

# Age-related risk of major adverse cardiac event risk and coronary artery disease extent and severity by coronary CT angiography: results from 15 187 patients from the International Multisite CONFIRM Study

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## Aims

Prior studies evaluating the prognostic utility of cardiac CT angiography (CCTA) have been largely constrained to an all-cause mortality endpoint, with other cardiac endpoints generally not reported. To this end, we sought to determine the relationship of extent and severity of coronary artery disease (CAD) by CCTA to risk of incident major adverse cardiac events (MACEs) (defined as death, myocardial infarction, and late revascularization).

## Methods and results

We identified subjects without prior known CAD who underwent CCTA and were followed for MACE. CAD by CCTA was defined as none (0% luminal stenosis), mild (1–49% luminal stenosis), moderate (50–69% luminal stenosis), or severe ( $\geq 70\%$  luminal stenosis), and  $\geq 50\%$  luminal stenosis was considered as obstructive. CAD severity was judged on per-patient, per-vessel, and per-segment basis. Time to MACE was estimated using univariable and multivariable Cox proportional hazards models. Among 15 187 patients ( $57 \pm 12$  years, 55% male), 595 MACE events (3.9%) occurred at a  $2.4 \pm 1.2$  year follow-up. In multivariable analyses, an increased risk of MACE was observed for both non-obstructive [hazard ratio (HR) 2.43,  $P < 0.001$ ] and obstructive CAD (HR: 11.21,  $P < 0.001$ ) when compared with patients with normal CCTA. Risk-adjusted MACE increased in a dose–response relationship based on the number of vessels with obstructive CAD  $\geq 50\%$ , with increasing hazards observed for non-obstructive (HR: 2.54,  $P < 0.001$ ), obstructive one-vessel (HR: 9.15,  $P < 0.001$ ), two-vessel (HR: 15.00,  $P < 0.001$ ), or three-vessel or left main (HR: 24.53,  $P < 0.001$ ) CAD.

Among patients stratified by age  $< 65$  vs.  $\geq 65$  years, older individuals experienced higher risk-adjusted hazards for MACE for non-obstructive, one-, and two-vessel, with similar event rates for three-vessel or left main ( $P < 0.001$  for

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all) compared with normal individuals age <65. Finally, there was a dose relationship of CAD findings by CCTA and MACE event rates with each advancing decade of life.

## Conclusion

Among individuals without known CAD, non-obstructive, and obstructive CAD are associated with higher MACE rates, with different risk profiles based on age.

## Keywords

Age • Major adverse cardiac events • Coronary artery disease • Prognosis • coronary CT angiography

## Introduction

Coronary artery disease (CAD) is the leading cause of morbidity and mortality worldwide.<sup>1,2</sup> The severity and prevalence of CAD increases with age,<sup>3</sup> with patients older than 75 years more likely having multi-vessel CAD.<sup>4</sup> However, the presence of CAD in young patients is not benign and is associated with significant morbidity and mortality.<sup>5</sup> Invasive coronary angiography (ICA) has traditionally been used as an anatomic standard for the diagnosis and prognosis of CAD. Coronary CT angiography (CCTA) of 64-detector rows or greater has emerged as a non-invasive modality that demonstrates high diagnostic performance compared with ICA.<sup>6,7</sup> While CAD findings by CCTA have been examined for their prognostic utility in several prior investigations, published studies to date have been generally restricted to single centres and limited to measures of obstructive CAD and all-cause mortality endpoints.<sup>8–11</sup> Further, given smaller sample sizes, these studies were constrained to evaluating cohorts in entirety and thus, were not able to discern differences in risk of major adverse cardiac events (MACEs), particularly based on differences in age.<sup>5,12</sup> To this end, we sought to determine in a prospective international multisite registry of 15 187 patients the relationship of the extent and severity of CAD by CCTA to risk of incident MACEs and further, to examine this relationship as a function of age.

## Methods

### Study population

Study patients were identified from the CONFIRM (Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter) registry, a dynamic, international, multicentre, observational cohort study that prospectively collects clinical, procedural, and follow-up data on patients who underwent  $\geq 64$ -detector row CCTA between 2005 and 2009 at 12 centres in 6 countries (Canada, Germany, Italy, Korea, Switzerland, and the USA). The rationale, design, site-specific patient characteristics, and follow-up durations have been described previously.<sup>13</sup> Patients undergoing CCTA at eight centres for whom the MACE follow-up were screened for the present study analysis, while those individuals with known CAD, as defined by prior myocardial infarction (MI) or coronary revascularization, or cardiac transplantations were excluded.

### CCTA protocol and image reconstruction

CCTA scans were performed on a variety of different scanner platforms as previously described.<sup>14</sup> The scan parameters were as follows:  $64 \times 0.625/0.750$ -mm collimation, tube voltage 100 or 120 mV, effective 400–650 mA. Dose reduction strategies were utilized as previously described,<sup>14</sup> and the phase with the least amount of coronary artery

motion was chosen for analysis. CCTAs were evaluated by an array of post-processing imaging techniques, and every arterial segment was scored in an intent-to-diagnose fashion.

