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CLINICAL RESEARCH
Interventional cardiology

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 EvaluatioN For Clinical Outcomes: An InteRnational Multicenter Registry)

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Aims To date, the therapeutic benefit of revascularization vs. medical therapy for stable individuals undergoing invasive coronary angiography (ICA) based upon coronary computed tomographic angiography (CCTA) findings has not been examined.

Methods and results We examined 15 223 patients without known coronary artery disease (CAD) undergoing CCTA from eight sites and six countries who were followed for median 2.1 years (interquartile range 1.4–3.3 years) for an endpoint of all-cause mortality. Obstructive CAD by CCTA was defined as a ≥50% luminal diameter stenosis in a major coronary artery. Patients were categorized as having high-risk CAD vs. non-high-risk CAD, with the former including patients with at

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least obstructive two-vessel CAD with proximal left anterior descending artery involvement, three-vessel CAD, and left main CAD. Death occurred in 185 (1.2%) patients. Patients were categorized into two treatment groups: revascularization ($n = 1103$; 2.2% mortality) and medical therapy ($n = 14\,120$, 1.1% mortality). To account for non-randomized referral to revascularization, we created a propensity score developed by logistic regression to identify variables that influenced the decision to refer to revascularization. Within this model (C index 0.92, $\chi 2 = 1248$, $P < 0.0001$), obstructive CAD was the most influential factor for referral, followed by an interaction of obstructive CAD with pre-test likelihood of CAD ($P = 0.0344$). Within CCTA CAD groups, rates of revascularization increased from 3.8% for non-high-risk CAD to 51.2% high-risk CAD. In multivariable models, when compared with medical therapy, revascularization was associated with a survival advantage for patients with high-risk CAD [hazards ratio (HR) 0.38, 95% confidence interval 0.18–0.83], with no difference in survival for patients with non-high-risk CAD (HR 3.24, 95% CI 0.76–13.89) (*P*-value for interaction = 0.03).

Conclusion In an intermediate-term follow-up, coronary revascularization is associated with a survival benefit in patients with high-risk CAD by CCTA, with no apparent benefit of revascularization in patients with lesser forms of CAD.

Keywords Computed tomography • Coronary revascularization • Medical therapy • Coronary artery disease

Introduction

Numerous large-scale clinical studies have observed a distinct survival benefit for both percutaneous and surgical coronary revascularization when compared with medical therapy in stable patients with high-risk angiographic coronary artery disease (CAD) as demonstrated by invasive coronary angiography (ICA).[1,2] Recently, coronary computed tomographic angiography (CCTA) has emerged as a novel non-invasive alternative for angiographic assessment of CAD extent and severity, with high diagnostic performance when compared with ICA, and prognostic value for prediction of adverse events based upon CCTA-identified CAD.[3–5] Although the management of patients without obstructive CAD by CCTA is considered straightforward, little evidence is available regarding appropriate management of patients who are found to have high-grade coronary stenoses on CCTA. Whether CCTA findings can stratify individuals with CAD who may benefit from coronary revascularization vs. medical therapy remains unexplored. The goal of the present study was to determine the relative therapeutic impact of coronary revascularization vs. medical therapy on survival from a large international, multicentre, observational cohort of patients undergoing CCTA.

Methods

Patients

This study represents 15 223 stable patients without known CAD or suspected acute coronary syndrome from the CONFIRM Registry (Coronary CT Angiography EvaluatioN For Clinical Outcomes: An InteRnational Multicenter Registry), which has been previously described.[6] CONFIRM enrolled consecutive adults ≥18 years of age between 2005 and 2009 who underwent ≥64-detector row CCTA for suspected CAD. Eight of 12 centres for which follow-up for coronary revascularization was available are represented in the present study (Cedars Sinai Medical Center, Los Angeles, CA; Harbor UCLA Medical Center, Los Angeles, CA; Tennessee Heart and Vascular Institute, Hendersonville, TN; Capital Cardiology Associates, Albany, NY; University of Munich, Munich, Germany; Ottawa Heart Institute, Ontario, Canada; Henry Ford Medical Center, Detroit, Michigan; Yonsei Medical Center, Seoul, Korea; University Hospital, Zurich, Switzerland; William Beaumont Hospital, Royal Oak, MI; Walter Reed Armey Medical Center, Washington DC; University Hospital of Parma, Parma, Italy). Institutional review board approval was obtained at each centre. Individuals with known CAD, as defined by prior myocardial infarction or prior coronary revascularization, were excluded from the present study analysis (*Figure 1*).

