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ORIGINAL INVESTIGATIONS

Impact of Complete Revascularization in the ISCHEMIA Trial

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ABSTRACT

BACKGROUND Anatomic complete revascularization (ACR) and functional complete revascularization (FCR) have been associated with reduced death and myocardial infarction (MI) in some prior studies. The impact of complete revascularization (CR) in patients undergoing an invasive (INV) compared with a conservative (CON) management strategy has not been reported.

OBJECTIVES Among patients with chronic coronary disease without prior coronary artery bypass grafting randomized to INV vs CON management in the ISCHEMIA (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches) trial, we examined the following: 1) the outcomes of ACR and FCR compared with incomplete revascularization; and 2) the potential impact of achieving CR in all INV patients compared with CON management.

METHODS ACR and FCR in the INV group were assessed at an independent core laboratory. Multivariable-adjusted outcomes of CR were examined in INV patients. Inverse probability weighted modeling was then performed to estimate the treatment effect had CR been achieved in all INV patients compared with CON management.

RESULTS ACR and FCR were achieved in 43.4% and 58.4% of 1,824 INV patients. ACR was associated with reduced 4-year rates of cardiovascular death or MI compared with incomplete revascularization. By inverse probability weighted modeling, ACR in all 2,296 INV patients compared with 2,498 CON patients was associated with a lower 4-year rate of cardiovascular death or MI (difference −3.5; 95% CI: −7.2% to 0.0%). In comparison, the event rate difference of cardiovascular death or MI for INV minus CON in the overall ISCHEMIA trial was −2.4%. Results were similar but less pronounced with FCR.

CONCLUSIONS The outcomes of an INV strategy may be improved if CR (especially ACR) is achieved. (International Study of Comparative Health Effectiveness With Medical and Invasive Approaches [ISCHEMIA]; NCT01471522)
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ABBREVIATIONS AND ACRONYMS

ACR = anatomic complete revascularization

CABG = coronary artery bypass grafting

CON = conservative

CR = complete revascularization

FCR = functional complete revascularization

ICR = incomplete revascularization

INV = invasive

IPW = inverse probability weight/weighting

MI = myocardial infarction

PCI = percutaneous coronary intervention

Despite advances in coronary artery bypass graft surgery (CABG) and percutaneous coronary intervention (PCI), reduced rates of cardiovascular death and myocardial infarction (MI) have not been demonstrated in most randomized trials of revascularization compared with medical therapy in chronic coronary disease (CCD).[1-3] One factor that may have contributed to these neutral results is not achieving complete revascularization (CR) of all diseased coronary artery segments. In a large-scale randomized trial of patients with ST-segment elevation myocardial infarction (STEMI) and multivessel disease, PCI of all anatomically obstructive lesions in noninfarct arteries reduced cardiovascular death or MI compared with infarct artery recanalization alone.[4] An equivalent trial, however, has not been performed in patients with CCD (or non-STEMI), although achieving CR has been associated with reduced cardiovascular death and MI in the majority of >50 observational CCD studies.[5]

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Furthermore, the rate of incomplete revascularization (ICR) has been reported to be greater after PCI than after CABG (56% vs 25%, respectively, in a meta-analysis of 35 studies and 89,883 patients[6]), a finding that may contribute to differences in outcomes between these procedures in complex CCD. Not all studies, however, have shown an association between ICR and adverse outcomes, and few reports have adjusted for imbalances in baseline clinical and anatomic characteristics that may affect prognosis. Moreover, most prior studies neither prespecified a CR definition nor assessed the extent of revascularization at an independent quantitative coronary angiography (QCA) core laboratory. Whether the goal of revascularization should be to restore perfusion to all atherosclerotic diseased segments or only to those that are flow-limiting is also undetermined.[5] Finally, the potential impact of achieving CR in CCD patients undergoing invasive (INV) compared with conservative (CON) management has not been reported.

In the ISCHEMIA (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches) trial, 5,179 patients with CCD and at least moderate ischemia were randomized to an initial INV strategy (angiography and revascularization with PCI or CABG as appropriate per site discretion) plus medical therapy vs an initial CON strategy of medical therapy alone with angiography and revascularization reserved for medical therapy failure. The rates of cardiovascular death or MI between the groups were not statistically different at median 3.2-year follow-up.[3] An analysis of the extent of revascularization in ISCHEMIA was prespecified, and a comprehensive QCA methodology was developed to prospectively assess the completeness of both anatomic and functional (ischemic) revascularization.[7] The present report describes the findings from the ISCHEMIA Completeness of Revascularization study on cardiovascular events. The impact of CR on quality-of-life outcomes will be reported separately.[8]

METHODS

THE ISCHEMIA TRIAL. The design and principal results from the ISCHEMIA trial have been published.[3,9] Patients with CCD and at least moderate ischemia on a stress test were randomized 1:1 to INV vs CON management at 320 sites in 37 countries. The major exclusion criteria included unacceptable angina or NYHA functional class III or IV heart failure (HF), left

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ventricular ejection fraction (LVEF) <35%, estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2 or dialysis, acute coronary syndrome (ACS) within 2 months, prior PCI or CABG within 1 year, and left main (LM) or nonobstructive coronary artery disease (CAD) (<50% stenosis in all major coronary arteries) on a blinded computed tomographic angiography scan performed before randomization in patients with an eGFR ≥60 mL/min/1.73 m^2. Shortly after enrollment began, the protocol was modified to exclude patients with prior CABG because a large proportion were found to be unsuitable for revascularization. The primary endpoint was a composite of cardiovascular death, MI, or hospitalization for unstable angina, HF, or resuscitated cardiac arrest. The major secondary outcome was the composite of cardiovascular death or MI. The study was approved by the Institutional Review Board or ethics committee at each site, and all patients provided written informed consent. The trial was funded by the U.S. National Heart, Lung, and Blood Institute with additional support from industry, and is registered at clinicaltrials.gov (NCT01471522).

COMPLETENESS OF REVASCULARIZATION SUBSTUDY OBJECTIVES AND METHODOLOGY. The present study had 2 principal objectives: 1) to assess the frequency and outcomes of anatomic complete revascularization (ACR) and functional (ischemic) complete revascularization (FCR) compared with ICR in CCD patients assigned to INV in whom revascularization was performed; and 2) to assess the impact that achieving CR in all patients randomized to INV management might have had compared with CON management.

Prespecified definitions were developed for ACR and FCR that accounted for reference vessel diameter (RVD), diameter stenosis (DS) severity, and the myocardial distribution of ischemia.[7] QCA was performed at an independent angiographic core laboratory (Cardiovascular Research Foundation) blinded to clinical outcomes. For ACR, revascularization was required of all lesions with QCA-DS ≥50% in vessels with QCA-RVD ≥2.0 mm. This was determined by QCA of the PCI-procedure angiograms and by core laboratory review of the baseline angiogram and operative reports after CABG (accounting for diseased side branches and retrograde flow into diseased segments). For FCR, the lesions requiring revascularization (all in vessels with RVD ≥2.0 mm) were determined by a combination of stenosis severity and certainty of localization of ischemia. Significant lesions were those with localizing pressure wire-based abnormal physiology plus QCA-DS ≥30%; with localizing noninvasive stress (nuclear, echocardiography, or cardiac magnetic resonance) imaging evidence of ischemia in the vessel distribution plus QCA-DS ≥50%; with nonlocalizing severe ischemia by electrocardiographic stress test without imaging plus QCA-DS ≥60%; or with QCA-DS ≥70% in the absence of ischemia. Further details are provided in Supplemental Figures 1 to 3.[7]

ANALYSIS COHORTS AND ENDPOINTS. Specific analysis cohorts were comprised for each study objective. Patients with prior CABG enrolled before the protocol amendment were excluded from all analyses given their fundamental differences in eligibility for revascularization and QCA analytic challenges. INV patients were also excluded if angiographic images or operative reports necessary for core laboratory assessment of CR were absent or incomplete. The Objective 1 cohort included all INV patients in whom revascularization with PCI (including planned staged procedures), CABG, or a hybrid approach (planned PCI plus CABG) was performed within 6 months and before a primary endpoint event, and in whom at least 1 qualifying lesion was present meeting the prespecified anatomic or ischemic criteria necessitating revascularization. The Objective 2 cohort included all INV patients in whom the extent of revascularization could be assessed and all CON patients.

