 (1.08–2.71)	0.023
Obstructive 3 Vx Dx & LM	2.86(1.57–5.23)	0.001
Non obstructive 1 segment	1.04 (0.53–2.05)	0.90
Non obstructive > 1 segment	1.73 (1.07–2.79)	0.025
Obstructive CAD	1.94 (1.25–3.00)	0.003

^a Adjusted for age & sex.

absence of CAD in coronary CTA was associated with a low rate of incident death (annualized mortality: 0.69%; 95% CI: 0.5–0.95%). Using multivariable Cox regression analysis considering age and sex, time to all-cause mortality was predicted by per-vessel obstructive 1- or 2-vessel CAD as well as 3 vessel/left main CAD (Table 3). Further analysis of the burden of non-obstructive disease, as determined by number of segments involved, showed that >1 segment of non-obstructive CAD predicted mortality (Table 3). Mortality rate after a mean of 5.6 years follow-up in those with no CAD was 3.95%. Mortality increased to 9.48% in patients with non-obstructive CAD and to 13.5% in patients with obstructive CAD (p for trend < 0.001).

3.4. Effect of per-patient and per-vessel CAD in coronary CTA on MACE

In the MACE cohort, the presence of any form of CAD, obstructive (HR: 6.63; 95% CI: 3.91–11.26; p < 0.001) or non-obstructive

(HR: 2.20; 95% CI: 1.31–3.67; p = 0.003) predicted MACE (Fig. 2). There was an increased hazard for MACE with increasing CAD severity (Table 4). The incidence of MACE increased from 5.6% in those without CAD to 13.24% in those with non-obstructive disease and to 36.28% in those with obstructive CAD (p < 0.001) for trend (Table 5).

4. Discussion

This sub-study of the CONFIRM long term registry signifies the first prospective international multicenter dataset to correlate CAD diagnosed on coronary CTA in individuals with no modifiable risk factors to long-term (>5 year) all-cause mortality. This analysis builds on prior work which noted a relationship between CCTA diagnosed disease and MACE in the medium-term, but did not show this relationship with all-cause mortality.⁴ Importantly, there was a relationship between the severity of obstructive CAD and long term all-cause mortality. Also, we observed a relationship

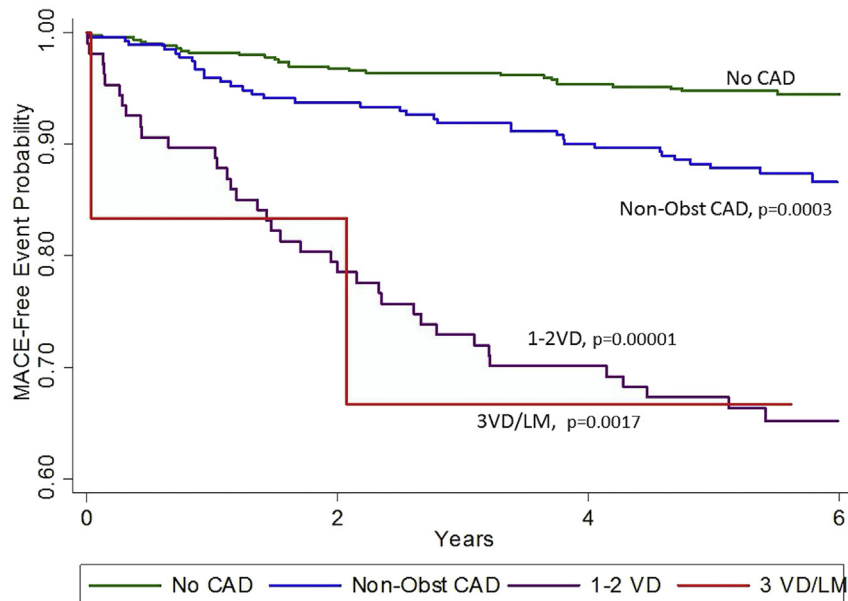


Figure 2. Unadjusted Kaplan–Meier curve for MACE-free survival on the basis of the presence of no CAD, non-obstructive CAD, 1&2 vessel obstructive CAD and 3 vessel obstructive & left main CAD for individuals without modifiable CAD risk factors (p values based on log-rank tests).

Table 4

Hazard Ratio Of MACE Stratified By Presence And Extent Of CAD On A Per-Patient And Per-Vessel Basis.

CCTA result	Univariable hazard ratio HR (95% CI)	P-value	Risk-adjusted ^a hazard ratio HR (95% CI)	P-value
Per-patient CAD				
Non Obstructive CAD	2.42 (1.48–3.97)	<0.001	2.20 (1.31–3.67)	0.003
Obstructive CAD	7.71 (4.77–12.48)	<0.001	6.63 (3.91–11.26)	<0.001
Per-vessel CAD				
Non Obstructive CAD	2.42 (1.48–3.97)	<0.001	2.20 (1.31–3.68)	0.003
Obstructive 1VD	7.75 (4.63–12.98)	<0.001	6.65 (3.79–11.65)	<0.001
Obstructive 2VD	7.71 (3.64–16.35)	<0.001	6.62 (3.00–14.61)	<0.001
Obstructive 3VD/LM	7.23 (1.72–30.36)	0.007	6.48 (1.53–27.51)	0.011

^a Adjusted for age, sex and family history.

