

Complete Revascularization and Angina-Related Health Status in the ISCHEMIA Trial



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ABSTRACT

BACKGROUND The impact of complete revascularization (CR) on angina-related health status (symptoms, function, quality of life) in chronic coronary disease (CCD) has not been well studied.

OBJECTIVES Among patients with CCD randomized to invasive (INV) vs conservative (CON) management in ISCHEMIA (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches), we compared the following: 1) the impact of anatomic and functional CR on health status compared with incomplete revascularization (ICR); and 2) the predicted impact of achieving CR in all INV patients compared with CON.

METHODS Multivariable regression adjusting for patient characteristics was used to compare 12-month health status after independent core laboratory-defined CR vs ICR in INV patients who underwent revascularization. Propensity-weighted modeling was then performed to estimate the treatment effect had CR or ICR been achieved in all INV patients, compared with CON.

RESULTS Anatomic and functional CR were achieved in 43.3% and 57.8% of 1,641 INV patients, respectively. Among revascularized patients, CR was associated with improved Seattle Angina Questionnaire Angina Frequency compared with ICR after adjustment for baseline differences. After modeling CR and ICR in all INV patients, patients with CR and ICR each had greater improvements in health status than CON, with better health status with CR than ICR. The projected benefits of CR were most pronounced in patients with baseline daily/weekly angina and not seen in those with no angina.

CONCLUSIONS Among patients with CCD in ISCHEMIA, health status improved more with CR compared with ICR or CON, particularly in those with frequent angina. Anatomic and functional CR provided comparable improvements in quality of life. (International Study of Comparative Health Effectiveness With Medical and Invasive Approaches [ISCHEMIA]; NCT01471522) (J Am Coll Cardiol 2023;82:295-313) © 2023 by the American College of Cardiology Foundation.

Randomized controlled trials have shown that, in patients with chronic coronary disease (CCD), the addition of revascularization to guideline-directed medical therapy (GDMT), ie, an “invasive strategy” (INV), has no significant impact

on mortality or overall major adverse cardiovascular events, but does improve angina-related health status (patients’ symptoms, function, quality of life [QoL]) compared with GDMT alone, ie, a “conservative strategy” (CON).¹⁻⁷ However, the completeness



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Christopher M. O'Connor, MD, served as Guest Editor-in-Chief for this paper.

ABBREVIATIONS AND ACRONYMS

- ACR** = anatomic complete revascularization
CABG = coronary artery bypass grafting
CCD = chronic coronary disease
CON = conservative treatment strategy
CR = complete revascularization
FCR = functional complete revascularization
ICR = incomplete revascularization
INV = invasive treatment strategy
PCI = percutaneous coronary intervention
QCA = quantitative coronary angiography

of revascularization achieved in INV, both in clinical trials and practice, varies considerably because of underlying disease severity and operators' skills. This variation may affect the observed outcomes of invasive treatment because of incomplete revascularization (ICR) resulting in less improvement in patients' health status than that which could be achieved with more complete revascularization (CR).

Numerous observational studies have attempted to examine the effect of CR vs ICR on clinical outcomes in patients with coronary artery disease. However, these studies have been limited, because patients have often been preselected for revascularization candidacy; differences in the patient populations with CR vs ICR have not been adequately adjusted for; and the most contemporary revascularization techniques have not been included, resulting in variable conclusions.⁸ Furthermore, most of these studies have focused on clinical events and not QoL or other patient-reported outcomes.

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In ISCHEMIA (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches), 5,179 patients with CCD and at least moderate ischemia were randomized to an initial INV strategy (angiography and revascularization with percutaneous coronary intervention [PCI] or coronary artery bypass grafting [CABG] as appropriate per clinician discretion plus GDMT) vs an initial CON strategy (GDMT alone with angiography and revascularization reserved for medical therapy failure). With a median follow-up of 3.2 years, the differences between the groups in the rates of cardiovascular death or myocardial infarction (MI) were not statistically different, but the INV group had significant improvements in angina-related health status, with minimal benefits in asymptomatic patients and larger benefits in those with baseline angina.^{6,7} An analysis of the completeness of revascularization in ISCHEMIA was prespecified, and a comprehensive quantitative coronary angiography (QCA) methodology was developed to prospectively assess the completeness of both anatomic and functional (ischemic)

revascularization.⁹ Stone et al¹⁰ have separately reported the effect of CR on major adverse cardiovascular events in the ISCHEMIA trial. The present report describes the impact of CR on angina-related health status. Collectively, these data provide a complete picture of the potential benefits of achieving CR in patients with CCD.