The prespecified primary outcome for the present analysis was the 4-year composite of cardiovascular death or MI, the endpoints most likely affected by CR. The primary MI definition from ISCHEMIA was used for all principal analyses. As a sensitivity analysis, the secondary MI definition from ISCHEMIA was used.[7] Additional outcomes analyzed included the ISCHEMIA trial composite primary endpoint and its components and all-cause death. All outcomes data are reported, although the 4-year results are emphasized because the number of patients with follow-up declined substantially thereafter.

STATISTICAL METHODOLOGY. Categorical variables were compared using the chi-square test. Continuous variables were compared using the Wilcoxon rank sum test. Parallel analyses were performed for ACR and FCR and for each clinical endpoint. Unadjusted cumulative event probabilities were estimated using the Kaplan-Meier method for endpoints that were not subject to competing risks (eg, all-cause death) and with a nonparametric cumulative incidence function estimator for endpoints that were subject to competing risks (eg, cardiovascular death, for which noncardiovascular death is a competing risk).

TABLE 1 Multivariable Predictors of Complete Revascularization

	Anatomic CR		Functional CR	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Geography of enrollment				
Asia vs North America	0.90 (0.59-1.35)	0.60	0.82 (0.55-1.22)	0.32
Europe vs North America	0.96 (0.69-1.33)	0.80	0.86 (0.62-1.19)	0.36
Latin America/other vs North America	1.19 (0.77-1.83)	0.44	0.91 (0.60-1.38)	0.66
Clinical characteristics				
Age, per 5 y	0.95 (0.89-1.03)	0.22	0.97 (0.90-1.04)	0.35
Female	1.06 (0.78-1.43)	0.71	0.93 (0.69-1.24)	0.61
Hypertension	0.85 (0.64-1.12)	0.25	0.93 (0.71-1.23)	0.62
Diabetes mellitus	1.43 (1.11-1.84)	0.006	1.35 (1.06-1.73)	0.02
Current smoker	0.88 (0.60-1.28)	0.49	0.87 (0.61-1.23)	0.42
Prior myocardial infarction	1.03 (0.72-1.46)	0.89	0.95 (0.67-1.33)	0.74
History of heart failure	1.26 (0.67-2.37)	0.48	1.53 (0.84-2.79)	0.16
History of cerebrovascular disease or stroke	0.84 (0.54-1.33)	0.46	0.76 (0.48-1.18)	0.22
Peripheral arterial disease	1.19 (0.65-2.16)	0.58	0.72 (0.41-1.26)	0.25
Prior PCI	0.73 (0.52-1.03)	0.07	0.84 (0.60-1.16)	0.29
Left ventricular ejection fraction, per 5%	0.96 (0.89-1.04)	0.36	1.01 (0.93-1.09)	0.87
Body mass index, per 5 kg/m^2	0.85 (0.74-0.97)	0.02	0.80 (0.70-0.92)	0.001
eGFR, per 5 mL/min/1.73 m^2	1.01 (0.98-1.04)	0.59	1.00 (0.97-1.03)	0.92
SAQ7-AF score, per 5 points	1.00 (0.96-1.03)	0.77	1.00 (0.97-1.03)	0.86
NYHA functional class, II vs I or none	1.15 (0.83-1.60)	0.41	1.06 (0.77-1.46)	0.72
Qualifying stress test (core laboratory assessment)				
Imaging stress test performed	1.34 (0.94-1.91)	0.10	1.23 (0.88-1.73)	0.22
Moderate ischemia vs absent or mild	0.86 (0.55-1.34)	0.51	0.71 (0.45-1.11)	0.13
Severe ischemia vs absent or mild	1.01 (0.65-1.56)	0.97	1.01 (0.65-1.57)	0.98
Baseline invasive coronary angiography (core laboratory assessment)				
Diseased vessels: 2 vs <2	0.41 (0.29-0.57)	<0.0001	0.56 (0.40-0.77)	0.0004
Diseased vessels: 3 vs <2	0.37 (0.22-0.62)	0.0002	0.55 (0.36-0.83)	0.005
Duke Jeopardy score (per 1 U)	1.20 (1.07-1.34)	0.001	1.07 (0.96-1.19)	0.21
Number of lesions	0.37 (0.31-0.44)	<0.0001	0.41 (0.35-0.48)	<0.0001
SYNTAX score per 5	0.89 (0.79-1.00)	0.05	0.91 (0.82-1.01)	0.09
CTOs: 1 vs 0	0.53 (0.39-0.71)	<0.0001	0.46 (0.36-0.60)	<0.0001
CTOs: 2+ vs 0	0.86 (0.48-1.55)	0.62	0.54 (0.32-0.91)	0.02
Left main disease	2.60 (1.23-5.48)	0.01	1.30 (0.65-2.58)	0.46
Proximal LAD disease	1.41 (1.06-1.87)	0.02	1.47 (1.12-1.93)	0.005
Number of lesions with mod/sev calcification	1.16 (1.05-1.29)	0.005	1.02 (0.93-1.12)	0.70
Number of lesions with mod/sev tortuosity	0.93 (0.81-1.06)	0.25	0.92 (0.82-1.03)	0.17
Procedural data				
First revascularization CABG vs PCI	2.29 (1.64-3.21)	<0.0001	1.89 (1.39-2.58)	<0.0001
Fractional flow reserve done	0.97 (0.71-1.33)	0.87	1.23 (0.91-1.67)	0.18
Intravascular ultrasound done	1.05 (0.49-2.26)	0.90	1.03 (0.47-2.23)	0.95

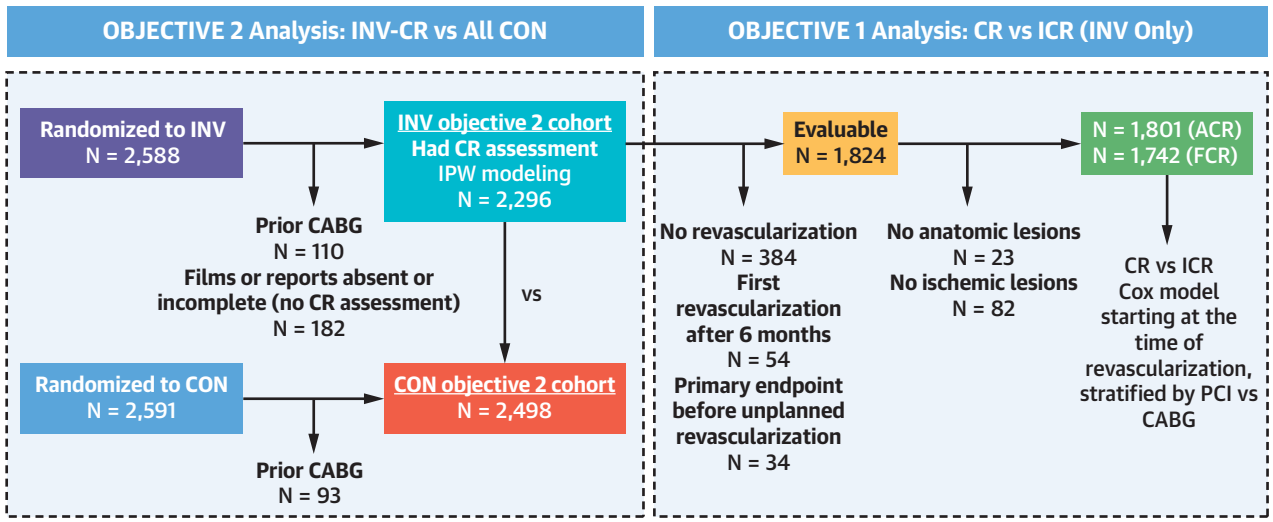
CABG = coronary artery bypass grafting surgery; CR = complete revascularization; CTO = chronic total occlusion; eGFR = estimated glomerular filtration rate; LAD = left anterior descending coronary artery; mod/sev = moderate or severe; PCI = percutaneous coronary intervention; SAQ7-AF – Seattle Angina Questionnaire 7, Angina Frequency; SYNTAX = Synergy Between Percutaneous Coronary Intervention With TAXUS and Cardiac Surgery.