Prior to the initiation of the scan, we prospectively collected information on the presence of categorical cardiac risk factors in each individual.[7] Systemic arterial 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. Dyslipidaemia was defined as known but untreated dyslipidaemia, 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

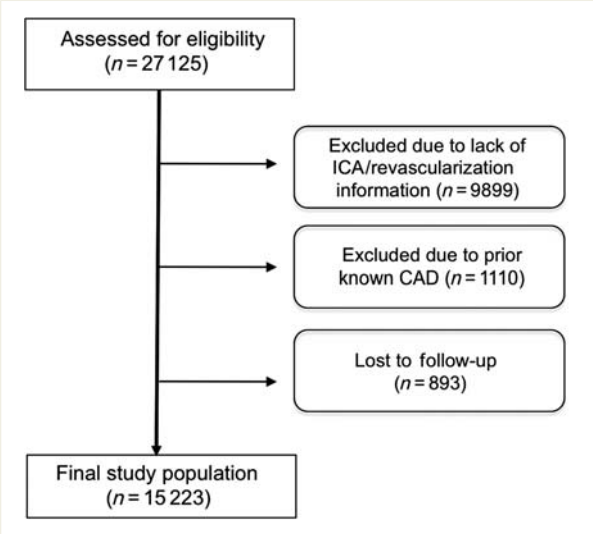

Figure 1 Study flow chart.

disease was determined by patient query. Symptom presentation was classified into one of four categories: typical chest pain/dyspnoea; atypical chest pain; non-cardiac pain or asymptomatic.

Scan protocol and image reconstruction

Coronary computed tomographic angiography scans were performed on a variety of different scanner platforms (Lightspeed VCT, GE Healthcare, Milwaukee, WI; Somatom Definition CT, Siemens, Erlangen, Germany; Somatom Definition Flash CT, Siemens, Ehrlangen, Germany) in accordance to performance guidelines from the Society of Cardiovascular Computed Tomography (SCCT).[8] Imaging of a test-bolus of contrast was performed at 2 mm superior to the takeoff of the left main coronary artery for precise timing of contrast injection. During the CCTA acquisition, 80–140 cc of iodinated contrast (Isovue 370, Bracco Diagnostics, Princeton, NJ; Omnipaque, GE Healthcare, Princeton, NJ; Visipaque, GE Healthcare, Princeton, NJ; or Imeron 350; Bracco Atlana Pharma, Konstanz, Germany) was injected followed by a 50 cc saline flush. Contrast timing was performed to optimize uniform contrast enhancement of the coronary arteries. The scan parameters were 64 × 0.625/0.750 mm collimation, tube voltage 100 or 120 mV, effective 400–650 mA. Dose reduction strategies—including ECG-gated tube current modulation, reduced tube voltage, and prospective axial triggering—were employed whenever feasible.

Helical or axial scan data were obtained with retrospective or prospective ECG gating, respectively. Images were reconstructed immediately after completion of the scan to identify motion-free coronary artery images. Optimal phase reconstruction was assessed by comparison of different phases, if available, and the phase with the least amount of coronary artery motion was chosen for analysis. Multiple phases were employed for image interpretation if motion-free images were different for different arteries. Coronary computed tomographic angiographys were evaluated by an array of post-processing imaging techniques, including axial, multiplanar reformat, maximum intensity projection, and short axis cross-sectional views. In all individuals, irrespective of image quality, every arterial segment was scored in an intent-to-diagnose fashion. If a coronary artery segment was uninterpretable despite these multiple techniques, the unevaluable segment was scored similar to the most proximal segment that was evaluable.

Non-invasive coronary artery analysis by CCTA

All scans were analysed by level III-equivalent cardiologists or radiologists with experience interpreting several thousand CCTA scans in direct accordance with the SCCT guidelines.[9] Coronary computed tomographic angiography interpretation was uniform across all study sites, with coronary segments visually scored for the presence of coronary plaque using a 16-segment coronary artery model in an intent-to-diagnose fashion. In each coronary artery segment, coronary atherosclerosis was defined as tissue structures $>1\ mm^2$ that existed either within the coronary artery lumen or adjacent to the coronary artery lumen that could be discriminated from surrounding pericardial tissue, epicardial fat, or the vessel lumen itself. Coronary atherosclerotic lesions were quantified for stenosis by visual estimation. Luminal diameter stenosis severity was scored as none (0% luminal stenosis), mild (1–49% luminal stenosis), moderate (50–69% luminal stenosis), or severe (≥70% luminal stenosis). Percent obstruction of 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. In instances in which plaque was highly calcified, 2D oblique images were also visualized without maximal intensity projection (i.e. 0.625–0.75 mm isotropic voxel resolution) or multiplanar reformats with cross-sectional views to minimize partial volume averaging artefact of calcium.

For purposes of classification for per-vessel analyses, we considered four arterial territories: left main artery (LM); left anterior descending (LAD) artery; left circumflex (LCx) artery; and right coronary artery (RCA). Obstructive CAD in the diagonal branches, obtuse marginal branches, and posterolateral branches was considered as part of the LAD, LCx and RCA system, respectively. The posterior descending artery was considered as part of the RCA or LCx system, depending upon the coronary artery dominance. A ≥50% stenosis in the left main artery was considered obstructive in all models. Extent of obstructive CAD was defined by ≥50% stenosis in 0, 1, 2, or 3 coronary artery vessels.