METHODS

The design and primary results of the ISCHEMIA trial have been published.^{6,7,11} Although functional complete revascularization (FCR) was encouraged by protocol, individual treating physicians determined the completeness of revascularization achieved. 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. Although the primary endpoint was a composite of cardiovascular death, MI, or hospitalization for unstable angina, heart failure, or resuscitated cardiac arrest, a major secondary outcome was angina-related health status.⁷ The protocol was approved by the Institutional Review Board at New York University Grossman School of Medicine (the clinical coordinating center) and by the Institutional Review Board and ethics committee at each participating site. The present study had 2 principal objectives: 1) to assess the frequency of anatomic complete revascularization (ACR) and FCR and their effects on angina-related health status outcomes in CCD patients treated with a planned revascularization; and 2) to compare the health status outcomes of the strategies of INV with CR vs INV with ICR vs CON among all patients.

Prespecified definitions were developed for ACR and FCR that accounted for vessel size, stenosis severity, and the myocardial distribution of ischemia as determined by QCA and review of operative reports after CABG. Categorization was performed by an independent angiographic core laboratory (Cardiovascular Research Foundation) blinded to clinical outcomes including health status. A complete description of the classification of ACR and FCR was published previously.⁹ Briefly, ACR was defined as revascularization of all vessels and side branches with a QCA reference vessel diameter ≥ 2.0 mm and diameter stenosis $\geq 50\%$. FCR was defined as

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revascularization of all stenotic vessels with reference vessel diameter ≥ 2.0 mm with significant lesions as determined by localization of ischemia using intracoronary hemodynamics based on pressure wire assessment, noninvasive ischemia imaging, electrocardiographic stress testing, or QCA angiographic diameter stenosis $\geq 70\%$.

ANALYTIC COHORTS. Specific analysis cohorts were comprised to meet each of the study objectives. Few patients with prior CABG were enrolled in the ISCHEMIA trial, and these were excluded from all present analyses given core laboratory analytic challenges. Patients were also excluded because of administrative errors in angina-related health status form completion at 5 sites. For INV group assessment of CR, patients were excluded if angiographic images or operative reports necessary for core laboratory assessment were absent or incomplete.