### Non-invasive coronary artery assessment by CCTA

The visual interpretation of CCTA at all the study sites was performed by level III equivalent cardiologist and all coronary segments were scored using a 16-segment coronary artery model. Coronary atherosclerotic lesions were graded by visual estimation using a 4-point grading system: none (0% luminal stenosis), mild (1–49% luminal stenosis), moderate (50–69% luminal stenosis), or severe ( $\geq 70\%$  luminal stenosis). Per cent obstruction of the coronary artery lumen was based on a comparison of the luminal diameter of the segment exhibiting obstruction to the luminal diameter of the most normal-appearing site immediately proximal to the plaque.

Plaque severity was graded on a per-patient, per-vessel, and per-segment basis. Per-patient severity was defined by the maximal stenosis in any coronary segment at the  $\geq 50\%$  stenosis threshold, with a  $\geq 50\%$  stenosis left main considered obstructive. Per-vessel CAD severity was defined by the presence of a  $\geq 50\%$  stenosis in 0, 1, 2, or 3 coronary artery vessels.

Per-segment CAD severity was judged for individual coronary artery segments as we have previously described.<sup>15</sup> Briefly, a segment stenosis score was calculated as a measure of the overall coronary artery plaque burden, and was graded and summed for each coronary segment as none to severe plaque (0–3) based on the extent of obstruction, with a total score ranging from 0 to 48. A segment involvement score was employed as a measure of overall coronary artery plaque distribution, and was calculated as the total number of coronary artery segments exhibiting plaque, irrespective of the degree of luminal stenosis within each segment (minimum = 0; maximum = 16). We further examined risk in association with any severe proximal stenosis in the left anterior descending, left circumflex, or right coronary vessels.

### Clinical endpoints

The primary study endpoint was time to MACE, defined as death, MI and late revascularization (defined as  $>90$  days after CCTA). Follow-up procedures were approved by all study centres' IRB. The death status was gathered by clinical visits, telephone contacts, questionnaires sent by mail, or by query of the national death registry.

### Statistical analysis

SPSS 12.0 (www.SPSS.com, Chicago, IL, USA) and SAS 9.2 (www.sas.com, Cary, NC, USA) were used for all statistical analyses. Categorical variables are presented as frequencies and continuous variables as means  $\pm 1$  SD. Variables were compared with  $\chi^2$  statistic for categorical variables and by Student's unpaired t test for continuous variables. Patients who underwent early revascularization procedures  $\leq 90$  days were excluded from all survival analyses. Time to event from all MACE events and event rates were

calculated using univariable Cox proportional hazards models. In each case, the proportional hazards assumption was met. Adjusted models were also devised including multivariable stepwise models adjusting for baseline demographics, cardiac risk factors, typicality of angina and pre-test likelihood of obstructive CAD. Adjusted models were also developed to test first order interactions related to age and study site. A two-tailed *P*-value <0.05 was considered statistically significant.

## Results

### Clinical characteristics of the study cohort

Among 17 226 consecutive patients undergoing CCTA at eight centres for whom the MACE follow-up and per-segment CAD data were available, 1110 patients with a history of MI, coronary revascularization, and cardiac transplant were excluded; and an additional 929 (5%) patients were lost to follow-up and excluded. The final analysis cohort consisted of 15 187 patients. The study cohort was middle-aged ( $57 \pm 12$  years, 55% male) with a high prevalence of CAD risk factors and symptoms. Patients presented predominantly with typical or atypical angina, with the majority of individuals intermediate or high pre-test likelihood of obstructive CAD. Given their history of prior CAD, excluded patients had a higher pre-test likelihood of CAD (Table 1).

### Clinical characteristics associated with CAD and MACE

Survival was examined after a mean follow-up of  $2.4 \pm 1.2$  years (median = 2.1, inter-quartile range 1.4–3.3 years), at which point 595 MACE events were recorded (182 deaths, 191 MI, 283 late revascularization). Among patients  $\geq 65$  vs.  $< 65$  years old, a higher incidence was observed for each individual component of MACE, including for all-cause mortality [122 (3.0%) vs. 60 (0.5%),  $P < 0.001$ ], non-fatal MI [82 (2.0%) vs. 109 (1.0%),  $P < 0.001$ ], and late revascularization [138 (3.4%) vs. 145 (1.3%),  $P < 0.001$ ]. In the case of multiple event types, time to the earliest event constituted time to MACE. For the survival analyses, early revascularization was excluded and 507 MACE events were analysed. Increasing severity of CAD was associated with male gender, diabetes, hypertension, dyslipidaemia, family history of CAD, current smoking, typical angina and high pre-test likelihood of CAD ( $P \leq 0.002$  for all) (Table 2). In univariable Cox proportional hazards models, increased hazards for MACE was associated with advanced age, male gender, diabetes, hypertension, untreated dyslipidaemia, current smoking, family history of CAD, and pre-test CAD likelihood (Table 3).