For Objective 1, analyses were performed in the INV group with follow-up beginning at the time of first revascularization. Multivariable predictors of CR vs ICR were identified using logistic regression adjusted for the covariates in Table 1. Adjusted outcomes of CR vs ICR were compared in Cox models adjusting for the same covariates and PCI vs CABG.

For Objective 2, statistical analysis focused on inferring the outcomes that would be observed had a large cohort resembling ISCHEMIA participants achieved CR after randomization compared with CON. As a nonrandomized comparison, statistical adjustments were used to control for differences between INV participants who did and did not undergo CR. The determinants of receiving vs not receiving CR were included in the adjustment procedure.

For endpoints subject to competing risks, we fit separate parallel Cox models for the endpoint and competing risk event. Because randomization was before invasive angiography, we required a CR

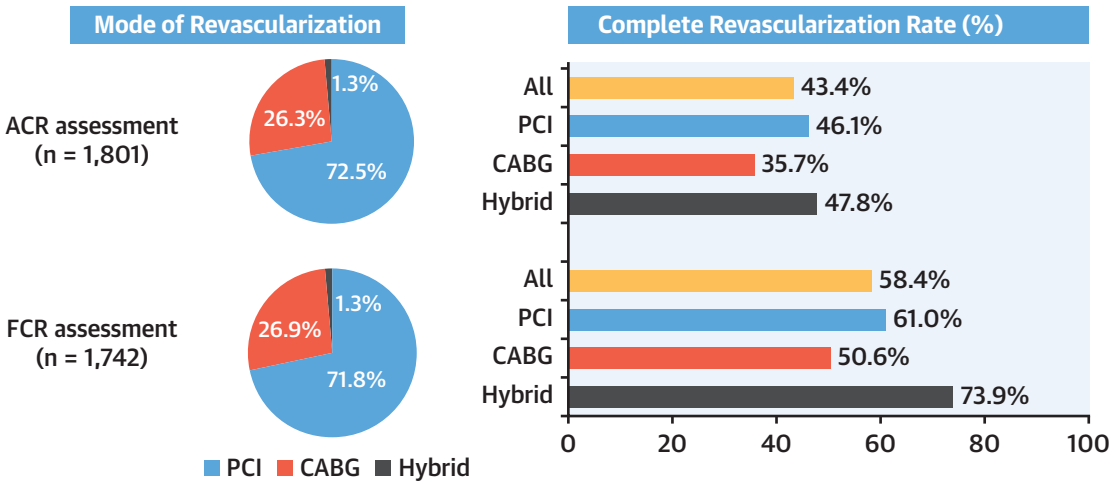
FIGURE 1 **Derivation of the Patient Cohorts**



For Objective 1 **(right)**, among invasive treatment strategy (INV)–assigned patients, the impact of achieving anatomic complete revascularization (ACR) and functional complete revascularization (FCR) vs incomplete revascularization (ICR) was assessed in 1,801 and 1,742 patients, respectively. For Objective 2 **(left)**, IPW with complete revascularization (CR) as a time-dependent variable was used to estimate the hypothetical ideal treatment effect for 2,296 INV-assigned patients without prior coronary artery bypass grafting (CABG) in whom the completeness of revascularization could be assessed by the angiographic core laboratory and who received CR at the time of randomization, compared with conservative treatment strategy (CON) management in 2,498 patients without prior CABG. IPW = inverse probability weighting; PCI = percutaneous coronary intervention.

definition that allowed all ISCHEMIA participants, regardless of anatomy, to be candidates for the strategy. Patients without significant lesions at baseline according to the prespecified ACR and FCR criteria in the previous text[7] were thus included as a distinct stratum within each Cox model and were considered to have CR; exclusion of such participants was not possible because of the lack of invasive angiography in the CON group. Instead, we relied on randomization to ensure an approximately equal prevalence of such participants in each treatment group. Among patients with significant lesions, CR was modeled as a time-dependent covariate with a regression parameter (HR) that was also assumed to be time-varying. Inverse-probability weights (IPWs) were incorporated in the Cox models to account for exclusion of patients with missing data and to adjust for nonrandom selection for CR. To construct the IPWs, we fit 2 models: 1) a logistic regression model predicting availability of an evaluable invasive baseline angiogram using baseline covariates available for all participants (region of enrollment, age, sex, hypertension, diabetes, smoking, prior MI, HF, NYHA functional class, cerebrovascular disease, peripheral arterial disease, prior PCI, LVEF, body mass index [BMI], eGFR, Seattle Angina Questionnaire 7 Angina Frequency, and stress test type and severity of ischemia); and 2) a Cox model predicting achievement of CR based on the model 1 covariates plus the following additional covariates from the baseline angiogram: number of diseased vessels, Duke jeopardy score,[10] SYNTAX score,[11] number of chronic total occlusions (CTOs), moderate/severe calcification,[12] moderate/severe tortuosity,[13] use of fractional flow reserve, use of intravascular ultrasound, numbers of anatomically and functionally significant lesions as defined in the ACR and FCR assessment algorithms, respectively, and the presence of obstructive LM and proximal left anterior descending (PLAD) disease. Within each combination of patient and week of follow-up, the data were weighted inversely by the product of the patient's predicted probability of having an evaluable angiogram (model 1) multiplied by the predicted probability of the patient's observed CR history (model 2). The goal of this weighting adjustment was to mimic a trial in which selection for CR and its timing were assigned randomly.[14] Before fitting weighted Cox models, the IPW's ability to balance measured covariates was assessed by summarizing covariate distributions of patients with and without CR within each week of follow-up in the weighted cohort. After confirming satisfactory balance and fitting the weighted Cox models, the resulting estimated hazard rate functions were

FIGURE 2 **Mode and Completeness of Revascularization in Revascularized Invasive Treatment Strategy Patients**



(Left) The type of first revascularization procedure performed in 1,824 patients assigned to an invasive management strategy in whom revascularization was completed within 6 months after randomization. **(Right)** Rates of anatomic complete revascularization **(top)** and functional complete revascularization **(bottom)** achieved in all patients and by revascularization modality. PCI was performed in approximately three-quarters of patients. In these unadjusted analyses, complete revascularization was achieved more frequently with PCI than coronary artery bypass grafting. Abbreviations as in Figure 1.

evaluated under the condition that CR was achieved on the day of randomization. Hazard rates were then converted into cumulative event probabilities (cumulative incidence functions) representing the event rates that would be expected had INV participants all achieved prompt CR.