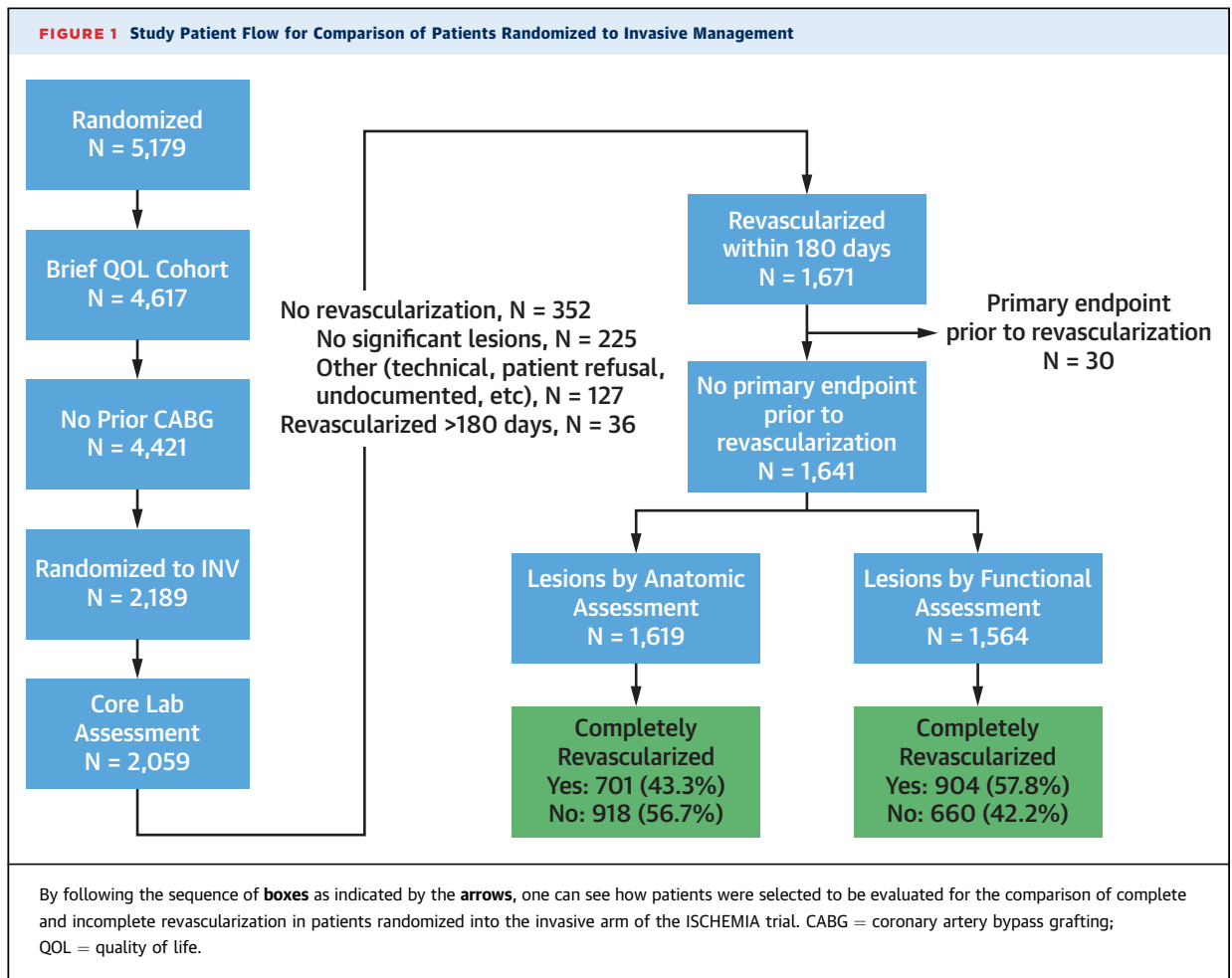
The Objective 1 cohort included all INV patients in whom revascularization with PCI (including planned staged procedures), CABG, or a hybrid approach (planned PCI plus CABG) was performed within 6 months of randomization and before a primary endpoint event, and in whom at least 1 qualifying lesion was present that met the prespecified anatomic or ischemic criteria for revascularization. Thus, for Objective 1, patients who did not undergo revascularization were excluded from the analyses. The Objective 2 cohort included all INV patients in whom CR vs ICR could be assessed, and all CON patients. Some INV patients who were not revascularized because no qualifying anatomically or functionally significant lesions were found on angiography were included in the cohort, because they were deemed to be adequately vascularized at baseline. Similarly, INV patients with qualifying anatomic or functional lesions who did not receive revascularization within 6 months were treated as incompletely revascularized.

HEALTH STATUS OUTCOMES. To quantify angina-specific health status (symptoms, function, and QoL) among participants who underwent randomization, surveys were administered before randomization; at months 1.5, 3, and 6; and every 6 months thereafter until trial termination. The surveys included the 7-item Seattle Angina Questionnaire (SAQ), the Rose Dyspnea Scale, and the EuroQol-5 Dimensions Visual Analogue Scale.¹²⁻¹⁴ The 7-item SAQ was the primary outcome for the health status assessments and has been shown to be highly valid, reliable, and sensitive to clinical change.¹² The SAQ captures the frequency of angina (SAQ Angina Frequency score) and the disease-specific effect of angina on patients' physical

function (SAQ Physical Limitation score) and QoL score over the previous 4 weeks; these scores are averaged to obtain the SAQ Summary score, an overall measure of patients' disease-specific health status. SAQ scores range from 0 to 100, with higher scores indicating less frequent angina, better function, and better QoL.¹⁵ SAQ Angina Frequency scores of 0 to 30, 31 to 60, 61 to 99, and 100 have been shown to validly reflect angina that occurs daily, weekly, several times per month ("monthly"), and no angina (freedom from angina), respectively, as assessed with daily diaries.¹⁶ The Rose Dyspnea Scale has 4 items indicating whether patients experience breathlessness with different activities (scores range from 0 to 4, with higher scores indicating dyspnea with milder activities). The prespecified primary endpoint of this substudy was SAQ Angina Frequency at 12 months, reflecting a time for the benefits of both INV and CON strategies to have been achieved and stable.⁷

STATISTICAL ANALYSES. Baseline clinical, angiographic, and procedural characteristics were compared across patient groups. Categorical variables were summarized as percentages and were compared using chi-square tests. Continuous variables were summarized as mean \pm SD or median (IQR) and were compared using Wilcoxon rank-sum tests. Parallel analyses were performed for ACR and FCR and for each health status endpoint.