### CAD findings for patients experience MACE vs. No MACE

Compared with patients who did not experienced an MACE event at follow-up, patients who did experience an MACE event had significantly more severe CAD in the majority of coronary segments (Table 4).

### Per-patient, per-vessel and per-segment CAD severity and risk of MACE

In both univariable as well as multivariable Cox regression analysis considering age, and CAD risk factors, MACE was predicted by

**Table 1** Demographics of the entire registry and study cohort

	Entire registry n (%) or means $\pm$ SD	Study cohort n (%) or means $\pm$ SD
Total	27 125	15 187
Age*	$57.7 \pm 12.7$	$56.8 \pm 11.8$
Male gender	14 997 (55)	8363 (55)
Diabetes*	4067 (15)	1958 (13)
Diabetes/meds*	4128 (15)	2015 (13)
Family history of premature CAD*	9849 (37)	4431 (30)
Hyperlipidaemia*	14 906 (56)	8248 (55)
Hyperlipidaemia/meds*	15 666 (58)	8890 (59)
Hypertension*	13 582 (51)	7196 (48)
Hypertension/meds*	16 084 (60)	9353 (62)
Current smoker*	4994 (19)	2476 (16)
History of PAD/CVD*	485 (4)	354 (5)
Chest pain <sup>a</sup>		
Typical angina	3556 (16)	1468 (10)
Atypical angina	8860 (39)	6246 (43)
Non-cardiac	2699 (12)	1325 (9)
Asymptomatic	7796 (34)	5387 (37)
Pre-test CAD likelihood <sup>b</sup>		
Low <10%	6477 (28)	4485 (31)
Intermediate 10–90%	14 137 (62)	8849 (62)
High >90%	2153 (9)	967 (7)

\**P*-value for differences in percentages for study cohort vs. excluded patients <0.05.

<sup>a</sup>Typicality of chest pain and pre-test likelihood of CAD missing from registry in 4214 patients and 4358, respectively.

maximal per-patient non-obstructive and obstructive CAD (Table 5, Figure 1). By both univariable and multivariable Cox models, per-vessel obstructive CAD was related to a dose–response increased hazards for MACE for one-vessel, two-vessel, three-vessel, or LM CAD (Table 5, Figure 2). Similarly, in both univariable and multivariable Cox regression analysis, higher rates of incident MACE were associated with higher numbers of coronary segments with plaque, with stenosis-adjusted segments with plaque, with any severe proximal stenosis and with any plaque within the LM artery (Table 5). Sixty-two MACE events occurred in patients with no angiographic luminal narrowing by CCTA resulting in an annual event rate of 0.36% (Figure 1). On the other hand, 146 MACE events occurred in patients with non-obstructive CAD by CCTA resulting in an annual event rate of 1.22%, while there were 299 MACE events occurred in patients with obstructive CAD resulting in an annual event rate of 6.85%.

### Age-stratified impact of CCTA-visualized CAD on MACE from all-causes

Individuals <65 years old had lower pre-test probability of CAD than those  $\geq 65$  years (pre-test probability low 36 vs. 18%; intermediate 59 vs. 69%, high 4 vs. 13%,  $\chi^2 P < 0.0001$ ). When compared with

**Table 2** Clinical characteristics of study group stratified by normal, non-obstructive, and obstructive CAD by CCTA

	Normal (n = 7015) n (%)	Non-obstructive CAD (n = 5374) n (%)	Obstructive CAD (n = 2798) n (%)	P-value
Age, mean ± SD	52.0 ± 11.6	60.0 ± 10.3	62.7 ± 10.1	<0.0001
Male	3180 (45.4)	3256 (60.6)	1927 (68.9)	<0.0001
Diabetes	611 (8.8)	760 (14.2)	587 (21.1)	<0.0001
Hypertension	2836 (41.0)	2694 (51.0)	1666 (60.2)	<0.0001
Dyslipidaemia	3284 (47.5)	3107 (58.4)	1857 (66.9)	<0.0001
Family history of premature CAD	1882 (27.5)	1551 (29.6)	998 (36.5)	<0.0001
Current smoking	1047 (15.1)	830 (15.6)	599 (21.6)	<0.0001
Chest pain Typicality <sup>a</sup>				<0.0001
Typical	580 (8.7)	425 (8.3)	463 (17.4)	
Atypical	3314 (49.8)	1994 (39.0)	938 (35.2)	
Non-cardiac	592 (8.9)	479 (9.4)	254 (9.5)	
Asymptomatic	2168 (32.6)	2211 (43.3)	1008 (37.9)	
Pre-test CAD Likelihood <sup>b</sup>				<0.0001
Low	2375 (36.0)	1543 (30.4)	567 (21.5)	
Intermediate	3951 (59.9)	3210 (63.3)	1688 (64.0)	
High	266 (4.0)	318 (6.3)	383 (14.5)	
Revascularization <90 days	14 (0.2)	58 (1.1)	709 (25.3)	<0.0001

<sup>a</sup>Chest pain typicality and <sup>b</sup>pre-test likelihood of CAD missing in 761 and 886 patients, respectively.