Per-segment analysis was judged for individual coronary artery segments that included the LM artery; proximal, mid-, and distal LAD; first and second diagonal branch; proximal and distal LCx; first and second obtuse marginal branch; proximal, mid-, and distal right coronary artery; left and right posterolateral artery; and posterior descending artery. Coronary artery disease severity was calculated using clinical coronary artery plaque scores, as we have previously described.[7,10] For assessment of the severity of CAD, a modified Duke CAD index, combining the location and degree of stenosis, was employed that we have previously demonstrated to provide incremental and linear gradations of prognostic risk of incident death in relations to extent and severity of CAD. Within the Duke CAD index, eight groups are present: Group 0 = No CAD; Group 1 = ≥1 segment with 1–49% stenosis; Group 2 = ≥2 segments with 1–49% stenosis AND at ≥1 proximal segment with any stenosis; Group 3 = ≥1 segment with 50–69% stenosis; Group 4 = ≥2 segments with 50–69% stenosis OR ≥1 segment with ≥70% stenosis; Group 5 = ≥3 segments with 50–69% stenosis OR ≥2 segments with ≥70% stenosis OR pLAD with ≥70% stenosis; Group 6 = ≥3 segments with ≥70% stenosis OR ≥2 segments with ≥70% stenosis AND pLAD with ≥70% stenosis); Group 7 = left main with ≥50% stenosis. Based upon these gradations and their associated prognosis, patients were also categorized into two separate groups that included non-high-risk CAD (Groups 0–4) and high-risk CAD (Groups 5–7).

Further, we examined the extent of CAD as determined by the number of major epicardial coronary vessels that possessed obstructive CAD (as defined by ≥50% stenosis), ranging from no CAD to three-vessel CAD. If a left main coronary stenosis of ≥50% was present, this was considered for the purposes of the study analysis equivalent to three-vessel CAD.

Statistical analysis and study design

SAS 9.2 (www.sas.com, Cary, NC) or SPSS 12.0 and 17.0 (www.SPSS.com, Chicago, IL) were used for all statistical analyses. Categorical variables are presented as frequencies and percentages. Continuous variables are presented as means ± 1 standard deviation or medians (interquartile range) when appropriate. Variables were compared with χ^2 statistic for categorical variables and by Student's unpaired *t*-test or Wilcoxon non-parametric test where appropriate for continuous variables. We further examined individuals undergoing post-CCTA coronary revascularization vs. medical therapy alone. Given the observational nature of the present cohort study, we employed statistical measures to account for non-random allocation of individuals to medical therapy or coronary revascularization. Post-test coronary revascularization was defined as having occurred in the first 90 days following CCTA, and was selected based upon our 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)

while revascularization occurring after this time occurs as a result of a worsening clinical state.[11] Post-test medical therapy vs. revascularization was adjusted via a propensity score that accounted for the decision to refer an individual for revascularization and allocated patient assignment to treatment type in a manner similar to that for a randomized clinical trial, as we have previously described.[12] In order to accomplish this, we performed a two-step process that entailed the development of the propensity score followed by execution of a multivariable Cox proportional hazards model that included the propensity score. The propensity score was developed using a logistic regression model that summarized predictors of referral of patients to revascularization vs. medical therapy. All potential factors known to influence this referral pattern were include a priori into the propensity score development with significant factors retained in the final model. All variables demonstrating significance (using $P < 0.10$ for interaction) were included in the final propensity score, which represented a summary measure for prediction of referral for revascularization.

Time to death from all causes was calculated using univariate Cox proportional hazards models to determine the relationship of medical therapy vs. coronary revascularization for time of freedom from death by all causes. We also performed a multivariable risk-adjusted Cox proportional hazards model. 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. A hazard ratio and 95% confidence interval was calculated from the Cox models. Model overfitting procedures were carefully considered. A two-tailed *P*-value of <0.05 was considered statistically significant.

Follow-up

The primary endpoint was time to death from all causes. Follow-up procedures were approved by all study centres' institutional review boards. Death status for non-US centres was gathered by clinical visits, telephone contacts, and questionnaires sent by mail; with verification of all reported events by hospital records or direct contact with a patient's attending physician. Death status for US centres was ascertained either by query of the Social Security Death Index or by scripted interview by experienced physician and/or nurse study investigators.

Results

Clinical characteristics of the study cohort

Baseline characteristics are listed in *Table 1*. Comparing with patients undergoing medical therapy, patients undergoing coronary revascularization were older, more likely to be male, more likely to possess CAD risk factors including hypertension, diabetes, dyslipidaemia, smoking, and family history of CAD. Patients undergoing revascularization also possessed greater rates of typical angina, obstructive CAD, and higher pre-test likelihood of CAD.