RESULTS

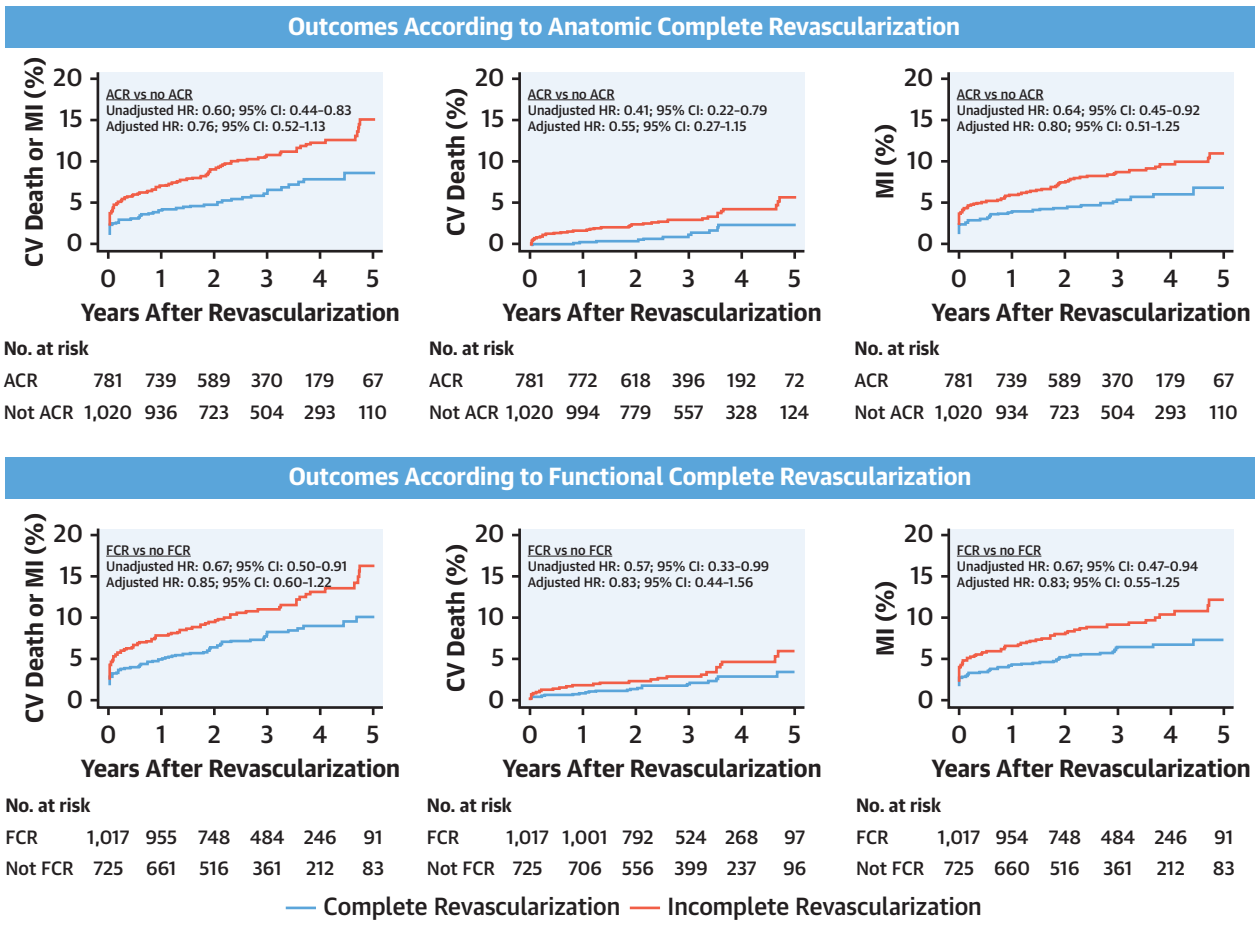
PATIENT POPULATIONS AND ANALYSIS COHORTS. As shown in Figure 1, among 2,588 patients randomized to INV, 292 were excluded either because of prior CABG or unavailability of films or reports required for core laboratory CR assessment. After further excluding those in whom revascularization was not performed within 6 months or before a primary endpoint event and those without qualifying lesions, Objective 1 (assessment of the frequency and impact of ACR and FCR in INV-assigned patients) was evaluable in 1,801 and 1,742 patients, respectively. For Objective 2 (assessment of the potential impact of having obtained CR in all INV patients), IPW adjustment to model ACR or FCR was performed on 2,296 INV-assigned patients who were then compared with 2,498 CON-assigned patients.

OBJECTIVE 1. Frequency and predictors of CR in INV. Among 1,801 INV patients evaluable for ACR assessment, PCI, CABG, and hybrid revascularization were performed in 1,305 (72.5%), 473 (26.3%), and 23 (1.3%), respectively. ACR was achieved in 781 (43.4%) patients. Among 1,742 INV patients evaluable for FCR assessment, PCI, CABG, and hybrid revascularization were performed in 1,251 (71.8%), 468 (26.9%), and 23 (1.3%), respectively. FCR was achieved in 1,017 (58.4%) patients. ACR and FCR results per revascularization modality are shown in Figure 2.

Baseline characteristics and treatment of INV patients with vs without ACR and FCR are shown in Supplemental Tables 1 to 5 and Supplemental Tables 6 to 10, respectively. By multivariable analysis (Table 1), independent clinical predictors of both ACR and FCR included diabetes mellitus as well as lower BMI. Independent angiographic predictors of CR included less extensive CAD (fewer number of diseased vessels and lesions, lower SYNTAX score, absence of CTOs) and LM or PLAD disease. Finally, despite the higher unadjusted rates of CR after PCI compared with CABG, after adjustment for between-group differences in baseline clinical and angiographic characteristics, revascularization by CABG rather than PCI was an independent predictor of both ACR and FCR. Age, sex, renal function, LV function, severity of ischemia and enrollment geography were unrelated to achievement of CR.

Impact of CR compared with ICR in INV. Outcomes in INV patients with vs without ACR and FCR are

FIGURE 3 **Relationship Between Complete Revascularization and Outcomes With Invasive Management**



The 5-year time-to-first event rates are shown for cardiovascular (CV) death or myocardial infarction (MI) **(left)**, CV death **(middle)**, and MI **(right)** in 1,824 invasive treatment-assigned patients according to the achievement of ACR **(top)** and FCR **(bottom).** Complete revascularization was associated with reduced rates of both CV death and MI (more so after ACR than FCR), although the relative reduction was attenuated after adjustment for differences in baseline clinical and angiographic characteristics. Abbreviations as in **Figure 1**.

shown in **Figure 3**, **Table 2**, and Supplemental Tables 11 to 13. In unadjusted analyses, both ACR and FCR compared with ICR were strongly associated with reduced rates of cardiovascular death and MI during follow-up. However, after accounting for differences in clinical and anatomic characteristics in patients with CR vs ICR, the benefits of both ACR and FCR were attenuated. These results were consistent using the secondary MI definition (Supplemental Tables 14 and 15).

OBJECTIVE 2. Patient characteristics and IPW modeling. Among 2,296 INV patients evaluable for CR assessment, PCI, CABG, and hybrid revascularization were performed in 1,341 (58.4%), 489 (21.3%), and 28 (1.2%) respectively, and 438 (19.1%) of patients were treated medically without revascularization within 6 months. ACR and FCR were achieved in 1,000 (43.6%) and 1,344 (58.5%) patients, respectively (**Figure 4**). Baseline characteristics and treatment of all 2,296 INV patients, and those with vs without ACR and FCR compared with 2,498 CON patients are shown in Supplemental Tables 16 to 19 and Supplemental Tables 20 to 23, respectively. IPW adjustment mitigated the baseline differences between patients with and without CR (Supplemental Figure 4).

