



# Coronary revascularization vs. medical therapy following coronary-computed tomographic angiography in patients with low-, intermediate- and high-risk coronary artery disease: results from the CONFIRM long-term registry

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## Aims

To identify the effect of early revascularization on 5-year survival in patients with CAD diagnosed by coronary-computed tomographic angiography (CCTA).

## Methods and results

We examined 5544 stable patients with suspected CAD undergoing CCTA who were followed a median of 5.5 years in a large international registry. Patients were categorized as having low-, intermediate-, or high-risk CAD based on CCTA findings. Two treatment groups were defined: early revascularization within 90 days of CCTA ( $n = 1171$ ) and medical therapy ( $n = 4373$ ). To account for the non-randomized referral to revascularization, we developed a propensity score by logistic regression. This score was incorporated into Cox proportional hazard models to calculate the effect of revascularization on all-cause mortality. Death occurred in 363 (6.6%) patients and was more frequent in medical therapy. In multivariable models, when compared with medical therapy, the mortality benefit of revascularization varied significantly over time and by CAD risk ( $P$  for interaction 0.04). In high-risk

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CAD, revascularization was significantly associated with lower mortality at 1 year (hazard ratio [HR] 0.22, 95% confidence interval [CI] 0.11–0.47) and 5 years (HR 0.31, 95% CI 0.18–0.54). For intermediate-risk CAD, revascularization was associated with reduced mortality at 1 year (HR 0.45, 95% CI 0.22–0.93) but not 5 years (HR 0.63, 95% CI 0.33–1.20). For low-risk CAD, there was no survival benefit at either time point.

## Conclusions

Early revascularization was associated with reduced 1-year mortality in intermediate- and high-risk CAD detected by CCTA, but this association only persisted for 5-year mortality in high-risk CAD.

## Keywords

coronary-computed tomographic angiography • CAD • revascularization

## Introduction

The benefit of coronary revascularization on survival in stable patients with obstructive coronary artery disease (CAD) remains a subject of active study. Older studies suggested a benefit among high-risk CAD patients<sup>1</sup> but this benefit has not been observed in lower risk CAD patients or in recent large-scale clinical trials of mostly intermediate risk CAD patients.<sup>2,3</sup> Recently, the emergence of coronary-computed tomographic angiography (CCTA) to non-invasively detect CAD has raised further questions about invasive treatment of visualized obstructive lesions. Patients undergoing CCTA for suspected CAD are more likely to have downstream revascularization procedures performed<sup>4</sup> and prior research has observed a mortality benefit for early revascularization following CCTA in patients with high-risk CAD in the short-term.<sup>5</sup> However, the long-term impact of revascularization on CAD detected by CCTA remains unknown. The goal of the present study was to determine the long-term impact of coronary revascularization compared with medical therapy on all-cause survival, and its interaction with the severity of CAD by CCTA, from a large international, observational cohort.

## Methods

### Patients

This was a study of stable patients without known CAD or suspected acute coronary syndrome undergoing CCTA from the long-term CONFIRM registry (Coronary CT Angiography Evaluation For Clinical Outcomes: An International Multicenter Registry), the methods of which have been previously described.<sup>6</sup> CONFIRM enrolled consecutive adults  $\geq 18$  years of age between 2005 and 2009 who underwent  $\geq 64$ -detector row CCTA for suspected CAD. The long-term registry includes data on 12 086 subjects who underwent CCTA at 17 centres in 9 countries (Austria, Canada, Germany, Israel, Italy, Portugal, South Korea, Switzerland, and USA). Institutional review board approval was obtained at each site, and the study complies with the Declaration of Helsinki.

This analysis excluded patients with sites that did not collect revascularization data ( $n = 5139$ ). Patients with known CAD, as defined by prior myocardial infarction or prior coronary revascularization ( $n = 1026$ ) or those with missing basic demographic or CCTA data ( $n = 238$ ) were excluded. Additionally, patients with myocardial infarction prior to any revascularization procedure within the first 7 days after the CCTA ( $n = 139$ ) were excluded from this analysis in order to minimize the misclassification of potentially unstable patients. The final sample included 5544 patients from 12 clinical sites.

As detailed elsewhere,<sup>5–7</sup> prior to the scan, demographic and categorical cardiac risk factor data were systematically collected for each consecutive patient. Hypertension was defined as a documented history of high blood pressure or treatment with anti-hypertensive medications. Diabetes

mellitus was defined by diagnosis of diabetes made previously by a physician and/or use of insulin or oral hypoglycemic agents. Dyslipidemia was defined as known but untreated dyslipidemia, or current treatment with lipid-lowering medications. A positive smoking history was defined as current smoking or cessation of smoking within 3 months of testing. Family history of coronary heart disease was determined by patient query, and it was defined as a primary relative with a diagnosis early in life (i.e. mother  $< 65$  years of age or father  $< 55$  years of age). Symptom presentation was classified into one of three categories: typical chest pain/dyspnea, atypical chest pain, and non-cardiac pain/asymptomatic.