Clinical treatment and events

Individuals were followed for a median of 2.1 years (interquartile range 1.4–3.3 years). Among individuals undergoing revascularization ($n = 1109$), most ($n = 1103$) had the procedure within the first 90 days. More patients undergoing post-CCTA coronary revascularization did so by percutaneous coronary intervention (PCI) ($n = 913$; 82.8%) when compared with coronary artery bypass surgery (CABG) ($n = 228$; 20.7%), with a small minority undergoing both PCI and CABG ($n = 38$, 3.5%). Coronary revascularization rates differed in relation to the extent and severity of CAD, with 3.8% (534 of 14 111), and 51.2% (569 of 1.112) of

Table 1 Baseline characteristics of the study groups

	Medical therapy	Revascularization	*P*-value
n	14 120	1103	
Male sex, % (*n*)	54 (7599)	71 (783)	<0.0001
Hypertension, % (*n*)	47 (6570)	59 (647)	<0.0001
Diabetes mellitus, % (*n*)	12 (1700)	24 (261)	<0.0001
Hypercholesterolaemia, % (*n*)	54 (7533)	67 (734)	<0.0001
Smoking, % (*n*)	16 (2239)	22 (244)	<0.0001
Family history of CAD, % (*n*)	29 (4020)	39 (421)	<0.0001
Typicality			<0.0001
Asymptomatic, % (*n*)	31 (4116)	24 (251)	
Non-cardiac angina, % (*n*)	5 (659)	5 (50)	
Atypical angina, % (*n*)	36 (4774)	29 (305)	
Typical angina or dyspnoea, % (*n*)	29 (3862)	42 (445)	
Age, mean (range)	56 (18–92)	63 (29–94)	<0.0001
Extent of stenosis by CCTA			<0.0001
Non-obstructive (<50%), % (*n*)	87 (12 284)	13 (139)	
Obstructive (≥50%), % (*n*)	13 (1836)	87 (964)	
Pre-test likelihood of CAD, median (range)	0.46 (0.003–0.943)	0.67 (0.003–0.943)	<0.0001[a]

[a]Differences tested using Wilcoxon test.

revascularization occurring in patients with non-high-risk CAD and high-risk CAD, respectively ($P < 0.01$).

During follow-up, a total of 185 deaths occurred (1.22% of the entire population), with the majority of deaths occurring in the first year ($n = 85$), followed to a lesser degree during the second year ($n = 53$) and more than 2 years ($n = 44$) after testing. As stratified by treatment method, death occurred in 1.14% (161 of 14 120) of those treated with medical therapy and 2.18% (24 of 1103) of those treated with coronary revascularization

Propensity score

From the logistic regression analysis, the most significant predictors of referral to coronary revascularization were presence of obstructive CAD and pre-test probability of CAD as calculated by the method of Diamond and Forrester[13] *Table 2*. Family history of CAD was significantly associated with referral to revascularization and was thus included in the propensity score. At a 0.10 significance level for interactions, the interaction between pre-test probability of CAD and obstructive CAD was significant ($P = 0.0344$) and was also included in the final propensity score model (C index 0.91, $\chi^2 = 1248$, $P < 0.0001$).

Survival analysis

The final Cox regression model for prediction of all-cause mortality included the following variables: age (linear and non-linear); male gender; hypertension; dyslipidaemia; diabetes; angina typicality; smoking; treatment type (revascularization vs. medical therapy); CAD severity categorized as non-high-risk CAD vs. high-risk CAD; the interaction of treatment and CAD severity; and the propensity score predicting referral to revascularization *Table 3*. When checking the proportional hazards assumptions for the Cox model, a significant time effect was observed to interact with CAD severity. 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 CAD severity, the second was a three-way interaction between time, CAD severity, and treatment. The final hazard ratios estimate the effect of treatment (revascularization vs. medical therapy) at different levels of CAD severity, and are given at the median follow-up time of 2.1 years.

The univariate relationship between CAD severity and death with respect to revascularization vs. medical therapy can be observed in *Figures 2* and *3*. *Figure 2* depicts the overall mortality of high-risk and non-high-risk CAD patients in the revascularization and medical therapy groups. A survival benefit with revascularization was seen for patients with high-risk CAD, whereas patients with less severe CAD demonstrated lower mortality rates when treated with medical therapy alone. *Figure 3* illustrates the mortality rate with the respective treatments by the extent of CAD as defined by number of major epicardial vessels with obstructive CAD. In patients with single-vessel CAD, no significant difference in mortality was observed between those undergoing and not undergoing revascularization. However, an observational survival benefit for those undergoing revascularization was observed in patients with two-vessel disease, with a trend towards benefit noted for patients with three-vessel disease.

Univariate Cox proportional hazards models of survival in relationship to revascularization or medical therapy can be seen in *Table 3*. In multivariable Cox proportional hazards models, when compared with medical therapy, revascularization was associated with a survival advantage for patients with high-risk CAD (hazards ratio 0.38, 95% confidence interval 0.18–0.83), with no difference in survival for patients with non-high-risk CAD (HR 3.24, 95% CI 0.76–13.89) at the median follow-up period (*P*-value for interaction of revascularization and high-risk CAD and time = 0.03). Using the final Cox model, we also evaluated subgroups to determine whether any particular cohort benefited more from coronary revascularization *Figure 4*. Improvement in survival was evident for all subgroups when high-risk CAD was treated with revascularization with no specific subgroup benefiting substantially more than another.