For Objective 1, analyses were performed comparing INV patients in whom CR vs ICR was achieved within 6 months of randomization. Unadjusted health status scores at baseline, 1.5, 3, 6, and 12 months were compared using Wilcoxon rank-sum tests. Proportional odds models for 1-year outcomes were used to compare patients with CR and ICR, adjusting for patient, clinical and angiographic variables, including baseline health status score, age, sex, geographic region, hypertension, diabetes, smoking status, prior MI, heart failure, cerebrovascular disease/prior stroke, peripheral arterial disease, prior PCI, left ventricular ejection fraction, body mass index (BMI), glomerular filtration rate, NYHA functional class, stress imaging modality, degree of ischemia on stress test, number of diseased vessels, Duke jeopardy score, SYNTAX score, number of chronic total occlusion (CTO) lesions, presence of calcification or tortuosity, use of intravascular ultrasound, fractional flow reserve, total number of anatomic and ischemic lesions, left main disease, proximal left anterior descending artery disease, and the initial mode of revascularization (PCI or CABG). Results are expressed as ORs of better health status with CR vs ICR.



For Objective 2, we compared 3 groups of patients: 1) INV patients with CR; 2) INV patients with ICR; and 3) CON patients. Two stages of propensity weighting were used to balance the 3 groups. The first-stage propensity weights compared CON vs INV patients and incorporated the fact that some patients randomized to INV treatment did not receive angiography ($n = 130$). These weights were obtained from a multinomial model of CON vs INV with angiography vs INV without angiography on patient demographic, clinical, stress testing/coronary computed tomographic angiography factors and baseline health status scores, as described in the previous text. The second stage of propensity weighting accounted for differences between completely and incompletely revascularized patients, among those with significant lesions found on angiography. This propensity model included all covariates from the first model, as well as angiographic characteristics listed in the previous text. Patients with no significant lesions were assigned a second-stage weight of 1. These weights

were then multiplied by the first stage weights. All weights were calculated as the reciprocal of the probability of being the given group. The final resulting weights thus provided estimates of outcomes if all patients in ISCHEMIA were treated as follows: 1) invasively with CR; 2) invasively with ICR; or 3) conservatively. Differences in 1-year health status outcomes were estimated using propensity-weighted linear models (logistic regression for the binary outcome of freedom from angina). CIs were obtained using bootstrapped SEs.

Of the 4,421 patients without prior CABG who formed the basis for both objectives, 1-year health status outcomes were missing in 8% ($n = 348$: 218 missed follow-up assessments, 13 study withdrawals, 65 lost to follow-up, 50 deaths, and 2 caused by study termination). Multiple imputation using chained equations was used to account for missing 1-year scores.¹⁷ The imputation model included all patient characteristics described above and all health status scores from baseline through 1 year.