### CCTA performance and interpretation

Standardized protocols for image acquisition, as defined by the Society of Cardiovascular-Computed Tomography (SCCT), were employed at all participating sites.<sup>8</sup> Specific details of CCTA procedures have been defined in detail elsewhere.<sup>6</sup> All scans were analysed by level III-equivalent cardiologists or radiologists in direct accordance with SCCT guidelines. Each site applied a standard 16-segment anatomic segmental analysis for image interpretation. In all individuals, irrespective of image quality, every arterial segment was scored in an intent-to-diagnose fashion. All segments were coded for the presence and severity of coronary stenosis and were scored as normal (0% luminal stenosis), mild-moderate (1–49%), moderate (50–69%) or severe ( $\geq 70\%$ ). If a coronary artery segment was uninterpretable despite multiple reformatting techniques, the un-evaluable segment was scored similar to the most proximal segment that was evaluable. Extent of obstructive CAD was defined by  $\geq 50\%$  stenosis in 0, 1, 2, or 3 coronary artery vessels. Left main artery disease was grouped with three-vessel obstructive coronary artery disease. All imaging findings were site-adjudicated; primary imaging data were not available for review.

Coronary artery disease severity was determined by both clinical plaque scores and the modified Duke CAD score. Plaque scores included segment stenosis score (SSS, range 0–48) and the segment involvement score (SIS, range 0–16) as previously described.<sup>7</sup> As in prior work,<sup>5</sup> CAD severity was also assessed using the modified Duke score. The groups include: Group 0 = No CAD; Group 1 =  $\geq 1$  segment with 1–49% stenosis; Group 2 =  $\geq 2$  segments with 1–49% stenosis AND at  $\geq 1$  proximal segment with any stenosis; Group 3 =  $\geq 1$  segment with 50–69% stenosis; Group 4 =  $\geq 2$  segments with 50–69% stenosis OR  $\geq 1$  segment with  $\geq 70\%$  stenosis; Group 5 =  $\geq 3$  segments with 50–69% stenosis OR  $\geq 2$  segments with  $\geq 70\%$  stenosis OR proximal LAD with  $\geq 70\%$  stenosis; Group 6 =  $\geq 3$  segments with  $\geq 70\%$  stenosis OR  $\geq 2$  segments with  $\geq 70\%$  stenosis AND proximal LAD with  $\geq 70\%$  stenosis; Group 7 = left main with  $\geq 50\%$  stenosis. Based upon these gradations and their associated prognoses, patients were categorized into three separate groups: low-risk (Groups 0–2), intermediate-risk (Groups 3–4), and high-risk (Groups 5–7).

### Post-test outcomes

Patients were followed prospectively over the course of at least 5 years (median 5.5 years, interquartile range 5.1–6.2 years). The primary

outcome measure was all-cause mortality. As in previous work,<sup>5</sup> the primary exposure was early post-CCTA revascularization. Early revascularization was defined as having occurred in the first 90 days following CCTA, and was selected based upon prior published studies that have indicated that this timeframe is consistent with treatment based upon test findings (i.e. within a general episode of care).<sup>9,10</sup>

Follow-up procedures were approved by all study centres' institutional review boards. All-cause mortality was adjudicated by trained study personnel or by querying of national medical databases. Myocardial infarction was site-adjudicated through a combination of direct questioning of patients using a scripted interview as previously described.<sup>6</sup> Late revascularization was not available as an endpoint for the present analysis.

## Statistical analysis and study design

Categorical variables are presented as frequencies and percentages. Continuous variables are presented as means  $\pm$  1 SD or medians (interquartile range) when appropriate. Variables were compared with  $\chi^2$  statistic for categorical variables and by Student's unpaired *t*-test or Wilcoxon non-parametric test where appropriate for continuous variables.

In order to examine the effects of early revascularization vs. medical therapy alone on the primary outcome, we performed a two-step statistical procedure similar to prior work.<sup>5,11</sup> We developed a propensity score for early revascularization, then performed multivariable Cox proportional hazards regression adjusted for the propensity score. The propensity score was developed using a backward stepwise logistic regression model that summarized predictors of referral of patients to revascularization or medical therapy. All potential factors known to influence this referral pattern were included in the propensity score development with significant factors (as defined by  $P \leq 0.10$ ) retained, to define a summary measure for likelihood of revascularization. It must be noted that the CONFIRM long-term study sites were somewhat different than those in the previously reported short-term study,<sup>5</sup> and therefore the propensity score presented here was constructed de novo.