Impact of achieving CR in all INV patients compared with CON. The 4-year unadjusted event rates in the INV group (all patients and according to whether ACR or FCR was achieved) compared with CON are shown in Supplemental Tables 24 and 25. Outcomes after IPW-adjustment to model CR in all

TABLE 2 Objective 1: Outcomes With Complete vs Incomplete Revascularization

	Anatomic Complete Revascularization Present vs Absent		Functional Complete Revascularization Present vs Absent	
	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Cardiovascular death or MI	0.60 (0.44-0.83)	0.76 (0.52-1.13)	0.67 (0.50-0.91)	0.85 (0.60-1.22)
Cardiovascular death	0.41 (0.22-0.79)	0.55 (0.27-1.15)	0.57 (0.33-0.99)	0.83 (0.44-1.56)
MI	0.64 (0.45-0.92)	0.80 (0.51-1.25)	0.67 (0.47-0.94)	0.83 (0.55-1.25)
All-cause death	0.65 (0.42-1.02)	0.66 (0.39-1.13)	0.80 (0.53-1.21)	0.90 (0.55-1.47)
Primary endpoint[a]	0.61 (0.45-0.82)	0.79 (0.55-1.14)	0.71 (0.54-0.94)	0.96 (0.68-1.34)

Outcomes are shown in 1,824 invasive management-assigned patients who had a revascularization procedure performed within 6 months after randomization. [a]Composite rate of cardiovascular death, myocardial infarction (MI), or hospitalization for unstable angina, heart failure, or resuscitated cardiac arrest.

patients in the INV group compared with all patients in the CON group are shown in **Figure 5**, **Table 3**, and Supplemental Tables 26 and 27. Modeling the achievement of ACR in all INV patients was associated with a reduction in the adjusted 4-year rate of cardiovascular death or MI of −3.5% (95% CI: −7.2% to 0.0%) compared with CON. Modeling the achievement of FCR in all INV patients was associated with a reduction in the adjusted 4-year rate of cardiovascular death or MI of −2.7% (95% CI: −5.9% to 0.3%). These results were consistent in a sensitivity analysis using covariate-adjusted Cox models (Supplemental Tables 28 and 29).

To place these outcomes in perspective, the results of INV vs CON management in the overall ISCHEMIA trial intention-to-treat (ITT) population that includes patients with ICR as well as with CR (but excluding patients with prior CABG) are shown in Supplemental Table 30. The INV strategy in the overall ISCHEMIA trial resulted in a reduction in the 4-year rate of cardiovascular death or MI of −2.4% (95% CI: −4.5% to −0.2%) compared with CON management in patients without prior CABG.

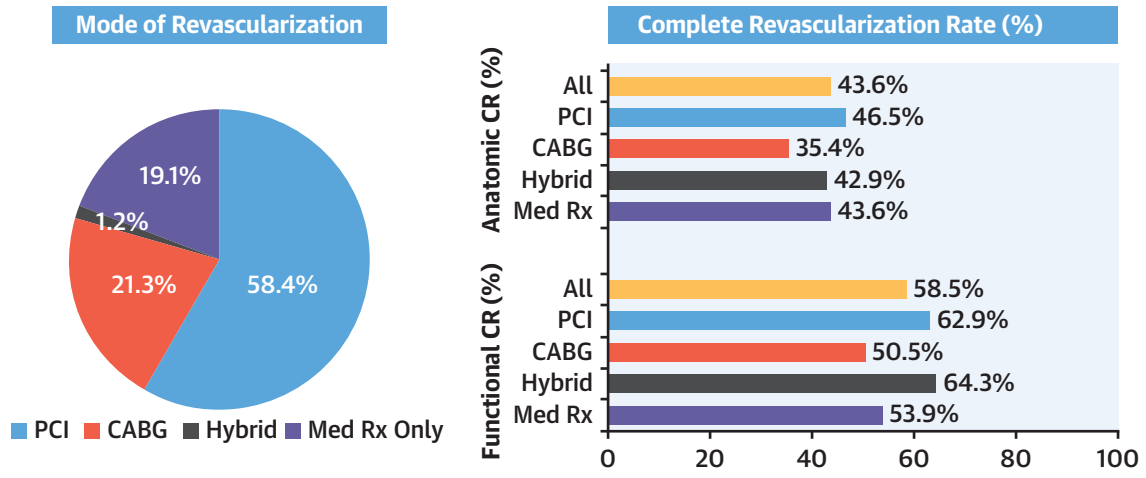
DISCUSSION

The **Central Illustration** summarizes the major findings from the ISCHEMIA Completeness of Revascularization study.

1. By QCA core laboratory assessment, only 43.4% and 58.4% of revascularization procedures in INV-assigned patients achieved prespecified criteria for ACR and FCR respectively. These rates were nearly identical for the entire INV cohort (43.6% and 58.5%, respectively), among whom 19.1% of patients were treated with medical therapy only (by definition affording CR status to those patients without qualifying severe lesions at baseline).
2. Independent predictors of CR were less extensive CAD (lower SYNTAX score and absence of CTO lesions), LM or PLAD disease, and diabetes and lower BMI.
3. Unadjusted CR rates were higher after PCI than CABG. However, after accounting for the substantial differences in baseline clinical characteristics and coronary anatomy between the groups, revascularization by CABG rather than PCI was an independent predictor of CR.
4. Among INV patients undergoing revascularization, achieving ACR and FCR were strongly associated with lower rates of cardiovascular death and MI. However, after adjusting for comorbidities and extent of disease, the magnitude of these associations was attenuated.
5. An INV strategy in which all patients achieved ACR at the time of randomization was associated with an absolute 3.5% lower 4-year rate of cardiovascular death or MI compared with CON in a model-based simulation using IPW to adjust for nonrandom treatment selection. This reduction compares with an absolute 2.4% lower 4-year rate of cardiovascular death or MI with the INV approach compared with CON in the overall ISCHEMIA trial, not accounting for the extent of revascularization.
6. The results with FCR were directionally similar as with ACR, but in most analyses, the benefits were not as pronounced.

In unadjusted analyses, ACR and FCR compared with ICR were strongly associated with reduced 4-year rates of cardiovascular death or MI (HRs: 0.60 and 0.67, respectively). These risk reductions were lessened (HRs: 0.76 and 0.85, respectively) and were no longer significant after accounting for baseline covariates and the extent of CAD. In this regard, most prior studies that reported large benefits of CR in

FIGURE 4 Mode and Completeness of Revascularization in All Invasive Treatment Strategy Patients



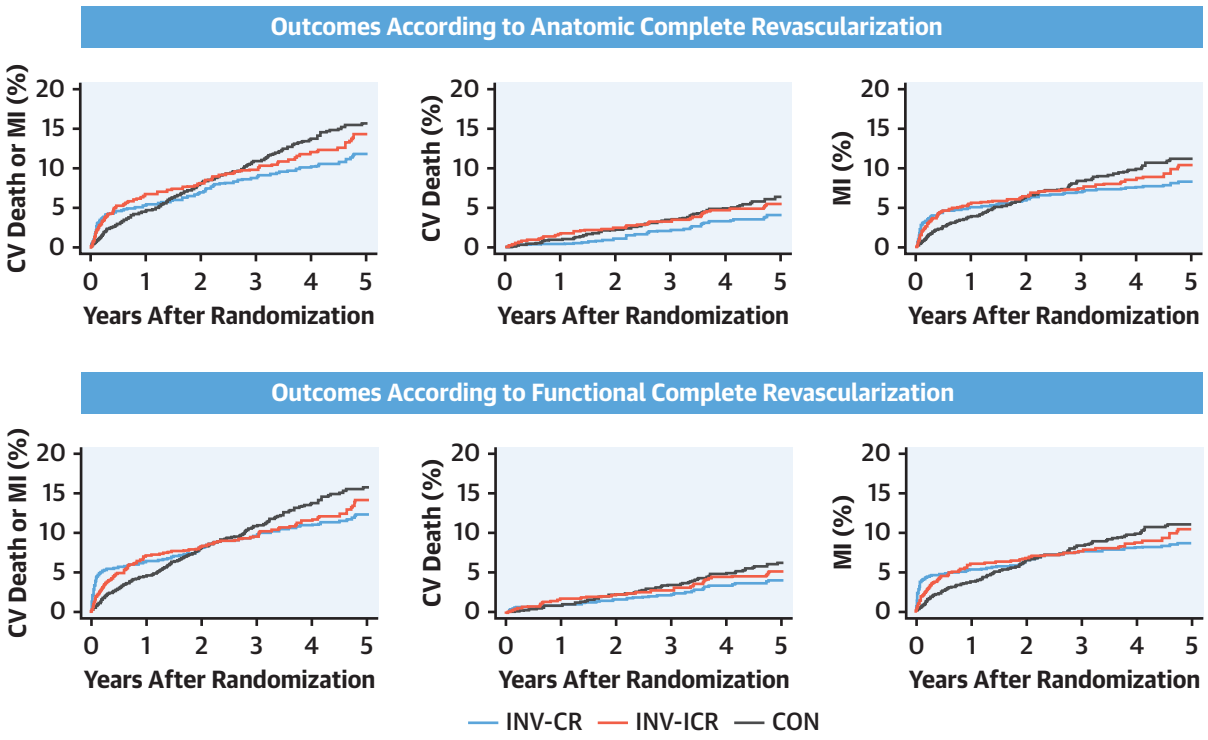
(Left) The type of first revascularization procedure performed or treatment with medical therapy alone in 2,296 patients within 6 months after randomization to an invasive management strategy. **(Right)** Rates of anatomic CR **(top)** and functional CR **(bottom)** achieved in all patients and by treatment modality. In these unadjusted analyses, CR was achieved more frequently with PCI than CABG. Abbreviations as in Figure 1.

