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ORIGINAL RESEARCH

Outcomes with revascularisation versus conservative management of participants with 3-vessel coronary artery disease in the ISCHEMIA trial

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ABSTRACT

BACKGROUND: Whether revascularisation (REV) improves outcomes in patients with three-vessel coronary artery disease (3V-CAD) is uncertain.

AIMS: Our objective was to evaluate outcomes with REV (percutaneous coronary intervention [PCI] or coronary artery bypass graft surgery [CABG]) versus medical therapy in patients with 3V-CAD.

METHODS: ISCHEMIA participants with 3V-CAD on coronary computed tomography angiography without prior CABG were included. Outcomes following initial invasive management (INV) with REV (PCI or CABG) versus initial conservative management (CON) with medical therapy alone were evaluated. Regression modelling was used to estimate the outcomes if all participants were to undergo prompt REV versus those assigned to CON. Outcomes were cardiovascular (CV) death/myocardial infarction (MI), death, CV death, and quality of life. Bayesian posterior probability for benefit (Pr [benefit]) for 1 percentage point lower 4-year rates with REV versus CON were evaluated.

RESULTS: Among 1,236 participants with 3V-CAD (612 INV/624 CON), REV was associated with lower 4-year CV death/MI (adjusted 4-year difference: –4.4, 95% credible interval [CrI] –8.7 to –0.3 percentage points, Pr [benefit]=94.8%) when compared with CON, with similar results for PCI versus CON (–5.8, 95% CrI: –10.8 to –0.5 percentage points, Pr [benefit]=96.4%) and CABG versus CON (–3.7, 95% CrI: –8.8 to 1.5 percentage points, Pr [benefit]=84.7%). Adjusted 4-year REV versus CON differences were as follows: death –1.2 (95% CrI: –4.7 to 2.2) percentage points, CV death –2.3 (95% CrI: –5.5 to 0.8) percentage points, with similar results for PCI and for CABG. The Pr (benefit) for death with REV (PCI or CABG) versus CON was 49-63%. The adjusted 12-month Seattle Angina Questionnaire-7 summary score differences favoured REV: REV versus CON 4.6 (95% CrI: 2.7-6.4) percentage points; PCI versus CON 3.6 (95% CrI: 1.2-5.8) percentage points and CABG versus CON 4.3 (95% CrI: 1.5-6.9) percentage points with high Pr (benefit).

CONCLUSIONS: In participants with 3V-CAD, REV (either PCI or CABG) was associated with a lower 4-year CV death/MI rate and improved quality of life, with similar results for PCI versus CON and CABG versus CON. The differences in all-cause mortality between REV and CON were small with wide confidence intervals. (ClinicalTrials.gov: NCT01471522)

KEYWORDS: miscellaneous; multiple vessel disease; prior percutaneous intervention

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In patients with stable coronary artery disease (CAD), revascularisation (REV) improves angina-related quality of life (QoL)[1-3]. Whether REV improves cardiovascular outcomes in patients with stable CAD, and especially in those with three-vessel CAD (3V-CAD), is unknown and has been hotly debated[4,5]. Randomised trials in the 1970s and 1980s showed an improvement in survival with coronary artery bypass graft surgery (CABG) when compared with medical therapy in patients with 3V-CAD[6]. However, medical therapy was very limited compared with contemporary practice. The outcomes of patients with 3V-CAD in contemporary practice with guideline-directed medical therapy (GDMT) are not known.

In the ISCHEMIA trial, there was no heterogeneity of treatment effect in the comparison of randomised treatment groups (initial invasive [INV] vs initial conservative [CON] strategy) for the primary endpoint based on the number of diseased vessels on coronary computed tomography angiography (CCTA)[7]. However, a subgroup of interest was identified in an analysis of randomised participants who had CCTA evaluable for the modified Duke prognostic index. In that prior analysis, the 4-year rate of cardiovascular (CV) death or myocardial infarction (MI) was lower with the INV strategy (INV vs CON difference 6.3% [95% confidence interval CI : 0.2-12.4%]; $p_{interaction}$=0.33) in the most severe CAD subgroup (defined as Duke 6: three-vessel disease [3VD] based on ≥70% stenosis or two-vessel disease [2VD] based on ≥70% stenosis including the proximal left anterior descending artery [LAD])[8]. However, the outcomes based on actual REV received (only 80% of participants randomised to INV were revascularised) or outcomes restricted to 3VD were not explored. Accordingly, in the current analysis we sought to evaluate what the outcomes of REV would be if all participants were to receive REV compared with CON, as well as separately evaluating percutaneous coronary intervention (PCI) versus CON and CABG versus CON in the subset of participants with 3V-CAD who were randomised in the ISCHEMIA trial.

Editorial, see page e1260

Impact on daily practice

This *post hoc* analysis of participants with three-vessel coronary artery disease (3V-CAD) randomised in the ISCHEMIA trial suggests that revascularisation (with either percutaneous coronary intervention or coronary artery bypass graft surgery) was associated with a lower 4-year rate of cardiovascular death or myocardial infarction, despite early procedural risk, and with a significantly improved quality of life, but the impact on overall mortality was similar with wide confidence intervals when compared with initial conservative management. These associations should be considered in the management of patients with 3V-CAD.

Methods

The authors declare that all supporting data are available online. A list of non-author collaborators for indexing in PubMed is included in **Supplementary Appendix 1**.

STUDY POPULATION

The design and principal results of the ISCHEMIA trial have previously been published[7,9]. The study was approved by the institutional review boards of the participating sites. In brief, 5,179 participants with stable CAD and site-determined moderate or severe ischaemia were randomised 1:1 to either INV, consisting of coronary angiography and REV (PCI or CABG) if suitable, plus GDMT, or to CON of GDMT alone, with coronary angiography and REV reserved for failure of GDMT. Notable exclusion criteria included participants with known left main disease, recent acute coronary syndrome, left ventricular ejection fraction (LVEF) <35% or participants with an unacceptable level of angina at enrolment. Among participants randomised to INV, 80% were revascularised: 76% of them with PCI and 24% with CABG[7].

Participants who had a core laboratory-interpreted CCTA with 3V-CAD based on ≥50% stenosis severity and without prior CABG were included in the present analysis. Participants with CCTA of poor quality that were not evaluable for diseased vessels were excluded. We note that the available number of evaluable CCTA studies for this analysis is larger than in a prior ISCHEMIA trial CCTA analysis that used the modified Duke prognostic index, because that index requires assessment of whether stenosis severity is ≥70%[8].

STUDY PROCEDURES

Participants randomised to INV underwent coronary angiography and were scheduled to undergo REV, if feasible, using contemporary techniques, including 2nd-generation drug-eluting stents, physiology guidance for PCI and use of at least the left internal mammary artery graft for CABG. Coronary angiography and revascularisation were only allowed in the CON group in case of refractory symptoms or a suspected primary endpoint event. Both groups received secondary prevention measures that included lifestyle and pharmacological interventions.

STUDY ENDPOINTS

Endpoints of interest were the composite of CV death or MI, composite of death or MI, other composite outcomes including stroke, and individual components of the composite outcome. Health status outcomes included symptoms,

Abbreviations

CABG	coronary artery bypass graft surgery	**INV**	invasive management
CAD	coronary artery disease	**MI**	myocardial infarction
CON	conservative management	**PCI**	percutaneous coronary intervention
CV	cardiovascular	**QoL**	quality of life

function and QoL. The definitions of outcomes have been described previously[7]. MI included the study's primary definition of both procedural MI and spontaneous MI.

Participants' health status at 12 months post-randomisation was assessed using the 7-item Seattle Angina Questionnaire (SAQ-7), the Rose Dyspnea Scale (RDS), and the European Quality of Life-5 Dimension visual analogue scale (EQ-5D VAS). The SAQ-7 encompasses 3 domains assessing angina-related health status over the previous 4 weeks, quantified by angina frequency, physical limitation, and QoL scores; a summary score was also derived integrating all 3 domains[10]. All scores range from 0 to 100, with higher scores denoting better health status. The RDS assesses the presence of dyspnoea with 4 common physical activities, with a score of 0 indicating no dyspnoea and a score of 4 indicating significant limitations due to dyspnoea[11]. The EQ-5D VAS assesses general health status; scores range from 0 to 100, with a score of 0 indicating the worst possible health and a score of 100 indicating perfect health[12].

STATISTICAL ANALYSIS

Detailed statistical methods are presented in **Supplementary Appendix 2**. Briefly, we studied the hypothesis that, on average, patients resembling ISCHEMIA participants with 3V-CAD and no prior CABG would benefit from a strategy of upfront REV compared to CON. Outcomes of REV and CON were based on data from the randomised INV and CON groups, respectively. INV-assigned participants were excluded if they had missing data for key invasively measured angiographic covariates (n=47). Statistical adjustments were implemented to account for this exclusion and to address the fact that not all remaining INV-assigned participants underwent prompt upfront revascularisation. We also adjusted for censoring (i.e., incomplete follow-up) in the analysis of time-to-event clinical endpoints. By making these adjustments, we sought to recover the true treatment effect that would be observed in an ideal setting of no missing angiographic covariates, no censoring, and 100% adherence to an INV strategy of prompt upfront revascularisation.

We performed separate analyses for each method of revascularisation and each endpoint. For clinical endpoints, the statistical framework was a set of discrete-time longitudinal logistic regression models adjusting for the covariates listed in **Supplementary Table 1**. We used these models to estimate a patient's weekly risk as a function of time since randomisation, time since INV-assigned revascularisation, and baseline covariates. Weekly risk estimates were then combined to produce an estimate of each patient's cumulative risk over a 4-year time horizon. This calculation was performed twice per patient. The first estimate described the patient's risk if assigned to INV and given prompt REV. The second estimate described the patient's risk if assigned to CON. We then averaged each of these estimates across participants to produce an overall estimate of the difference in risk under a strategy of REV compared to CON.

For QoL outcomes, the statistical framework was a set of proportional odds models. Missing health status scores were imputed using multiple imputation methods, as described in **Supplementary Appendix 2**. We performed separate analyses for each method of REV and for each outcome. For each analysis, we estimated separate models for INV and CON, adjusting for the covariates listed in **Supplementary Table 1** as well as the baseline health status score for the given outcome. Using these models, we predicted the score for each participant in the study's INV cohort under each treatment strategy. We then estimated the standardised outcome for each treatment strategy as the average of the predicted scores. We defined the primary measure of treatment effect for each QoL outcome to be the between-group difference in the REV versus CON, PCI versus CON, and CABG versus CON standardised outcomes at 12 months.

We used a Bayesian statistical approach to implement the above analyses. This methodology allows us to calculate the probability of various outcomes directly, making the results especially relevant and understandable in clinical and practical terms[13,14]. For example, we were able to calculate the probability that REV produces a 4-year cumulative risk that is lower than CON by a margin of at least 1 (defined in this report for simplicity as probability for benefit [Pr{benefit}]), 3, or 5 percentage points. Details are presented in **Supplementary Appendix 2**.

Results

A total of 1,283 participants with no prior CABG, with a prerandomisation CCTA that was evaluable for diseased vessels, revealing 3V-CAD, were identified, among whom 47 participants randomised to INV but with missing key angiographic covariates were excluded **(Supplementary Figure 1)**. Among the remaining 1,236 participants included in this analysis, 612 were randomised to INV and 624 to CON. Among those in the INV group, 510 (83.3%) underwent REV, including 292 who underwent PCI and 218 who underwent CABG, within 180 days post-randomisation. In the CON group, 89 participants (14.3%) underwent REV within the 4-year follow-up.

BASELINE CHARACTERISTICS

Baseline characteristics of the INV versus CON groups and the comparisons of REV versus CON, PCI versus CON, and CABG versus CON are presented in **Table 1**, **Supplementary Table 2** and **Supplementary Table 3**. There were no major differences except for a higher proportion of participants with prior stroke, higher estimated glomerular filtration rate (eGFR) and lower SAQ angina frequency score (more angina) among those randomised to INV compared with CON. For the PCI versus CON comparison, there were no major differences except for QoL domains, with a lower SAQ summary score, lower SAQ angina frequency score and lower SAQ QoL score, indicating worse symptoms in the PCI group. Conversely, the PCI group had lower proportions of participants with left main disease and proximal LAD disease when compared with CON **(Supplementary Table 3)**. For the CABG versus CON comparison, there were no major differences between the groups except for a greater proportion of participants with prior stroke, a greater proportion from Europe, a lesser proportion from Asia and North America, and a greater proportion of participants with severe ischaemia and left main disease in the CABG group when compared with CON **(Table 1, Supplementary Table 2, Supplementary Table 3).**

Table 1. Baseline characteristics.

	INV N=612	INV: REV N=510	INV: PCI N=292	INV: CABG N=218	CON N=624	p-value INV vs CON	p-value REV vs CON	p-value PCI vs CON	p-value CABG vs CON
Age, years	64 (57-70)	63 (57-69)	63 (55-69)	64 (59-70)	64 (57-69)	0.56	0.92	0.28	0.26
Male	521/612 (85.1)	432/510 (84.7)	238/292 (81.5)	194/218 (89.0)	526/624 (84.3)	0.74	0.91	0.34	0.11
Hypertension	438/610 (71.8)	370/508 (72.8)	212/292 (72.6)	158/216 (73.1)	449/622 (72.2)	0.93	0.86	0.96	0.85
Diabetes	261/612 (42.6)	216/510 (42.4)	121/292 (41.4)	95/218 (43.6)	289/624 (46.3)	0.22	0.20	0.19	0.54
Current smoker	80/611 (13.1)	59/509 (11.6)	33/292 (11.3)	26/217 (12.0)	78/623 (12.5)	0.94	0.85	0.45	0.69
Previous myocardial infarction	105/612 (17.2)	85/510 (16.7)	46/292 (15.8)	39/218 (17.9)	104/623 (16.7)	0.89	1.00	0.79	0.76
Known heart failure	20/612 (3.3)	18/510 (3.5)	11/292 (3.8)	7/218 (3.2)	13/624 (2.1)	0.26	0.19	0.21	0.49
Previous stroke	22/612 (3.6)	19/510 (3.7)	9/292 (3.1)	10/218 (4.6)	10/624 (1.6)	0.04*	0.04*	0.22	0.03*
History of peripheral arterial disease	32/610 (5.2)	23/509 (4.5)	12/291 (4.1)	11/218 (5.0)	20/621 (3.2)	0.10	0.33	0.62	0.31
Previous percutaneous coronary intervention	108/611 (17.7)	81/509 (15.9)	50/292 (17.1)	31/217 (14.3)	101/624 (16.2)	0.53	0.97	0.79	0.58
Left ventricular ejection fraction, %	60 (55-64)	60 (55-65)	60 (56-65)	60 (55-65)	60 (55-65)	0.95	0.59	0.26	0.67
eGFR, mL/min/1.73 m^2	88 (74-103)	88 (74-102)	88 (73-102	88 (74-102)	84 (72-98)	0.02*	0.03*	0.07	0.09
SAQ-7 summary score	76 (62-89)	75 (62-88)	74 (58-88)	77 (65-89)	78 (64-90)	0.10	0.06	0.02*	0.68
SAQ-7 angina frequency score	80 (70-100)	80 (70-100)	80 (60-100)	80 (70-100)	90 (70-100)	0.02*	0.003*	0.0002*	0.38
SAQ-7 physical limitation score	92 (67-100)	92 (67-100)	92 (67-100)	92 (75-100)	92 (75-100)	0.85	0.94	0.55	0.55
SAQ-7 quality of life score	63 (50-88)	63 (50-85)	63 (38-75)	63 (50-88)	63 (50-88)	0.07	0.06	0.04*	0.36
History of angina	549/612 (89.7)	457/510 (89.6)	259/292 (88.7)	198/218 (90.8)	553/624 (88.6)	0.60	0.66	1.00	0.44

Data are presented as n/N (%) or mean (95% credible interval). *Value holds statistical significance. CABG: coronary artery bypass graft surgery; CON: conservative management; eGFR: estimated glomerular filtration rate; INV: invasive management; PCI: percutaneous coronary intervention; REV: revascularisation; SAQ: Seattle Angina Questionnaire

There were no major differences in physiological measurements, risk factor goals, medication use at baseline and at the last visit, or procedural details between the groups, except for a greater use of clopidogrel in the PCI group and a higher medication adherence in the REV, PCI, and CABG groups when compared with the CON group at the last visit **(Supplementary Table 4, Supplementary Table 5)**. The overall 4-year mortality rate was 9.0% for CON in patients with 3V-CAD, compared with 6.4% for CON in the overall trial, reflecting the higher anatomical risk of this subset.

CLINICAL OUTCOMES: REV VERSUS CON

Compared with CON, REV was associated with a lower 4-year CV death or MI rate (4-year between-group difference: –4.4 percentage points, 95% credible interval [CrI]: –8.7 to –0.3 percentage points, Pr [benefit]=94.8%) **(Figure 1, Table 2, Supplementary Table 6)**. REV was associated with an early procedural risk with a 6-month CV death/procedural MI (pMI) difference of 6.0 (95% CrI: 4.0 to 8.3) percentage points but lower 4-year CV death/spontaneous MI (sMI) (–8.1 percentage points, 95% CrI: –12.0 to –4.5 percentage points, Pr [benefit] >99.9%) **(Supplementary Table 6)**. For other composite endpoints, the Pr (benefit) with REV was between 73% and 87% **(Table 2, Supplementary Table 7)**.

In contrast, the estimated between-group differences for all-cause death (4-year between-group difference, REV minus CON, –1.2 percentage points, 95% CrI: –4.7 to 2.2 percentage points, Pr [benefit]=55.6%) **(Supplementary Figure 2)** and CV death (–2.3 percentage points, 95% CrI: –5.5 to 0.8 percentage points, Pr [benefit]=78.7%) **(Table 2, Supplementary Figure 2, Supplementary Figure 3)** were imprecise with wide credible intervals. However, the probability for harm (Pr [harm]) with REV for the all-cause death rate and CV death rate was only 10.6% and 1.9%, respectively.

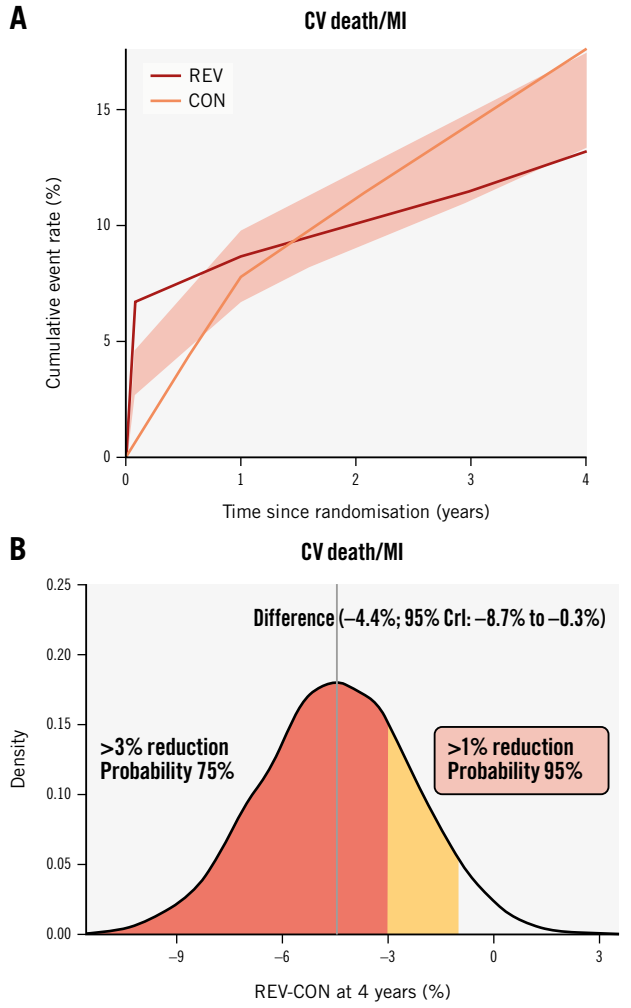


Figure 1. *Revascularisation versus CON in participants with 3-vessel disease. A) Cumulative risk estimates for the outcome of CV death or MI; (B) the posterior distribution of the absolute difference in the risk of CV death or MI at 4 years for REV versus CON. The concentration of values around –4 indicates a benefit of revascularisation rather than CON by ~4 percentage points. CON: conservative strategy; CrI: credible interval; CV: cardiovascular; MI: myocardial infarction; REV: revascularisation*

CLINICAL OUTCOMES: PCI VERSUS CON

Compared with CON, PCI was associated with a lower 4-year CV death or MI rate (4-year between-group difference: –5.8 percentage points, 95% CrI: –10.8 to –0.5 percentage points, Pr [benefit]=96.4%) **(Figure 2, Table 2, Supplementary Table 8)**. PCI was associated with an early procedural risk with a 6-month CV death/pMI difference of 3.5 (95% CrI: 1.4 to 6.1) percentage points but lower 4-year CV death/sMI (–7.4 percentage points, 95% CrI: –11.6 to –2.9 percentage points, Pr [benefit]=99.8%) **(Supplementary Table 8)**. For other composite endpoints the Pr (benefit) with PCI was between 90% and 95% **(Table 2, Supplementary Table 7)**.

In contrast, the estimated between-group differences for all-cause death (–0.9 percentage points, 95% CrI: –5.0 to 3.4 percentage points, Pr [benefit]=49.2%) and CV death (–1.5 percentage points, 95% CrI: –5.3 to 2.6 percentage points, Pr [benefit]=60.1%) **(Table 2, Supplementary Figure 4, Supplementary Figure 5)** were imprecise with wide credible intervals. However, the Pr (harm) with PCI for the all-cause death rate and CV death rate were only 18.6% and 9.8%, respectively.