Discussion

The present results of this large multinational registry of patients without known CAD undergoing CCTA provide evidence that

Table 2 Logistic regression model predicting referral to revascularization

Variable	β coefficient (95% CI)	χ^2	*P*-value
Intercept	−3.48 (−3.68 to −3.28)	1177.43	<0.0001
Family history of CAD	0.1848 (0.03–0.34)	5.6449	0.0175
DF pre-test probablility	0.3749 (0.18–0.57)	14.7235	0.0001
Obstructive CAD	–	1110.59	<0.0001
Normal	1	Reference	Reference
Non-obstructive	−0.3437 (−0.57 to −0.12)	8.9508	0.0028
Obstructive CAD	2.8367 (2.64–3.03)	792.3851	<0.0001
DF probability vs. Obstructive CAD	–	6.7387	0.0344
Normal vs. DF_probability	1	Reference	Reference
Non-obstructive vs. DF_probability	−0.2872 (−0.51 to −0.06)	6.2515	0.0124
Obstructive CAD vs. DF_probability	−0.1778 (−0.38 to 0.02)	3.1141	0.0776

Table 3 Cox proportional hazards model predicting death by any cause

Effect	Univariate			Multivariate		
	Hazard ratio	95% CI	*P*-value	Hazard ratio	95% CI	*P*-value
Male sex	0.9	0.66–1.22	0.502	1.17	0.85–1.61	0.3326
Hypertension	2.31	1.66–3.22	<0.0001	1.8	1.28–2.54	0.0007
Dyslipidaemia	0.67	0.50–0.91	0.0104	0.67	0.49–0.91	0.01
Diabetes	1.77	1.25–2.50	0.0013	1.83	1.29–2.60	0.0007
Age, linear	1.09	1.07–1.11	<0.0001	0.87	0.81–0.97	0.002
Age vs. age, non-linear	1.001	1.001–1.001	<0.0001	1.002	1.001–1.002	<0.0001
Typicality of chest pain						
Asymptomatic	1	Reference	Reference	1	Reference	Reference
Non-cardiac	1.61	0.88–2.95	0.1215	1.31	0.71–2.42	0.3834
Atypical	0.46	0.29–0.71	0.0006	0.47	0.30–0.74	0.0012
Typical/dyspnoea	1.21	0.84–1.72	0.3029	1.1	0.77–1.59	0.5943
Smoker	1.72	1.22–2.41	0.0018	2.2	1.56–3.12	<0.0001
Treatment (revasc vs. medical Tx)	0.69	0.42–1.12	0.1308	N/A	N/A	0.4484
High-risk vs. low-risk CAD	1.49	0.95–2.34	0.0836	N/A	N/A	0.5821
Revasc vs. high-risk CAD	N/A	N/A	0.0899	N/A	N/A	0.0161
High risk vs. time	N/A	N/A	0.3652	N/A	N/A	0.4477
High risk vs. time vs. early revasc			0.1179			0.03
Revasc vs. medical Tx (high-risk CAD at 2.1 year follow-up)	0.52	0.30–0.89		0.38	0.18–0.83	
Revasc vs. medical Tx (low-risk CAD at 2.1 year follow-up)	0.87	0.46–1.64		3.24	0.76–13.9	
Propensity	51.6	21.9–121.4	<0.0001	4.84	1.41–16.6	0.012

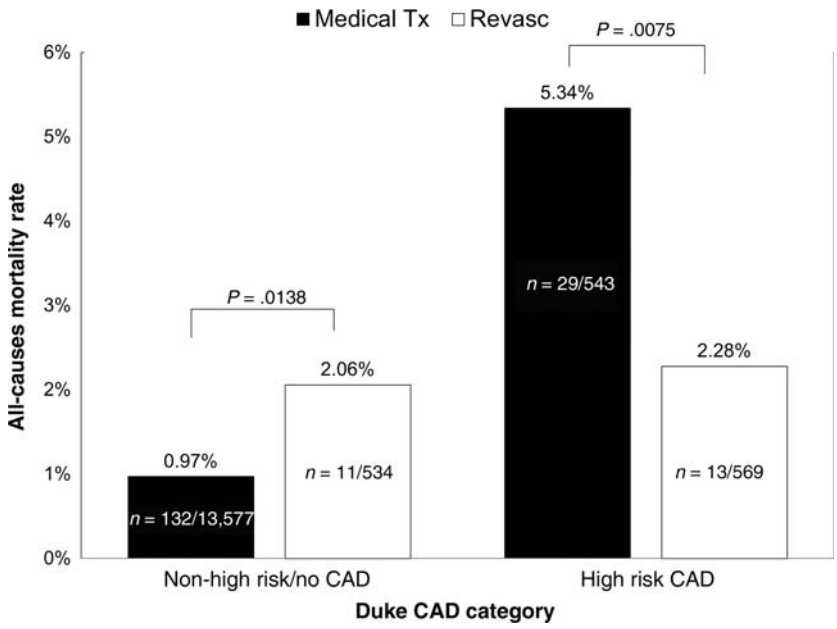

Figure 2 Observed death rates for patients with obstructive coronary artery disease undergoing medical therapy (medical Tx) or revascularization (revasc) by high-risk vs. non-high-risk coronary artery disease.