**Table 3** Clinical characteristics associated with MACE event

Variable	Univariable HR (95% CI)	P-value
Age	1.07 (1.06–1.07)	<0.001
Male gender	1.40 (1.17–1.68)	<0.001
Diabetes	2.34 (1.91–2.86)	<0.001
Hypertension	2.01 (1.67–2.41)	<0.001
Hyperlipidaemia	1.41 (1.18–1.70)	<0.001
Current smoking	1.33 (1.07–1.65)	0.01
Family history of premature CAD	1.45 (1.20–1.74)	<0.001
Pre-test CAD Likelihood per 10% increments	1.09 (1.06–1.13)	<0.001

individuals without CAD in patients <65 years, patients ≥65 years experienced higher hazards for MACE for non-obstructive, one-vessel, and two-vessel obstructive CAD than patients <65 years, with similar rates of MACE for three-vessel or left main obstructive CAD (Table 6, Figure 3). A dose–response relationship of MACE risk was observed per increasing decade of life (Figure 4).

We also separately compared the individual components of MACE including death, MI, and late revascularization among patients <65 and ≥65 years old (Table 7). All the individual components of MACE were higher for individuals ≥65 than <65 years for normal, non-obstructive, one-, two-, and three-vessel or left main obstructive CAD than patients <65 years (Table 7).

## Age-stratified impact of early vs. late revascularization

We examined whether symptom-driven early revascularization (≤90 days) incidence differed by age, and noted differences among individuals ≥65 vs. <65 years for typical angina (14.3 vs. 10.6%,  $P = 0.035$ ), atypical angina (8.8 vs. 3.4%,  $P < 0.001$ ), non-cardiac pain (9.7 vs. 3.1%,  $P < 0.001$ ), and shortness of breath (7.6 vs. 4.7%,  $P = 0.001$ ). When compared with individuals without CAD in patients with <65 years, patients with ≥65 years experienced higher hazards for MACE for late revascularization [hazard ratio (HR) 11.67, 95% confidence interval (CI) 6.90–19.73,  $P = 0.002$ ], while patients <65 years experienced higher hazards for MACE for late revascularization (HR: 17.73, 95% CI: 11.40–27.57,  $P = 0.002$ ).

## Discussion

In this present study, we observed an independent prognostic value of both non-obstructive and obstructive CAD for future MACE on a per-patient, per-vessel and per-segment basis. We further observed the risk of future MACE based on CAD findings by CCTA as it related to age, and identified a heightened risk for future MACE for individuals <65 vs. ≥65 years of age, even when adjusted for measures of CAD, when compared with their similar aged counterparts without evident CAD by CCTA. We further observed a dose–response relationship of MACE risk with each advancing decade of life. To our knowledge, the current study represents the first prospective large-scale multicentre international study to examine the incidence of MACE based on CCTA findings of CAD with adequate power (beta > 0.90, alpha > 0.001) to

**Table 4** Coronary artery stenosis severity by segment for individuals with MACE vs. without MACE

Coronary segment	No MACE (n = 14 592)			MACE (n = 595)			P-value (%)	P-value (stenosis score)
	n	% with any CAD	Stenosis score	n	% with any CAD	Stenosis score		
Left main artery	2227	16	0.17 ± 0.40	224	39	0.45 ± 0.63	<0.001	<0.0001
Left anterior descending artery								
Proximal	5486	38	0.46 ± 0.67	410	73	1.17 ± 0.99	<0.001	<0.0001
Mid	3938	29	0.38 ± 0.69	329	60	1.01 ± 1.05	<0.001	<0.0001
Distal	1218	9	0.12 ± 0.41	146	27	0.41 ± 0.79	<0.001	<0.0001
Diagonal artery 1	1318	10	0.14 ± 0.47	144	29	0.47 ± 0.86	<0.001	<0.0001
Diagonal artery 2	583	5	0.07 ± 0.33	53	13	0.22 ± 0.64	<0.001	<0.0001
Left circumflex artery								
Proximal	2380	17	0.20 ± 0.49	250	45	0.66 ± 0.88	<0.001	<0.0001
Distal	1235	9	0.13 ± 0.45	156	30	0.47 ± 0.84	<0.001	<0.0001
Obtuse Marginal 1	922	7	0.10 ± 0.41	123	25	0.45 ± 0.90	<0.001	<0.0001
Obtuse Marginal 2	382	6	0.08 ± 0.37	50	20	0.31 ± 0.70	<0.001	<0.0001
Right coronary artery								
Proximal	3015	21	0.26 ± 0.57	299	53	0.78 ± 0.93	<0.001	<0.0001
Mid	2351	17	0.23 ± 0.58	267	50	0.84 ± 1.04	<0.001	<0.0001
Distal	1465	11	0.15 ± 0.46	198	38	0.54 ± 0.83	<0.001	<0.0001
Right PL artery	116	1	0.02 ± 0.17	11	4	0.07 ± 0.35	<0.001	0.0003
Left PL artery	14	0.3	0.01 ± 0.11	3	3.5	0.08 ± 0.44	<0.001	<0.0001
Posterior descending artery	494	4	0.05 ± 0.29	74	15	0.25 ± 0.67	<0.001	<0.0001