Univariate and multivariate propensity-adjusted Cox proportional hazards models were then used to determine the relationship of early revascularization or medical therapy for time to death by all causes. This approach controlled for the effect of baseline differences in the comparator cohorts as well as the impact of non-randomized treatment allocation on survival. Hazard ratios (HR) and 95% confidence intervals (95% CI) were calculated from the Cox models for the endpoint of all-cause mortality. For coherence, sensitivity analyses were performed using the final multivariable Cox model in selected subgroups of interest as well as for the secondary outcome of first major adverse cardiac event (MACE = death or non-fatal acute coronary syndrome). Model over-fitting procedures and interaction testing were carefully considered. A two-tailed *P* value of  $< 0.05$  for association and  $P < 0.10$  for interaction was considered statistically significant. Analyses were performed using SAS 9.3 (Cary, NC) and STATA version 13 (College Station, TX).

## Results

### Clinical characteristics of the study cohort

Baseline characteristics of the patient sample categorized by initial treatment strategy are listed in Table 1. Compared with patients undergoing medical therapy, patients undergoing early revascularization were older, more likely to be male, and more likely to have CAD risk factors including hypertension, hyperlipidemia, diabetes, tobacco use, and a family history of CAD. Patients undergoing early

**Table 1** Demographics

	Medical therapy (n=4373)	Early revascularization (n=1171)	P value
Age (years) $\pm$ SD	59.4 $\pm$ 12.0	63.3 $\pm$ 10.1	<0.0001
Male sex % (n)	61.1 (2672)	72.4 (848)	<0.001
Cardiovascular risk factors % (n)			
Hypertension	53 (2305)	63 (733)	<0.001
Hyperlipidemia	51.6 (2247)	64.3 (746)	<0.001
Diabetes	14.8 (643)	25.5 (297)	<0.001
Current smoker	20.3 (878)	25.7 (299)	<0.001
Family history of premature CAD	29.4 (1269)	32.6 (375)	<0.001
Chest pain, % (n)			<0.001
Typical	28.9 (1248)	41.8 (483)	
Atypical	25.9 (1120)	23.8 (275)	
Non-cardiac/asymptomatic	45.2 (1949)	34.4 (397)	
Presence of CAD by CCTA % (n)			<0.001
Normal	41.4 (1799)	2.5 (29)	
Non-obstructive CAD	36.8 (1608)	5.8 (68)	
Obstructive CAD	22.1 (966)	91.7 (1074)	
Duke CAD Score % (n)			<0.001
Low-risk (Score 0–2)	77.9 (3407)	8.3 (97)	
Intermediate-risk (Score 3–4)	13.2 (576)	35.8 (419)	
High-risk (Score 5–7)	8.9 (390)	55.9 (655)	

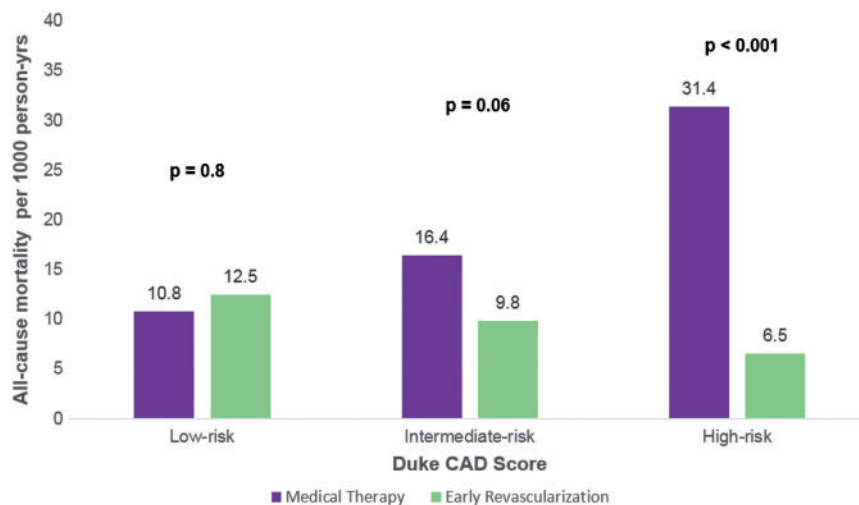
CCTA, coronary-computed tomographic angiography.

revascularization were more likely to have typical angina, obstructive CAD as defined by CCTA, and an intermediate- or high-risk Duke score than those treated medically.