TABLE 1 Baseline Characteristics of Invasively Managed Patients With CR and ICR

	Anatomic CR			Functional CR		
	CR (n = 701)	ICR (n = 918)	P Value	CR (n = 904)	ICR (n = 660)	P Value
Age, y	63.4 ± 9.7	64.1 ± 9.2	0.147	63.6 ± 9.5	64.1 ± 9.3	0.403
Female	181 (25.8)	174 (19.0)	<0.001	208 (23.0)	125 (18.9)	0.052
Hypertension	509 (72.9)	721 (78.7)	0.006	671 (74.5)	523 (79.5)	0.021
Diabetes	295 (42.1)	367 (40.0)	0.393	370 (40.9)	264 (40.0)	0.711
Prior MI	125 (17.9)	197 (21.5)	0.074	161 (17.8)	146 (22.2)	0.034
Peripheral vascular disease	31 (4.4)	46 (5.0)	0.582	34 (3.8)	42 (6.4)	0.017
Ejection fraction, %	61.0 ± 8.0	60.0 ± 8.1	0.005	60.9 ± 8.0	59.7 ± 8.0	0.001
Body mass index, kg/m ²	28.3 ± 4.8	29.0 ± 4.8	0.003	28.3 ± 4.6	29.2 ± 5.0	0.001
SAQ Summary Score	72.1 ± 18.8	73.3 ± 19.0	0.158	72.6 ± 19.0	73.2 ± 18.7	0.624
SAQ Angina Frequency Score	79.5 ± 19.7	79.8 ± 20.8	0.334	79.9 ± 20.2	79.5 ± 20.4	0.838
Rose Dyspnea Scale	1.2 ± 1.3	1.2 ± 1.3	0.293	1.2 ± 1.3	1.2 ± 1.3	0.327
# of vessels ≥70% (coronary CTA)			<0.001			<0.001
0	48 (8.7)	25 (3.6)		48 (6.8)	16 (3.2)	
1	171 (31.1)	178 (25.5)		220 (31.1)	122 (24.1)	
2	82 (14.9)	144 (20.7)		111 (15.7)	110 (21.7)	
3	39 (7.1)	114 (16.4)		61 (8.6)	92 (18.2)	
SYNTAX score			<0.001			<0.001
<23	577 (82.3)	499 (54.4)		697 (77.1)	329 (49.8)	
23 to <33	99 (14.1)	250 (27.2)		159 (17.6)	186 (28.2)	
≥33	25 (3.6)	169 (18.4)		48 (5.3)	145 (22.0)	
Duke Jeopardy Score			<0.001			<0.001
1	45 (6.4)	24 (2.6)		40 (4.4)	10 (1.5)	
2	159 (22.7)	117 (12.7)		196 (21.7)	71 (10.8)	
3	166 (23.7)	174 (19.0)		200 (22.1)	127 (19.2)	
4	162 (23.1)	217 (23.6)		221 (24.4)	148 (22.4)	
5	113 (16.1)	183 (19.9)		158 (17.5)	135 (20.5)	
6	36 (5.1)	135 (14.7)		56 (6.2)	114 (17.3)	
7	20 (2.9)	68 (7.4)		33 (3.7)	55 (8.3)	
Number of anatomic lesions			<0.001			<0.001
1	343 (48.9)	45 (4.9)				
2	214 (30.5)	212 (23.1)		508 (56.2)	92 (13.9)	
3	84 (12.0)	253 (27.6)		253 (28.0)	208 (31.5)	
4	48 (6.8)	172 (18.7)		97 (10.7)	165 (25.0)	
5	10 (1.4)	129 (14.1)		40 (4.4)	116 (17.6)	
6	1 (0.1)	58 (6.3)		4 (0.4)	49 (7.4)	
7	0 (0.0)	33 (3.6)		1 (0.1)	21 (3.2)	
8	1 (0.1)	9 (1.0)		0 (0.0)	6 (0.9)	
9	0 (0.0)	5 (0.5)		1 (0.1)	2 (0.3)	
10	0 (0.0)	1 (0.1)		0 (0.0)	1 (0.2)	
11	0 (0.0)	1 (0.1)				
Number of CTOs			<0.001			<0.001
0	475 (67.9)	411 (44.8)		587 (65.0)	249 (37.7)	
1	194 (27.7)	401 (43.7)		275 (30.5)	315 (47.7)	
2	30 (4.3)	87 (9.5)		39 (4.3)	78 (11.8)	
≥3	1 (0.1)	18 (2.1)		2 (0.2)	17 (2.8)	

Values are mean ± SD or n (%).