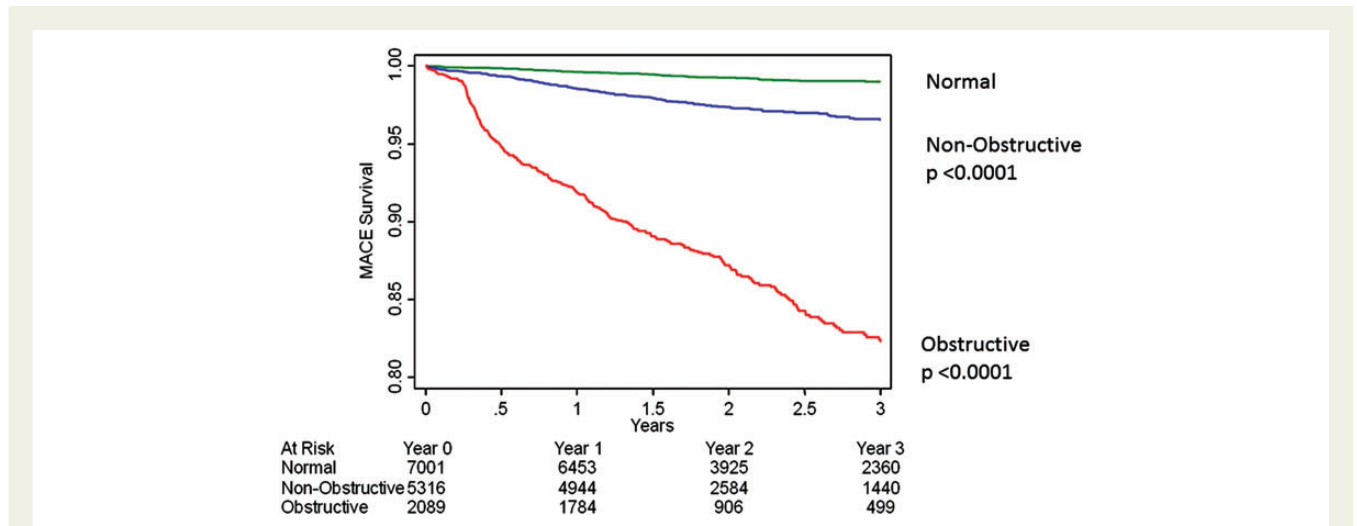
**Table 5** Univariable and adjusted hazards ratio for MACE events by per-patient, per-vessel and per-segment analysis by obstructive CAD

CCTA Result	Univariable HR (95% CI)	P-value	Risk-adjusted HR (95% CI)	P-value
Per-patient analysis				
Normal (reference)	1.00		1.00	
Non-obstructive	3.31 (2.46–4.46)	<0.001	2.43 (1.77–3.34)	<0.001
Obstructive CAD	18.40 (14.00–24.20)	<0.001	11.21 (8.26–15.22)	<0.001
Per-vessel analysis				
Normal (reference)	1.00		1.00	
Non-obstructive	3.31 (2.46–4.46)	<0.001	2.54 (1.85–3.49)	<0.001
One-vessel obstructive	13.57 (10.10–18.22)	<0.001	9.15 (6.62–12.63)	<0.001
Two-vessel obstructive	23.65 (17.04–32.82)	<0.001	15.00 (10.47–21.49)	<0.001
Three-vessel or left main	47.08 (32.99–67.19)	<0.001	24.53 (16.38–36.72)	<0.001
Per-segment analysis				
Segment involvement score (per segment involved)	1.31 (1.28–1.34)	<0.001	1.22 (1.19–1.25)	<0.001
Segment stenosis score (per segment severity)	1.18 (1.16–1.19)	<0.001	1.14 (1.12–1.15)	<0.001
Presence of proximal stenosis	5.30 (4.26–6.59)	<0.001	3.10 (2.44–3.94)	<0.001
Presence of left main stenosis	3.77 (3.13–4.53)	<0.001	2.19 (1.79–2.67)	<0.001