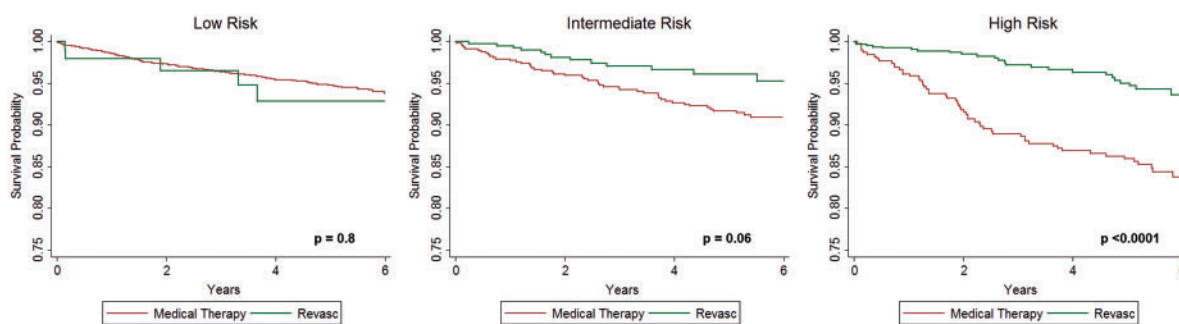
### Clinical treatment and events

Among the 1171 individuals undergoing early revascularization, 1001 (85.5%) underwent percutaneous coronary intervention (PCI) and 170 (14.5%) coronary artery bypass surgery (CABG). Revascularization was performed in 2.7% of patients with low-risk CAD, 42.1% with intermediate risk CAD, and 62.7% with high risk CAD ( $P < 0.001$ ). During follow-up, a total of 363 deaths occurred (6.6% of the entire population). As stratified by the initial treatment method, death occurred in 318 (7.3%) of patients treated with medical therapy and 45 (3.8%) of patients treated with early coronary revascularization ( $P < 0.001$ ).

The unadjusted relationship between CAD severity and incidence of all-cause mortality with respect to early revascularization vs. medical therapy can be observed in Figure 1. The unadjusted incidence of death was significantly increased for medical therapy in high-risk (3.1 vs. 1.0%,  $P < 0.001$ ), trended toward increased in intermediate-risk (1.6 vs. 1.0%,  $P = 0.06$ ) but not increased in low-risk CAD (1.1 vs. 1.3%,  $P = 0.8$ ). The observed survival differences in the intermediate



**Figure 1** Incidence of all-cause mortality by treatment and Duke CAD score. The unadjusted incidence of death was significantly increased for medical therapy in high-risk, trended toward increased in intermediate-risk, but was not increased in low-risk CAD.



**Figure 2** Kaplan–Meier survival curves by severity of CAD. The five unadjusted observed survival differences were similar in low risk (A) but diverged early in the intermediate (B) and high risk groups (C).

and high risk groups emerged early in the study period and persisted over the 5-year study period (Figure 2A–C).

## Propensity score

The logistic regression analysis results are shown in Table 2. Significant predictors of referral to coronary revascularization included age, sex, hyperlipidemia, typicality of symptoms, the pre-test probability of CAD as calculated by the method of Diamond and Forrester,<sup>12</sup> the presence of obstructive CAD, clinical plaque scores, and clinical site). Interactions between sex and symptom typicality as well as age and SSS were also significant and included in the final propensity score model (C-index 0.92,  $\chi^2 = 15.2$ ,  $P = 0.056$ ).

## Survival analysis

Univariate Cox proportional hazards models predicting all-cause mortality are shown in Table 3. The final multivariable Cox regression

model included age (linear and non-linear), hypertension, diabetes, smoking, symptom typicality, Duke CAD score, early revascularization (vs. medical therapy), and the propensity score predicting referral to revascularization. When checking the proportional hazards assumptions for the Cox model, a significant time effect was observed to interact with Duke CAD score. To account for this, two additional terms were added to the final Cox regression model; the first was a two-way interaction between time and the Duke CAD score, and the second was a three-way interaction between time, Duke CAD score, and early revascularization.

Using the final multivariable model, the hazard ratios for early revascularization for all-cause mortality were estimated at both 1 year and 5 years. When compared with medical therapy, early revascularization was associated with lower mortality at both 1 year and 5 years for patients with high risk CAD (Figure 3). In contrast, in patients with intermediate risk CAD, early revascularization was