Table 5

All Cause Mortality And MACE Rates Stratified By The Presence And Severity Of CAD.

Event	Normal n (%)	Non-obstructive CAD n (%)	Obstructive CAD n (%)	P-value (trend)
Overall cohort n = 1884	936	496	452	
Death	37 (4.0)	47 (9.5)	61 (13.5)	<0.001 (<0.001)
MACE cohort n = 885	500	272	113	
MACE	28 (5.6)	36 (13.2)	41 (36.3)	<0.001 (<0.001)

between the presence of nonobstructive atherosclerosis in >1 coronary segment and mortality. However, while the presence of any obstructive disease conferred an incremental risk of MACE, there was no significant difference in MACE rates when stratified by the extent of obstructive disease. This may reflect the fact that the majority of our MACE events were late revascularizations.

Our study is in keeping with prior published data from phase 1 of the CONFIRM registry which analyzed all patients suspected of having CAD, regardless of risk factors, for a median of 2.3 years. In that larger cohort (n = 24 775) individuals had increased mortality associated with both obstructive and non-obstructive disease.⁷ Other investigators have shown that after more than 6 years of follow-up, 3-vessel non-obstructive and any obstructive CAD, diagnosed by coronary CTA, were independent predictors of mortality in a multivariable model with an influence of the burden of CAD on mortality.⁸

Accurately estimating the pre-test likelihood of significant CAD

is fundamental to determine subsequent decisions for diagnostic testing and resultant management.⁸ In our cohort, the vast majority of individuals (92%) were classed as either low or intermediate pre-test likelihood of obstructive CAD. This is at odds to the observed rates of obstructive CAD (24%) and non-obstructive CAD (26.3%). This highlights a discrepancy between the clinical assessment of CAD and the presence and extent of CAD demonstrated by coronary CTA, which is potentially particularly pronounced in individuals without traditional modifiable risk factors. These findings are not dissimilar to the vast amount of data emphasizing that coronary calcium is a better predictor of cardiac events than traditional risk factors. Hou et al. demonstrated an incremental value of coronary calcium and coronary CTA for predicting MACE, with areas under the receiver-operating characteristic curves improving to from 0.71 for clinical risk factors alone to 0.82 and 0.93, respectively (both $p < 0.001$).⁹

In our cohort, those deemed as low pretest likelihood of CAD

had lower all-cause mortality, while patients with a high pre-test likelihood of CAD showed a signal towards increased mortality. It is however important to acknowledge that the Diamond Forrester pre-test model was designed to assess probability of having significant CAD in symptomatic patients and not to predict downstream events.⁶ In addition, the Diamond Forrester risk score was developed for use in higher risk individuals planned for invasive coronary angiography and not low-risk cohorts such as ours or other groups typically scheduled for coronary CTA. Recently, risk tools using clinical risk factors and coronary CTA findings in combination have been developed. For example, an optimized prognostic score, the “CONFIRM Score”,¹⁰ integrates the distribution and severity of disease as identified on coronary CTA and clinical risk factors to determine risk. It resulted in an impressive net reclassification improvement of 49% compared to a clinical risk score, the NCEP ATP III score,¹¹ in predicting all-cause mortality.¹⁰ These findings, similar to our analysis, emphasize the clinical importance of CAD identified by coronary CTA.

This study is not without limitations. Firstly, the details of downstream management decisions are not known and therefore the potential impact such decisions may have on downstream events is unclear. Importantly however, although information regarding downstream management was lacking, treatment bias would result in a reduction of events in those with atherosclerosis. Secondly, although all-cause mortality was the primary outcome, the precise cause of death for each patient was not available. This is particularly important considering that almost 4% of patients without any atherosclerosis died after 5.6 years of follow-up. This, however, must be interpreted in the context of the baseline population annualised death rate in this age group, which is approximately 1%.¹² Thirdly, our study focused entirely on stenosis assessment without taking into consideration other information available from coronary CTA such as plaque characteristics which may also influence the likelihood of ischemia and outcomes.^{13,14}

5. Conclusion

In individuals without modifiable cardiovascular risk factors undergoing coronary CTA, long-term mortality was predicted by the presence of more than 1 segment of non-obstructive plaque, obstructive 1- or 2-vessel CAD as well as 3 vessel/left main CAD. In addition, any degree of CAD, whether non-obstructive or obstructive, predicted MACE over the same time period.

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Conflict of interests

None declared.

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