CLINICAL OUTCOMES: CABG VERSUS CON

Compared with CON, the effect of CABG on CV death or MI (4-year between-group difference –3.7 percentage points, 95% CrI: –8.8 to 1.5 percentage points, Pr [benefit]=84.7%) was directionally similar to that observed with PCI **(Figure 3, Supplementary Table 9)**. CABG was associated with an early procedural risk with 6-month CV death/pMI difference of 9.2 (95% CrI: 5.9 to 13.1) percentage points but lower 4-year CV death/sMI (–9.8 percentage points, 95% CrI: –13.9 to –5.6 percentage points, Pr [benefit] >99.9%) **(Supplementary Table 9)**. For other composite endpoints, the Pr (benefit) with CABG was between 50% and 69% **(Table 2, Supplementary Table 7)**.

In contrast, the estimated between-group differences for all-cause death (–1.7 percentage points, 95% CrI: –5.6 to 2.6 percentage points, Pr [benefit]=63.1%) **(Table 2, Supplementary Figure 6)** and CV death (–3.3 percentage points, 95% CrI: –6.8 to 0.3 percentage points, Pr [benefit]=90.3%) **(Table 2, Supplementary Figure 7)** were imprecise with wide credible intervals. However, the Pr (harm) with CABG for the all-cause death rate and CV death rate were only 10.6% and 0.9%, respectively.

QUALITY OF LIFE OUTCOMES

The effects of REV, PCI and CABG when compared with CON on 12-month health status are outlined in **Figure 4**. REV, PCI and CABG improved the 12-month SAQ-7 summary score when compared with CON. The between-group differences were 4.6 points (95% CrI: 2.7 to 6.4) for REV versus CON: 3.6 points (95% CrI: 1.2 to 5.8) for PCI versus CON and 4.3 points (95% CrI: 1.5 to 6.9) for CABG versus CON. There was a 90% probability that REV, PCI and CABG improved SAQ-7 scores by 3.4, 2.1 and 2.6 points, respectively, when compared with CON. The effects of PCI and CABG compared with CON were directionally consistent for other SAQ QoL endpoints **(Figure 4)**.

Discussion

In this analysis, comparing outcomes with the specific mode of revascularisation received compared to the conservative strategy, among participants with 3V-CAD (≥50% stenosis) and no prior CABG in the CCTA-evaluable ISCHEMIA trial cohort, REV was associated with a >90% probability of at least a 1 percentage point lower 4-year CV death or MI rate when compared with CON. PCI had a >90% probability of at least a 1 percentage point lower 4-year CV death or MI rate when compared with CON, and CABG had an 85% probability of at least a 1 percentage point lower 4-year CV death or MI rate when compared with CON. Moreover, angina-related QoL was substantially improved by REV, PCI and CABG compared with CON **(Central illustration)**.

Table 2. Posterior probability for revascularisation, PCI or CABG versus CON in participants with 3-vessel disease.

Treatment effect, %	CV death/MI	All death/MI	All death	CV death	All death/MI/stroke	CV death/MI/stroke
REV vs CON						
>5% lower	39.5	23.4	2.0	4.2	13.6	25.2
>3% lower	74.7	56.2	16.0	31.7	41.4	59.5
>1% lower	94.8*	85.2	55.6	78.7	73.4	87.2
Any lower	98.3*	93.1*	75.5	92.4*	84.8	94.0*
Any higher	1.7	6.9	24.5	7.6	15.2	6.0
>1% higher	0.5	2.6	10.6	1.9	7.1	2.1
>3% higher	<0.1	0.2	0.8	<0.1	1.0	0.2
>5% higher	<0.1	<0.1	<0.1	<0.1	0.1	<0.1
PCI vs CON						
>5% lower	61.8	49.4	2.6	3.5	44.0	56.9
>3% lower	85.9	76.8	16.4	22.0	72.2	82.0
>1% lower	96.4*	93.2*	49.2	60.1	90.3*	95.2*
Any lower	98.4*	96.4*	67.7	78.2	95.0*	97.9*
Any higher	1.6	3.6	32.4	21.8	5.1	2.1
>1% higher	0.7	1.7	18.6	9.8	2.4	0.7
>3% higher	0.1	0.3	3.8	1.5	0.3	0.1
>5% higher	<0.1	<0.1	0.3	0.1	<0.1	<0.1
CABG vs CON						
>5% lower	32.0	18.4	5.3	17.3	8.7	17.0
>3% lower	61.0	43.0	27.1	57.5	24.7	40.3
>1% lower	84.7	69.0	63.1	90.3*	50.0	67.2
Any lower	91.9*	79.6	78.4	96.5*	62.9	79.1
Any higher	8.1	20.4	21.6	3.5	37.1	20.8
>1% higher	3.9	12.1	10.6	0.9	26.2	12.6
>3% higher	0.6	3.4	1.8	0.1	9.3	3.7
>5% higher	0.1	0.7	0.2	<0.1	2.4	0.9

The treatment effect is defined as the difference in the cumulative risk for REV, PCI or CABG vs CON at 4 years post-randomisation. *Indicates probabilities that are high (defined as >90%). CABG: coronary artery bypass graft surgery; CON: conservative management; CV: cardiovascular; MI: myocardial infarction; PCI: percutaneous coronary intervention; REV: revascularisation

However, the posterior probability of at least a 1 percentage point lower 4-year rate of all-cause death with REV, PCI or CABG was estimated at 49-63% when compared with CON. For context, a coin flip has a 50% probability of either outcome. The estimated differences in death were imprecise, with wide credible intervals indicating uncertainty. Of note, the probability for harm (at least a 1 percentage point higher rate of death over 4 years) with either revascularisation modality was 11-19%.

A meta-analysis by Yusuf et al of trials of CABG versus no CABG that were done in the 1970s and 1980s showed a mortality benefit with CABG at 5 years (p<0.001) that narrowed at 10 years (p=0.03) of follow-up[6]. Two of the 3 large trials included in this meta-analysis failed to show a statistically significant reduction in mortality with CABG **(Supplementary Table 10)**. Of note, the studies included a proportion of patients with left main disease (which was excluded in ISCHEMIA). Medical therapy has greatly advanced since that time, and in ISCHEMIA, 95% of participants were on statins, 66% were on high-intensity statin therapy, the median achieved low-density lipoprotein cholesterol was 64 mg/dl, and the median achieved systolic blood pressure was 129 mmHg. Despite this, the 4-year mortality rate of 9.0% for CON in the current analysis, which excluded those without CCTA, e.g., high-risk chronic kidney disease patients, was higher than the 4-year mortality rate of 6.4% for CON in the overall trial, reflecting the higher anatomical risk subset of patients with 3V-CAD. In the current analysis, restricted to participants with 3V-CAD, REV, PCI and CABG were associated with an early procedural risk. The posterior probabilities of a 1 percentage point lower 4-year rate of death were 55.6%, 49.2% and 63.1% with REV, PCI and CABG, respectively, when compared with CON, indicating uncertainty regarding whether there is a lower rate of all-cause mortality. Randomised trials published since the meta-analysis by Yusuf et al have shown similar findings. In the BARI2D trial, neither the PCI nor the CABG stratum reduced death when compared with medical therapy (CABG vs medical therapy; p=0.33)[15]. Similar results of no significant difference between CABG and medical therapy for death were observed in the MASS II trial at 10 years of follow-up[16] and in other trials of patients with chronic coronary disease and preserved left ventricular (LV) function **(Supplementary Table 10)**. Meta-analyses of randomised trials in chronic coronary disease and preserved LV function have similarly

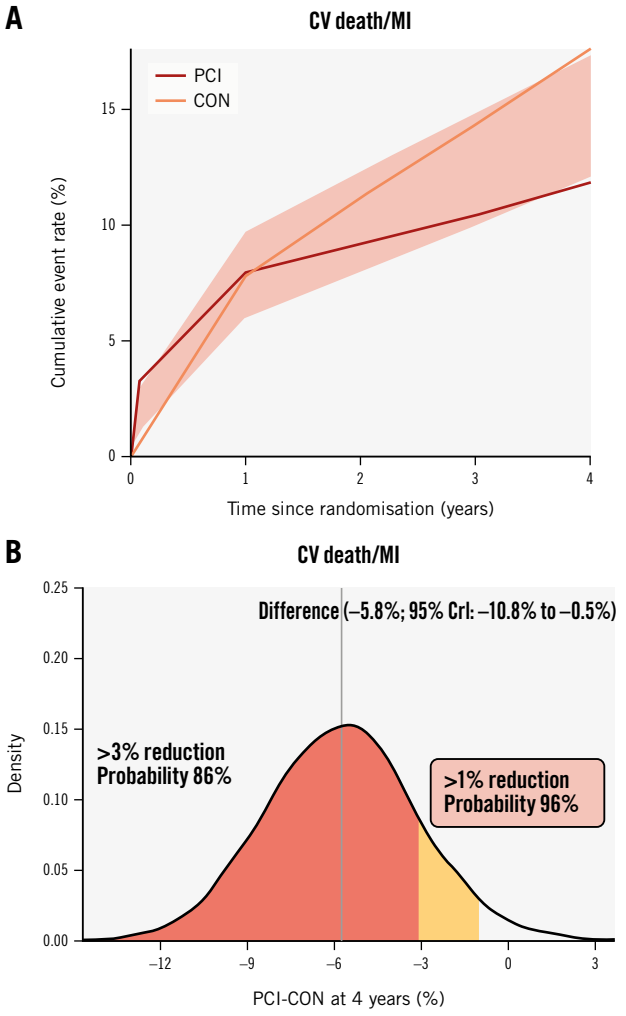


Figure 2. *PCI versus CON in participants with 3-vessel disease. A) Cumulative risk estimates for the outcome of CV death or MI; (B) the posterior distribution of the absolute difference in the risk of CV death or MI at 4 years for PCI versus CON. The concentration of values around –6 indicates a benefit to PCI rather than CON by ~6 percentage points. CON: conservative strategy; CrI: credible interval; CV: cardiovascular; MI: myocardial infarction; PCI: percutaneous coronary intervention*

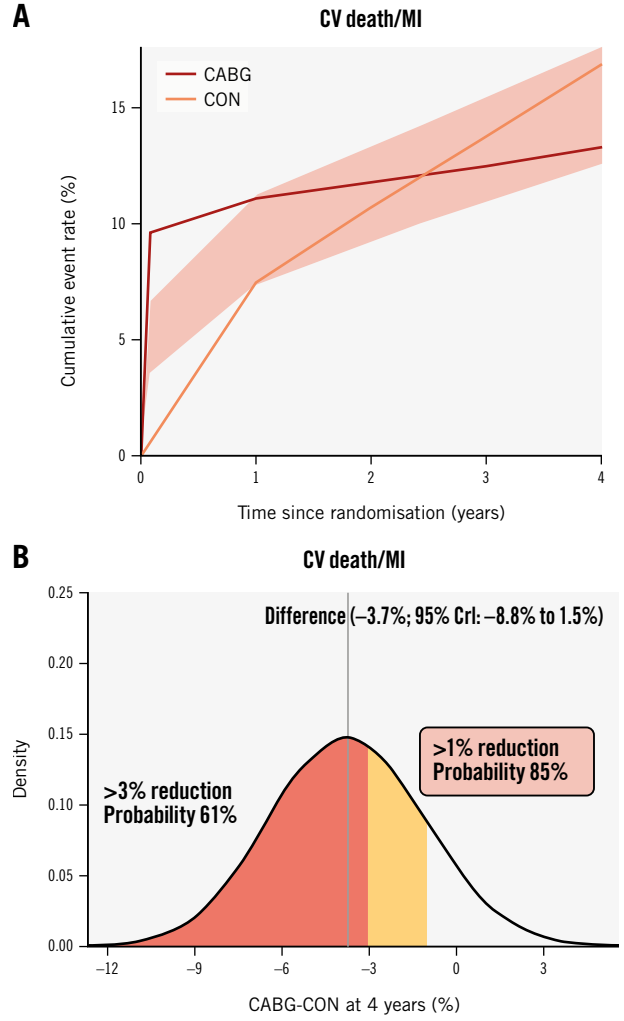


Figure 3. *CABG versus CON in participants with 3-vessel disease. A) Cumulative risk estimates for the outcome of CV death or MI; (B) the posterior distribution of the absolute difference in the risk of CV death or MI at 4 years for CABG versus CON. The concentration of values around –4 indicates a benefit to CABG rather than CON by ~4 percentage points. CABG: coronary artery bypass graft surgery; CrI: credible interval; CON: conservative strategy; CV: cardiovascular; MI: myocardial infarction*

shown no significant difference in overall mortality with revascularisation (PCI or CABG)[17], or with CABG, when compared with medical therapy[18]. However, in an individual patient-level data meta-analysis of 4 randomised controlled trials (MASS I, MASS II, STICHES and BARI2D), CABG increased mortality within 30 days (hazard ratio [HR] 4.81, 95% CI: 1.95-11.83) but reduced long-term death (HR 0.79, 95% CI: 0.69-0.89) when compared with medical therapy. In the subgroup with preserved LV function (≥50%), there was a non-significant reduction in mortality with CABG (HR 0.81, 95% CI: 0.60-1.10)[19].

Navarese et al, in a meta-analysis that included older trials, showed a 21% reduction (risk ratio [RR] 0.79, 95% CI: 0.67-0.93) in CV death with revascularisation, with a consistent effect even when trials of CABG were excluded[20]. In the current analysis from ISCHEMIA, REV, PCI and CABG were associated with an imprecise lower 4-year rate of CV death. The posterior probabilities of a 1 percentage point lower 4-year CV death rate were 78.7%, 60.1% and 90.3% with REV, PCI and CABG, respectively, versus CON. In the interim longer-term follow-up of the entire trial cohort (ISCHEMIA-EXTEND), there was a lower 7-year CV mortality (HR 0.78, 95% CI: 0.63-0.96) but a higher non-CV mortality (HR 1.44, 95% CI: 1.08-1.91) with INV compared with CON, with no difference in overall mortality[21].

Finally, REV with either PCI or CABG for 3V-CAD was associated with a lower 4-year rate of the composite of CV death or MI despite an early procedural risk **(Supplementary**

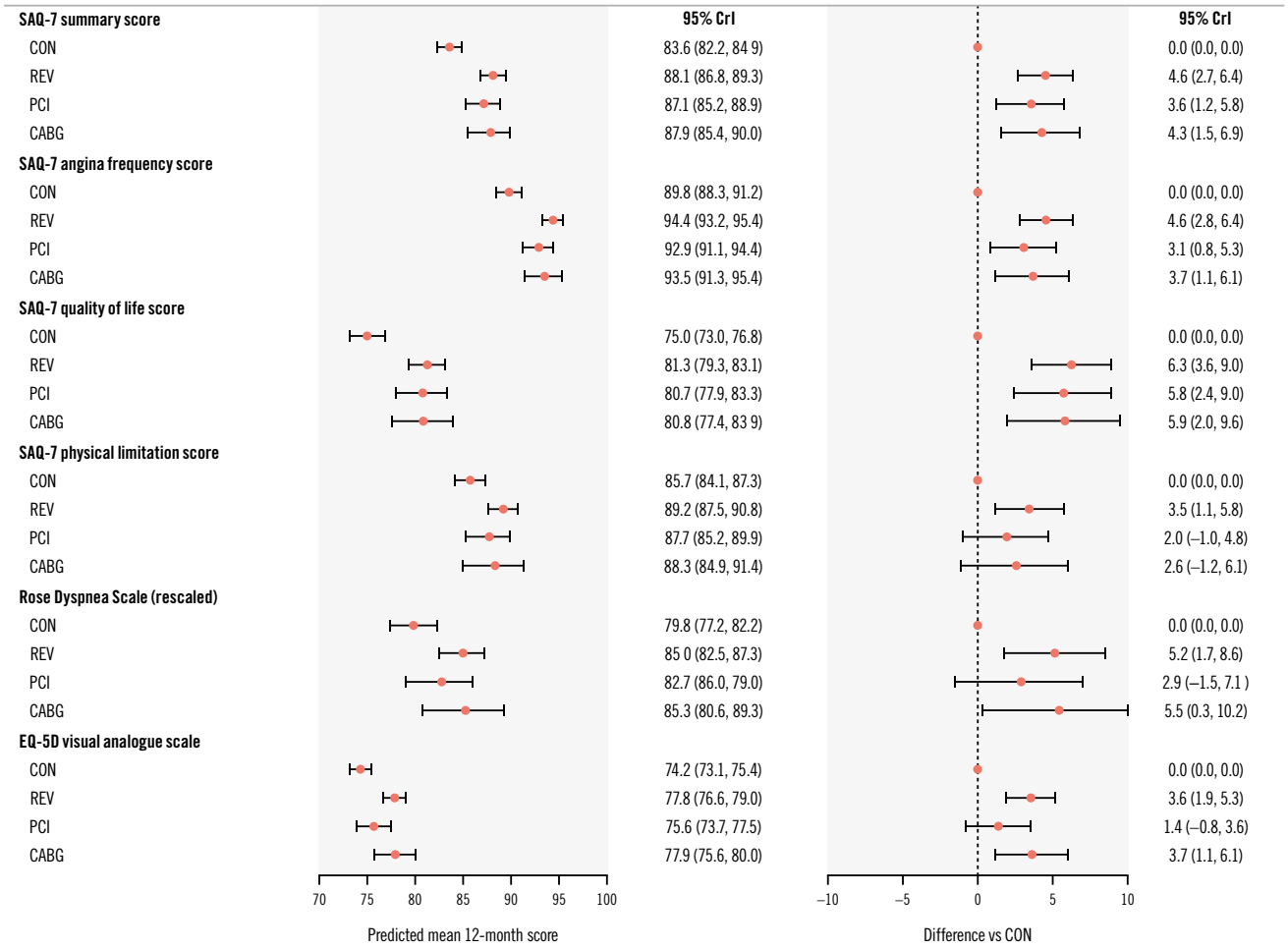


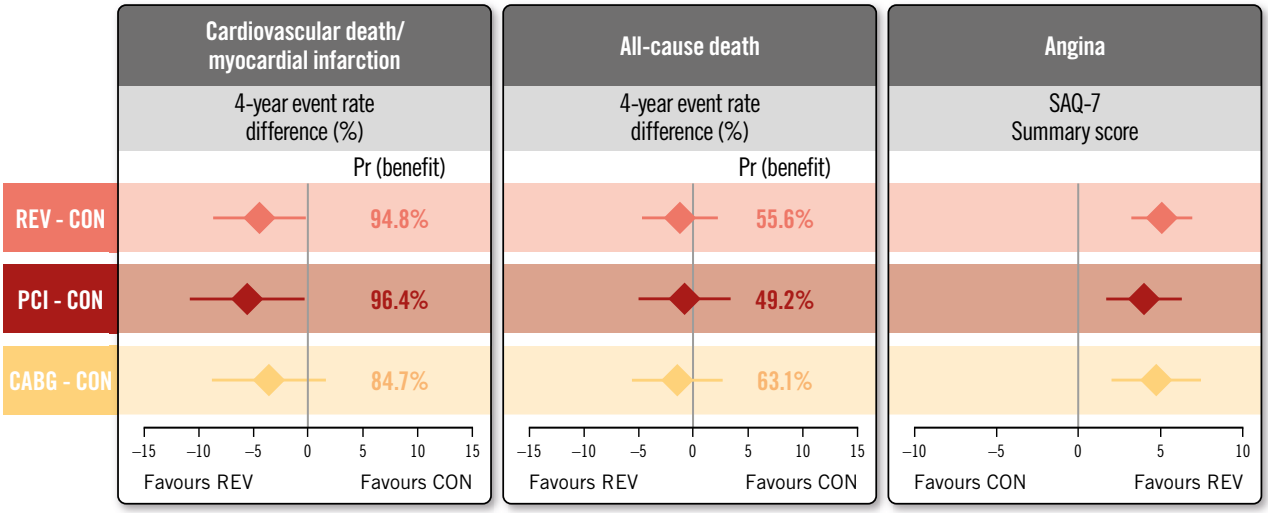
Figure 4. *Effect of revascularisation, PCI, CABG versus CON on QoL outcomes. CABG: coronary artery bypass graft surgery; CON: conservative strategy; CrI: credible interval; PCI: percutaneous coronary intervention; QoL: quality of life; REV: revascularisation ; SAQ: Seattle Angina Questionnaire*

Table 6, Supplementary Table 8, Supplementary Table 9). Bayesian analysis showed that the probability of at least a 3 percentage point lower 4-year rate of CV death or MI was >80% with PCI when compared with CON and was 61% with CABG when compared with CON, whereas the probability of at least a 1 percentage point lower 4-year rate of CV death or MI was >80% with both modalities. The relatively lower posterior probability of the advantage of CABG versus CON for the outcome of CV death or MI was driven by the higher upfront risk of CV death and an even higher risk of procedural MI when compared with PCI versus CON. For the composite outcomes that excluded procedural MI, there was a >90% probability of at least a 3 percentage point lower 4-year CV death or sMI rate with PCI and at least a 5 percentage point lower 4-year CV death or sMI rate with CABG when compared with CON **(Supplementary Table 7)**.

Finally, both PCI and CABG improved angina-related QoL when compared with CON, a critical outcome from patients' perspectives. There was a 90% probability that REV, PCI and CABG improved SAQ-7 scores by 3.4, 2.1 and 2.6 points, respectively, when compared with CON.