**Table 2** Logistic regression results for creation of propensity score

Variable	Odds ratio (95% CI)	P value
Age	1.03 (1.00–1.06)	0.04
Sex	1.33 (0.95–1.87)	0.10
Hyperlipidemia	1.46 (1.19–1.80)	<0.001
Symptom typicality		<0.001
Asymptomatic/non-cardiac chest pain	Reference	
Atypical angina	1.45 (0.97–2.15)	
Typical angina	2.22 (1.30–3.77)	
Diamond-Forrester probability	1.67 (0.99–2.81)	0.06
Obstructive CAD		<0.001
Normal	Reference	
Non-obstructive	0.75 (0.41–1.37)	
Obstructive	5.83 (3.12–10.89)	
SIS (log-transformed)	0.29 (0.17–0.50)	<0.001
SSS (log-transformed)	32.1 (11.58–88.97)	<0.001
Site		<0.001
A	0.29 (0.17–0.49)	
B	1.02 (0.65–1.59)	
C	5.16 (3.37–7.91)	
D	0.27 (0.19–0.38)	
E	0.07 (0.03–0.17)	
F	0.89 (0.62–1.29)	
G	1.72 (0.76–3.92)	
H	0.58 (0.38–0.88)	
I	0.48 (0.34–0.68)	
J	1.25 (0.42–3.69)	
Sex vs. typicality	0.77 (0.60–0.99)	0.04
Age vs. SSS	0.98 (0.96–0.99)	0.001

SIS, Segment Involvement Score; SSS, Segment Stenosis Score.

associated with reduced mortality at 1 year but not at 5 years, while in low-risk CAD there was no survival benefit from early revascularization at either time point. There was a significant interaction between severity of CAD and revascularization that increased over time ( $P$  value for interaction of revascularization, Duke CAD score, and time = 0.039).

Sensitivity analyses for coherence were performed using the final multivariable model. Findings were similar after the exclusion of obstructive left main artery disease, in models stratified by revascularization technique (PCI vs. CABG), and using the outcome of MACE.

## Discussion

In this large, international observational registry of stable patients without known CAD undergoing CCTA, we observed a mortality benefit persisting to 5 years for early post-test coronary revascularization in patients with high-risk CAD. This includes patients with multivessel obstructive CAD, obstructive disease of the proximal left anterior descending artery, and/or obstructive disease of the left

main coronary artery. In contrast, patients with lesser severity of CAD undergoing early revascularization did not experience any sustained change in survival over this longer time frame.

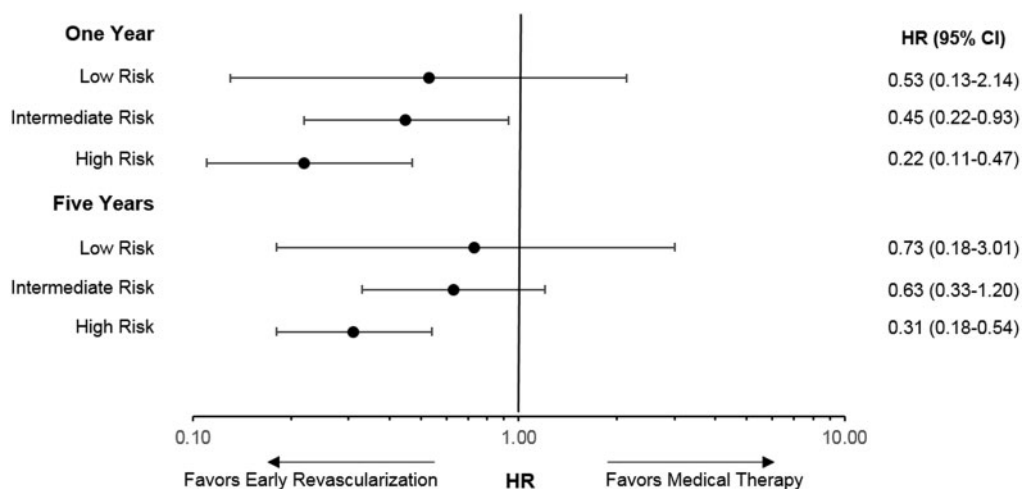
Our findings expand upon the prior literature from this registry on the relative benefit of early post-test revascularization vs. medical therapy for CAD detected by CCTA. In a study by Min *et al.* of 15 223 CONFIRM registry patients with a median follow-up of 2.1 years, patients with high risk CAD (Duke CAD score 5–8) undergoing revascularization had reduced mortality (HR 0.38, 95% CI 0.18–0.83) while those with lower risk CAD (Duke CAD score 0–4) did not (HR 3.24, 95% CI 0.76–13.89,  $P$  for interaction 0.03). While the overall study population was larger in the prior study, the long-term follow-up presented here had nearly 4 times the number of deaths and over twice as much time available for analysis. Notably, this longer term study demonstrates the durability of mortality benefit for early revascularization among patients with high-risk CAD, and the persistent absence of long-term benefit among those with low-risk CAD. It is interesting that the intermediate-risk patients demonstrated an early mortality benefit that dissipated over the long term, although given the wide confidence interval, a smaller protective benefit cannot be excluded among these patients.