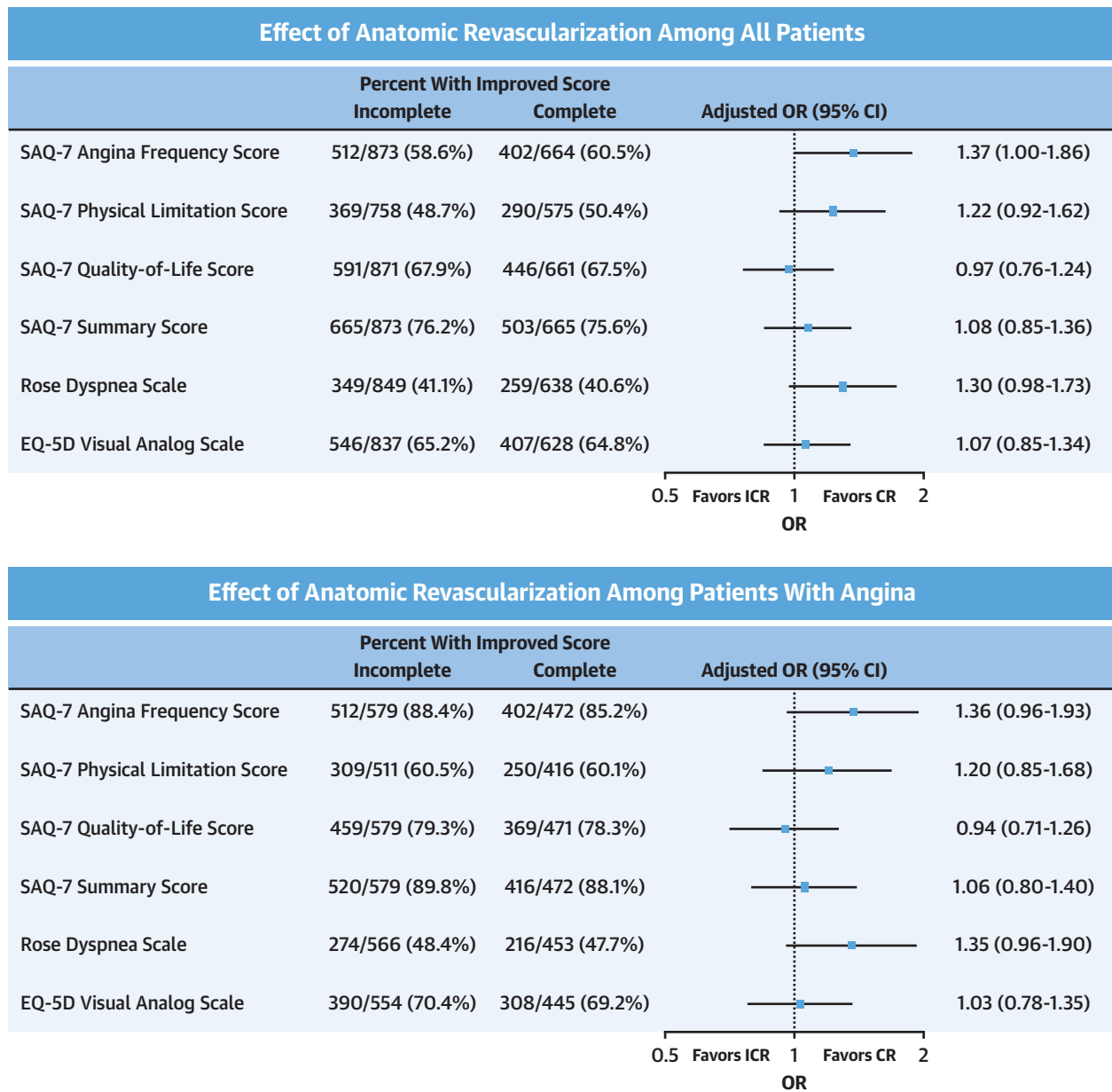
CABG = coronary artery bypass grafting; CR = complete revascularization; CTA = computed tomographic angiography; CTO = chronic total occlusion; ICR = incomplete revascularization; MI = myocardial infarction; PCI = percutaneous coronary intervention; SAQ = Seattle Angina Questionnaire.

In all regression and propensity models, continuous covariate effects were fit using restricted cubic splines to accommodate nonlinear associations. Analyses were conducted using SAS version 9.4 (SAS Institute, Inc) and R version 3.6.3 (R Foundation for Statistical Computing).¹⁸

RESULTS

Of the 5,179 patients with CCD and at least moderate ischemia in the ISCHEMIA trial, 4,421 had no prior CABG and available health status assessments and formed the cohort for both objectives.