Taken in aggregate, the results from this analysis and those of other contemporary trials indicate uncertainty regarding whether there is a lower rate of death with either routine prompt PCI or CABG when compared with a strategy of GDMT and revascularisation reserved for failure of medical therapy. As medical therapy has further advanced since ISCHEMIA with the use of low-dose rivaroxaban, sodium-glucose cotransporter-2 inhibitors, proprotein convertase subtilisin/kexin type 9 inhibitors and glucagon-like peptide-1 receptor agonists, the absolute difference in mortality between REV plus medical therapy versus medical therapy alone may be even lower. Nonetheless, revascularisation was safe, with a low probability of higher mortality when compared with CON. The decision to consider REV in patients with 3V-CAD should thus be based on symptom control and other outcomes including a potential reduction in the composite of CV death or MI, as well as patient preferences weighing the upfront risks of REV versus improved long-term outcomes. This is concordant with the 2021 ACC/AHA/SCAI revascularisation guidelines that downgraded CABG to a Class 2b recommendation to improve survival based on a detailed review of prior trials (such as BARI2D) and

Effect of revascularisation, PCI, CABG versus CON on clinical and QoL outcomes in patients with 3-vessel CAD without prior CABG in the ISCHEMIA trial (N=1,236).



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CABG: coronary artery bypass graft surgery; CAD: coronary artery disease; CON: conservative strategy; PCI: percutaneous coronary intervention; Pr (benefit): probability of >1 percentage point reduction over 4 years; QoL: quality of life; REV: revascularisation; SAQ: Seattle Angina Questionnaire

newer evidence including meta-analyses with and without ISCHEMIA[4]. The analysis is also concordant with the newer Class 2a recommendation by the 2021 guidelines for revascularisation to lower the risk of cardiovascular events such as spontaneous MI, unplanned urgent revascularisations, or cardiac death[4]. Similarly, the 2018 European Society of Cardiology (ESC) and European Association for Cardio-Thoracic Surgery (EACTS) guideline on myocardial revascularisation lists 2V- or 3V-CAD with stenosis >50% as an indication for revascularisation to improve prognosis in patients with impaired LV function (LVEF ≤35%) but not in those without impaired LV function[22]. Patients with LVEF <35% were excluded from ISCHEMIA. Finally, the 2023 ACC/AHA Guideline for the Management of Patients with Chronic Coronary Disease gave a Class 1 recommendation for CABG to improve survival in patients with multivessel disease only in the setting of severe LV dysfunction[5].

Limitations

This study has a number of important limitations. First, despite using data from a randomised trial, the current ISCHEMIA analysis was observational and susceptible to bias. After randomising patients to INV versus CON, the timing of REV and the choice of PCI versus CABG for INV was left to the local Heart Team. The clinical profiles of patients selected for PCI and CABG differed from one another and from the overall INV group. We used regression modelling combined with direct standardisation to adjust for non-random treatment selection. This technique can only control for differences that were explicitly measured and incorporated in the adjustment procedure. Residual bias from unmeasured differences may have influenced the findings. An additional assumption is that all INV participants were eligible to receive REV. If REV was not an option for some INV participants due to unmeasured anatomical or clinical factors, the observed differences in outcomes may be partly a reflection of different patients rather than different treatments. Moreover, this observational analysis estimated outcomes for a patient population enrolled in ISCHEMIA. Of the 4,976 participants in the ISCHEMIA cohort with no prior CABG, 2,911 (58.5%) had a core lab-interpreted CCTA that was evaluable for the number of diseased vessels based on the 50% threshold. To extend results to the general 3V-CAD population with no prior CABG with or without an evaluable CCTA, one must assume that there were no systematic differences affecting the outcomes for participants who did versus did not have an evaluable CCTA. Notwithstanding these considerations, the results are consistent with meta-analyses of randomised trials showing lack of a significant reduction in death with REV when compared with medical therapy alone in patients with chronic coronary disease without left main involvement or LV dysfunction. Second, ISCHEMIA was not powered to demonstrate a difference in all-cause death. Given the wide credible intervals, we cannot exclude a clinically meaningful lower (or higher) mortality with either PCI or

CABG in patients with 3V-CAD. Third, we used a 50% diameter stenosis severity threshold for the inclusion criteria (in addition to at least moderate ischaemia on a stress test), consistent with the majority of trials of CABG versus medical therapy listed in **Supplementary Table 10** and also in the recently published FAME 3 trial[24]; whether the results would be different were REV restricted to more severe lesions is unknown. Fourth, the use of internal mammary artery grafting was ~92%, and it is not known if the results would have been different with greater use of this or with multiarterial grafts. Fifth, we used a CCTA definition of 3VD for entry criteria, given that patients randomised to CON did not routinely undergo coronary angiography. However, this should not differentially affect the INV and CON groups. Finally, longer-term follow-up from this trial (presently planned up to 10 years) is required to examine whether a late survival difference emerges with REV.

Conclusions

In this analysis, among participants with 3V-CAD randomised in ISCHEMIA without prior CABG, revascularisation (PCI or CABG) was associated with a lower 4-year rate of CV death or MI despite an early procedural risk. Moreover, REV improved angina-related quality of life. However, the estimated difference in the rate of death with revascularisation (PCI or CABG) compared with conservative management was imprecise, with wide credible intervals indicating uncertainty. The posterior probability of at least a 1 percentage point lower 4-year rate of death with revascularisation overall, with PCI, or with CABG was estimated at 49-63% when compared with conservative management. The probability of at least a 1 percentage point higher rate of death over 4 years with either REV modality was 11-19%.

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Conflict of interest statement

S. Bangalore reports grants from the National Heart, Lung, and Blood Institute during the conduct of the study; grants and personal fees from Abbott; personal fees from Biotronik, Pfizer, Amgen, and Reata outside of the submitted work. G. Rhodes reports NIH funding. D.J. Maron reports grants from the National Heart, Lung, and Blood Institute during the conduct of the study. R. Anthopolos reports grants from the National Heart, Lung, and Blood Institute during the conduct of the study. S.M. O'Brien reports grants from the National Heart, Lung, and Blood Institute during the conduct of the study. D.B. Mark reports grants from National Heart, Lung, and Blood Institute during the conduct of the study; and grants from HeartFlow and Merck, outside the submitted work. H.R. Reynolds reports grants from the National Heart, Lung, and Blood Institute during the conduct of the study; and non-financial support from Abbott, Siemens, and BioTelemetry, outside of the submitted work. J.A. Spertus reports grants from National Heart, Lung, and Blood Institute during the conduct of the study; personal fees from Bayer, Novartis, AstraZeneca, Amgen, Janssen, and United Healthcare; and grants from American College of Cardiology, outside the submitted work; in addition, he has a patent copyright to the Seattle Angina Questionnaire with royalties paid; is on the Board of Directors for Blue Cross Blue Shield of Kansas City; and reports equity in Health Outcomes Sciences. G.W. Stone has received speaker honoraria from Medtronic, Pulnovo, and Infraredx; has served as a consultant to Valfix, TherOx, Robocath, HeartFlow, Ablative Solutions, Vectorious, Miracor, Neovasc, Abiomed, Ancora, Elucid Bio, Occlutech, CorFlow, Apollo Therapeutics, Impulse Dynamics, Cardiomech, Gore Medical, Amgen, Adona Medical, and Millennia Biopharma; and has equity/options from Ancora, Cagent, Applied Therapeutics, Biostar family of funds, SpectraWAVE, Orchestra Biomed, Aria, Cardiac Success, Valfix, and Xenter; his daughter is an employee at Medtronic; for institutional disclosure, his employer, Mount Sinai Hospital, receives research support from Abbott, Abiomed, Bioventrix, Cardiovascular Systems Inc, Philips, Biosense Webster, Shockwave Medical, Vascular Dynamics, Pulnovo, and V-Wave. H.D. White reports grants from National Heart, Lung, and Blood Institute during the conduct of the study; reports receiving grant support paid to the institution and fees for serving on a steering committee for the ODYSSEY OUTCOMES trial (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab) from Sanofi-Aventis and Regeneron Pharmaceuticals; for the ACCELERATE study (A Study of Evacetrapib in High-Risk Vascular Disease) from Eli Lilly; for the STRENGTH trial (Outcomes Study to Assess Statin Residual Risk Reduction With EpaNova in High CV Risk Patients With Hypertriglyceridemia) from Omthera Pharmaceuticals; for the HEART-FID study (Randomized Placebo-Controlled Trial of FCM as Treatment for Heart Failure With Iron Deficiency) from American Regent; for the CAMELLIA-TIMI study (A Study to Evaluate the Effect of Long-term Treatment With BELVIQ [Lorcaserin HC] on the Incidence of Major Adverse Cardiovascular Events and Conversion to Type 2 Diabetes Mellitus in Obese and Overweight Subjects With Cardiovascular Disease or

Multiple Cardiovascular Risk Factors) from Eisai Inc; for the dal-GenE study (Effect of Dalcetrapib vs Placebo on CV Risk in a Genetically Defined Population With a Recent ACS) from DalCor Pharma UK Inc; for the AEGIS-II study from CSL Behring; for the SCORED trial (Effect of Sotagliflozin on Cardiovascular and Renal Events in Patients With Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk) and the SOLOIST-WHF trial (Effect of Sotagliflozin on Cardiovascular Events in Patients With Type2 Diabetes Post Worsening Heart Failure) from Sanofi-Aventis Australia Pty Ltd; and for the CLEAR Outcomes Study (Evaluation of Major Cardiovascular Events in Patients With, or at High Risk for, Cardiovascular Disease Who Are Statin Intolerant Treated With Bempedoic Acid. [ETC-1002] or Placebo) from Esperion Therapeutics Inc; he was on the advisory board for Genentech, Inc.; and received lecture fees from AstraZeneca. Y. Xu reports grants from the National Heart, Lung, and Blood Institute during the conduct of the study. J.S. Hochman is the PI for the ISCHEMIA trial for which, in addition to support by the National Heart, Lung, and Blood Institute grant, devices and medications were provided by Abbott, Medtronic, Abbott Laboratories (formerly St. Jude Medical, Inc.), Royal Philips NV (formerly Volcano Corporation), Arbor Pharmaceuticals, LLC, AstraZeneca Pharmaceuticals, LP, Merck Sharp & Dohme Corp., Omron Healthcare, Inc., Sunovion Pharmaceuticals, Inc., Espero BioPharma, and Amgen, Inc.; and received financial donations from Arbor Pharmaceuticals LLC and AstraZeneca Pharmaceuticals LP. The other authors have no conflicts of interest to declare.

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Supplementary data

Supplementary Appendix 1. ISCHEMIA committees, CCC, trial-related personnel.
Supplementary Appendix 2. Statistical appendix.
Supplementary Table 1. Adjustment covariates for regression models.
Supplementary Table 2. Baseline characteristics.
Supplementary Table 3. Baseline stress test and CCTA results for each analysis group.
Supplementary Table 4. Physiological measurements, risk factors, and medications for each analysis group at baseline and the last visit.
Supplementary Table 5. Procedural details.
Supplementary Table 6. Cumulative risk estimates of outcomes over time for revascularisation versus CON in patients with 3-vessel disease.
Supplementary Table 7. Posterior probability for revascularisation, PCI or CABG versus CON in patients with 3-vessel disease for MI separated into procedural (p) or spontaneous (s).
Supplementary Table 8. Cumulative risk estimates of outcomes over time for PCI versus CON in patients with 3-vessel disease.
Supplementary Table 9. Cumulative risk estimates of outcomes over time for CABG versus CON in patients with 3-vessel disease.
Supplementary Table 10. Trials of stable coronary artery disease testing revascularisation versus medical therapy with CABG as one of the revascularisation modalities.
Supplementary Figure 1. Consort diagram.
Supplementary Figure 2. Revascularisation versus CON in patients with 3-vessel disease: outcome of death.
Supplementary Figure 3. Revascularisation versus CON in patients with 3-vessel disease: outcome of CV death.
Supplementary Figure 4. PCI versus CON in patients with 3-vessel disease: outcome of death.
Supplementary Figure 5. PCI versus CON in patients with 3-vessel disease: outcome of CV death.
Supplementary Figure 6. CABG versus CON in patients with 3-vessel disease: outcome of death.
Supplementary Figure 7. CABG versus CON in patients with 3-vessel disease: outcome of CV death.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-24-00240

Supplementary data

Supplementary Appendix 1. ISCHEMIA committees, CCC, trial-related personnel.

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	Raymond W. Little, MD	Holly Little			Houston, TX	Houston Heart & Vascular Associates (5)
	Brandi D. Zimbelman, FNP-C	Tiffany Little				
	Charles Y. Lui, MD	Nona A Eskelson, RN	Stephen McKellar	Charles Lui	Salt Lake City, UT	Salt Lake City VA Medical Center (4)
	Brigham R. Smith, MD					
	Daniel P. Vezina, MD, MSC					
	Lillian L. Khor, MBBCh, MSc					

	Josephine D. Abraham, MD, MPH					
	David A. Bull, MD					
	Stephen H. McKellar, MD, MSc					
	David Booth, MD	Yvonne Taul, RN			Lexington, KY	Lexington VA Medical Center (4)
	John Kotter, MD	Caroline Rodgers, RN				
	Ahmed Abdel-Latif, MD, PhD	Jennifer Isaacs, MS				
		Viktoria Bulkley				
	Bob Hu, MD	Renee Kaneshiro			Palo Alto, CA	Palo Alto Medical Foundation Research Institute (4)
	Arthur J. Labovitz, MD				Tampa, FL	University of South Florida (4)
	Michael Berlowitz, MD	Bonnie J. Kirby, RN, MSN				
	Philip Rogal, MD	Nhi N. Tran, MS				
	Christopher McFarren, MD	Catherine Jahrsdorfer, RN, BSN				
	Fadi Matar, MD					
	Christiano Caldeira, MD					
	David J. Maron, MD				Stanford, CA	Stanford University School of Medicine (4)
	Fatima Rodriguez, MD, MPH	Reem Yunis, PhD				
	Ingela Schnittger, MD	Jhina Patro				
	William F. Fearon, MD					
	Prakash Deedwania, MD	Antonia Vega			Fresno, CA	UCSF - Fresno Community Regional Medical Center (4)
	Kiran Reddy, MD					
	Joseph Sweeny, MD	Hugo Bloise-Adames			New York, NY	Icahn School of Medicine
		Santa Jimenez				

		Nicole Saint Vrestil				at Mount Sinai (4)
		Reyna Bhandari				
	Christopher Spizzieri, MD	Danielle Schade			Camp Hill, PA	Holy Spirit Hospital Cardiovascular Institute (4)
		Roxanne Yost				
	Claudia P Hochberg, MD	Paula Beardsley			Boston, MA	Boston Medical Center (4)
		Denise Fine				
	William D. Salerno, MD	Jana Tancredi, RN, MA/MSN, CCRN			Saddle Brook, NJ	Hackensack University Medical Center (4)
		Patricia Arakelian				
		Susan Mathus				
		Deborah O'Neill				
	Ray Wyman, MD	Joy Burkhardt, CCRP	Sharo Raissi	Ray Wyman	Torrance, CA	Torrance Memorial Medical Center (4)
		Suellen Hosino, RN, BSN, CCRP	John Stoneburner			
		Oksana A. Lubyanaya, BA			Santa Ana, CA	Coastal Heart Medical Group (4)
		Jose D. Salas, BS				
	Amer Zarka, MD	Maria Aguirre				
	Anil V. Shah, MD	Manu Dhawan				
		Diana Parra				
		Tri Tran				
	Thomas Haldis, DO	Catherine Weick, BSRT(R)(VI)			Fargo, ND	Sanford Health (4)
		Katie Fowler-Lehman, BSN				
		Natalie Spitzer, BSN				
		Casey Riedberger				
		Catherine Weick				
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		Raven R. Dwyer, MPH	Leora Balsam			
		Dalisa Espinosa, MBS	Aubrey Galloway			

		Kirsten J. Quiles, MS	Gene Grossi			
			Didier Loulmet			
			Charles Schwartz			
	Saket Girotra, MD	Carrie Drum, RN			Iowa City, IA	University of Iowa Hospitals and Clinics (4)
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		Amy Ollinger, RN				
	Omar Almousalli, MD	Elizabeth Capasso-Gulve	Bill Daily	Norbert Urbanski	Fairview Heights, IL	Advanced Heart Care Group (4)
		Alaine Melanie Loehr				
		Marlowe Mosley				
	Mayil S. Krishnam, MD	Shirin Heydari, MS	Jeffrey Milliken	Pranav Patel	Orange, CA	University of California Irvine Medical Center (3)
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	Pranav M. Patel, MD	Edgar Karanjah, MD				
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	Michael A. Gibson, MD	Pam Singh				
	Byron J. Allen, MD					
	Rita Coram, MD	Anne Marie Webb, BSN	Ramesh Singh		Louisville, KY	University of Louisville (3)
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		Heidi Wilson, BS				
	Sabu Thomas, MD, MSc	Angela Kim, BS	Peter Knight	Frederick Ling	Rochester, NY	University of Rochester (3)
	Ronald G Schwartz, MD, MS	Patrick Wilmot, BS				
	Wei Chen, MD, MS					
	Mahfouz El Shahawy, MD	Ramona Stevens	Thomas Kelly	John Culp	Sarasota, FL	Cardiovascular Center of Sarasota (3)
	James Stafford, MD	Loriane Black			Baltimore, MD	University of Maryland Medical Center (3)

	William B. Abernethy, MD	Amber B. Hull, RN			Asheville, NC	Asheville Cardiology Associates (3)
		Olivia J. Lim, RN				
		Helen C. Tucker				
		Natasha C. Putnam, RN				
		Linda L. Hall				
		Tia Cauthren				
		Trish Tucker				
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		Jan Orga	Evelio Rodriguez			
	Thomas M. Meyer, MD	Joyce R. White, MSN NP-C			Lynchburg, VA	Stroobants Cardiovascular Center (3)
	Ronald G. Morford, MD	Cynthia Baumann, RN				
	Bruce Rutkin, MD	Vidya Seeratan			Manhasset, NY	Northwell Health - Manhasset (3)
	Sabahat Bokhari, MD	Magnolia Jimenez	Michael Argenziano	Giora Weisz	New York, NY	Columbia University Medical Center (3)
	Seth I. Sokol, MD	Cidney Schultz, RN	Alfred Culliford	Seth Sokol	Bronx, NY	Jacobi Medical Center (3)
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			Aubrey Galloway			
			Gene Grossi			
			Didier Loulmet			
	Jay Meisner, MD		Charles Schwartz			
	Ihab Hamzeh, MD		Matthew Wall Jr.	Mahboob Alam	Houston, TX	Baylor College of Medicine (3)
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	Matthew Wall Jr., MD	Araceli Boan				
	Veronica Lenges De Rosen, MD					
	Mahboob Alam, MD					
	Michael C. Turner, MD	Christine R Hinton				Cardiovascular

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		Cheryl A. Allardyce, BSN, RN				
		Lindsey N. Sikora, BSN, RN				
		Jennifer H. Czerniak, RN				
		Jennifer A. Mull, MSN, RN				
		Elizabeth Ferguson				
		Frances Laube				
	Nicolas W. Shammas, MD, MS	Gail A Shammas, BSN, RN			Davenport, IA	Midwest Cardiovascular Research Foundation (3)
		Lori Christensen				
		Holly Park				
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	Patricia K. Nguyen, MD	Davis Vo, BS			Palo Alto, CA	VA Palo Alto Healthcare System (2)
		James Hirsch				
	Matthew Jezior, MD	Jody Bindeman	Jared Antevil	Matthew Jezior	Bethesda, MD	Walter Reed National Military Medical Center (2)
		Sara Salkind				
		Dalisa Espinosa, MBS	Arun Singh	Paul Gordon	Providence, RI	Miriam Hospital (2)
		Lori-Ann Desimone, BSN				
	Paul C. Gordon, MD	Lina Felix-Stern				
	Thomas Crain, MD	Jassira Gomes				
		Catherine Gordon, BSN				
		Aimee Mann				

	Robert Stenberg, MD	Theresa McCreary			Johnstown, PA	Conemaugh Valley Memorial Hospital (2)
	Ronald P. Pedalino, MD	Stanley E. Cobos, BA	Alfred Culliford	James Slater	Brooklyn, NY	NYU-HHC Kings County Hospital Center (2)
		Raven R. Dwyer, MPH	Leora Balsam			
		Dalisa Espinosa, MBS	Aubrey Galloway			
		Kirsten J. Quiles, MS	Gene Grossi			
			Didier Loulmet			
			Charles Schwartz			
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		Dalisa Espinosa, MBS				
		Kirsten J. Quiles, MS				
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		Karen Hultberg	Leora Balsam			
		Tauqir Huk	Aubrey Galloway			
		Afshan Hussain	Gene Grossi			
			Didier Loulmet			
			Charles Schwartz			
	Mohammed Al-Amoodi, MD	Yesenia Zambrano, BS			Yuma, AZ	Yuma Regional Medical Center (2)
		Sarah Medina Rodriguez				
		Trudie Milner				
	David Wohns, MD	Abbey Mulder, RN			Grand Rapids, MI	Spectrum Health (2)
		Stacie Van Oosterhout, MEd				
	Ellis W. Lader, MD	Martha Meyer, RN, MSN			Kingston, NY	Mid Valley Cardiology (1)
	Michael Mumma, MD	Nancy L. Clapp, RN, BA, CCRC			Sarasota, FL	Sarasota Memorial