reducing death and MI did not adjust their outcomes for these confounding factors.[5] These findings emphasize the importance of accounting for the severity of coronary disease and other comorbidities when evaluating the prognostic impact of CR. Nonetheless, the adjusted point estimates remained in favor of CR, consistent with a SYNTAX trial report in which the extent of residual disease was an independent predictor of mortality after adjusting for these covariates.[15] Considering the present findings in the context of prior results,[5] we believe it is likely that CR is associated with an improved prognosis, although the magnitude of this effect may be less than generally advocated from prior unadjusted studies.

A novel aspect of the present study is that within the context of a randomized trial, we were able to model the potential effect that CR may have had on an INV compared with a CON approach had all INV patients been completely revascularized. In the fully adjusted analysis, an INV strategy with ACR in all patients yielded 4-year reductions in cardiovascular death or MI, cardiovascular death alone, MI alone, and the ISCHEMIA trial 5-component primary composite endpoint of −3.5%, −1.7%, −2.3%, and −3.5%, respectively, compared with CON. To place these outcomes in perspective, from the overall ISCHEMIA trial (also excluding prior CABG patients), in whom INV outcomes included anatomic ICR in 56.4% of patients, the magnitude of these reductions with INV compared with CON were −2.4%, −0.9%, −1.3%, and −2.5% respectively. These comparative outcomes represent a best-case scenario that ACR may deliver because they assume no penalty of greater procedural complications in attempting to achieve CR in the complex lesions that most commonly result in ICR (eg, CTOs, diffuse disease). Moreover, all-cause mortality was nearly identical with INV vs CON and was not affected by achievement of CR.

Both ACR and FCR have been linked with improved outcomes in prior studies,[5] but which of these 2 approaches is preferable is uncertain. In a small (n = 100) randomized trial, the 6-month rates of adverse cardiovascular events and graft patency after CABG were similar with an anatomy-guided vs ischemia-guided approach.[16] In the larger randomized FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) (n = 1,005) and FAVOR-III China (Comparison of Quantitative Flow Ratio Guided and Angiography Guided Percutaneous Intervention in Patients with Coronary Artery Disease) (n = 3,825) trials,[17,18] an ischemia-guided approach was superior to an angiography-guided approach of lesion selection for PCI in patients with CCD and stabilized ACS. In contrast, the randomized FUTURE (FUnctional Testing Underlying coronary REvascularization) trial (n = 927) was stopped early for increased mortality in patients in whom PCI was limited to functionally significant lesions compared with revascularization of all lesions with an angiographic DS >50%.[19] In the FLOWER-MI (Flow Evaluation to Guide Revascularization in Multivessel

FIGURE 5 **Outcomes After Complete and Incomplete Revascularization Compared With Conservative Management**



The 5-year IPW-adjusted time-to-first event rates are shown for CV death or MI **(left)**, CV death **(middle)**, and MI **(right)** according to the achievement of anatomic CR **(top)** and functional CR **(bottom)** in 2,296 patients assigned to INV management compared with 2,498 patients assigned to conservative (CON) management (excluding patients with prior CABG from both groups). CR (especially anatomic CR) was associated with reduced rates of both CV death and MI compared with both ICR and CON management. The outcomes in INV patients with ICR were roughly comparable to or slightly better than those in the CON group. Abbreviations as in Figures 1 and 3.

ST-Elevation Myocardial Infarction) trial (n = 1,163), patients with recent STEMI and multivessel disease randomized to ACR compared with FCR had similar 1-year rates of major adverse cardiovascular events but fewer cardiovascular hospitalizations, in part because of a 5.6% rate of MI arising from nonischemic deferred lesions in the FCR group.[20] Although FLOWER-MI was confined to STEMI, plaque rupture and thrombosis of high-risk thin-cap fibroatheromas may result in ACS and MI in CCD patients in the absence of ischemia.[21-23] The finding in the present study that ACR was associated with superior outcomes compared with FCR is also consistent with our previous report from ISCHEMIA that the extent of CAD was more strongly related to death and MI than the severity of ischemia.[24] Further studies are required to verify whether a strategy of achieving ACR is preferable to FCR because these approaches may not only affect prognosis but also resource utilization; an ACR-guided approach necessitates more stents and contrast use during PCI and additional grafts during surgery whereas an FCR-guided approach requires more diagnostic testing.

By QCA, less than one-half of INV patients achieved ACR and slightly more than one-half achieved FCR. These rates are lower than those reported from many but not all prior studies[5] and suggest ample opportunity for improvement. Although ISCHEMIA was a randomized trial with specific entry criteria rather than a "real-world" registry, these results may be generalizable because randomization occurred before angiography, resulting in a less biased CCD population than in prior studies. Because most physicians would agree CR is desirable, the observation that CR rates were slightly higher with PCI compared with CABG in unadjusted analyses suggests operators are selecting reasonably appropriate patients for PCI. Nonetheless, PCI achieved ACR in only 46.1% of patients, and the superiority of CABG in achieving both ACR and FCR was evident in multivariable analysis.

TABLE 3 Objective 2: 4-Year Adjusted Outcomes With Complete Revascularization Compared With Conservative Management

	ISCHEMIA Trial Modeled for Complete Revascularization in INV Group[a]					Overall ISCHEMIA Trial (ITT)[a]
	4-y Kaplan-Meier Estimated Event Rates, %			Difference (95% CI), %		Difference (95% CI), %
	INV With ACR (n = 2,296)	INV With FCR (n = 2,296)	CON (n = 2,498)	INV With ACR (n = 2,296) vs CON (n = 2,498)	INV With FCR (n = 2,296) vs CON (n = 2,498)	All INV (n = 2,478) vs CON (n = 2,498)
Cardiovascular death or MI	10.2	10.7	13.7	−3.5 (−7.2 to 0.0)	−2.7 (−5.9 to 0.3)	−2.4 (−4.5 to −0.2)
Cardiovascular death	3.2	2.7	4.9	−1.7 (−4.0 to 0.4)	−1.5 (−3.5 to 0.4)	−0.9 (−2.3 to 0.6)
MI	7.6	9.0	9.9	−2.3 (−5.4 to 0.7)	−1.8 (−4.6 to 0.9)	−1.3 (−3.1 to 0.5)
All-cause death	6.3	5.5	6.3	0.0 (−4.0 to 3.1)	0.0 (−2.5 to 2.3)	0.0 (−1.6 to 1.7)
Primary endpoint[b]	11.7	11.7	15.3	−3.5 (−7.4 to 0.2)	−2.1 (−5.3 to 1.2)	−2.5 (−4.8 to −0.3)

Outcomes are shown in 2,296 invasive treatment strategy (INV)-assigned patients modeled to have achieved anatomic complete revascularization (ACR) or functional complete revascularization (FCR) vs 2,498 conservative treatment strategy (CON)-assigned patients. [a]Excluding patients with prior coronary artery bypass graft surgery from both groups. [b]Composite rate of cardiovascular death, myocardial infarction (MI), or hospitalization for unstable angina, heart failure, or resuscitated cardiac arrest.

