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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
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 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. 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 and prior research has observed a mortality benefit for early revascularization following CCTA in patients with high-risk CAD in the short-term. 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 Internaional Multicenter Registry), the methods of which have been previously described. CONFIRM enrolled consecutive adults ≥18 years of age between 2005 and 2009 who underwent ≥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 at 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 miscategorization of potentially unstable patients. The final sample included 5544 patients from 12 clinical sites.

As detailed elsewhere, 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. Specific details of CCTA procedures have been defined in detail elsewhere. 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 (≥70%). If a coronary artery segment was uninterpretable despite multiple reformating techniques, the un-evaluable segment was scored similar to the most proximal segment that was evaluable. Extent of obstructive CAD was defined by ≥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. As in prior work, CAD severity was also assessed using the modified Duke score. The groups include: Group 0 = No CAD; Group 1 = ≥1 segment with 1–49% stenosis; Group 2 = ≥2 segments with 1–49% stenosis AND ≥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 proximal LAD with ≥70% stenosis; Group 6 = ≥3 segments with ≥70% stenosis OR ≥2 segments with ≥70% stenosis AND proximal LAD with ≥70% stenosis; Group 7 = left main with ≥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, 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). 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. 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 ± 1 SD or medians (inter-quartile range) when appropriate. Variables were compared with χ² 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. 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 < 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, 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 variable 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 variable models were then used to determine the relationship of early revascularization. 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

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 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

Table 1
<table>
<thead>
<tr>
<th>Medical therapy (n=4373)</th>
<th>Early revascularization (n=1171)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) ± SD</td>
<td>59.4 ± 12.0</td>
<td>63.3 ± 10.1</td>
</tr>
<tr>
<td>Male sex % (n)</td>
<td>61.1 (2672)</td>
<td>72.4 (848)</td>
</tr>
<tr>
<td>Cardiovascular risk factors % (n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>53 (2305)</td>
<td>63 (733)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>51.6 (2247)</td>
<td>64.3 (746)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>14.8 (643)</td>
<td>25.5 (297)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>20.3 (878)</td>
<td>25.7 (299)</td>
</tr>
<tr>
<td>Family history of premature CAD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presence of</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>41.4 (1799)</td>
<td>2.5 (29)</td>
</tr>
<tr>
<td>Non-obstructive CAD</td>
<td>36.8 (1608)</td>
<td>5.8 (68)</td>
</tr>
<tr>
<td>Obstructive CAD</td>
<td>22.1 (966)</td>
<td>91.7 (1074)</td>
</tr>
<tr>
<td>Duke CAD Score % (n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low-risk (Score 0–2)</td>
<td>77.9 (3407)</td>
<td>8.3 (97)</td>
</tr>
<tr>
<td>Intermediate-risk (Score 3–4)</td>
<td>13.2 (576)</td>
<td>35.8 (419)</td>
</tr>
<tr>
<td>High-risk (Score 5–7)</td>
<td>8.9 (390)</td>
<td>55.9 (655)</td>
</tr>
</tbody>
</table>

CCTA, coronary-computed tomographic angiography.
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,12 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
anterior descending artery, and/or obstructive disease of the left
without known CAD undergoing CCTA, we observed a mortality
in this large, international observational registry of stable patients
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 revasculari-
zation 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 sus-
tained 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 bene-
fit 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 demon-
strated 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,10,13 which may reflect lower inclu-
sion of patients with high-risk CAD. In contrast, the CONFIRM regis-
try was explicitly designed to determine the prognostic value of
CCTA findings.6 Entry was not restricted to patients with suspected
CAD alone, but rather was representative of physician referral at nu-
merous high-volume sites around the world. As such, patients at
higher risk or with known CAD were enrolled, as were lower risk pa-
tients 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 per-
formed 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.6
Our study contributes to literature documenting the adverse
prognosis of increasing anatomic CAD (detected both invasively and
by CCTA)14 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,1 a finding
that persists in clinical guidelines of stable ischemic heart disease.15
Conversely, on the whole contemporary randomized trials of
intermediate-to-high risk CAD2,3 have not identified an association
between revascularization and a subsequent reduction of death as
compared with OMT. Furthermore, in COURAGE, there was no sig-
ificant interaction between treatment strategy and angiographic se-
vensity for mortality benefit,16 a finding reflected in our observations
of patients with low and intermediate risk CAD. However, these tri-
als had several limitations. First, inclusion was contingent on pre-trial
invasive angiography, raising concerns of negative selection bias
against patients with high-risk CAD.17 Second, percutaneous revascu-
larization 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.18
Third, patients with the highest risk CAD (i.e. left main) were

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.03 (1.00–1.06)</td>
<td>0.04</td>
</tr>
<tr>
<td>Sex</td>
<td>1.33 (0.95–1.87)</td>
<td>0.10</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>1.46 (1.19–1.80)</td>
<td>&lt;0.001</td>
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<tr>
<td>Symptom typicality</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Asymptomatic/non-cardiac chest pain</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>Atypical angina</td>
<td>1.45 (0.97–2.15)</td>
<td></td>
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<tr>
<td>Typical angina</td>
<td>2.22 (1.30–3.77)</td>
<td></td>
</tr>
<tr>
<td>Diamond-Forrester probability</td>
<td>1.67 (0.99–2.81)</td>
<td>0.06</td>
</tr>
<tr>
<td>Obstructive CAD</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Normal</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>Non-obstructive</td>
<td>0.75 (0.41–1.37)</td>
<td></td>
</tr>
<tr>
<td>Obstructive</td>
<td>5.83 (3.12–10.89)</td>
<td></td>
</tr>
<tr>
<td>SIS (log-transformed)</td>
<td>0.29 (0.17–0.50)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SSS (log-transformed)</td>
<td>32.1 (11.58–88.97)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Site</td>
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<td>&lt;0.001</td>
</tr>
<tr>
<td>A</td>
<td>0.29 (0.17–0.49)</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>1.02 (0.65–1.59)</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>5.16 (3.73–7.91)</td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>0.27 (0.19–0.38)</td>
<td></td>
</tr>
<tr>
<td>E</td>
<td>0.07 (0.03–0.17)</td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>0.89 (0.62–1.29)</td>
<td></td>
</tr>
<tr>
<td>G</td>
<td>1.72 (0.76–3.92)</td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>0.58 (0.38–0.88)</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>0.48 (0.34–0.68)</td>
<td></td>
</tr>
<tr>
<td>J</td>
<td>1.25 (0.42–3.69)</td>
<td></td>
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<tr>
<td>Sex vs. typicality</td>
<td>0.77 (0.60–0.99)</td>
<td>0.04</td>
</tr>
<tr>
<td>Age vs. SSS</td>
<td>0.98 (0.96–0.99)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

SIS, Segment Involvement Score; SSS, Segment Stenosis Score.
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.15,19 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

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

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

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.

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, 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 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 a primary endpoint.

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 other journal. All cohort participants provided written informed consent, and the appropriate ethics committees approved the study.

Conflict of interest: None declared.

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Relationship with Industry

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

References