		Heather Barrentine				Hospital (1)
	Lekshmi Dharmarajan , MD	Jenne M. Jose, PA	Alfred Culliford	James Slater	Bronx, NY	NYU-HHC Lincoln Medical and Mental Health Center (1)
		Stanley E. Cobos, BA	Leora Balsam			
		Raven R. Dwyer, MPH	Aubrey Galloway			
		Dalisa Espinosa, MBS	Gene Grossi			
		Kirsten J. Quiles, MS	Didier Loulmet			
		Jenne Manchery	Charles Schwartz			
	Joseph F.X. McGarvey Jr, MD	Vera McKinney, RN			Doylestown, PA	Doylestown Health Cardiology (1)
		Linda Schwarz, RN				
	Thomas R. Downes, MD (till Dec. 2016)	Scott M. Kaczkowski			Loveland, CO	Medical Center of the Rockies (1)
	Gary J. Luckasen, MD (from Dec. 2016)	Adam J. Jaskowiak				
		Joel Klitch				
	Benjamin Cheong, MD	Debra Dees			Houston, TX	Baylor St. Luke's Medical Center (1)
	Srinivasa Potluri, MD	Precilia Vasquez			Plano, TX	Baylor Research Institute at Legacy Heart Center (1) **
	Ronald A. Mastouri, MD		Arthur Coffey	Jeffery Breall	Indianapolis, IN	Indiana University/Krannert Institute of Cardiology (1)
	Jeffery A. Breall, MD, PhD	Elise L. Hannemann, RN, CCRC	Daniel Beckman			
	George E. Revtyak, MD	Judy Mae Foltz, RN,CCRC	Yousef Mahomed			
	Jonathan W. Bazeley, MD					
	Dayuan Li, MD	Emily DeRosa			St. Paul, MN	HealthEast Saint Joseph's Hospital (1)
		Beth Jorgenson				
		Joyce Riestenberg-Smith				
	Kenneth Giedd, MD				New York, NY	Beth Israel

						Medical Center (1)
	Wayne Old, MD	Rebecca Bariciano			Chesapeake, VA	Cardiovascular Associates, Ltd. (1)
	Francis Burt, MD				Bethlehem, PA	Saint Luke's Hospital and Health Network (1)
	Kozhaya Sokhon, MD	Jessica Waldron			Sugar land, TX	Medicus Alliance Clinical Research Org., Inc. (1)
		Michelle Mayon				
	Deepika Gopal, MD				Plano, TX	The Heart Hospital Baylor (1)
	Uma S. Valeti, MD	Gretchen Ann Peichel, RN			Minneapolis, MN	University of Minnesota (1)
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		Lucilla Garcia				
		Maria Thottam				
India (941)						
Country Leader						
Balram Bhargava, DM						
		Anjali Anand, MSc		Chakanalil Sajeev	Calicut	Government Medical College (208)
	Sajeev Chakanalil Govindan, MD, DNB, DM, PhD	Janitha Raj, B.Tech				
	Rajesh Gopalan Nair, MD, DNB, DM	Reshma Ravindran, MSc				
		Rajalekshmi VS, MSc, MScCRRA				
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	Nagaraja Moorthy, MD, DM	Soundarya Nayak,				

		BE(Biotech) PGDICRCDM				Sciences and Research (149)
	Satvic Cholenahally Manjunath, MD, DM	Mahevamma Mylarappa, GNM (General Nursing)				
	Suryaprakash Narayanappa, MBBS					
	Neeraj Pandit, MD, DM	Sheromani Bajaj	Vijay Gupta	Neeraj Pandit	New Delhi	Dr Ram Manohar Lohia Hospital (101)
	Ranjit Kumar Nath, MD, DM	Vandana Yadav, Msc,PGDACR	Vijay Grover			
		Girish Mishra, Msc, PGDACR				
	S.K. Dwivedi, DM	Roma Tewari, PG		Sudhanshu Dwivedi	Lucknow	King George's Medical University, Department of Cardiology (100)
	V.S. Narain, DM	Meenakshi Mishra, PG				
	Sharad Chandra, DM	Shivali Patel				
		Suman Singh, PG				
	Gurpreet S. Wander, DM		Sarju Ralhan		Ludhiana	Hero DMC Heart Institute, Dayanand Medical College and Hospital (83)
	Rohit Tandon, MD		Rajiv Gupta			
	Sarju Ralhan, M.Ch (CTVS)	Baljeet Kaur, MSc (Biotechnology)				
	Naved Aslam, DM	Sonika Gupta, MBA, B. Pharmacy				
	Abhishek Goyal, DM					
	Balram Bhargava, DM	Chandini Suvarna, BDS	Milind Hote	Balram Bhargava	New Delhi	All India Institute Of Medical Sciences (67)
	G.Karthikeyan, DM					
	S.Ramakrishnan, DM					
	Sandeep Seth, DM					
	Rakesh Yadav, DM					
	Sandeep Singh, DM					
	Ambuj Roy, DM					
	Neeraj Parakh, DM					
	Sunil Kumar Verma, DM					
	Rajiv Narang, DM					
	Sundeep Mishra, DM					

	Nitish Naik, DM					
	Gautam Sharma, DM					
	Shiv Kumar Choudhary, M.Ch					
	Chetan Patel, DNB					
	Gurpreet Gulati, MD					
	Sanjeev Sharma, MD					
	V K Bahl, DM					
	Anoop Mathew, MD	Binoy Mannekkattukudy Kurian		Louie Fischer	Kolencherry	MOSC Medical College Hospital (39)
	Eapen Punnoose, MD					
	Milind Avdhoot Gadkari, MD	Sheetal Rupesh Karwa, BHMS		Milind Gadkari	Pune	KEM Hospital Pune (35)
	Siddharth Gadage, MD DNB	Suvarna Kolhe, MSc				
	Tapan Umesh Pillay, BHMS MSc					
	Santhosh Satheesh, MBBS, MD, DM	R. J. Vindhya, B.Sc. (Bio-Technology), MSc (Bio-Informatics)	Saichandran BV	Santhosh Satheesh	Pondicherry	Jawaharlal Institute of Postgraduate Medical Education & Research (JIPMER) (31)
		Peeyush Jain, MD	Zile Meharwal	Atul Mathur	New Delhi	Fortis Escort Heart Institute
		Ashok Seth, MD				-31
		Zile Singh Meharwal, MD				
	Atul Mathur, MD	Atul Verma, MD				
	Upendra Kaul, MD	Mona Bhatia, MD				
		Ankush Sachdeva, MD				
		Thounaojam Indira Devi, RN				
		Nungshi Jungla, RN				
	Johann Christopher, MD, DNB	K. Manjula Rani, MSc.		Johann Christopher	Hyderabad	Gurunanak CARE

	Rajeev Menon, MD, DNB	M. Sowjanya Reddy, BSc				Hospital (27)
	Nirmal Kumar, MD, DNB	K. Preethi, BSc				
	Abraham Oomman, MD, DM, DNB	Rinu R sidh, MSc (Clinical Research)		Robert Mao	Chennai	Apollo Research and Innovation (23)
	Robert Mao, MD, DM	Ramakrishnan T., B.Tech(Biotechnology)				
	Hilda Solomon, PhD	Rajesh Francis, MSc (Clinical Research)				
	Sudhir Naik, MD, DM	Vamshi Priya P., MSc	Sanjay Agarwal	Pratap Chandra	Hyderabad	Apollo Research & Innovations (13)
	Sajeeda Parveen Khan, MBBS, (Dip.Card)					
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	Nirmal Kumar, MD			Nirmal Kumar		
	Purvez Grant, MD	Shweta Hande, BHMS, PGDCR	Ranjeet Jagtap	Purvez Grant	Pune	Ruby Hall Clinic,Grant Medical Foundation (10)
		Poonam Sonawane, B.ScMicrobiology, ACCR	Vinayak Karmarkar			
			Manoj Pradhan			
	Ranjan Kachru, MD	Abhishek Dubey		Tapan Ghose	New Delhi	Fortis Healthcare Fl.t Lt. Rajan Dhall Hospital (4)
		Kavita Rawat				
	Ajit Kumar VK, MD, DM		Jayakumar Karunakaran	Harikrishnan Sivadasanpillai	Trivandrum	Sree Chitra Tirunal Institute for Medical Sciences and Technology (3)
	Sanjay Ganapathi, MD, DM					
	Jayakumar K, MS, M.Ch	Vineeth CP				
	Harikrishnan Sivadasanpillai, MD, DM	Manas Chacko, RN				
	Bijulal Sasidharan, MD, DM	Suresh Babu				
	Kapilamoorthy TR, MD					
	Johann Christopher, MD	Sowjanya Reddy	Rajashe Khas	Rajeev Menon	Hyderabad	

	Praneeth Polamuri, MD	Manjula Rani				CARE Hospital (3)
	Upendra Kaul, MD	Priyadarshani Arambam	Sanjay Pandey	Upendra Kaul	New Delhi	Batra Hospital and Medical Research Centre (BHMRC) (3)
		Bebek Singh				
United Kingdom (539)						
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Roxy Senior, MBBS, MD, DM						
Keith AA Fox, MBChB *(past)*						
Country Coordinators						
Grace M. Young , MSc, BSc (Hons)						
Kathryn Carruthers *(past)*						
	Roxy Senior, MBBS, MD, DM		Richard Trimlett	Ahmed Elghamaz	Harrow	Northwick Park Hospital Harrow/ Royal Brompton Hospital London (202)
	Ahmed Elghamaz, MB BCh					
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	Benoy N Shah, MD, MBBS, BSc (Hons)	Christopher Kinsey				
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	Edward D Nicol, MD, BMedSci, MBBS, DTM&H	Ikraam Hassan, RN				
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		Karen Swan, RN				
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	Jeet Thambyrajah, MD		Enoch Akowuah			
			Jonathan Ferguson			
			Andrew Goodwin			
			Simon Kendall			
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	John R Davies, MBBS, PhD					
	Steven J. Lindsay, MD	Craig Atkinson, RN	Kalyana Javagula	Steven Lindsay	Bradford	Bradford Royal Infirmary (20)
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	Haqeel Jamil, MD	Manitha Vinod, RN				
	Osama Raheem, MD					
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		Julie Morrow	Steven Griffin			
		Kay Rowe				
	Patrick Donnelly, MD	Stephanie Kelly, RN			Belfast	South Eastern Health and Social Care (17)
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		Dawn Turnbull				
	Anoop Chauhan, MD	Catherine Fleming	Andrew Duncan	Anoop Chauhan	Blackpool	Blackpool Teaching Hospitals (16)
		Arijit Ghosh	Joseph Zacharias			
		Karen Gratrix				
		Stephen Preston				
	Craig Barr, MD	Anne Cartwright	Maciej Matuszewski	Matthew Banks	Dudley	Russells Hall

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	Ian Webb, PhD, MA		Ranjit Deshpande			
			Lindsay John			
			Olaf Wendler			
			Donald Whitaker			
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		James Harrison, BSc(Hons), PG dip				
	Peter OKane, MD	Nicki Lakeman	Geoff Tsang	Peter OKane	Bourneouth	Royal Bournemouth Hospital (13)
		Anja Ljubez				
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			Yasir Abu-Omar			
	Dwayne S. G. Conway, MD	Judith Wright	David O'Regan	Dwayne Conway	Wakefield	Pinderfields Hospital (11)
		Donna Exley	Betsy Evans			
			Kalyana Javagula			
			Pankaj Kaul			
			Joe McGoldrick			
			Chris Munsch			
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		Mervyn Andiapen, RN				University College London Hospitals NHS Foundation Trust
		Amy J. Richards, BSc	Shyam Kolvekar	Alex Sirker		BartsHealth NHS Trust

				Elliot Smith		
						-11
	Stephen P Hoole, MD	Lisa Wong, MSc	John Dunning	Stephen Hoole	Cambridge	Papworth Hospital (10)
			Yasir Abu-Omar			
	Fraser N. Witherow, MD	Melanie J. Munro, RGN	Sunil Ohri	Fraser Witherow	Dorchester	Dorset County Hospital (8)
			Geoff Tsang			
	Nicola Johnston, MB, Bch BAO, MRCP, MD		Alastair Graham	Simon Walsh	Belfast	Belfast Trust (7)
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	Simon Walsh, MB, Bch BAO, MD	Caroline Brown, RN	Simon MaGowan			
	Hanna Douglas, MB, Bch BAO, MRCP, MD		Onyekwelu Nzewi			
			Harry Parissis			
			Pushpinder Sidhu			
	Matthew Luckie, MD	Thabitha Charles		Nadim Malik	Manchester	Central Manchester University Hospital (7)
		Laurel Kolakaluri				
		Hannah Phillips				
	Jolanta Sobolewska, MD	Louise Morby, RN			Oldham	The Pennine Acute Hospitals NHS Trust (6)
		Karen Hallett, RN				
		Carolyn Corbett, RN				
		Lynne Winstanley				
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	Niket Patel, MD					
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	Mahmud Al-Bustami, MBBS		Julien Gaer			

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		Joanne Taaffe		Nick West		
	Robert Henderson, MD	Jane Burton	David Richens	Robert Henderson	Nottingham	Nottingham University Hospitals (4)
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	Surendra Naik, PhD	Rachel King	Surenda Naik			
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		Ammani Brown, MSc BA RN			Clydebank	University of Glasgow (4)
		Andrew Docherty, RN				
	Colin Berry, BSc MB ChB, PhD	Lisa McCloy, RN				
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	Giles Roditi, MB ChB	Craig Paterson, PhD				
		Wenda Crawford, RN				
		Joanne Kelly, RN				
		Lorraine McGregor, RN				
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	Jason D. Glover, MBBS	Janet P Knight, RN	Tony De Souza	Jason Glover	Basingstoke	Hampshire Hospitals NHS Foundation Trust (2)
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	Darrel P. Francis, MD, MA		Jonathan Anderson			
			Roberto Casula			
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Country Leaders						

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Shaun Goodman, MD, MSc						
Gilbert Gosselin, MD						
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		Christine Masson				
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	Shaiful Azmi Yahaya, MD	Irni Yusnida, RN				
		Humayrah Hashim				
** Countries participated in Economics Quality of Life (EQoL) Questionnaires*						
***This site received one participant in transfer that was randomized at another site*						

Supplementary Appendix 2. Statistical appendix.

SECTION I: CLINICAL OUTCOMES

Statistical analyses focused on adjusting for potential biases arising from non-randomized treatment comparisons, censoring of time-to-event endpoints, and missing data. In particular, we sought to recover the treatment effect that would be observed in an ideal setting if all eligible INV participants adhered to a strategy of prompt upfront revascularization and all eligible INV and CON participants were followed for 4 years. We performed separate parallel analyses for three methods of revascularization (PCI, CABG, and either PCI or CABG, abbreviated REV) and ten endpoints (death, CV death, death or MI, CV death or MI, death or procedural MI, CV death or procedural MI, death or spontaneous MI, CV death or spontaneous MI, death or MI or stroke, CV death or MI or stroke).

Among those who had a core lab interpreted CCTA (N=3826) that was evaluable for number of diseased vessels based on a 50% stenosis threshold (N=2911), we analyzed a subset of 1283 participants with 3V-CAD and no prior CABG. Of the 1283 studied participants, 624 were randomized to CON, and 659 were randomized to INV. From the INV group, we excluded 47 participants who had missing data for key invasively measured angiographic covariates. Statistical adjustments were implemented to account for this exclusion and to address the fact that not all remaining INV-assigned participants underwent prompt upfront revascularization. The final study cohort consisted of 612 INV participants and 624 CON participants (total n = 1236).

To facilitate computation, follow-up time was discretized into weekly time intervals. The analysis dataset was structured to contain a record for each combination of patient ID and week of follow-up, with follow-up beginning at randomization and ending at first occurrence of the endpoint of interest or censoring. Logistic regression models were used to estimate a patient's weekly risk as a function of time since randomization, time since INV-assigned revascularization, and baseline covariates. These models were estimated separately for INV and CON. The outcome variable was a binary indicator of whether the event of interest did or did not occur in a given week. Time since randomization was modeled as a piecewise-constant function with cut-points at weeks 52 and 156 (1 and 3 years). Time since revascularization in INV was modeled as a piecewise-constant function with a cut-point at week 4.

After fitting the above models, weekly event probability functions from the models were converted into treatment- and covariate-specific cumulative incidence functions (CIFs). The CIF represents the cumulative probability of an event as a function of follow-up time conditional on treatment group, timing of revascularization in INV, and patient covariates. Risk estimates were calculated twice per patient. The first estimate described the patient's risk if assigned to INV and given prompt REV. The second estimate described the patient's risk if assigned to CON.

Standardized CIFs were calculated by applying the treatment- and covariate-specific CIF equations to covariate data from 612 participant in the study's INV cohort. For each of these participants, we predicted their cumulative event probability if assigned to CON and again if assigned to INV and given prompt revascularization. A standardized CIF for each treatment was

then obtained by calculating the average of the 612 covariate-specific CIFs. The treatment effect was estimated by subtracting the standardized CIFs for CON minus REV.

A Bayesian statistical was adopted for the above analysis. A key advantage of the Bayesian approach is the ability to express analysis results in terms of clinically relevant probabilities (e.g., the probability that revascularization is associated with lower 4-year risk compared to CON). Some accessible and well-written introductions to Bayesian analysis include O'Hagan and Luce (2003), Spiegelhalter, Abrams, and Myles (2004), and Goodman (1999).

Bayesian inference uses probabilities to express beliefs about model parameters before and after observing the study data. Pre-study beliefs are represented mathematically in the form of a "prior distribution". Briefly, the prior distribution expresses the relative likelihood of different possible numerical estimates of all unknown model parameters before observing study data. After specifying the prior distribution, a formula known as Bayes' Theorem is then used to combine prior beliefs with study data to arrive at an updated set of post-study beliefs, i.e., the "posterior distribution". The posterior distribution is then manipulated to produce appropriate summary estimates and to determine the likelihood of various clinical hypotheses.

A key step in Bayesian analysis is the specification of the prior distribution. Due to limited prior information, our goal was to select a prior distribution that would allow inferences to be driven by the study data as opposed to strong prior beliefs. Toward this end, we specified a set of diffuse independent normal distributions with mean = 0 and SD = 100 for all regression parameters.

Technical Details

Causal inference considerations

We used the framework of potential outcomes (Hernán and Robins, 2020; Imbens and Rubin, 2015) to define and clarify the "treatment effect" parameter that our study sought to estimate. Under the potential outcomes framework, each patient is assumed to have an unobserved set of variables describing what the patient's outcome status would be (i.e., their time from randomization to the event of interest) hypothetically under each possible treatment strategy. For example, let $Y^{(a)}$ denote a patient's potential outcome under a strategy of "revascularization at week a for all patients who survive until week a", where a is a whole number such as 1,2,3, etc. Similarly, let $Y^{(\text{con})}$ denote a patient's potential outcome hypothetically if assigned to ISCHEMIA's CON treatment strategy. The potential outcomes of interest in the current study are $Y^{(a=1)}$ and $Y^{(\text{con})}$. They are referred to as potential outcomes (aka, counterfactual outcomes) because they describe what would be observed, perhaps contrary to fact, if the patient were to receive a particular treatment. A key challenge for causal inference is the fact that variables $Y^{(a=1)}$ and $Y^{(\text{con})}$ are never observed simultaneously for the same patient. For example, if a patient is randomized to CON, then $Y^{(\text{con})}$ is observed and $Y^{(a=1)}$ is missing. If a patient is randomized to INV and receives revascularization during week 1, then $Y^{(a=1)}$ is observed and Y^{con} is missing. If a patient is randomized to INV and receives revascularization after week 1, then both $Y^{(a=1)}$ and $Y^{(\text{con})}$ are missing.

In order to define the treatment effect of interest, we assume that patients in ISCHEMIA are a random sample from a hypothetical large population, i.e., a super-population. Analysis then focuses on inferring population-level distributions of $Y^{(a=1)}$ and $Y^{(\text{con})}$ subject to the limitations of observational analysis. Estimation of $Y^{(\text{con})}$'s population-level distribution is relatively straightforward because the ~50% of patients for whom Y^{con} is observed are a representative random sample from the larger ISCHEMIA population. Inference for $Y^{(a=1)}$ is relatively more challenging because INV participants with non-missing $Y^{(a=1)}$ are a small and non-representative subset. To the extent that INV patients undergoing prompt revascularization might differ from others assigned to INV or CON (e.g., being systematically lower or higher risk), a simple unadjusted comparison with CON may reflect differences in patient selection rather than the true treatment effect of interest. Our statistical adjustment was designed to recover the true treatment effect that would be observed hypothetically if patients receiving each treatment strategy were similar in terms of observable baseline characteristics.

The statistical literature on causal inference describes conditions for valid treatment effect estimation using non-randomized observational data. In general, valid inference is possible when patients who receive each treatment are exchangeable in the sense of having identical counterfactual outcome distributions within strata formed by the cross-classification of a set of pre-treatment covariates. Loosely speaking, this means that patients with a given combination of covariates who are selected for a particular treatment are like a random sample from the overall population of patients who have that combination of covariates. When treatment decisions are made repeatedly over time (e.g., receiving or not receiving revascularization at week 2 after not receiving revascularization at week 1), the exchangeability condition must be met at all time points when the treatments are given. Moreover, if the outcome data for some patients are censored, the patients with and without censoring must be exchangeable at all time points at which censoring occurs.