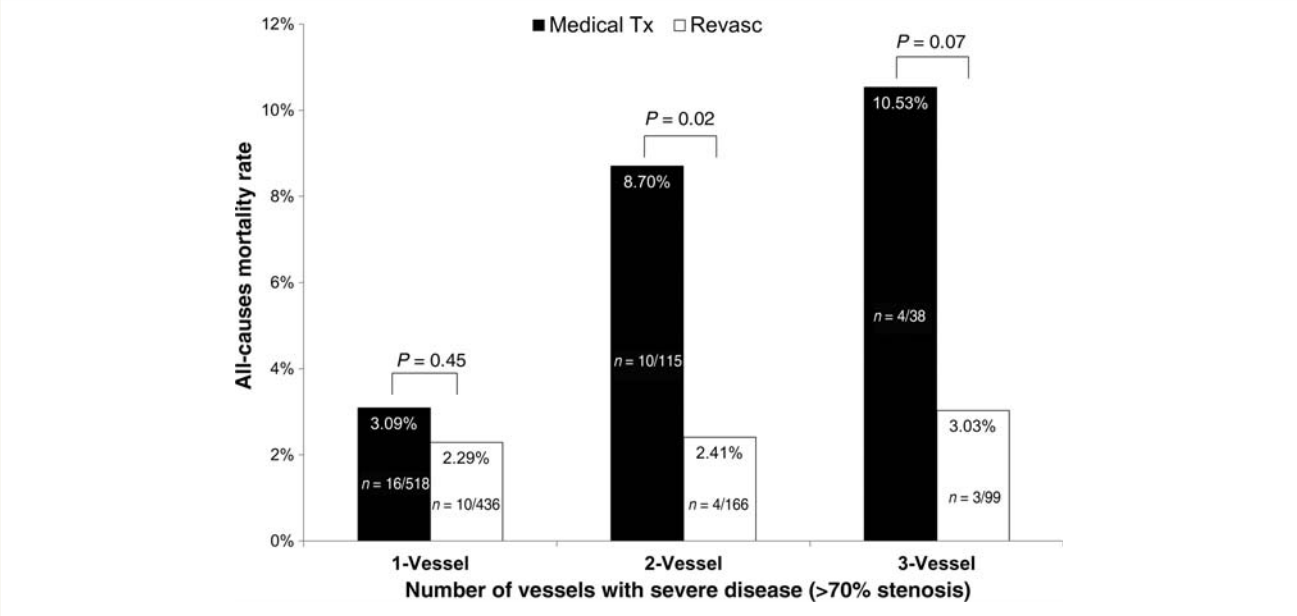

Figure 3 Observed death rates for patients undergoing medical therapy (medical Tx) or revascularization (revasc) by obstructive coronary stenosis for one-, two-, or three-vessels.