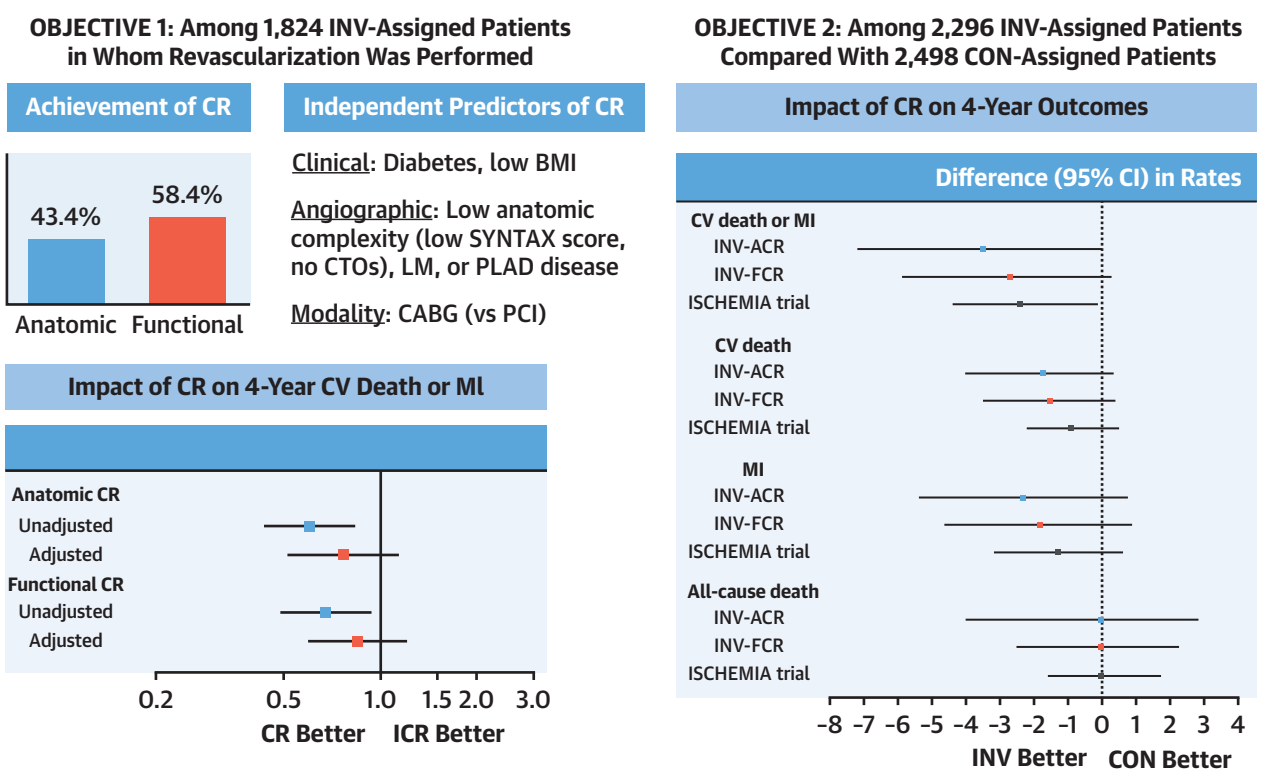
ISCHEMIA = International Study of Comparative Health Effectiveness with Medical and Invasive Approaches; ITT = intention-to-treat.

Some prior studies have also reported that CR is prognostically more strongly associated with outcomes after PCI than after CABG,[5,6,25] an issue not yet examined in ISCHEMIA. Although these findings collectively suggest that the INV outcomes in ISCHEMIA may have been improved had a greater proportion of INV-assigned patients been triaged to CABG, whether the higher CR rates that CABG may have achieved in these relatively lower-risk, less-complex PCI patients would have offset potentially greater surgical risks and resulted in improved net outcomes is unknown and can only be answered through randomized trials.

Importantly, the impact that CR in all INV patients may have had compared with CON management was assessed in the present study through IPW modeling. The ability to achieve CR is not always predictable, and whether striving for CR (especially ACR) in all cases of PCI and CABG would safely improve outcomes is unknown; the present results are therefore hypothesis-generating, warranting randomized trials of standard vs "more complete" revascularization in CCD (as have been done in STEMI[4,5]). Randomized trials are also warranted to establish whether an ACR strategy is preferable to a FCR approach (as suggested in the present study), and to identify whether an optimal threshold exists for "reasonable" ICR that might afford similar prognostic gains as CR with less patient risk and resource consumption.[5,15] Absent such trials (which will be difficult to conduct), our results, in concert with prior reports, conceptually support judicious attempts to achieve CR, especially ACR.

STUDY LIMITATIONS. First, because the treatment comparisons were not randomized, an important influence of unmeasured confounders cannot be excluded. Absent randomization, the findings represent associations and not causality. Second, although ISCHEMIA is the largest randomized trial to date to assess the impact of CR and arguably the most rigorous in terms of methodology, because of the contracted size of the CR cohorts (~50% of all INV patients), the 95% CIs around the point estimates for their effects were wider than for those from the entire unadjusted population. Third, the frequency of CR and its impact are dependent on the specific analysis parameters and definitions of ACR and FCR utilized, eg, the minimum RVD and DS of lesions required to be treated.[26] Future substudies will examine the impact of varying these and other variables. Fourth, for the Objective 2 analysis, 191 (8.3%) and 236 (10.3%) INV patients treated with medical therapy alone in whom obstructive lesions meeting the prespecified criteria were not present by core laboratory analysis were considered to have ACR and FCR respectively at baseline. Although these proportions are small and this approach is logical (the condition of CR is, by definition, met if at postprocedure the coronary tree is free from obstructive disease, regardless of treatment), unfortunately a sensitivity analysis excluding participants without significant lesions was not possible because of the lack of invasive angiography data in CON participants. Instead, our analysis strategy relied on randomization to ensure an approximately equal prevalence of participants without significant lesions in INV and CON. Fifth, a formal comparison of ICR vs CON would be of interest but was not performed. Because all patients with ICR by definition have significant lesions, a fair comparison of ICR vs CON would require eliminating CON participants without significant lesions. This was not possible because of the CON group's lack of invasive angiography. Nonetheless, as seen in Figure 5, the outcomes in INV patients with ICR were roughly

CENTRAL ILLUSTRATION **Impact of Complete Revascularization in the ISCHEMIA trial**



Stone GW, et al. J Am Coll Cardiol. 2023;82(12):1175–1188.

Objective 1 **(left)** assessed the frequency and impact of complete revascularization (CR) among patients assigned to invasive (INV) management. Objective 2 **(right)** assessed the impact that achieving CR in all patients assigned to INV would have had compared with conservative (CON) management. In the **right graph**, INV-anatomic complete revascularization (ACR) and INV-functional complete revascularization (FCR) vs CON represent the inverse probability weight (IPW)-modeled differences in rates. INV vs CON for the ISCHEMIA trial represents the unadjusted differences in rates from the overall ISCHEMIA trial intention-to-treat cohort. See text for details. BMI = body mass index; CABG = coronary artery bypass graft; CTO = chronic total occlusion; CV = cardiovascular; ICR = incomplete revascularization; ISCHEMIA = International Study of Comparative Health Effectiveness with Medical and Invasive Approaches; LM = left main; MI = myocardial infarction; PCI = percutaneous coronary intervention; PLAD = proximal left anterior descending artery; SYNTAX = Synergy Between Percutaneous Coronary Intervention With TAXUS and Cardiac Surgery.

comparable to or slightly better than those in the CON group. Sixth, the present analysis did not account for the use of medical therapies and other risk factor modification strategies, which vary over time and may be conditioned by whether CR vs ICR is obtained. Seventh, although outcomes were adjusted for global LVEF, assessment of regional myocardial viability, which may impact the utility of revascularizing individual vessels, was not available. Moreover, most ISCHEMIA participants had preserved LV function. The results do not apply, therefore, to patients with severely reduced contractile reserve. In this regard, the STICH (Surgical Treatment for Ischemic Heart Failure) trial demonstrated improved 10-year survival after surgical revascularization in patients with LVEF ≤35%,[27] although an analysis examining the impact of CR from that trial has not been reported. Similarly, given the ISCHEMIA trial inclusion criteria, the present results do not apply to patients with ACS within 2 months or those who are highly symptomatic, have LM disease, or have minimal or no ischemia. Finally, the present analysis did not consider the impact of the use of guideline-directed medical therapy (GDMT) and recommended lifestyle changes or goal achievement on the effects of CR. GDMT was strongly recommended for both the INV and CON strategies and did not vary significantly between the 2 approaches.[3] In addition, GDMT prescription and goal achievement varied over time during follow-up; consideration of their impact on

the effects of CR would thus require a sophisticated time-varying analysis that was beyond the scope of the present report.