In a randomized treatment group comparison, randomization guarantees that the treatment groups are exchangeable. When treatment comparisons are not randomized, as in the current analysis, we must assume that the key determinants of receiving treatment were measured and included in the adjustment procedure. Although this exchangeability condition is unlikely to be true in a literal sense, we sought to reduce the risk of large violations of exchangeability by adjusting for a large number of relevant pre-treatment covariates.

In the current analysis, variables measured by invasive angiography are critical in order for the exchangeability assumption to be plausible. A complicating factor is that data from invasive angiography were missing for 100% of CON participants and for 47 of this study's INV participants. Addressing this challenge required the use of customized statistical methodology, as detailed below.

Mathematical form of regression models

Let X denote baseline covariates that are available for all patients; let Z denote angiographic covariates; let M be an indicator of whether Z is observed ($M = 1$) or missing ($M = 0$); let G denote the patient's randomization assignment (inv, con); let Y_t denote a patient's event status at week t (1=event on or before week t, 0=no event as of week t); let C_t be an indicator of whether

Y_t is observed ($C_t = 1$) or unobserved due to prior censoring ($C_t = 0$); and let $R_t =$ one plus the number of weeks between an INV patient's revascularization procedure and week t, or set $R_t = 0$ if an INV patient has not yet undergone revascularization by week t. As usual when analyzing time-to-event outcomes, we assumed that censoring is non-informative. For patients in the INV group, we assumed that a patient's missing data status M is ignorable conditional on covariates X and Z; in other words, M does not add prognostic information above and beyond the covariate information encoded in X and Z.

Modeling focused on the following sets of weekly event probabilities:

- $p_t^{\text{con}}(x) = P(Y_t = 1 | Y_{t-1} = 0, C_t = 1, X = x, G = \text{con})$ (CON)
- $p_t^{\text{inv}}(x, z, r_t) = P(Y_t = 1 | Y_{t-1} = 0, C_t = 1, X = x, Z = z, M = 1, R_t = r_t, G = \text{inv})$ (INV)

The specific modeling assumptions were:

- $\log \frac{p_t^{\text{con}}(x)}{1-p_t^{\text{con}}(x)} = \beta_1 I(t \leq 52) + \beta_2 I(52 < t \leq 156) + \beta_3 I(t > 156) + \tilde{x}'\beta_4$
- $\log \frac{p_t^{\text{inv}}(x,z,r_t)}{1-p_t^{\text{inv}}(x,z,r_t)} = \beta_5 I(t \leq 52) + \beta_6 I(52 < t \leq 156) + \beta_7 I(t > 156) + \tilde{x}'\beta_8 + \tilde{z}'\beta_9 + \beta_{10} I(1 \leq r_t \leq 4) + \beta_{11} I(r_t > 4)$

where $\tilde{x}$ and $\tilde{z}$ represent functions that translate x and z into specific mathematical representations, and $\beta_1, \ldots, \beta_{11}$ represent unknown coefficients to be estimated from the data. Note that β_{10} describes the difference in the (log) odds of an event at week t for a patient who was event-free the prior week and was recently revascularized ($1 \leq R_t \leq 4$) compared to a patient with the same combination of covariates who was event-free the prior week and has not yet received revascularization ($R_t = 0$). Parameter β_{11} has a similar interpretation but pertains to patients with remote ($R_t > 4$) rather than recent ($1 \leq R_t \leq 4$) revascularization.

Covariate-specific CIFs

After fitting the above models, weekly event probability functions from the models were converted into treatment- and covariate-specific cumulative incidence functions (CIFs). The CIF represents the cumulative probability of an event as a function of follow-up time conditional on treatment group, timing of revascularization in INV, and patient covariates. For CON, the covariate-specific CIF was calculated as

$$F_t^{\text{con}}(x; \beta) = 1 - q_1^{\text{con}}(x; \beta) \times q_2^{\text{con}}(x; \beta) \times \cdots \times q_t^{\text{con}}(x; \beta)$$

where $q_t^{\text{con}}(x; \beta) = 1 - p_t^{\text{con}}(x; \beta)$ and $p_t^{\text{con}}(x; \beta)$ is as defined above. For INV, weekly probability functions were evaluated under the condition that revascularization was performed at the time of randomization ($t = 1$), such that $R_t = t$ for all t. The covariate-specific CIF for prompt revascularization was then calculated as

$$F_t^{\text{a=1}}(x, z; \beta) = 1 - q_1^{\text{inv}}(x, z, r_t = 1; \beta) \times q_2^{\text{inv}}(x, z, r_t = 2; \beta) \times \cdots \times q_t^{\text{inv}}(x, z, r_t = t; \beta)$$

where $q_t^{\text{inv}}(x, z, r_t; \beta) = 1 - p_t^{\text{inv}}(x, z, r_t; \beta)$ and $p_t^{\text{inv}}(x, z, r_t; \beta)$ is as defined above.

Standardized CIFs

Standardized CIFs were calculated by applying the treatment- and covariate-specific CIF equations to covariate data from 612 patients in the study's INV cohort. We assumed that all 612 patients were eligible to receive revascularization at the time of randomization. For each of these patients, we then predicted their cumulative event probability if assigned to CON and again if assigned to INV and given prompt revascularization. A standardized CIF for each treatment was obtained by calculating the average of the 612 covariate-specific CIFs. Let (x_i, z_i) denote covariates for the i-th patient from the study's INV cohort, $i = 1,2,\ldots,612$. The standardized CIF for CON was calculated as $F_t^{\text{con}}(\beta) = (1/612)\sum_{i=1}^{612} F_t^{\text{con}}(x = x_i; \beta)$. The standardized CIF for prompt revascularization was calculated as $F_t^{a=1}(\beta) = (1/612)\sum_{i=1}^{612} F_t^{a=1}(x = x_i, z = z_i; \beta)$. Our primary measure of treatment effect was the difference in standardized CIFs for CON versus prompt revascularization at $t^* = 208$ weeks (4 years), that is, $\delta_{t^*}(\beta) = F_{t^*}^{a=1}(\beta) - F_{t^*}^{\text{con}}(\beta)$.

Bayesian computation

Bayesian computation was based on Markov Chain Monte Carlo (MCMC) sampling as implemented in the Rstan software package 'brms'. Sampling was run for 6000 iterations after an initial burn-in period; thus, we obtained 6000 sets of sampled regression parameters. Convergence of the MCMC procedure was confirmed through evaluation of trace plots, autocorrelation plots, and effective sample size.

To calculate estimates and measures of uncertainty for CIFs and related quantities, we noted that each unknown single-number quantity of interest (e.g., the CIF at a single time point) could be expressed as a function $f(\beta)$ of the unknown model coefficients, β. Point estimates (posterior means) were calculated as $\hat{f} = (1/6000)\sum_{m=1}^{6000} f\,(\beta^{(m)})$, where $\beta^{(m)}$ is the set of regression coefficients sampled on the m-th iteration of the MCMC procedure. A two-sided equal tail 95% credible interval for $f(\beta)$ was obtained by calculating the 2.5th and 97.5th empirical quantiles across the set of numbers $f\left(\beta^{(1)}\right), f\left(\beta^{(2)}\right), \ldots, f\left(\beta^{(6000)}\right)$, i.e., the 150th smallest value and 150th largest value, out of 6000.

Additional information for research statisticians

Conditions for valid causal interpretation

In order to relate F_t^{con} and $F_t^{a=1}$ to counterfactual outcomes, some additional notation is required. Recall that $Y^{(\text{con})}$ represents a patient's counterfactual outcome if assigned to CON, and $Y^{(a)}$ represents a patient's counterfactual outcome under an INV strategy of revascularization at week a for all patients who survive until week a. Let $Y_t^{(\text{con})} = I(Y^{(\text{con})} \leq t)$ indicate a patient's counterfactual event status at week t under CON, and let $Y_t^{(a)} = I(Y^{(a)} \leq t)$ indicate a patient's counterfactual event status at week t under an INV strategy of revascularization at week a. Let

$$p_t^{(\text{con})}(x) = P\left(Y_t^{(\text{con})} = 1 \middle| Y_{t-1}^{(\text{con})} = 0, X = x\right)$$

be the counterfactual weekly event probability at week t conditional on covariates $X = x$ if assigned to CON and let

$$p_t^{(a)}(x, z) = P\left(Y_t^{(a)} = 1 \middle| Y_{t-1}^{(a)} = 0, X = x, Z = z\right)$$

be the counterfactual weekly event probability at week t conditional on covariates $X = x, Z = z$ under a strategy of revascularization at week a for all patients. Let $\bar{r}_t(a)$ be a function that returns the value of R_t at week t hypothetically if revascularization is given at week a, i.e., $\bar{r}_t(a) = 1 + t - a$ if $t \geq a$ and $\bar{r}_t(a) = 0$ if $t < a$. Finally, let $M^{(\text{inv})}$ denote a patient's counterfactual missing data status for angiography variables hypothetically if randomized to INV (0=missing, 1=non-missing). According to this definition, a patient's actual observed missing data status for angiography variables is $M = I(G = \text{inv}) \times M^{(\text{inv})}$.

In the paragraphs below, our goal is to outline conditions leading to the equalities $p_t^{\text{con}}(x) = p_t^{(\text{con})}(x)$ and $p_t{}^{\text{inv}}(x, z, r_t = \bar{r}_t(a)) = p_t^{(a)}(x, z)$, in other words, conditions that allow $p_t^{\text{con}}(x)$ and $p_t{}^{\text{inv}}(x, z, \bar{r}_t(a))$ to be interpreted in terms of counterfactual outcomes, i.e., causally.

For patients who are assigned to CON, the outcome $Y^{(\text{con})}$ is observed and so $Y_t = Y_t^{(\text{con})}$ for all t. Hence, we can replace Y_t with $Y_t^{(\text{con})}$ in the $p_t^{\text{con}}(x)$ definition; that is, $p_t^{\text{con}}(x) = P\left(Y_t^{(\text{con})} = 1 \middle| Y_{t-1}^{(\text{con})} = 0, C_t = 1, G = \text{con}, X = x\right)$. Due to randomization, it is reasonable to assume that the distribution of $Y_t^{(\text{con})}$ is identical among patients in both randomized treatment groups. This allows us to drop the condition $G = \text{con}$ from the right-hand side of the above probability. If we further assume that censoring is non-informative, this allows us to also drop the condition $C_t = 1$ from the right-hand side of the above probability. After dropping both of the above, we have

$$p_t^{\text{con}}(x) = P\left(Y_t^{(\text{con})} = 1 \middle| Y_{t-1}^{(\text{con})} = 0, X = x\right) = p_t^{(\text{con})}(x).$$

Under the same conditions, it follows that

$$F_t^{\text{con}}(x) = P\left(Y^{(\text{con})} \leq t \middle| X = x\right) = E(Y_t^{(\text{con})} | X = x)$$

and, hence,

$$F_t^{\text{con}} = \frac{1}{612}\sum_{i=1}^{612} P\left(Y^{(\text{con})} \leq t \middle| X = x_i\right) = \frac{1}{612}\sum_{i=1}^{612} E\left(Y_t^{(\text{con})} \middle| X = x_i\right).$$

This shows that F_t^{con} is an average of covariate-specific counterfactual means and probabilities.

For INV patients who have revascularization status $R_t = \bar{r}_t(a)$ on week t, the observed outcomes through week t are $Y_1^{(a)}, \ldots, Y_t^{(a)}$ so $Y_j = Y_j^{(a)}$ for $j \leq t$. Hence, we can replace Y_t with $Y_t^{(a)}$ in the $p_t^{\text{inv}}(x, z, r_t = \bar{r}_t(a))$ definition; that is, $p_t^{\text{inv}}(x, z, r_t = \bar{r}_t(a)) = P\left(Y_t^{(a)} = 1 \middle| Y_{t-1}^{(a)} = 0, R_t = \bar{r}_t(a), C_t = 1, G = \text{inv}, M = 1, X = x, Z = z\right)$. The equality $p_t^{\text{inv}}\left(x, z, r_t = \bar{r}_t(a)\right) = p_t^{(a)}(x, z)$ then follows by assuming that counterfactual outcomes are independent of assigned treatments R_t, censoring status C_t, randomization group G, and missingness status of angiographic covariates M within strata formed by the cross-classification of baseline variables represented by X and Z. Under these conditions, it follows that

$$F_t^{a=1}(x, z) = P(Y^{(a=1)} \leq t | X = x, Z = z)$$

and, hence,

$$F_t^{a=1} = \frac{1}{612}\sum_{i=1}^{612} P(Y^{(a=1)} \leq t | X = x_i, Z = z_i) = \frac{1}{612}\sum_{i=1}^{612} E(Y_t^{(a=1)} | X = x_i, Z = z_i).$$

This shows that $F_t^{a=1}$ is an average of covariate-specific counterfactual means and probabilities.

Finally, the above results allow us to rewrite δ_t as

$$\delta_t = \frac{1}{612}\sum_{i=1}^{612}\left\{E\left(Y_t^{(a=1)}\middle|X = x_i, Z = z_i\right) - E\left(Y_t^{(\text{con})}\middle|X = x_i\right)\right\}.$$

Justification for different covariates in models for revascularization and CON

The quantity δ_t differs from conventional model-based direct standardization because the standardization for prompt revascularization conditions on both X and Z whereas the standardization for CON only conditions on X. In order for δ_t to be a meaningful summary measure of treatment effect, an additional assumption is required. Specifically, we assume that the probability of non-missing invasive angiography data depends only on baseline covariates X and not on the results of the angiography itself, Z. In probability notation, the assumption is $M \perp Z|X$.

To justify δ_t under the above assumption, re-write it as

$$\delta_t = F_t^{a=1} - F_t^{\text{con}} = \frac{\sum_{i=1}^{N}\{F_t^{a=1}(x_i, z_i) - F_t^{con}(x_i)\}\, I(G_i = \text{inv}, M_i = 1)}{\sum_{i=1}^{N} I(G_i = \text{inv}, M_i = 1)},$$

where $N = 1283$ is the total sample size across both treatment groups, and subscript i is re-defined to refer to the i-th of these N participants. Also, let δ_t^* be the quantity to which δ_t converges in probability as N grows large if the study cohort was a random sample, i.e., $\delta_t \xrightarrow{p} \delta_t^*$. From the above δ_t expression, we can see that

$$\delta_t^* = E\{F_t^{a=1}(X, Z) - F_t^{con}(X)|G = \text{inv}, M = 1\}.$$

Under conditions already given above, we will show that

$$\delta_t^* = E\left\{Y_t^{(a=1)} - Y_t^{(\text{con})}\middle|M^{(\text{inv})} = 1\right\}.$$

In other words, δ_t^* is the population average of the causal contrast $Y_t^{(a=1)} - Y_t^{(\text{con})}$ among patients who would have non-missing angiography data if assigned to INV. To establish the above equality, first note that the event $G = \text{inv}, M = 1$ is equivalent to $G = \text{inv}, M^{(\text{inv})} = 1$. Also, by randomization, we have $G \perp (X, Z, M^{(\text{inv})})$. Finally, the assumption $M \perp Z|X$, together with the above assumptions, implies that $P(X, Z|G = \text{inv}, M = 1) = P(Z|X)P\left(X = x\middle|M^{(\text{inv})} = 1\right)$. It follows that

$$\begin{aligned}\delta_t^* = \sum_x \sum_z \Big\{&E\left(Y_t^{(a=1)}|X = x, Z = z\right) \\ &- E\left(Y_t^{(\text{con})}|X = x\right)\Big\}P(Z = z|X = x)P\left(X = x\middle|M^{(\text{inv})} = 1\right) \\ = \sum_x \Bigg\{&\left(\sum_z E\left(Y_t^{(a=1)}|X = x, Z = z\right)P(Z = z|X = x)\right) \\ &- E\left(Y_t^{(\text{con})}|X = x\right)\Bigg\}P\left(X = x\middle|M^{(\text{inv})} = 1\right)\end{aligned}$$

$$= \sum_{x} \{E(Y_t^{(a=1)} - Y_t^{(\text{con})} | X = x)\} P(X = x | M^{(\text{inv})} = 1)$$
$$= E(Y_t^{(a=1)} - Y_t^{(\text{con})} | M^{(\text{inv})} = 1).$$

The above discussion shows that δ_t^* represents the average causal effect of the two treatments within a defined subgroup of the overall population. Estimation of δ_t is justified by the observation that it is a sample analog of δ_t^* and that δ_t^* has a well-defined causal interpretation under the assumptions we outlined.

Alternative estimands

The main limitation of δ_t^* is that the subgroup it pertains to is not directly observable or of inherent clinical interest. Ideally, we would instead prefer to estimate the overall population treatment effect, $\delta_t^{\text{overall}} = E(Y_t^{(a=1)} - Y_t^{(\text{con})})$.

In a frequentist analysis, estimation of the quantity $\delta_t^{\text{overall}}$ would be relatively straightforward. For example, an inverse probability weighting (IPW) adjustment could be applied to the 612 INV participants with non-missing invasive angiography data. Let $w(x) = 1/P(M = 1|X = x)$ and define

$$\delta_t^{\text{ipw}} = \frac{\sum_{i=1}^{N} w(x_i)\{F_t^{a=1}(x_i, z_i) - F_t^{con}(x_i)\} I(G_i = \text{inv}, M_i = 1)}{\sum_{i=1}^{N} w(x_i) I(G_i = \text{inv}, M_i = 1)}.$$

This quantity would have the desirable property $\delta_t^{\text{ipw}} \xrightarrow{p} \delta_t^{\text{overall}}$.

Targeting $\delta_t^{\text{overall}}$ in a fully Bayesian statistical analysis is not straightforward, as it would require modeling and/or assigning a prior distribution to the unknown probability mass function $P(X, Z, M)$. The chosen approach avoids estimating $P(X, Z, M)$ by standardizing outcomes according to an observed empirical covariate distribution.

SECTION II: QUALITY-OF-LIFE OUTCOMES

Statistical methods

The statistical analyses for quality-of-life (QoL) focused on predicting outcomes hypothetically if a large patient population resembling the study's INV cohort (i.e., the subset with non-missing angiography data) were all to undergo revascularization or all assigned to CON. Again, analyses of the INV cohort were limited to 612 patients who had non-missing data for key invasively measured angiographic covariates. As previously noted, treatment was not randomized, as the timing of revascularization and choice of PCI or CABG was left to the local heart time. Consequently, we assume that the key determinants of receiving treatment were measured and included in the adjustment procedure. Although this exchangeability condition is unlikely to be true in a literal sense, we aim to reduce the risk of large violations of exchangeability by adjusting for a large number of relevant pre-treatment covariates.

For QoL outcomes, the statistical framework was a set of proportional odds models. We performed separate analyses for each method of revascularization (REV, PCI, CABG) and outcome (SAQ-7, RDS, EQ-5D). For each analysis, we estimated separate models for INV and CON, adjusting for the covariates listed in eTable 8 as well as the baseline health status score for the given outcome. Using these models, we predicted the score for each patient in the study's INV cohort under each treatment strategy. We then estimated the standardized outcome for each treatment strategy as the average of the predicted scores. We defined the primary measure of treatment effect for each QoL outcome to be the between group difference in the REV vs. CON, PCI vs. CON and CABG vs. CON standardized outcomes at 12 months.

We estimated the model parameters in a Bayesian statistical framework using Markov Chain Monte Carlo (MCMC) sampling. We specified diffuse Student's t prior distributions (degrees of freedom = 3, mean = 0, standard deviation (SD) = 10 times the SD of the respective covariate) for all regression parameters. We summarized between group differences by posterior means and equal-tailed 95% credible intervals (CrIs).

In the QoL analyses, we imputed missing health status scores using multiple imputation methods. Imputation models included all baseline and angiographic covariates listed in eTable 8, as well as treatment strategy and health status scores through 12 months. Thirty-two randomly imputed data sets were generated, models were fit on each data set, and the resulting posterior predicted outcomes were combined to obtain final posterior distributions incorporating uncertainty due to missingness.

Supplementary Table 1. Adjustment covariates for regression models.

	Clinical Outcomes		Quality-of-Life Outcomes	
	INV	CON	INV	CON
Baseline Covariates				
Region	X	X	X	X
Age	X	X	X	X
Sex	X	X	X	X
Hypertension	X	X	X	X
Diabetes	X	X	X	X
Smoking	X	X	X	X
Prior MI	X	X	X	X
History of Cerebrovascular Disease or Stroke	X	X	X	X
History of Peripheral Artery Disease	X	X	X	X
Prior PCI	X	X	X	X
Left Ventricular Ejection Fraction	X	X	X	X
Body Mass Index	X	X	X	X
Estimated Glomerular Filtration Rate	X	X	X	X
Seattle Angina Frequency Score	X	X	X	X
New York Heart Association Functional Class	X	X	X	X
Degree of Ischemia on Stress Test	X	X	X	X
Angiographic Covariates				
Duke Jeopardy Score	X		X	
SYNTAX Score	X		X	
Chronic Total Occlusion	X		X	
Moderate/Severe Calcification	X		X	
Moderate/Severe Tortuosity	X		X	
Number of Anatomic Lesions	X		X	
Number of Ischemic Lesions	X		X	
Left Main Disease	X		X	
Proximal Left Anterior Descending Artery Stenosis	X		X	
Time-Dependent Covariates				
Time Since Randomization	X	X		
Time Since Revascularization	X			

Supplementary Table 2. Baseline characteristics.