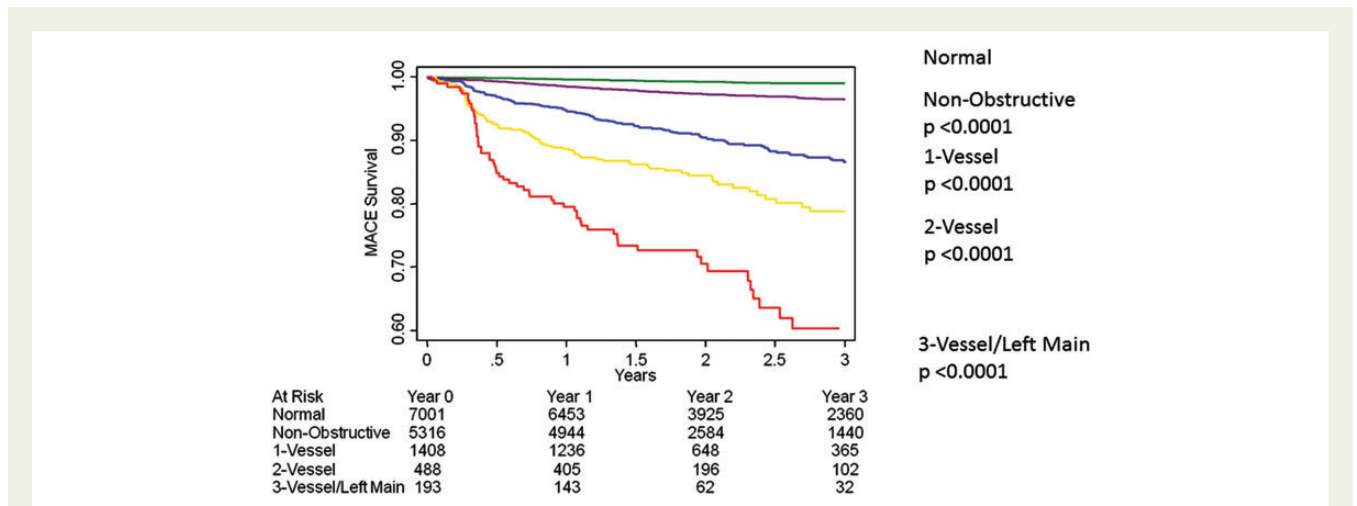
Hyperlipidaemia removed in multivariate analysis ( $P > 0.05$ ).

allow for differential age-related risk stratification based on CAD extent and severity by CCTA. These results are similar to prior studies, which have demonstrated that the extent and severity of

ischaemia has previously been shown to be a poor prognostic indicator.<sup>16–21</sup> Although, the ability of CCTA to detect anatomic coronary artery stenoses has been well established, prior studies have shown



**Figure 1** Unadjusted all-cause 3-year Kaplan–Meier MACE-free survival by the maximal per-patient presence of none, non-obstructive and obstructive CAD



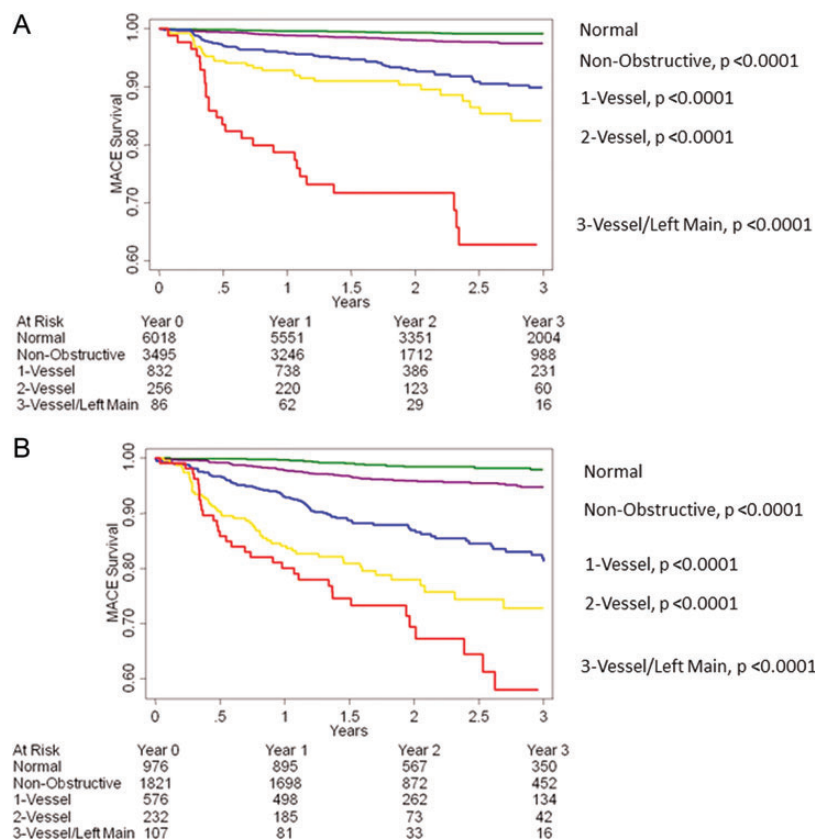
**Figure 2** Unadjusted all-cause 3-year Kaplan–Meier MACE-free survival by the presence, extent and severity of CAD by CCTA.