CONCLUSIONS

CR was achieved in approximately one-half of INV-assigned patients in the ISCHEMIA trial. CR (especially ACR) was strongly associated with freedom from cardiovascular death or MI in unadjusted analyses (as in most prior reports), but this effect was lessened after accounting for the confounding effects of the extent and complexity of CAD. The benefits of FCR were directionally similar to those of ACR but less pronounced. Had ACR been achieved in all randomized INV patients, the composite rate of cardiovascular death or MI may have been reduced by ~3.5% over 4 years compared with CON management, an ~1% absolute improvement (number needed-to-treat ~100) compared with the observed outcomes in the overall ISCHEMIA trial, which is a modest but desirable goal if CR may be safely achieved.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: In patients with chronic CAD participating in the ISCHEMIA trial, complete percutaneous or surgical revascularization of all obstructed major coronary arteries reduced the composite incidence of cardiovascular death or MI.

TRANSLATIONAL OUTLOOK: Further studies are necessary to determine whether complete revascularization of all diseased coronary artery segments improves prognosis compared with selective revascularization of segments associated with ischemia and myocardial viability.

REFERENCES

1. Boden WE, O'Rourke RA, Teo KK, et al. Optimal medical therapy with or without PCI for stable coronary disease. *N Engl J Med*. 2007;356:1503–1516.

2. Frye RL, August P, Brooks MM, et al. A randomized trial of therapies for type 2 diabetes and coronary artery disease. *N Engl J Med*. 2009;360:2503–2515.

3. Maron DJ, Hochman JS, Reynolds HR, et al. Initial invasive or conservative strategy for stable coronary disease. *N Engl J Med*. 2020;382:1395–1407.

4. Mehta SR, Wood DA, Storey RF, et al. Complete revascularization with multivessel PCI for myocardial infarction. *N Engl J Med*. 2019;381:1411–1421.

5. Gaba P, Gersh BJ, Ali ZA, Moses JW, Stone GW. Complete versus incomplete coronary revascularization: definitions, assessment and outcomes. *Nat Rev Cardiol*. 2021;18:155–168.

6. Garcia S, Sandoval Y, Roukoz H, et al. Outcomes after complete versus incomplete revascularization of patients with multivessel coronary artery disease: a meta-analysis of 89,883 patients enrolled in randomized clinical trials and observational studies. *J Am Coll Cardiol*. 2013;62:1421–1431.

7. Ali ZA, Horst J, Gaba P, et al. Standardizing the definition and analysis methodology for complete coronary artery revascularization. *J Am Heart Assoc*. 2021;10:e020110. https://doi.org/10.1161/JAHA.120.020110

8. Mavromatis K, Jones PG, Ali ZA, et al. Complete revascularization and angina-related health status in the ISCHEMIA trial. *J Am Coll Cardiol*. 2023;82:295–313.

9. Maron DJ, Hochman JS, O'Brien SM, et al. International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) trial: rationale and design. *Am Heart J*. 2018;201:124–135.

10. Califf RM, Phillips HR 3rd, Hindman MC, et al. Prognostic value of a coronary artery jeopardy score. *J Am Coll Cardiol*. 1985;5:1055–1063.

11. Sianos G, Morel MA, Kappetein AP, et al. The SYNTAX score: an angiographic tool grading the complexity of coronary artery disease. *EuroIntervention*. 2005;1:219–227.

12. Madhavan MV, Tarigopula M, Mintz GS, et al. Coronary artery calcification: pathogenesis and prognostic implications. *J Am Coll Cardiol*. 2014;63:1703–1714.

13. Konigstein M, Ben-Yehuda O, Redfors B, et al. Impact of coronary artery tortuosity on outcomes following stenting: a pooled analysis from 6 trials. *J Am Coll Cardiol Intv*. 2021;14:1009–1018.

14. Hernán MA, Robins JM. *Causal Inference: What If*. Boca Raton, FL: Chapman and Hall/CRC; 2020.

15. Farooq V, Serruys PW, Bourantas CV, et al. Quantification of incomplete revascularization and its association with five-year mortality in the synergy between percutaneous coronary intervention with taxus and cardiac surgery (SYNTAX) trial validation of the residual SYNTAX score. *Circulation*. 2013;128:141–151.

16. Thuesen AL, Riber LP, Veien KT, et al. Fractional flow reserve versus angiographically-guided coronary artery bypass grafting. *J Am Coll Cardiol*. 2018;72:2732–2743.

17. Tonino PA, De Bruyne B, Pijls NH, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. *N Engl J Med*. 2009;360:213–224.

18. Xu B, Tu S, Song L, et al. Angiographic quantitative flow ratio-guided coronary intervention (FAVOR III China): a multicentre, randomised, sham-controlled trial. *Lancet*. 2021;398:2149–2159.

19. Rioufol G, Dérimay F, Roubille F, et al. Fractional flow reserve to guide treatment of patients with multivessel coronary artery disease. *J Am Coll Cardiol*. 2021;78:1875–1885.

20. Puymirat E, Cayla G, Simon T, et al. Multivessel PCI guided by FFR or angiography for myocardial infarction. *N Engl J Med*. 2021;385:297–308.

21. Kedhi E, Berta B, Roleder T, et al. Thin-cap fibroatheroma predicts clinical events in diabetic patients with normal fractional flow reserve: the COMBINE OCT-FFR trial. *Eur Heart J*. 2021;42:4671–4679.

22. Lee JM, Choi KH, Koo BK, et al. Prognostic implications of plaque characteristics and stenosis severity in patients with coronary artery disease. *J Am Coll Cardiol*. 2019;73:2413–2424.

23. Waksman R, Di Mario C, Torguson R, et al. Identification of patients and plaques vulnerable to future coronary events with near-infrared spectroscopy intravascular ultrasound imaging: a prospective, cohort study. *Lancet*. 2019;394:1629–1637.

24. Reynolds HR, Shaw LJ, Min JK, et al. Outcomes in the ISCHEMIA trial based on coronary artery disease and ischemia severity. *Circulation*. 2021;144:1024–1038.

25. Head SJ, Mack MJ, Holmes DR Jr, et al. Incidence, predictors and outcomes of incomplete revascularization after percutaneous coronary intervention and coronary artery bypass grafting: a subgroup analysis of 3-year SYNTAX data. *Eur J Cardiothorac Surg*. 2012;41:535–541.

26. Rosner GF, Kirtane AJ, Genereux P, et al. Impact of the presence and extent of incomplete angiographic revascularization after percutaneous coronary intervention in acute coronary syndromes: the Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial. *Circulation*. 2012;125:2613–2620.

27. Velazquez EJ, Lee KL, Jones RH, et al. Coronary-artery bypass surgery in patients with ischemic cardiomyopathy. *N Engl J Med*. 2016;374:1511–1520.

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APPENDIX For a list of nonauthor collaborators as well as supplemental tables and figures, please see the online version of this paper.