	INV N=612	INV: REV N=510	INV: PCI N=292	INV: CABG N=218	CON N=624	P-value INV vs. CON	P-value REV vs. CON	P-value PCI vs. CON	P-value CABG vs. CON
Race						0.87	0.90	0.82	0.11
White	386 / 606 (63.7%)	324 / 506 (64.0%)	174 / 291 (59.8%)	150 / 215 (69.8%)	382 / 617 (61.9%)				
Black	21 / 606 (3.5%)	17 / 506 (3.4%)	9 / 291 (3.1%)	8 / 215 (3.7%)	22 / 617 (3.6%)				
Asian	195 / 606 (32.2%)	161 / 506 (31.8%)	104 / 291 (35.7%)	57 / 215 (26.5%)	207 / 617 (33.5%)				
Other or multiple races reported	4 / 606 (0.7%)	4 / 506 (0.8%)	4 / 291 (1.4%)	0 / 215 (0.0%)	6 / 617 (1.0%)				
Hispanic or Latino	98 / 612 (16.0%)	83 / 510 (16.3%)	44 / 292 (15.1%)	39 / 218 (17.9%)	97 / 624 (15.5%)	0.88	0.80	0.93	0.48
Region						0.75	0.66	0.53	**0.03**
North America	150 / 612 (24.5%)	118 / 510 (23.1%)	67 / 292 (22.9%)	51 / 218 (23.4%)	156 / 624 (25.0%)				
Europe	186 / 612 (30.4%)	157 / 510 (30.8%)	84 / 292 (28.8%)	73 / 218 (33.5%)	192 / 624 (30.8%)				
Asia	197 / 612 (32.2%)	168 / 510 (32.9%)	112 / 292 (38.4%)	56 / 218 (25.7%)	208 / 624 (33.3%)				
Other	79 / 612 (12.9%)	67 / 510 (13.1%)	29 / 292 (9.9%)	38 / 218 (17.4%)	68 / 624 (10.9%)				
Insulin-dependent diabetes	58 / 608 (9.5%)	50 / 506 (9.9%)	27 / 290 (9.3%)	23 / 216 (10.6%)	71 / 618 (11.5%)	0.31	0.44	0.38	0.83
History of cerebrovascular disease	49 / 611 (8.0%)	40 / 510 (7.8%)	23 / 292 (7.9%)	17 / 218 (7.8%)	36 / 621 (5.8%)	0.15	0.21	0.29	0.38
Body mass index, kg/m^2,	28 (25--31)	28 (25--31)	28 (25--31)	28 (25--31)	28 (25--31)	0.81	0.45	0.33	0.88
SAQ7 Angina Frequency score						**0.03**	**0.007**	**0.0005**	0.66
100	169 / 612 (27.6%)	132 / 510 (25.9%)	67 / 292 (22.9%)	65 / 218 (29.8%)	207 / 624 (33.2%)				
70 to 90	318 / 612 (52.0%)	269 / 510 (52.7%)	153 / 292 (52.4%)	116 / 218 (53.2%)	318 / 624 (51.0%)				
0 to 60	125 / 612 (20.4%)	109 / 510 (21.4%)	72 / 292 (24.7%)	37 / 218 (17.0%)	99 / 624 (15.9%)				
Heart Failure Status Over the Past Month						0.69	0.59	0.80	0.51
None	386 / 612 (63.1%)	326 / 510 (63.9%)	185 / 292 (63.4%)	141 / 218 (64.7%)	386 / 624 (61.9%)				
NYHA Class I	120 / 612 (19.6%)	93 / 510 (18.2%)	53 / 292 (18.2%)	40 / 218 (18.3%)	128 / 624 (20.5%)				
NYHA Class II	106 / 612 (17.3%)	91 / 510 (17.8%)	54 / 292 (18.5%)	37 / 218 (17.0%)	110 / 624 (17.6%)				
Type of stress testing						0.75	0.52	0.49	0.77

Nuclear	265 / 612 (43.3%)	213 / 510 (41.8%)	120 / 292 (41.1%)	93 / 218 (42.7%)	286 / 624 (45.8%)				
Echocardiography	130 / 612 (21.2%)	113 / 510 (22.2%)	67 / 292 (22.9%)	46 / 218 (21.1%)	121 / 624 (19.4%)				
Cardiac magnetic resonance imaging	25 / 612 (4.1%)	18 / 510 (3.5%)	12 / 292 (4.1%)	6 / 218 (2.8%)	22 / 624 (3.5%)				
Exercise treadmill test	192 / 612 (31.4%)	166 / 510 (32.5%)	93 / 292 (31.8%)	73 / 218 (33.5%)	195 / 624 (31.2%)				

Supplementary Table 3. Baseline stress test and CCTA results for each analysis group.

	Total	INV	INV: REV	INV: PCI	INV: CABG	CON
	(1236)	(612)	(510)	(292)	(218)	(624)
Stress test modality						
Stress imaging	849 / 1236 (68.7%)	420 / 612 (68.6%)	344 / 510 (67.5%)	199 / 292 (68.2%)	145 / 218 (66.5%)	429 / 624 (68.8%)
Severe	426 / 848 (50.2%)	209 / 420 (49.8%)	174 / 344 (50.6%)	95 / 199 (47.7%)	79 / 145 (54.5%)	217 / 428 (50.7%)
Moderate	353 / 848 (41.6%)	178 / 420 (42.4%)	150 / 344 (43.6%)	90 / 199 (45.2%)	60 / 145 (41.4%)	175 / 428 (40.9%)
Mild	42 / 848 (5.0%)	21 / 420 (5.0%)	14 / 344 (4.1%)	8 / 199 (4.0%)	6 / 145 (4.1%)	21 / 428 (4.9%)
None	27 / 848 (3.2%)	12 / 420 (2.9%)	6 / 344 (1.7%)	6 / 199 (3.0%)	0 / 145 (0.0%)	15 / 428 (3.5%)
Uninterpretable	0 / 848 (0.0%)	0 / 420 (0.0%)	0 / 344 (0.0%)	0 / 199 (0.0%)	0 / 145 (0.0%)	0 / 428 (0.0%)
Exercise stress test	387 / 1236 (31.3%)	192 / 612 (31.4%)	166 / 510 (32.5%)	93 / 292 (31.8%)	73 / 218 (33.5%)	195 / 624 (31.2%)
Severe	331 / 385 (86.0%)	161 / 191 (84.3%)	140 / 165 (84.8%)	77 / 93 (82.8%)	63 / 72 (87.5%)	170 / 194 (87.6%)
Moderate	32 / 385 (8.3%)	21 / 191 (11.0%)	16 / 165 (9.7%)	10 / 93 (10.8%)	6 / 72 (8.3%)	11 / 194 (5.7%)
Mild	5 / 385 (1.3%)	3 / 191 (1.6%)	3 / 165 (1.8%)	2 / 93 (2.2%)	1 / 72 (1.4%)	2 / 194 (1.0%)
None	5 / 385 (1.3%)	3 / 191 (1.6%)	3 / 165 (1.8%)	2 / 93 (2.2%)	1 / 72 (1.4%)	2 / 194 (1.0%)
Uninterpretable	12 / 385 (3.1%)	3 / 191 (1.6%)	3 / 165 (1.8%)	2 / 93 (2.2%)	1 / 72 (1.4%)	9 / 194 (4.6%)
Coronary anatomy by CCTA (≥50% stenosis)						
Left main	10 / 1231 (0.8%)	4 / 610 (0.7%)	4 / 509 (0.8%)	1 / 291 (0.3%)	3 / 218 (1.4%)	6 / 621 (1.0%)
Left anterior descending	1236 / 1236 (100.0%)	612 / 612 (100.0%)	510 / 510 (100.0%)	292 / 292 (100.0%)	218 / 218 (100.0%)	624 / 624 (100.0%)
Proximal LAD	715 / 1210 (59.1%)	344 / 601 (57.2%)	284 / 503 (56.5%)	157 / 287 (54.7%)	127 / 216 (58.8%)	371 / 609 (60.9%)
Left circumflex	1235 / 1236 (99.9%)	612 / 612 (100.0%)	510 / 510 (100.0%)	292 / 292 (100.0%)	218 / 218 (100.0%)	623 / 624 (99.8%)
Right coronary artery	1236 / 1236 (100.0%)	612 / 612 (100.0%)	510 / 510 (100.0%)	292 / 292 (100.0%)	218 / 218 (100.0%)	624 / 624 (100.0%)

CABG= coronary artery bypass graft surgery; CCTA = coronary computed tomography angiography; CON = conservative; INV= invasive; PCI= percutaneous coronary intervention; REV= revascularization

Supplementary Table 4. Physiological measurements, risk factors, and medications for each analysis group at baseline and the last visit.

Baseline Measurements	Total	INV	INV: REV	INV: PCI	INV: CABG	CON
	(1236)	(612)	(510)	(292)	(218)	(624)
Systolic blood pressure						
N	1227	607	506	290	216	620
Median	130.0	131.0	131.5	131.5	131.5	130.0
(Q1, Q3)	(120.0, 143.0)	(120.0, 145.0)	(120.0, 145.0)	(120.0, 144.0)	(120.0, 146.0)	(120.0, 141.0)
Diastolic blood pressure						
N	1227	607	506	290	216	620
Median	79.0	80.0	80.0	80.0	80.0	78.0
(Q1, Q3)	(70.0, 82.0)	(70.0, 83.0)	(70.0, 83.0)	(70.0, 84.0)	(70.0, 80.0)	(70.0, 82.0)
Total cholesterol (mg/dL)						
N	1216	599	500	289	211	617
Median	155.0	156.0	157.0	157.0	155.0	154.7
(Q1, Q3)	(130.6, 185.7)	(131.0, 187.0)	(131.5, 188.1)	(131.5, 186.0)	(132.0, 192.5)	(129.5, 185.6)
HDL cholesterol (mg/dL)						
N	1209	595	497	287	210	614
Median	41.0	41.0	41.0	41.0	40.8	41.4
(Q1, Q3)	(35.0, 49.5)	(35.0, 49.9)	(35.0, 49.1)	(35.6, 49.9)	(34.8, 48.3)	(34.8, 49.1)
LDL cholesterol (mg/dL)						
N	1195	591	493	286	207	604
Median	85.0	85.0	85.0	85.0	84.0	85.0
(Q1, Q3)	(64.0, 111.0)	(64.0, 111.5)	(65.0, 114.0)	(66.2, 113.0)	(65.0, 119.0)	(64.0, 109.2)
Triglycerides (mg/dL)						
N	1205	594	495	287	208	611
Median	126.0	130.1	131.0	132.7	125.2	124.0
(Q1, Q3)	(93.0, 182.0)	(95.7, 185.0)	(98.0, 185.8)	(101.4, 186.0)	(94.8, 184.0)	(91.0, 177.0)
HbA1c (%)						
N	873	425	350	197	153	448
Median	6.4	6.4	6.4	6.4	6.4	6.4
(Q1, Q3)	(5.8, 7.6)	(5.8, 7.6)	(5.8, 7.5)	(5.7, 7.4)	(5.8, 7.5)	(5.8, 7.6)
Body mass index						
N	1220	606	505	292	213	614
Median	27.6	27.7	27.8	28.0	27.6	27.6
(Q1, Q3)	(24.8, 31.1)	(25.0, 31.1)	(25.1, 31.2)	(25.1, 31.4)	(25.2, 30.9)	(24.6, 31.2)
Current smoking	158 / 1234 (12.8%)	80 / 611 (13.1%)	59 / 509 (11.6%)	33 / 292 (11.3%)	26 / 217 (12.0%)	78 / 623 (12.5%)

Medications						
Aspirin or aspirin alternative	1184 / 1220 (97.0%)	583 / 601 (97.0%)	488 / 503 (97.0%)	280 / 287 (97.6%)	208 / 216 (96.3%)	601 / 619 (97.1%)
Clopidogrel	324 / 1236 (26.2%)	176 / 612 (28.8%)	149 / 510 (29.2%)	87 / 292 (29.8%)	62 / 218 (28.4%)	148 / 624 (23.7%)
Anticoagulant	37 / 1226 (3.0%)	25 / 608 (4.1%)	18 / 506 (3.6%)	11 / 291 (3.8%)	7 / 215 (3.3%)	12 / 618 (1.9%)
Antiplatelet or anticoagulant	1200 / 1200 (100.0%)	594 / 594 (100.0%)	495 / 495 (100.0%)	285 / 285 (100.0%)	210 / 210 (100.0%)	606 / 606 (100.0%)
Statin	1165 / 1235 (94.3%)	579 / 612 (94.6%)	482 / 510 (94.5%)	274 / 292 (93.8%)	208 / 218 (95.4%)	586 / 623 (94.1%)
High-intensity statin	502 / 1194 (42.0%)	242 / 584 (41.4%)	203 / 485 (41.9%)	118 / 278 (42.4%)	85 / 207 (41.1%)	260 / 610 (42.6%)
Ezetimibe	41 / 1236 (3.3%)	19 / 612 (3.1%)	16 / 510 (3.1%)	9 / 292 (3.1%)	7 / 218 (3.2%)	22 / 624 (3.5%)
Ace inhibitor / ARB	806 / 1235 (65.3%)	400 / 611 (65.5%)	330 / 509 (64.8%)	187 / 292 (64.0%)	143 / 217 (65.9%)	406 / 624 (65.1%)
Adherent to medications	880 / 1177 (74.8%)	435 / 581 (74.9%)	364 / 485 (75.1%)	206 / 280 (73.6%)	158 / 205 (77.1%)	445 / 596 (74.7%)
Last Visit Measurements	**Total**	**INV**	**INV: REV**	**INV: PCI**	**INV: CABG**	**CON**
	(1236)	(612)	(510)	(292)	(218)	(624)
Systolic blood pressure						
N	1186	584	493	283	210	602
Median	129.0	130.0	130.0	130.0	130.0	127.5
(Q1, Q3)	(120.0, 139.0)	(120.0, 138.0)	(120.0, 139.0)	(119.0, 138.0)	(120.0, 140.0)	(119.0, 139.8)
Diastolic blood pressure						
N	1186	584	493	283	210	602
Median	75.0	74.0	74.0	75.0	74.0	75.0
(Q1, Q3)	(69.0, 80.0)	(69.0, 80.0)	(69.0, 80.0)	(69.0, 80.0)	(70.0, 80.0)	(69.0, 80.0)
Total cholesterol (mg/dL)						
N	1169	574	486	278	208	595
Median	128.0	128.0	128.0	128.5	128.0	128.0
(Q1, Q3)	(112.1, 150.8)	(112.1, 150.8)	(112.2, 150.8)	(113.0, 151.0)	(112.0, 148.1)	(112.0, 151.0)
HDL cholesterol (mg/dL)						
N	1167	573	485	277	208	594
Median	42.0	42.0	42.0	42.5	41.7	42.0
(Q1, Q3)	(34.9, 49.9)	(34.8, 50.0)	(34.8, 50.0)	(35.2, 50.0)	(34.0, 49.3)	(35.0, 49.4)
LDL cholesterol (mg/dL)						
N	1166	573	485	277	208	593
Median	63.0	63.0	63.0	64.0	62.3	62.0
(Q1, Q3)	(50.0, 81.0)	(50.3, 81.2)	(51.0, 81.0)	(51.0, 81.6)	(50.3, 78.9)	(49.9, 79.0)
Triglycerides (mg/dL)						

N	1168	573	486	278	208	595
Median	115.0	118.0	120.3	122.0	119.0	115.0
(Q1, Q3)	(85.0, 159.3)	(86.7, 164.6)	(86.2, 165.9)	(88.1, 164.9)	(84.1, 168.0)	(82.7, 155.4)
HbA1c (%)						
N	929	452	388	218	170	477
Median	6.4	6.4	6.3	6.3	6.4	6.4
(Q1, Q3)	(5.8, 7.4)	(5.7, 7.4)	(5.7, 7.4)	(5.8, 7.5)	(5.7, 7.3)	(5.8, 7.4)
Body mass index						
N	1166	575	486	282	204	591
Median	27.3	27.4	27.7	28.0	27.3	27.2
(Q1, Q3)	(24.6, 30.8)	(24.8, 30.6)	(24.8, 30.7)	(24.7, 31.1)	(24.9, 30.4)	(24.2, 30.9)
Current smoking	118 / 1152 (10.2%)	53 / 567 (9.3%)	38 / 482 (7.9%)	28 / 277 (10.1%)	10 / 205 (4.9%)	65 / 585 (11.1%)
Medications						
Aspirin or aspirin alternative	1135 / 1166 (97.3%)	560 / 576 (97.2%)	476 / 489 (97.3%)	277 / 283 (97.9%)	199 / 206 (96.6%)	575 / 590 (97.5%)
Clopidogrel	345 / 1190 (29.0%)	189 / 585 (32.3%)	168 / 494 (34.0%)	117 / 284 (41.2%)	51 / 210 (24.3%)	156 / 605 (25.8%)
Anticoagulant	62 / 1188 (5.2%)	33 / 583 (5.7%)	25 / 493 (5.1%)	10 / 283 (3.5%)	15 / 210 (7.1%)	29 / 605 (4.8%)
Antiplatelet or anticoagulant	1159 / 1159 (100.0%)	569 / 569 (100.0%)	481 / 481 (100.0%)	278 / 278 (100.0%)	203 / 203 (100.0%)	590 / 590 (100.0%)
Statin	1139 / 1190 (95.7%)	564 / 585 (96.4%)	476 / 494 (96.4%)	272 / 284 (95.8%)	204 / 210 (97.1%)	575 / 605 (95.0%)
High-intensity statin	829 / 1188 (69.8%)	412 / 584 (70.5%)	350 / 493 (71.0%)	200 / 283 (70.7%)	150 / 210 (71.4%)	417 / 604 (69.0%)
Ezetimibe	309 / 1190 (26.0%)	142 / 585 (24.3%)	121 / 494 (24.5%)	73 / 284 (25.7%)	48 / 210 (22.9%)	167 / 605 (27.6%)
Ace inhibitor / ARB	833 / 1190 (70.0%)	421 / 585 (72.0%)	356 / 494 (72.1%)	209 / 284 (73.6%)	147 / 210 (70.0%)	412 / 605 (68.1%)
Adherent to medications	968 / 1164 (83.2%)	492 / 573 (85.9%)	422 / 487 (86.7%)	245 / 280 (87.5%)	177 / 207 (85.5%)	476 / 591 (80.5%)

ACE= angiotensin converting enzyme; ARB= angiotensin receptor blocker; CABG= coronary artery bypass graft surgery; CCTA = coronary computed tomography angiography; CON = conservative; HDL=high density lipoprotein; INV= invasive; LDL= low density lipoprotein; PCI= percutaneous coronary intervention; REV= revascularization

Supplementary Table 5. Procedural details.

CABG Details	
Variable	**CABG (N = 218)**
No. of grafts	3 (3--4)
Any arterial grafts	203 / 218 (93.1%)
Internal mammary artery	
Yes, left only	162 / 218 (74.3%)
Yes, right only	5 / 218 (2.3%)
Yes, bilateral	33 / 218 (15.1%)
Concomitant valve procedure	3 / 218 (1.4%)
Cardio Pulmonary Bypass used	123 / 216 (56.9%)
PCI Details	
PCI performed on all ischemic lesions RV >=2.25 mm?	
Yes	244 / 292 (83.6%)
No	48 / 292 (16.4%)
Technically difficult	6 / 46 (13.0%)
Attempted but failed	15 / 46 (32.6%)
Intervening procedural complication	3 / 46 (6.5%)
Patient refused	NA
Staged procedure planned	5 / 46 (10.9%)
Distal disease not addressed	3 / 46 (6.5%)
Other	14 / 46 (30.4%)
For unknown/missing reason	NA
Was PCI performed on any non-ischemic lesion <=80% stenosis	
No	274 / 292 (93.8%)
Yes	18 / 292 (6.2%)
FFR not done: severe lesion by IVUS - MLA <4.0 mm2	1 / 18 (5.6%)
FFR not done: technical reasons	0
FFR not done: intervening procedural complications	0
FFR not done: other reasons	1 / 18 (5.6%)
FFR <=0.80	14 / 18 (77.8%)
FFR >0.80	2 / 18 (11.1%)
With severe lesion by IVUS - MLA <4.0 mm2	0
And IVUS not performed	2 / 2 (100.0%)
Stent use	273 / 292 (93.5%)
Drug-eluting stent use	264 / 272 (97.1%)
Bare metal stent use	9 / 272 (3.3%)
Drug-eluting stents	
Xience	117 / 264 (44.3%)
Promus Element	32 / 264 (12.1%)
Endeavor	4 / 264 (1.5%)
Resolute	105 / 264 (39.8%)
Taxus	1 / 264 (0.4%)
Biomatrix	3 / 264 (1.1%)
Other	19 / 264 (7.2%)

Supplementary Table 6. Cumulative risk estimates of outcomes over time for revascularisation versus CON in patients with 3-vessel disease.