**Table 6** Adjusted hazards ratio for MACE events for patients <65 vs. ≥65 years of age

Variable	<65 years old		≥65 years old	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Normal	1.00 (reference)	–	2.30 (1.29–4.11)	0.005
Non-obstructive	2.70 (1.82–4.00)	<0.001	6.19 (4.22–9.07)	<0.001
One-vessel Disease	11.35 (7.65–16.85)	<0.001	19.89 (13.57–29.14)	<0.001
Two-vessel Disease	17.41 (10.87–27.90)	<0.001	36.06 (23.74–54.78)	<0.001
Three-vessel disease or left main disease	47.61 (28.46–79.66)	<0.001	48.10 (30.13–76.77)	<0.001

its inability to reliably detect haemodynamically significant CAD.<sup>22,23</sup> Future studies are likely required to further assess the haemodynamic significance of these obstructive lesions on CCTA.

A recent study of 24 775 stable patients from CONFIRM registry assessed the prognostic value CCTA for the prediction of all-cause mortality.<sup>14</sup> In this large, multicentre, multinational study, both non-



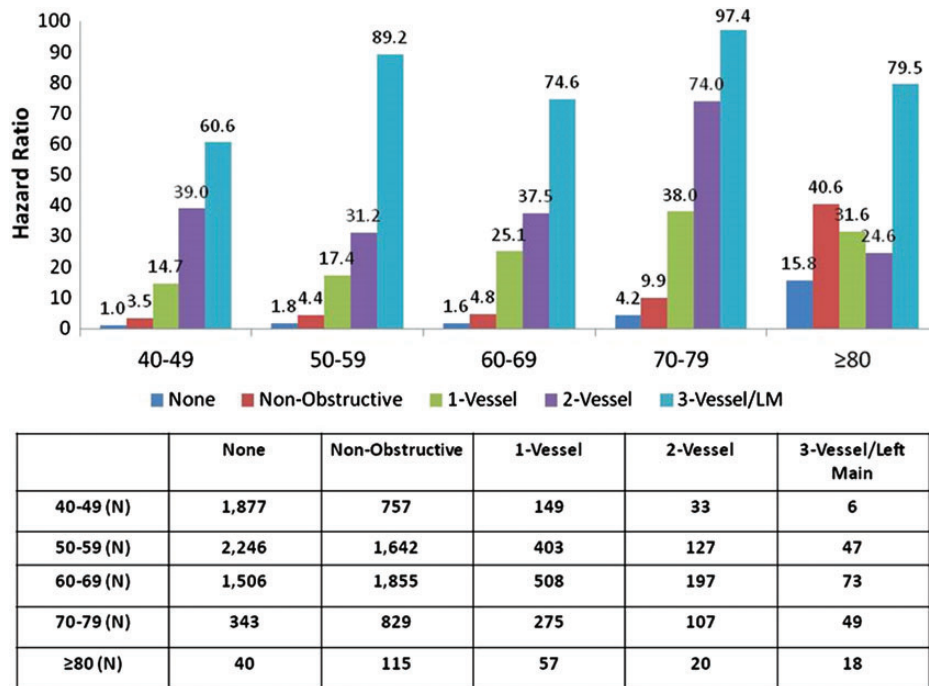
**Figure 3** Unadjusted all-cause 3-year Kaplan–Meier MACE-free survival by presence, extent and severity of CAD by CCTA as stratified by age  $<65$  (A) or  $\geq 65$  (B) years of age.

obstructive (HR: 1.60,  $P = 0.002$ ) and obstructive CAD (HR: 2.60,  $P < 0.0001$ ) were associated with increased all-cause mortality, with differences in multivariable risk-adjusted hazards for all-cause mortality noted for non-obstructive as well as increasing degrees of obstructive CAD. Importantly, the risk of 4-year death in this study was very low, indicating a 'warranty period' associated with a normal CCTA. As applied to MACE, Yiu *et al.*<sup>24</sup> assessed the prognostic significance of CCTA CAD findings for the prediction of MACE events in 2432 patients suspected of CAD. During 2.2-year follow-up, there were 59 (2.4%) MACE events, with significantly higher event rates noted in patients older than 60. The authors noted a dose-dependent increase in MACE risk based on the presence of CAD regardless of age or gender, with patients without evidence of CAD on CCTA having very low event rates ( $\leq 0.3\%$ ). These findings are in accordance with a recent meta-analysis applied to acute symptoms for which 1559 adult patients with symptoms suggestive of ACS underwent CCTA and were assessed for MACE at a  $\geq 30$  days after their initial presentation.<sup>25</sup> This study demonstrated a  $\geq 99\%$  negative predictive value of MACE based on the CCTA findings, suggesting the power of a normal CCTA to identify a low-risk population.