FIGURE 2 Health Status Outcomes in Invasively Managed and Revascularized Patients



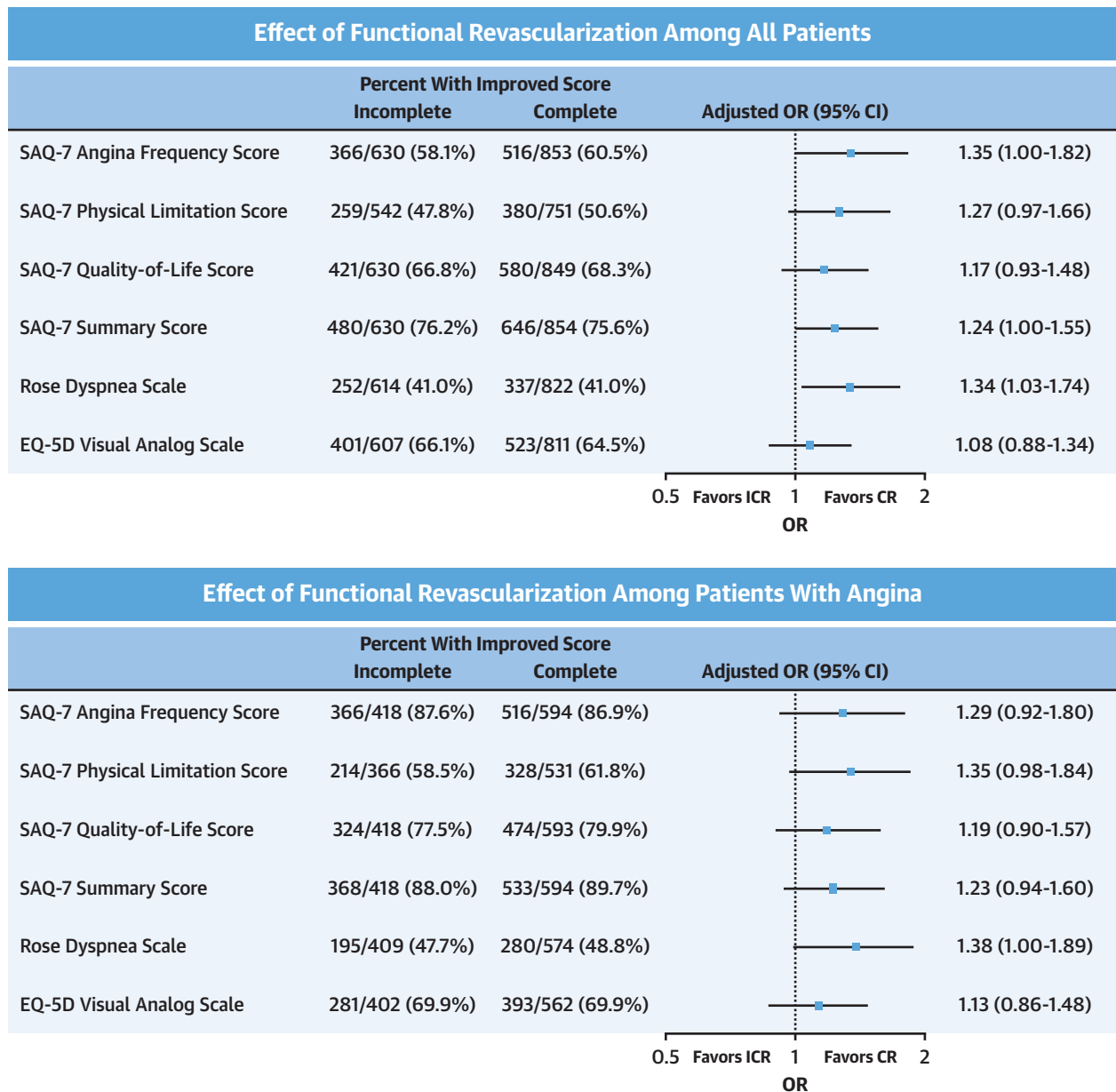
Patients achieving complete revascularization (CR) and incomplete revascularization (ICR) with improved health status score at 1 year are compared, using proportional odds models to adjust for patient, clinical, and angiographic variables. Results are expressed as percent of patients with improved health status (unadjusted) as well as ORs of better health status with CR vs ICR (adjusted). EQ-5D = EuroQoL 5 Dimensions; SAQ = Seattle Angina Questionnaire.