Event	Time	REV	CON	Treatment Effect: REV-CON (95% Credible Interval)
All Death	6 Months	1.9%	1.0%	0.9% (-0.2% to 2.2%)
All Death	1 Year	2.6%	1.9%	0.7% (-1.0% to 2.5%)
All Death	2 Years	4.0%	3.8%	0.2% (-1.8% to 2.2%)
All Death	3 Years	5.2%	5.5%	-0.3% (-2.9% to 2.4%)
All Death	**4 Years**	**7.6%**	**8.8%**	**-1.2% (-4.7% to 2.2%)**
All Death	5 Years	9.7%	11.8%	-2.1% (-7.1% to 2.8%)
CV Death	6 Months	1.6%	0.9%	0.7% (-0.3% to 2.0%)
CV Death	1 Year	2.1%	1.7%	0.4% (-1.2% to 2.0%)
CV Death	2 Years	2.9%	3.3%	-0.4% (-2.3% to 1.4%)
CV Death	3 Years	3.6%	4.8%	-1.2% (-3.5% to 1.1%)
CV Death	**4 Years**	**5.2%**	**7.5%**	**-2.3% (-5.5% to 0.8%)**
CV Death	5 Years	6.6%	9.8%	-3.2% (-7.8% to 1.0%)
All Death/MI	6 Months	7.9%	4.1%	3.8% (1.5% to 6.3%)
All Death/MI	1 Year	9.3%	7.9%	1.4% (-1.8% to 4.6%)
All Death/MI	2 Years	11.2%	11.5%	-0.3% (-3.6% to 3.1%)
All Death/MI	3 Years	13.0%	14.9%	-1.8% (-5.8% to 2.2%)
All Death/MI	**4 Years**	**15.5%**	**18.8%**	**-3.4% (-7.9% to 1.0%)**
All Death/MI	5 Years	17.7%	22.4%	-4.8% (-10.5% to 0.7%)
CV Death/MI	6 Months	7.6%	4.1%	3.6% (1.3% to 6.0%)
CV Death/MI	1 Year	8.7%	7.8%	0.9% (-2.2% to 3.9%)
CV Death/MI	2 Years	10.1%	11.2%	-1.1% (-4.4% to 2.2%)
CV Death/MI	3 Years	11.5%	14.4%	-2.8% (-6.7% to 0.9%)
CV Death/MI	**4 Years**	**13.2%**	**17.6%**	**-4.4% (-8.7% to -0.3%)**
CV Death/MI	5 Years	14.8%	20.7%	-5.9% (-11.2% to -0.8%)
All-Cause Death/ Procedural MI	6 Months	7.5%	1.4%	6.2% (4.1% to 8.4%)
All-Cause Death/ Procedural MI	1 Year	8.3%	2.7%	5.6% (3.1% to 8.2%)
All-Cause Death/ Procedural MI	2 Years	9.7%	4.8%	4.8% (2.1% to 7.7%)
All-Cause Death/ Procedural MI	3 Years	10.9%	6.8%	4.1% (0.8% to 7.5%)
All-Cause Death/ Procedural MI	**4 Years**	**12.8%**	**10.2%**	**2.7% (-1.3% to 6.5%)**
All-Cause Death/ Procedural MI	5 Years	14.6%	13.2%	1.4% (-3.8% to 6.2%)
CV Death/ Procedural MI	6 Months	7.3%	1.3%	6.0% (4.0% to 8.3%)
CV Death/ Procedural MI	1 Year	7.8%	2.4%	5.3% (3.0% to 7.9%)
CV Death/ Procedural MI	2 Years	8.6%	4.3%	4.3% (1.7% to 7.0%)
CV Death/ Procedural MI	3 Years	9.4%	6.0%	3.3% (0.2% to 6.4%)
CV Death/ Procedural MI	**4 Years**	**10.5%**	**8.7%**	**1.8% (-1.8% to 5.3%)**
CV Death/ Procedural MI	5 Years	11.5%	11.1%	0.4% (-4.2% to 4.8%)
All-Cause Death/Spontaneous MI	6 Months	2.4%	3.8%	-1.3% (-2.9% to 0.2%)
All-Cause Death/Spontaneous MI	1 Year	3.7%	7.3%	-3.6% (-6.1% to -1.1%)

All-Cause Death/Spontaneous MI	2 Years	5.2%	10.3%	-5.1% (-7.9% to -2.4%)
All-Cause Death/Spontaneous MI	3 Years	6.5%	13.1%	-6.5% (-9.9% to -3.2%)
All-Cause Death/Spontaneous MI	**4 Years**	**9.4%**	**16.4%**	**-7.0% (-11.0% to -3.2%)**
All-Cause Death/Spontaneous MI	5 Years	11.9%	19.5%	-7.6% (-12.8% to -2.6%)
CV Death/Spontaneous MI	6 Months	2.2%	3.8%	-1.6% (-3.0% to 0.0%)
CV Death/Spontaneous MI	1 Year	3.1%	7.2%	-4.1% (-6.5% to -1.6%)
CV Death/Spontaneous MI	2 Years	4.1%	10.0%	-5.9% (-8.6% to -3.2%)
CV Death/Spontaneous MI	3 Years	5.0%	12.6%	-7.5% (-10.9% to -4.4%)
CV Death/Spontaneous MI	**4 Years**	**7.1%**	**15.2%**	**-8.1% (-12.0% to -4.5%)**
CV Death/Spontaneous MI	5 Years	8.9%	17.6%	-8.7% (-13.7% to -4.0%)
All Death/MI/Stroke	6 Months	9.2%	4.2%	5.0% (2.6% to 7.6%)
All Death/MI/Stroke	1 Year	10.5%	8.0%	2.5% (-0.7% to 5.7%)
All Death/MI/Stroke	2 Years	12.8%	12.0%	0.7% (-2.7% to 4.2%)
All Death/MI/Stroke	3 Years	14.8%	15.7%	-0.9% (-5.0% to 3.3%)
All Death/MI/Stroke	**4 Years**	**17.5%**	**19.9%**	**-2.5% (-7.0% to 2.2%)**
All Death/MI/Stroke	5 Years	19.9%	23.7%	-3.9% (-9.7% to 1.8%)
CV Death/MI/Stroke	6 Months	8.9%	4.1%	4.8% (2.3% to 7.4%)
CV Death/MI/Stroke	1 Year	10.0%	7.9%	2.1% (-1.2% to 5.3%)
CV Death/MI/Stroke	2 Years	11.7%	11.7%	0.0% (-3.4% to 3.4%)
CV Death/MI/Stroke	3 Years	13.3%	15.2%	-1.9% (-5.8% to 2.1%)
CV Death/MI/Stroke	**4 Years**	**15.2%**	**18.7%**	**-3.5% (-7.9% to 0.8%)**
CV Death/MI/Stroke	5 Years	16.9%	22.0%	-5.0% (-10.5% to 0.3%)

CON= conservative; CV= cardiovascular; MI= myocardial infarction; REV= revascularization

Supplementary Table 7. Posterior probability for revascularisation, PCI or CABG versus CON in patients with 3-vessel disease for MI separated into procedural (p) or spontaneous (s).

Treatment Effect (%)	All Death/pMI	CV Death/pMI	All Death/sMI	CV Death/sMI
REV vs. CON				
>5% lower	<0.1	<0.1	83.8	**95.1**
>3% lower	0.2	0.4	**97.9**	**99.6**
>1% lower	3.5	6.2	**99.9**	**>99.9**
Any lower	9.1	16.2	**>99.9**	**>99.9**
Any higher	**90.9**	83.8	<0.1	<0.1
>1% higher	80.2	67.4	<0.1	<0.1
> 3% higher	43.3	25.3	<0.1	<0.1
> 5% higher	11.6	3.6	<0.1	<0.1
PCI vs. CON				
>5% lower	0.8	0.8	75.7	85.6
>3% lower	5.5	8.2	**93.3**	**97.3**
>1% lower	24.2	31.3	**98.9**	**99.8**
Any lower	39.0	50.3	**99.7**	**99.9**
Any higher	61.0	49.7	0.3	0.1
>1% higher	43.5	32.9	<0.1	<0.1
> 3% higher	17.0	9.3	<0.1	<0.1
> 5% higher	4.0	1.7	<0.1	<0.1
CABG vs. CON				
>5% lower	<0.1	<0.1	**91.1**	**98.8**
>3% lower	0.2	0.3	**98.3**	**99.9**
>1% lower	1.6	3.7	**99.8**	**>99.9**
Any lower	4.4	8.5	**99.9**	**>99.9**
Any higher	**95.6**	**91.5**	0.1	<0.1
>1% higher	**90.3**	82.4	<0.1	<0.1
> 3% higher	69.0	51.8	<0.1	<0.1
> 5% higher	39.0	22.0	<0.1	<0.1

Supplementary Table 8. Cumulative risk estimates of outcomes over time for PCI versus CON in patients with 3-vessel disease.

Event	Time	PCI	CON	Treatment Effect: PCI-CON (95% Credible Interval)
All Death	6 Months	1.6%	1.0%	0.5% (-0.6% to 2.0%)
All Death	1 Year	2.7%	1.9%	0.8% (-1.1% to 3.0%)
All Death	2 Years	4.1%	3.8%	0.3% (-2.0% to 3.0%)
All Death	3 Years	5.4%	5.5%	-0.1% (-3.1% to 3.3%)
All Death	**4 Years**	**7.9%**	**8.8%**	**-0.9% (-5.0% to 3.4%)**
All Death	5 Years	10.1%	11.8%	-1.7% (-7.3% to 4.0%)
CV Death	6 Months	1.4%	0.9%	0.5% (-0.6% to 2.0%)
CV Death	1 Year	2.4%	1.7%	0.7% (-1.1% to 2.8%)
CV Death	2 Years	3.4%	3.3%	0.0% (-2.2% to 2.5%)
CV Death	3 Years	4.2%	4.8%	-0.6% (-3.5% to 2.5%)
CV Death	**4 Years**	**6.0%**	**7.5%**	**-1.5% (-5.3% to 2.6%)**
CV Death	5 Years	7.5%	9.8%	-2.3% (-7.4% to 3.1%)
All Death/MI	6 Months	5.8%	4.1%	1.7% (-0.8% to 4.5%)
All Death/MI	1 Year	8.5%	7.9%	0.6% (-3.0% to 4.5%)
All Death/MI	2 Years	10.2%	11.5%	-1.3% (-5.3% to 3.0%)
All Death/MI	3 Years	11.8%	14.9%	-3.1% (-7.7% to 1.9%)
All Death/MI	**4 Years**	**13.9%**	**18.8%**	**-4.9% (-10.2% to 0.7%)**
All Death/MI	5 Years	15.8%	22.4%	-6.6% (-13.0% to -0.2%)
CV Death/MI	6 Months	5.5%	4.1%	1.4% (-1.1% to 4.4%)
CV Death/MI	1 Year	8.0%	7.8%	0.2% (-3.6% to 4.0%)
CV Death/MI	2 Years	9.2%	11.2%	-2.0% (-5.9% to 2.3%)
CV Death/MI	3 Years	10.5%	14.4%	-3.9% (-8.5% to 0.9%)
CV Death/MI	**4 Years**	**11.9%**	**17.6%**	**-5.8% (-10.8% to -0.5%)**
CV Death/MI	5 Years	13.2%	20.7%	-7.4% (-13.4% to -1.4%)
All-Cause Death/ Procedural MI	6 Months	5.0%	1.4%	3.6% (1.4% to 6.3%)
All-Cause Death/ Procedural MI	1 Year	7.1%	2.7%	4.4% (1.5% to 7.7%)
All-Cause Death/ Procedural MI	2 Years	8.2%	4.8%	3.4% (0.1% to 7.1%)
All-Cause Death/ Procedural MI	3 Years	9.3%	6.8%	2.5% (-1.4% to 6.7%)
All-Cause Death/ Procedural MI	**4 Years**	**10.9%**	**10.2%**	**0.7% (-3.9% to 5.5%)**
All-Cause Death/ Procedural MI	5 Years	12.4%	13.2%	-0.9% (-6.6% to 5.0%)
CV Death/ Procedural MI	6 Months	4.7%	1.3%	3.5% (1.4% to 6.1%)
CV Death/ Procedural MI	1 Year	6.5%	2.4%	4.0% (1.2% to 7.3%)
CV Death/ Procedural MI	2 Years	7.2%	4.3%	2.9% (-0.2% to 6.4%)
CV Death/ Procedural MI	3 Years	7.8%	6.0%	1.8% (-1.8% to 5.9%)
CV Death/ Procedural MI	**4 Years**	**8.7%**	**8.7%**	**0.1% (-4.1% to 4.7%)**
CV Death/ Procedural MI	5 Years	9.6%	11.1%	-1.5% (-6.6% to 3.8%)
All-Cause Death/Spontaneous MI	6 Months	2.4%	3.8%	-1.4% (-3.1% to 0.4%)
All-Cause Death/Spontaneous MI	1 Year	4.2%	7.3%	-3.1% (-5.8% to -0.1%)

All-Cause Death/Spontaneous MI	2 Years	5.6%	10.3%	-4.6% (-7.7% to -1.3%)
All-Cause Death/Spontaneous MI	3 Years	7.0%	13.1%	-6.0% (-9.8% to -2.0%)
All-Cause Death/Spontaneous MI	**4 Years**	**9.8%**	**16.4%**	**-6.6% (-11.3% to -1.9%)**
All-Cause Death/Spontaneous MI	5 Years	12.2%	19.5%	-7.2% (-13.2% to -1.1%)
CV Death/Spontaneous MI	6 Months	2.2%	3.8%	-1.5% (-3.2% to 0.3%)
CV Death/Spontaneous MI	1 Year	3.8%	7.2%	-3.4% (-6.2% to -0.5%)
CV Death/Spontaneous MI	2 Years	4.8%	10.0%	-5.1% (-8.2% to -1.9%)
CV Death/Spontaneous MI	3 Years	5.8%	12.6%	-6.7% (-10.4% to -3.0%)
CV Death/Spontaneous MI	**4 Years**	**7.8%**	**15.2%**	**-7.4% (-11.6% to -2.9%)**
CV Death/Spontaneous MI	5 Years	9.6%	17.6%	-8.0% (-13.3% to -2.4%)
All Death/MI/Stroke	6 Months	6.6%	4.2%	2.5% (-0.1% to 5.5%)
All Death/MI/Stroke	1 Year	9.5%	8.0%	1.5% (-2.1% to 5.4%)
All Death/MI/Stroke	2 Years	11.4%	12.0%	-0.7% (-4.7% to 3.6%)
All Death/MI/Stroke	3 Years	13.1%	15.7%	-2.6% (-7.3% to 2.3%)
All Death/MI/Stroke	**4 Years**	**15.3%**	**19.9%**	**-4.6% (-9.8% to 0.9%)**
All Death/MI/Stroke	5 Years	17.4%	23.7%	-6.3% (-12.7% to 0.1%)
CV Death/MI/Stroke	6 Months	6.3%	4.1%	2.2% (-0.3% to 5.1%)
CV Death/MI/Stroke	1 Year	8.9%	7.9%	1.0% (-2.6% to 4.8%)
CV Death/MI/Stroke	2 Years	10.4%	11.7%	-1.3% (-5.3% to 2.9%)
CV Death/MI/Stroke	3 Years	11.7%	15.2%	-3.5% (-8.1% to 1.4%)
CV Death/MI/Stroke	**4 Years**	**13.3%**	**18.7%**	**-5.4% (-10.5% to -0.2%)**
CV Death/MI/Stroke	5 Years	14.8%	22.0%	-7.2% (-13.2% to -1.0%)

CON= conservative; CV= cardiovascular; MI= myocardial infarction; PCI= percutaneous coronary intervention

Supplementary Table 9. Cumulative risk estimates of outcomes over time for CABG versus CON in patients with 3-vessel disease.

Event	Time	CABG	CON	Treatment Effect: CABG-CON (95% Credible Interval)
All Death	6 Months	2.6%	1.0%	1.6% (0.0% to 3.6%)
All Death	1 Year	3.2%	1.9%	1.2% (-0.8% to 3.6%)
All Death	2 Years	4.2%	3.8%	0.4% (-2.0% to 3.1%)
All Death	3 Years	5.2%	5.5%	-0.3% (-3.3% to 3.0%)
All Death	**4 Years**	**7.2%**	**8.8%**	**-1.7% (-5.6% to 2.6%)**
All Death	5 Years	8.9%	11.8%	-2.8% (-8.2% to 2.8%)
CV Death	6 Months	2.1%	0.9%	1.2% (-0.2% to 3.2%)
CV Death	1 Year	2.4%	1.7%	0.7% (-1.1% to 2.9%)
CV Death	2 Years	2.8%	3.3%	-0.5% (-2.6% to 1.9%)
CV Death	3 Years	3.2%	4.8%	-1.6% (-4.2% to 1.2%)
CV Death	**4 Years**	**4.1%**	**7.5%**	**-3.3% (-6.8% to 0.3%)**
CV Death	5 Years	4.9%	9.8%	-4.9% (-9.6% to -0.2%)
All Death/MI	6 Months	11.2%	4.1%	7.1% (3.4% to 11.2%)
All Death/MI	1 Year	12.4%	7.9%	4.5% (0.3% to 9.2%)
All Death/MI	2 Years	13.7%	11.5%	2.2% (-2.4% to 7.0%)
All Death/MI	3 Years	14.9%	14.9%	0.0% (-5.1% to 5.4%)
All Death/MI	**4 Years**	**16.4%**	**18.8%**	**-2.4% (-8.1% to 3.4%)**
All Death/MI	5 Years	17.9%	22.4%	-4.6% (-11.3% to 2.1%)
CV Death/MI	6 Months	10.8%	4.1%	6.7% (3.2% to 10.5%)
CV Death/MI	1 Year	11.6%	7.8%	3.8% (-0.3% to 8.1%)
CV Death/MI	2 Years	12.3%	11.2%	1.1% (-3.1% to 5.6%)
CV Death/MI	3 Years	13.1%	14.4%	-1.3% (-5.9% to 3.5%)
CV Death/MI	**4 Years**	**13.9%**	**17.6%**	**-3.7% (-8.8% to 1.5%)**
CV Death/MI	5 Years	14.7%	20.7%	-6.0% (-11.9% to 0.0%)
All-Cause Death/ Procedural MI	6 Months	11.0%	1.4%	9.6% (6.2% to 13.6%)
All-Cause Death/ Procedural MI	1 Year	11.7%	2.7%	9.0% (5.2% to 13.2%)
All-Cause Death/ Procedural MI	2 Years	12.5%	4.8%	7.7% (3.8% to 12.0%)

All-Cause Death/ Procedural MI	3 Years	13.3%	6.8%	6.5% (2.2% to 11.3%)
All-Cause Death/ Procedural MI	**4 Years**	**14.5%**	**10.2%**	**4.3% (-0.6% to 9.5%)**
All-Cause Death/ Procedural MI	5 Years	15.6%	13.2%	2.4% (-3.6% to 8.5%)
CV Death/ Procedural MI	6 Months	10.5%	1.3%	9.2% (5.9% to 13.1%)
CV Death/ Procedural MI	1 Year	10.8%	2.4%	8.4% (4.8% to 12.3%)
CV Death/ Procedural MI	2 Years	11.1%	4.3%	6.8% (3.1% to 10.9%)
CV Death/ Procedural MI	3 Years	11.4%	6.0%	5.4% (1.3% to 9.7%)
CV Death/ Procedural MI	**4 Years**	**11.8%**	**8.7%**	**3.2% (-1.4% to 7.9%)**
CV Death/ Procedural MI	5 Years	12.3%	11.1%	1.2% (-4.2% to 6.5%)
All-Cause Death/Spontaneous MI	6 Months	2.9%	3.8%	-0.9% (-2.8% to 1.3%)
All-Cause Death/Spontaneous MI	1 Year	4.0%	7.3%	-3.2% (-6.0% to -0.3%)
All-Cause Death/Spontaneous MI	2 Years	5.1%	10.3%	-5.1% (-8.3% to -1.8%)
All-Cause Death/Spontaneous MI	3 Years	6.2%	13.1%	-6.9% (-10.7% to -3.0%)
All-Cause Death/Spontaneous MI	**4 Years**	**8.2%**	**16.4%**	**-8.2% (-12.7% to -3.4%)**
All-Cause Death/Spontaneous MI	5 Years	10.0%	19.5%	-9.5% (-15.1% to -3.4%)
CV Death/Spontaneous MI	6 Months	2.5%	3.8%	-1.3% (-3.1% to 0.9%)
CV Death/Spontaneous MI	1 Year	3.2%	7.2%	-4.0% (-6.7% to -1.2%)
CV Death/Spontaneous MI	2 Years	3.7%	10.0%	-6.2% (-9.2% to -3.2%)
CV Death/Spontaneous MI	3 Years	4.3%	12.6%	-8.3% (-11.8% to -4.7%)
CV Death/Spontaneous MI	**4 Years**	**5.4%**	**15.2%**	**-9.8% (-13.9% to -5.6%)**
CV Death/Spontaneous MI	5 Years	6.4%	17.6%	-11.3% (-16.3% to -6.1%)
All Death/MI/Stroke	6 Months	13.1%	4.2%	8.9% (5.1% to 13.1%)
All Death/MI/Stroke	1 Year	14.4%	8.0%	6.4% (2.0% to 11.0%)
All Death/MI/Stroke	2 Years	15.9%	12.0%	3.8% (-0.8% to 8.7%)
All Death/MI/Stroke	3 Years	17.3%	15.7%	1.5% (-3.8% to 6.9%)
All Death/MI/Stroke	**4 Years**	**19.0%**	**19.9%**	**-1.0% (-6.7% to 4.9%)**
All Death/MI/Stroke	5 Years	20.6%	23.7%	-3.2% (-9.9% to 3.6%)
CV Death/MI/Stroke	6 Months	12.6%	4.1%	8.5% (4.7% to 12.8%)
CV Death/MI/Stroke	1 Year	13.6%	7.9%	5.7% (1.4% to 10.5%)
CV Death/MI/Stroke	2 Years	14.5%	11.7%	2.8% (-1.7% to 7.9%)
CV Death/MI/Stroke	3 Years	15.5%	15.2%	0.3% (-4.7% to 5.7%)

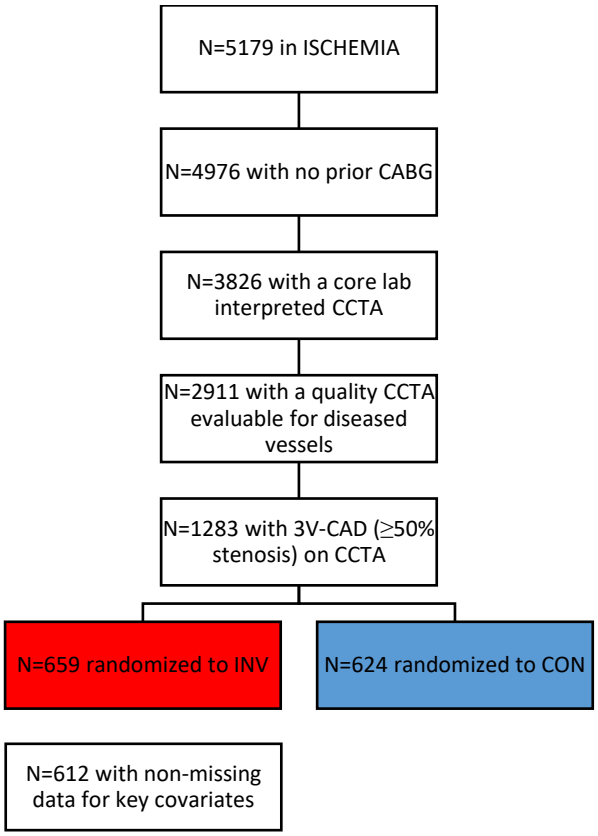
CV Death/MI/Stroke	**4 Years**	**16.4%**	**18.7%**	**-2.3% (-7.7% to 3.6%)**
CV Death/MI/Stroke	5 Years	17.4%	22.0%	-4.6% (-10.8% to 2.2%)

CABG= coronary artery bypass graft surgery; CON= conservative; CV= cardiovascular; MI= myocardial infarction

Supplementary Table 10. Trials of stable coronary artery disease testing revascularisation versus medical therapy with CABG as one of the revascularisation modalities.