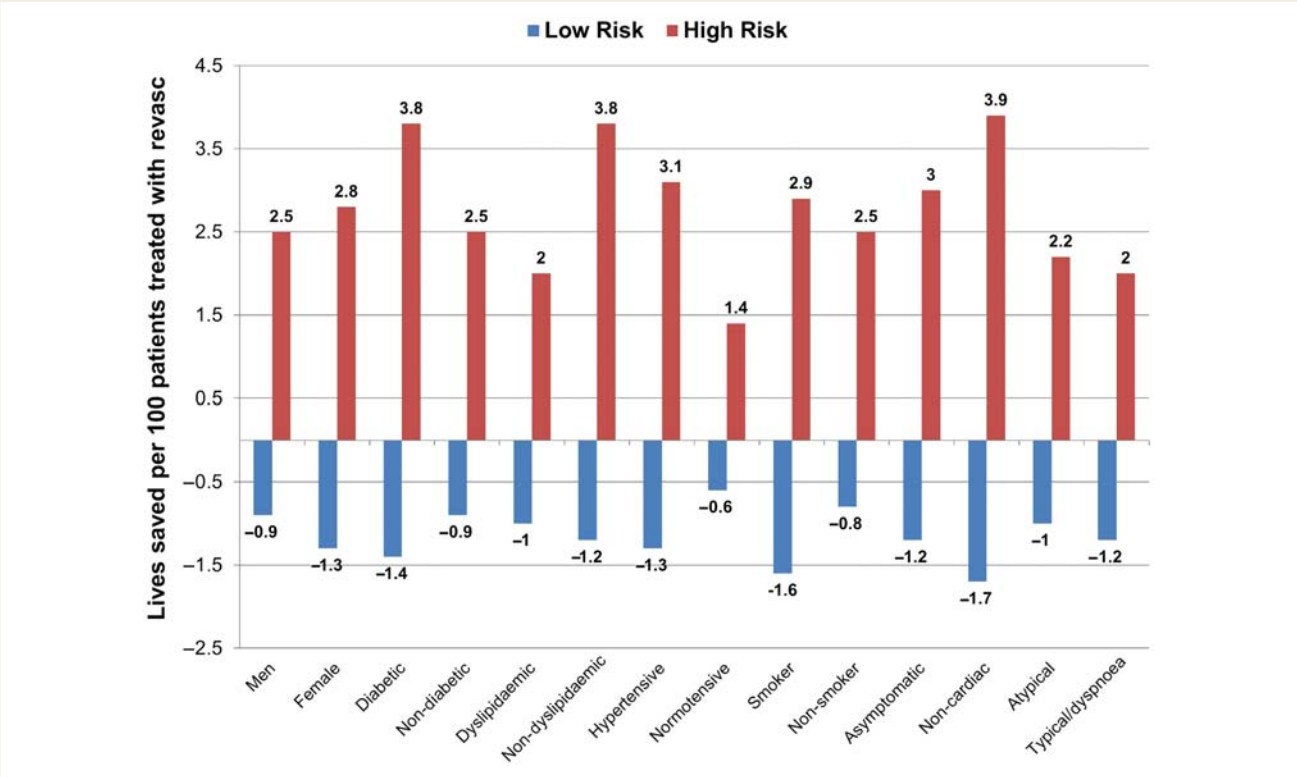

Figure 4 Predicted all-cause mortality rates in patients treated with medical therapy vs. coronary revascularization as stratified by non-high-risk coronary artery disease, and high-risk coronary artery disease. Exploratory analyses that do not reach statistical significance.

stable patients with high-risk CAD—inclusive of those with two-vessel obstructive CAD with proximal left anterior descending artery involvement, three-vessel obstructive CAD, and obstructive left main CAD—experience a survival benefit from undergoing revascularization when compared with standard medical therapy alone. In contradistinction, those with lesser forms of CAD—which represent the predominant majority of individuals undergoing CCTA—do not experience any difference in survival by undergoing revascularization. These results were evident in observed rates of mortality following revascularization as well as after adjustment for the assignment of individuals to revascularization vs. medical therapy. On the basis of the final Cox models, the benefits for revascularization in the high-risk CAD subset are suggestive of generalizability across a myriad of patient subgroups.

Our group has previously reported on the prognostic value of CCTA-identified CAD extent and severity, and has observed increased risk of death and major adverse cardiac events[14] for CCTA measures of high-risk CAD, obstructive CAD, and even for milder forms of non-obstructive CAD.[7,15–17] The prognostic value of CCTA-identified CAD is incremental to traditional measures of CAD risk assessment—including being additive to measures of left-ventricular function, myocardial perfusion, coronary artery calcium scores, and clinical evaluation—and generalizable across an array of patient subgroups including those without and with known CAD, diabetics, women, and asymptomatic patients.[17–22] In this article, we sought to further determine whether there exists a threshold of angiographic CAD above which revascularization might hold a relative therapeutic advantage over medical therapy alone. Given the large-scale international multisite nature of the CONFIRM registry, these results extend prior studies by examining the potential therapeutic benefit of CCTA-guided decision making. Future studies examining whether CCTA can improve appropriate referral to cardiac catheterization with intended coronary revascularization now appear warranted.

Recently, large-scale registries and randomized controlled trials (RCT) have suggested that ischaemia-guided revascularization may be superior to angiographically guided revascularization for reduction of events.[12,23,24] In particular, the recent FAME, or Fractional Flow Reserve vs. Angiography for Multivessel Evaluation, trial demonstrated a higher survival for patients undergoing revascularization based upon lesion-specific assessment of coronary artery stenosis haemodynamic significance.[25] Similarly, a prior large-scale registry from our own group has revealed that revascularization based upon a function of % ischaemic myocardium as judged by non-invasive myocardial perfusion testing may identify individuals who may benefit from coronary revascularization over medical therapy alone.[12] The results of the present study do not conflict with these prior landmark studies, and whether ischaemia-guided revascularization is superior to angiographically guided revascularization by CCTA is beyond the scope of the study. Rather, given the recent designation of CCTA by American College of Cardiology Appropriate Use Criteria as an appropriate alternative to functional stress for symptomatic individuals with suspected CAD, these data may be useful for practitioners to identify thresholds at which cardiac catheterization with intended revascularization after CCTA may be considered reasonable or not.[26]