Other recently reported CCTA studies have not had sufficient mortality rates to detect downstream mortality differences resulting from post-test revascularization,<sup>10,13</sup> which may reflect lower inclusion of patients with high-risk CAD. In contrast, the CONFIRM registry was explicitly designed to determine the prognostic value of CCTA findings.<sup>6</sup> Entry was not restricted to patients with suspected CAD alone, but rather was representative of physician referral at numerous high-volume sites around the world. As such, patients at higher risk or with known CAD were enrolled, as were lower risk patients who had a CCTA performed for other diagnostic purposes such as a family history of CAD. Although some of these indications are currently discouraged, most CCTAs in this study were performed in the years before the creation of appropriate use criteria, and their inclusion allow for an unbiased assessment of an ‘all comers’ population of individuals undergoing CCTA.<sup>6</sup>

Our study contributes to literature documenting the adverse prognosis of increasing anatomic CAD (detected both invasively and by CCTA)<sup>7,14</sup> and the debated role of subsequent revascularization following diagnostic imaging. Observational studies predating modern optimal medical therapy (OMT) demonstrated a survival benefit for predominantly surgical revascularization of high-risk CAD,<sup>1</sup> a finding that persists in clinical guidelines of stable ischemic heart disease.<sup>15</sup> Conversely, on the whole contemporary randomized trials of intermediate-to-high risk CAD<sup>2,3</sup> have not identified an association between revascularization and a subsequent reduction of death as compared with OMT. Furthermore, in COURAGE, there was no significant interaction between treatment strategy and angiographic severity for mortality benefit,<sup>16</sup> a finding reflected in our observations of patients with low and intermediate risk CAD. However, these trials had several limitations. First, inclusion was contingent on pre-trial invasive angiography, raising concerns of negative selection bias against patients with high-risk CAD.<sup>17</sup> Second, percutaneous revascularization was mostly performed with earlier stent generations, while a recent meta-analysis found a mortality benefit in trials using second-generation drug eluting stents compared with medical therapy.<sup>18</sup> Third, patients with the highest risk CAD (i.e. left main) were

**Table 3** Cox proportional hazard models for the prediction of all-cause mortality

	Univariate			Multivariate		
	HR	95% CI	P value	HR	95% CI	P value
Age (linear)	1.07	1.06–1.08	<0.001	0.88	0.82–0.94	<0.001
Age vs. age (non-linear)	1.00	1.00–1.01	<0.001	1.002	1.001–1.002	<0.001
Male sex	0.92	0.75–1.14	0.47			
Hypertension	1.73	1.39–2.16	<0.001	1.34	1.03–1.75	0.03
Hyperlipidemia	0.79	0.65–0.98	0.03			
Diabetes	1.81	1.43–2.30	<0.001	1.66	1.26–2.18	<0.001
Smoking	1.36	1.08–1.72	0.01	1.80	1.37–2.36	<0.001
Family history	0.69	0.54–0.89	0.004			
Symptoms						
Asymptomatic/non-cardiac	1.00	ref	ref	1	Ref.	Ref.
Atypical angina	0.67	0.50–0.90	0.009	0.70	0.51–0.95	0.02
Typical angina	1.26	1.00–1.58	0.05	1.03	0.78–1.37	0.84
Duke CAD Score						
Low-risk	1.00	ref	ref	1.00	Ref.	Ref.
Intermediate-risk	1.27	0.96–1.68	0.09	1.16	0.68–1.98	0.58
High-risk	1.71	1.33–2.21	<0.001	1.84	0.92–3.70	0.09
Early revascularization	0.73	0.53–0.99	0.046	0.48	0.12–1.98	0.31
Propensity score	1.69	1.10–2.57	0.015	1.005	0.37–2.75	0.99
Early revascularization vs. intermed-risk				0.86	0.18–4.03	0.84
Early revascularization vs. high-risk				0.42	0.09–1.99	0.28
Duke Score vs. time				0.96	0.88–1.05	0.38
Early revascularization vs. Duke Score vs. time				1.09	1.00–1.18	0.039



**Figure 3** Adjusted hazard of all-cause mortality for early revascularization. Early revascularization was associated with significant survival benefit at both 1 year and 5 years in high risk CAD. In intermediate CAD, there was benefit at 1 year but not at 5 years, while in low-risk CAD there was no difference at either time point.

systematically excluded, as they are from the ongoing ISCHEMIA trial [NCT 01471522]). Indeed, revascularization to reduce mortality in such patients has long been recommended by guidelines based primarily on the work of clinical trials predating modern OMT.<sup>15,19</sup>

In this context, it is possible that the patients in CONFIRM with high-risk CAD who were medically treated were inherently ‘sicker’, which may contribute to higher observed mortality despite careful statistical adjustment. This type of potential confounding is best mitigated by a

randomized controlled trial, and our findings draw attention to the continued need for such a study in high-risk patients.