The findings of these prior studies are in general agreement with the present study results and support the notion of a very low-risk state for patients with normal coronary arteries by CCTA; as well as an increasing risk of future MACE for both non-obstructive and

obstructive CAD. However, the results of the present study directly and substantively extend these prior findings by stratifying risk according to age. When dichotomized by age  $\geq 65$  vs.  $< 65$  years, patients  $< 65$  years old had lower hazards of MACE for non-obstructive, one-, and two-vessel CAD, when compared with those who were  $\geq 65$  years old, they had similar hazard rates for three-vessel and LM disease. When stratified based on individual components of MACE, younger patients with three-vessel or LM disease had higher hazard rates for MI and late revascularization compared with individuals  $\geq 65$  years old. The potential explanations for these findings are manifold, and may relate to more aggressive forms of atherosclerosis in younger patients with a greater extent and severity of CAD when compared with their age-related counterparts. Future studies examining the phenomena that underscore this increased risk should now be pursued.

Even when stratified in a more granular fashion—that is, according to increasing decade of life—we observed a dose–response relationship of CAD extent and severity to MACE. This relationship was generally linear in nature, but increased for patients  $\geq 80$  years. Conversely, we noted a very low MACE event rate for patients with normal coronary arteries by CCTA, even among older patients. Importantly, we noted higher MACE rates in the very elderly population even among those with non-obstructive CAD by CCTA. When examined for components of MACE, mortality dominated as an



**Figure 4** Unadjusted MACE hazard ratio based on decade of life.

**Table 7** Adjusted hazards ratio for individual MACE events for patients <65 vs. ≥65 years of age

Variable	<65 years old		≥65 years old	
	HR (95% CI)	P-value	HR (95% CI)	P-value
All-cause mortality				
Normal	1.00 (reference)		3.77 (1.82–7.81)	<0.001
Non-obstructive	1.80 (0.95–3.39)	0.07	7.49 (4.34–12.91)	<0.001
One-vessel disease	2.14 (0.85–5.40)	0.11	14.24 (7.90–25.65)	<0.001
Two-vessel disease	6.92 (2.72–17.56)	<0.001	18.67 (9.21–37.83)	<0.001
Three-vessel disease or left main disease	6.35 (1.45–27.75)	0.01	12.24 (4.50–33.31)	<0.001
Myocardial infarction				
Normal (reference)	1.00 (reference)		0.94 (0.28–3.22)	0.93
Non-obstructive	2.71 (1.49–4.94)	0.001	3.52 (1.83–6.76)	<0.001
One-vessel disease	4.15 (1.93–8.91)	<0.001	4.91 (2.18–11.03)	<0.001
Two-vessel disease	7.08 (2.75–18.22)	<0.001	12.46 (5.49–28.28)	<0.001
Three-vessel disease or left main disease	17.91 (6.40–50.13)	<0.001	13.09 (4.75–36.10)	<0.001
Late revascularization				
Normal	1.00 (reference)		2.41 (0.47–12.45)	0.29
Non-obstructive	10.44 (4.06–26.87)	<0.001	14.62 (5.52–38.67)	<0.001
One-vessel disease	71.05 (28.29–178)	<0.001	94.50 (37.42–239)	<0.001
Two-vessel disease	104 (39.47–274)	<0.001	195 (76.09–501)	<0.001
Three-vessel disease or left main disease	334 (124–894)	<0.001	327 (125–856)	<0.001

endpoint in this population and thus, it is conceivable that these increased death rates may represent those of a non-cardiac nature. Future studies with cause-specific endpoints may be useful to further describe these findings.

## Limitations

While this study addresses many of the shortcomings of prior smaller single-centre investigations evaluating the prognostic performance of



CAD findings by CCTA for the prediction of MACE, it is nevertheless not immune to measures of selection, referral, and misclassification bias, as is the case for all observational studies. The information regarding the downstream treatment based on CCTA findings were also unknown, and it remains possible that changes in medical therapy following CCTA may have altered study outcomes. However, salutary treatment regimens would most likely mitigate rather than strengthen the current study's findings. Given the increasing risk associated with CAD findings by CCTA—specifically as it relates to age—future prospective studies examining differential treatment strategies may be useful to further expound upon these present study findings. Furthermore, stress testing data were not available in our study cohort, and future studies are likely required to assess the haemodynamic significance of obstructive lesions on CCTA.

## Conclusion

In this large, prospective, multinational, multicentre CONFIRM registry, extent, and severity of CAD by CCTA is independent predictor of future cardiovascular events, with age-specific differences in risk. Importantly, normal coronary arteries by CCTA are associated with a low risk of future MACE, irrespective of age.

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