On its surface, the results of the present study may appear incongruous with recent RCTs that have challenged the notion that the addition of coronary revascularization to optimal medical therapy (OMT) is superior to OMT alone in stable patients with angiographically obstructive CAD.[27,28] Particularly germane to the present discussion are the results of the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial, which evaluated 2287 patients with angiographic obstructive CAD who were assigned to revascularization plus OMT vs. OMT alone. At a 4.6-year follow-up, no differences were noted between groups for MACE events or angina-related quality of life. And indeed, in the present study, for the vast majority of patients with CCTA-identified CAD—including those with angiographically obstructive CAD—no survival benefit was observed for those undergoing coronary revascularization vs. medical therapy alone. However, for a small minority of patients undergoing CCTA who were identified as having high-risk CAD (7.3%; 1112 of 15 223), a survival benefit from revascularization was observed. The propitious outcomes following revascularization in patients with angiographically high-risk CAD may be explained by differences in the CONFIRM and COURAGE cohorts. By design, the COURAGE trial systematically excluded patients with obstructive left main CAD and may have been affected by unobserved negative selection biases for patients with more high-risk forms of angiographic CAD.[29] In contrast, the present study assessed the outcomes of patients across the entire range of CAD severity—including those with high-risk CAD—without pre-defined selection criteria. Further, the present study design was an observational one, with no mandated post-test treatments and thus, medical regimens and medical compliance are unknown. In this regard, the patients in our registry are assumed to have achieved usual rather than OMT, which may have served to heighten the outcome disparities between the revascularization and medical therapy groups. In this real world comparative effectiveness study, whether the outcomes of patients with high-risk CAD taking an OMT regimen could be improved by revascularization cannot be properly tested. Given the observational nature of this study, all of its results should be considered hypothesis-generating rather than hypothesis-proving; future randomized trials further exploring the present findings should be performed to corroborate the present findings.

The present results harmonize with prior large-scale registries that have demonstrated a similar hazards reduction for death in patients with angiographically high-risk CAD treated with revascularization. Mark *et al.*[2] examined 9263 patients referred for invasive angiography during a 7-year period. In this cohort, a growing benefit for revascularization was noted for patients with increasingly severe CAD, with an almost 40% lower rate of cardiovascular death in patients with three-vessel obstructive CAD undergoing coronary artery bypass grafting in favour of medical therapy. Similarly, the Coronary Artery Surgery Study examined 11 508 patients for sudden death, comparing those treated with medical therapy vs. coronary revascularization by surgical methods.[1] In this cohort with high-risk CAD, a 25% lower rate of sudden death was observed in patients undergoing revascularization. Both of these studies identified the most favourable outcomes of patients with high-risk CAD to be related to surgical, as opposed to

percutaneous revascularization. Importantly, these investigations were performed in an era that preceded contemporary stent technologies. In the current study, we did not specifically examine the mortality differences associated with revascularization by percutaneous methods vs. CABG because to do so would have compromised statistical power and because angiographic data was not available for review. However, given the recent large-scale RCTs that have demonstrated a similar survival advantage among patients treated with surgical vs. percutaneous revascularization methods, we believe that combination of these methods into a single revascularization category is both contemporary in its scope as well as scientifically justified.[30–32]

This study is not without limitations. While the patient cohorts represent those from a diversity of clinical practice sites and countries, all study results are subject to the limitations of observational data. In particular, unobserved confounders and selection and/or referral biases may have affected our study results. It is notable to mention, however, that we performed careful statistical modelling to account for patterns of referral to coronary revascularization vs. medical therapy, in a manner that simulated an RCT design.[12] Further, we aimed to examine those patients who underwent revascularization as a response to CCTA findings and chose a 90-day window after CCTA performance to define early post-test revascularization. This window of time was chosen as lengthier periods of time after testing generally represent clinical worsening that exceeds the warranty of an episode of care for which the original test was ordered.[11,33,34]

Notably, in this prospective multicentre observational cohort study, post-CCTA treatment regimens were not mandated. Our study results may have differed, particularly in the high-risk CAD subset, if OMT had been mandated; future randomized studies addressing this issue may be warranted. Further, it should be noted that we examined baseline characteristics—including CAD risk factors—as binary variables, rather than as continuous ones. Thus, the duration of CAD risk factor presence and the severity of the risk remain unknown. Finally, we examined all-cause mortality as a primary endpoint, given its unparalleled clinical importance and freedom from ascertainment bias. Nevertheless, revascularization is not expected to affect rates of non-cardiac deaths and the relative therapeutic impact of revascularization vs. medical therapy specifically on cardiac death alone or on sudden cardiac death remains unknown.

Conclusion

In an intermediate-term follow-up of 15 223 patients without known CAD undergoing CCTA from an international multicentre observational cohort study, coronary revascularization in patients with high-risk CAD was associated with significantly lower rates of all-cause mortality when compared with medical therapy alone. In contrast, no apparent benefit of revascularization was realized for patients with lesser forms of CAD. These observational findings may be potentially useful as hypothesis-generating data upon which future randomized trials can be considered.

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