Recently, the presence of ischemia (detected either non-invasively or by invasive fractional flow reserve [FFR]) has been advocated over isolated angiographic findings to identify patients likely to benefit from revascularization rather than medical therapy.<sup>20</sup> Our study cannot test this hypothesis, as the CONFIRM registry did not collect the results of non-invasive ischemia testing or subsequently performed FFR. However, there remains considerable uncertainty about the incremental importance of ischemia beyond anatomic findings, including both ischemia detected non-invasively<sup>21</sup> and by invasive FFR.<sup>22</sup> We hope that replication of our methodology in secondary analyses of the ongoing ISCHEMIA trial or in the future with the newly available non-invasive FFR-CCTA may shed further light on this matter.

This study is not without limitations. First, although the patient cohorts represent a diversity of sites and countries, all results are subject to limitations of observational data including the presence of unobserved confounders and selection bias. However, we performed careful statistical modelling to account for patterns of referral to coronary revascularization vs. medical therapy within a clinically important 90-day post-test window, as has been previously reported.<sup>5,11</sup> Second, baseline characteristics, including CAD risk factors, were based on patient reporting and were considered binary variables in accordance to prior randomized and observational studies, rather than as continuous ones. Thus, the duration of CAD risk factor presence and the severity of the risk remain unknown. Likewise, the symptom severity, previous medical therapy and prior non-invasive or invasive testing results were unknown, and therefore the appropriateness of post-test revascularization cannot be ascertained. Third, inclusion in this international observational registry did not mandate the provision of post-test optimal medical therapy. As such, medical regimens, compliance, and lifestyle changes post-test are unknown but rather represent the 'real world' nature of treatment in a large international cohort. Prior studies have found an amplification of secondary preventive measures after cardiac CT demonstrating CAD,<sup>13,23</sup> but to what extent this was achieved in the present study remains unknown. Finally, we examined all-cause mortality as a primary endpoint, given its unparalleled clinical importance and freedom from ascertainment bias. Findings were coherent in a sensitivity analysis using an outcome of MACE consisting of all-cause mortality and acute coronary syndrome. Other outcomes (e.g. cause-specific mortality, stroke) were not uniformly available and deserve future study. In spite of these limitations, this study is the largest consecutive cohort of patients undergoing CCTA with long-term outcomes data available.

## Conclusion

In this large international long-term registry of patients without known CAD undergoing CCTA, early revascularization is associated with reduced mortality at 5 years in patients with high-risk CAD. No benefit from early revascularization was seen in patients with low-risk CAD, while early mortality benefits in patients with intermediate-risk CAD were not sustained at 5 years.

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The data presented in this article is original and has not been reported elsewhere, nor is this article under consideration with any

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J.K.M. reports being a consultant with HeartFlow, on the scientific advisory board of Arineta, having partial ownership in MDDX and Autoplaq, and receiving research support from GE Healthcare.