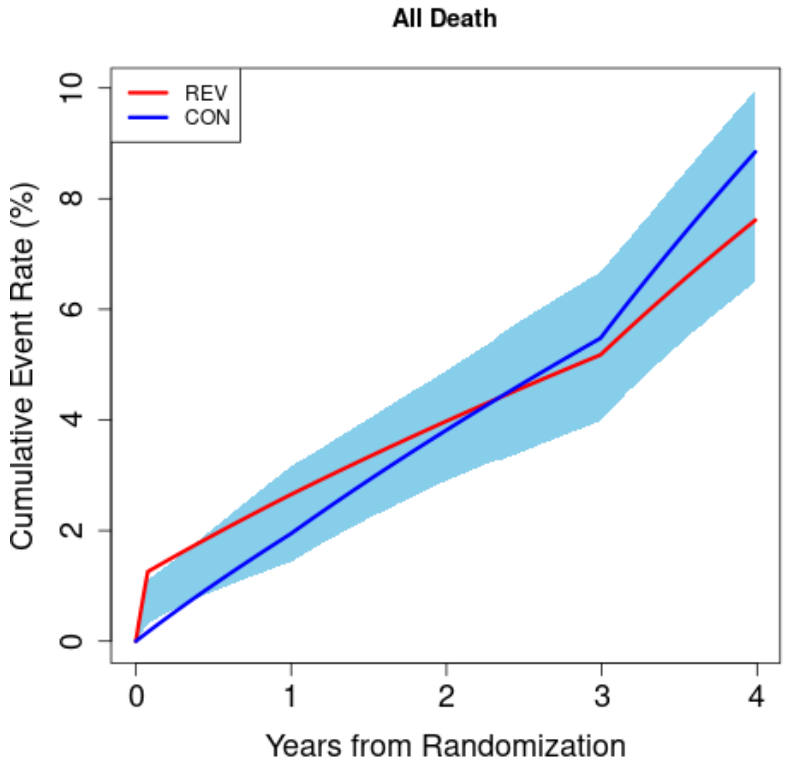
Trial	Publication Year	Number of patients who underwent CABG	Follow-up	Stenosis Criteria for Inclusion	Mortality Reduction with CABG	P-value for Mortality Difference
Trials with GDMT						
MASS II (20)	2010	203	10 years	>70%+documented ischemia	No	0.17
BARI 2D CABG Stratum (21)	2009	378	5 years	≥50%+documented ischemia	No	0.33
ISCHEMIA (5)	2020	530*	4 years	≥50%+documented ischemia	No	
Trials without GDMT						
CASS Study (22)	1983	390	10 years	≥70%	No	0.25
VA Study (23)	1984	332	11 years	≥50%	No	0.45
European Study (24)	1988	394	12 years	≥50%	Yes	0.02

* Represents participants randomized to invasive management who underwent CABG not restricted to whether they underwent CCTA or had 3-vessel disease



Supplementary Figure 1. Consort diagram.

A)



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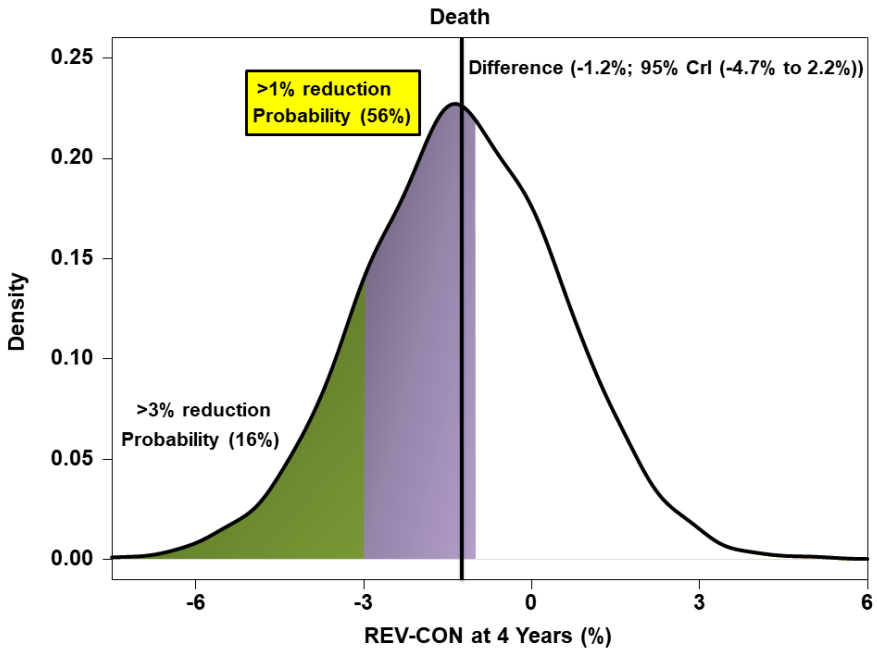
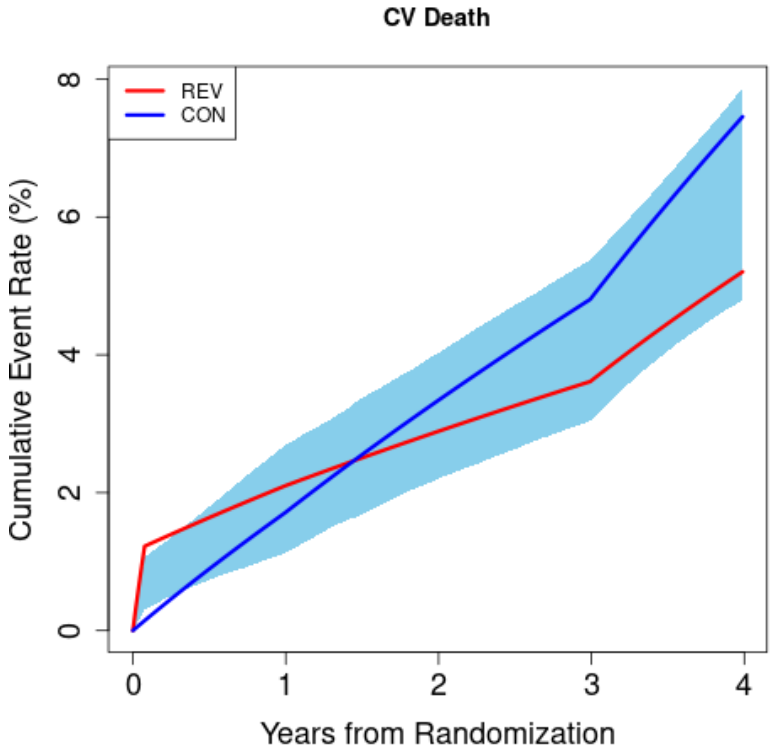


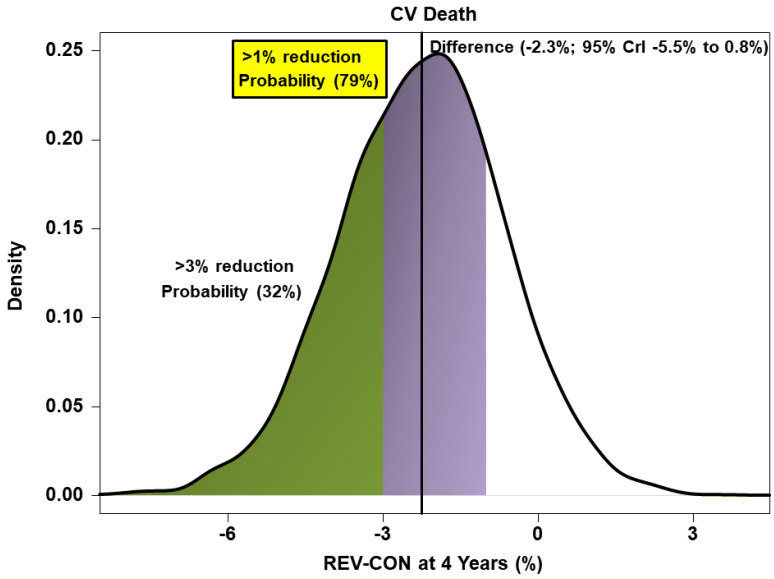
Supplementary Figure 2. Revascularisation versus CON in patients with 3-vessel disease: outcome of death.

A) Cumulative risk estimates for the outcome of death; B) Posterior probability for the outcome of death.

A)



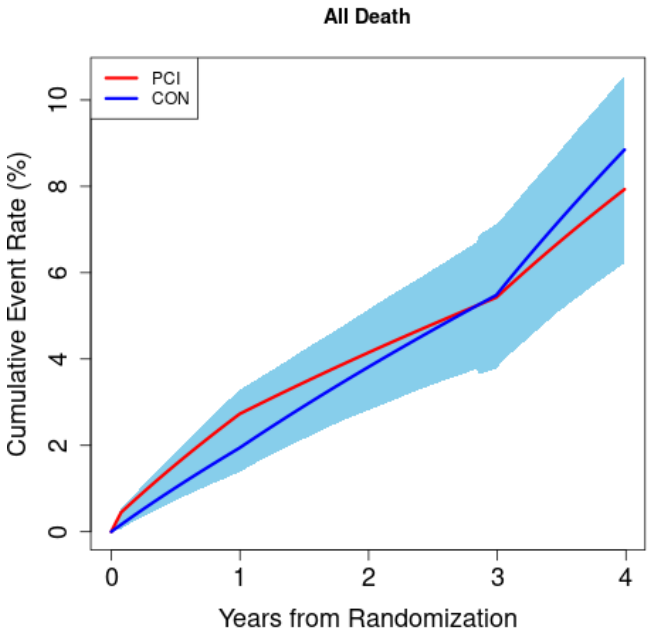
B)



Supplementary Figure 3. Revascularisation versus CON in patients with 3-vessel disease: outcome of CV death.

A) Cumulative risk estimates for the outcome of CV death; B) Posterior probability for the outcome of CV death.

A)



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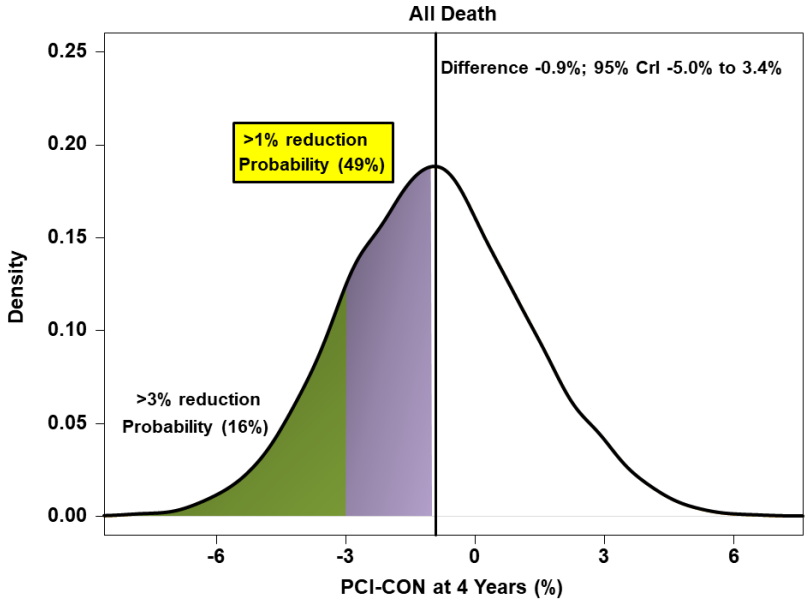
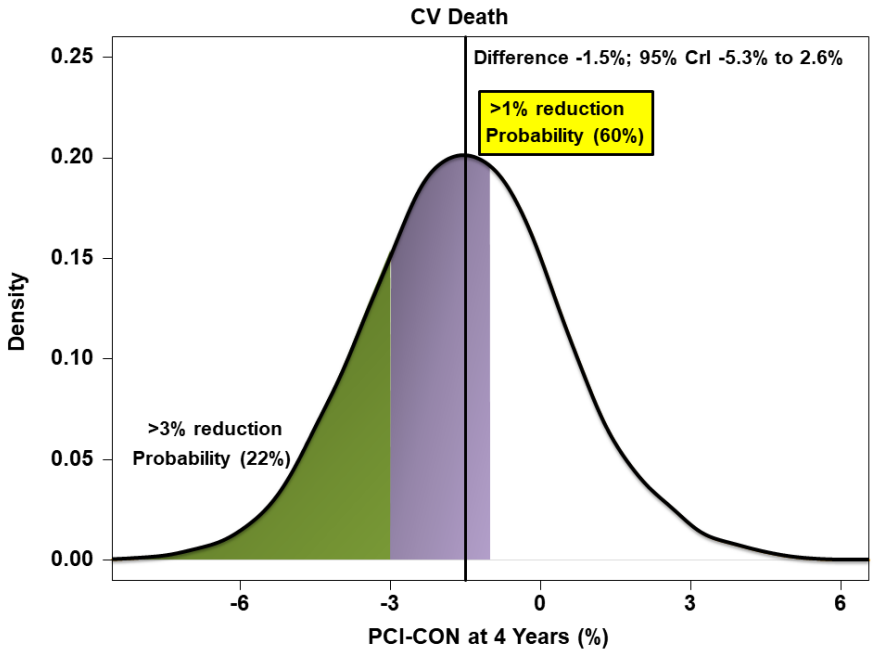


Supplementary Figure 4. PCI versus CON in patients with 3-vessel disease: outcome of death.

A) Cumulative risk estimates for the outcome of death; B) Posterior probability for the outcome of death.

A)

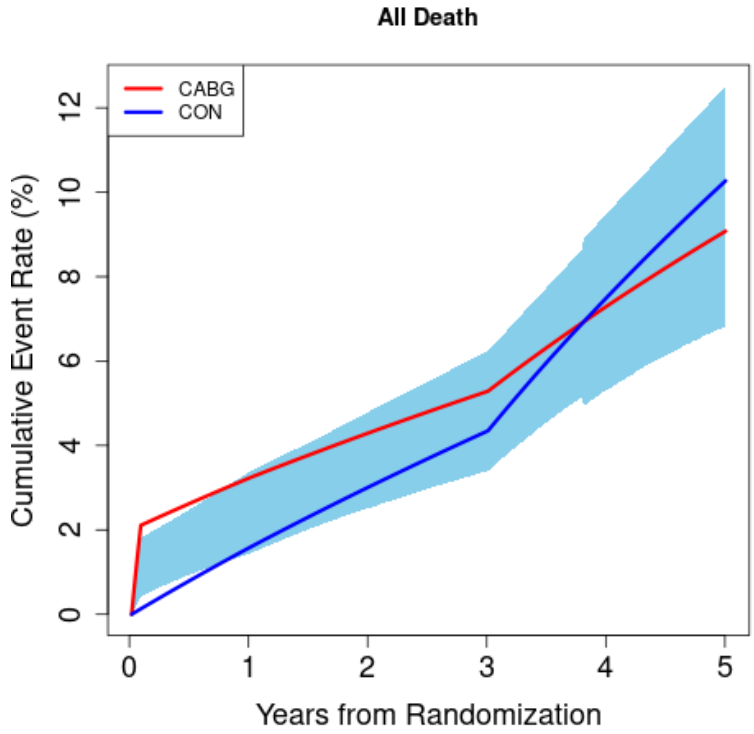
B)



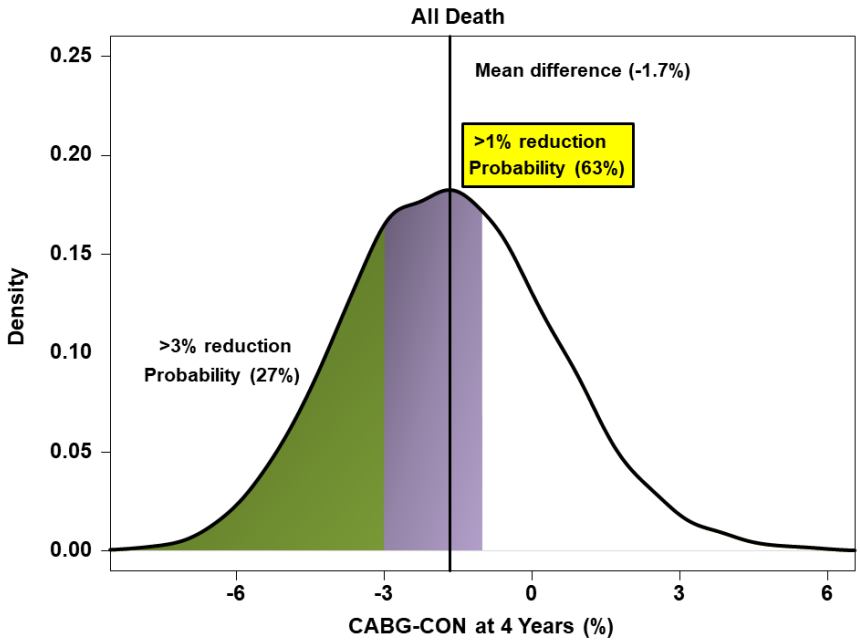
Supplementary Figure 5. PCI versus CON in patients with 3-vessel disease: outcome of CV death.

A) Cumulative risk estimates for the outcome of CV death; B) Posterior probability for the outcome of CV death.

A)



B)

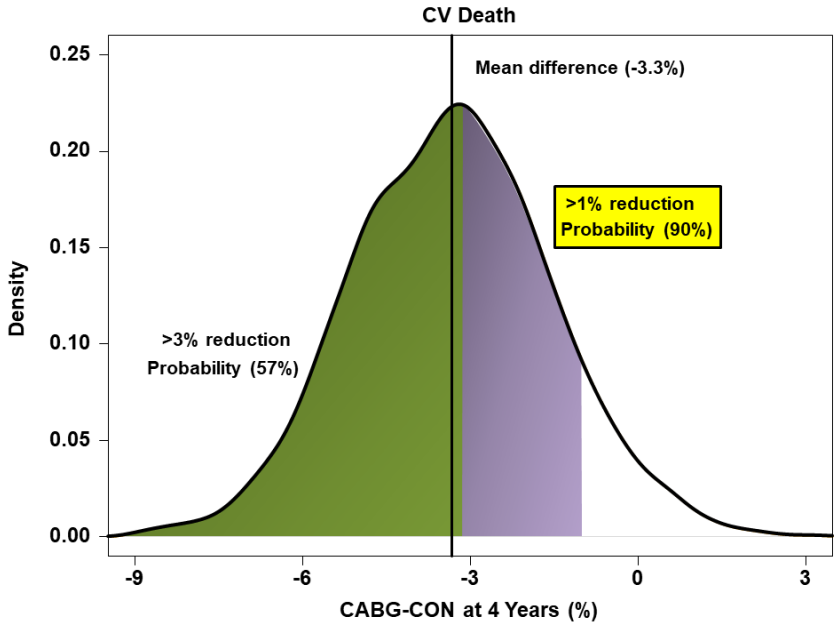


Supplementary Figure 6. CABG versus CON in patients with 3-vessel disease: outcome of death.

A) Cumulative risk estimates for the outcome of death; B) Posterior probability for the outcome of death.

A)

B)



Supplementary Figure 7. CABG versus CON in patients with 3-vessel disease: outcome of CV death.

A) Cumulative risk estimates for the outcome of CV death; B) Posterior probability for the outcome of CV death.