## References

1. Yusuf S, Zucker D, Peduzzi P, Fisher LD, Takaro T, Kennedy JW *et al.* Effect of coronary artery bypass graft surgery on survival: overview of 10-year results from randomised trials by the Coronary Artery Bypass Graft Surgery Trialists Collaboration. *Lancet* 1994;**344**:563–70.
2. Boden WE, O'Rourke RA, Teo KK, Hartigan PM, Maron DJ, Kostuk WJ *et al.* Optimal medical therapy with or without PCI for stable coronary disease. *N Engl J Med* 2007;**356**:1503–16.
3. The BARI 2D Study Group. A randomized trial of therapies for type 2 diabetes and coronary artery disease. *N Engl J Med* 2009;**360**:2503–15.
4. Douglas PS, Hoffmann U, Patel MR, Mark DB, Al-Khalidi HR, Cavanaugh B *et al.* Outcomes of anatomical versus functional testing for coronary artery disease. *N Engl J Med* 2015;**372**:1291–300.
5. Min JK, Berman DS, Dunning A, Achenbach S, Al-Mallah M, Budoff MJ *et al.* All-cause mortality benefit of coronary revascularization vs. medical therapy in patients without known coronary artery disease undergoing coronary computed tomographic angiography: results from CONFIRM (COronary CT Angiography EvaluationN For Clinical Outcomes: An International Multicenter Registry). *Eur Heart J* 2012;**33**:3088–97.
6. Min JK, Dunning A, Lin FY, Achenbach S, Al-Mallah MH, Berman DS *et al.* Rationale and design of the CONFIRM (COronary CT Angiography EvaluationN For Clinical Outcomes: An International Multicenter) registry. *J Cardiovasc Comput Tomogr* 2011;**5**:84–92.
7. Min JK, Dunning A, Lin FY, Achenbach S, Al-Mallah M, Budoff MJ *et al.* Age- and sex-related differences in all-cause mortality risk based on coronary computed tomography angiography findings results from the International Multicenter CONFIRM (Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter Registry) of 23,854 patients without known coronary artery disease. *J Am Coll Cardiol* 2011;**58**:849–60.
8. Abbara S, Arbab-Zadeh A, Callister TQ, Desai MY, Mamuya W, Thomson L *et al.* SCCT guidelines for performance of coronary computed tomographic angiography: a report of the Society of Cardiovascular Computed Tomography Guidelines Committee. *J Cardiovasc Comput Tomogr* 2009;**3**:190–204.
9. Shaw LJ, Peterson ED, Shaw LK, Kesler KL, DeLong ER, Harrell FE Jr *et al.* Use of a prognostic treadmill score in identifying diagnostic coronary disease subgroups. *Circulation* 1998;**98**:1622–30.
10. Douglas PS, Hoffmann U, Patel MR, Mark DB, Al-Khalidi HR, Cavanaugh B *et al.* Outcomes of Anatomical versus Functional Testing for Coronary Artery Disease. *N Engl J Med* 2015;**372**:1291–1300.
11. Hachamovitch R, Hayes SW, Friedman JD, Cohen I, Berman DS. Comparison of the short-term survival benefit associated with revascularization compared with medical therapy in patients with no prior coronary artery disease undergoing stress myocardial perfusion single photon emission computed tomography. *Circulation* 2003;**107**:2900–7.
12. Diamond GA, Forrester JS. Analysis of probability as an aid in the clinical diagnosis of coronary-artery disease. *N Engl J Med* 1979;**300**:1350–8.
13. Scot-Heart Investigators. CT coronary angiography in patients with suspected angina due to coronary heart disease (SCOT-HEART): an open-label, parallel-group, multicentre trial. *Lancet* 2015;**385**:2383–91.
14. Mancini GB, Bates ER, Maron DJ, Hartigan P, Dada M, Gosselin G *et al.* Quantitative results of baseline angiography and percutaneous coronary intervention in the COURAGE trial. *Circ Cardiovasc Qual Outcomes* 2009;**2**:320–7.

15. Montalescot G, Sechtem U, Achenbach S, Andreotti F, Arden C, Budaj A et al. 2013 ESC guidelines on the management of stable coronary artery disease: The Task Force on the management of stable coronary artery disease of the European Society of Cardiology. *Eur Heart J* 2013;**34**:2949–3003.
16. Mancini GB, Hartigan PM, Bates ER, Chaitman BR, Sedlis SP, Maron DJ et al. Prognostic importance of coronary anatomy and left ventricular ejection fraction despite optimal therapy: assessment of residual risk in the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation Trial. *Am Heart J* 2013;**166**:481–7.
17. Kereiakes DJ, Teirstein PS, Sarembock IJ, Holmes DR Jr, Krucoff MW, O'Neill WW et al. The truth and consequences of the COURAGE trial. *J Am Coll Cardiol* 2007;**50**:1598–603.
18. Windecker S, Stortecky S, Stefanini GG, da Costa BR, Rutjes AW, Di Nisio M et al. Revascularisation versus medical treatment in patients with stable coronary artery disease: network meta-analysis. *BMJ* 2014;**348**:g3859.
19. Wijns W, Kolh P, Danchin N, Di Mario C, Falk V, Folliguet T et al. Guidelines on myocardial revascularization. *Eur Heart J* 2010;**31**:2501–55.
20. De Bruyne B, Fearon WF, Pijls NH, Barbato E, Tonino P, Piroth Z et al. Fractional flow reserve-guided PCI for stable coronary artery disease. *N Engl J Med* 2014;**371**:1208–17.
21. Mancini GB, Hartigan PM, Shaw LJ, Berman DS, Hayes SW, Bates ER et al. Predicting outcome in the COURAGE trial (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation): coronary anatomy versus ischemia. *JACC Cardiovasc Interv* 2014;**7**:195–201.
22. Arbab-Zadeh A. Fractional flow reserve-guided percutaneous coronary intervention is not a valid concept. *Circulation* 2014;**129**:1871–8; discussion 8.
23. Cheezum MK, Hulten EA, Smith RM, Taylor AJ, Kircher J, Surry L et al. Changes in preventive medical therapies and CV risk factors after CT angiography. *JACC Cardiovasc Imaging* 2013;**6**:574–81.