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OBJECTIVE 1: COMPARISON OF INV TREATMENT WITH CR OR ICR. Of these 4,421 patients, 2,189 were randomized to INV. After exclusion of patients without core laboratory angiographic analysis (n = 130), without revascularization within 180 days (revascularization after 180 days, n = 36; no significant

lesions, n = 225; no revascularization for other reasons, n = 127), or with a clinical endpoint preceding revascularization (n = 30), 1,641 patients were evaluable for the assessment of the frequency of ACR and FCR in INV-assigned patients and their impact on health status outcomes (Figure 1). Of these, 1,619 had

FIGURE 2 Continued

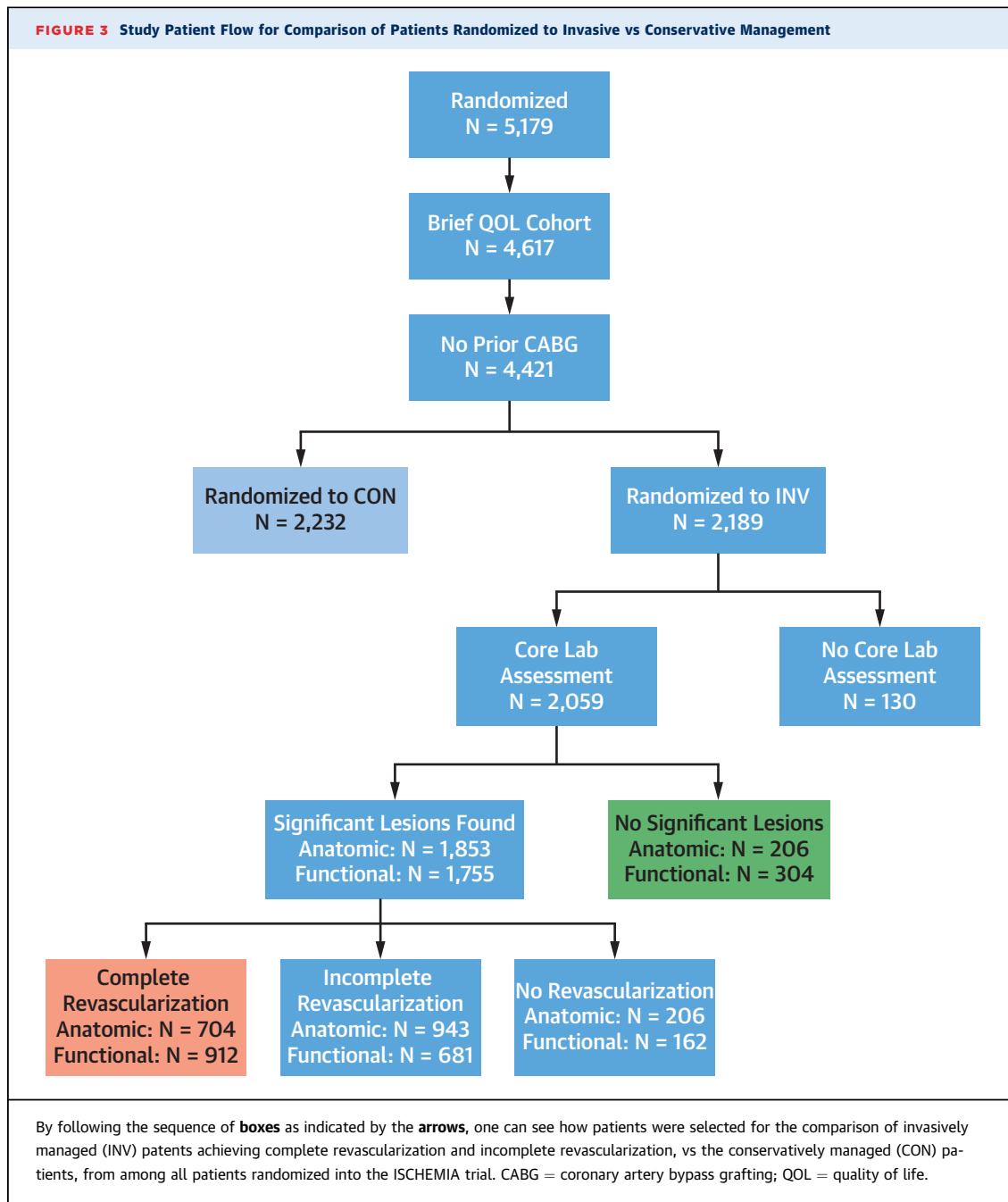


QCA-defined anatomic lesions, with 701 (43.3%) achieving ACR. Among 1,564 patients with QCA-defined functional lesions, 904 (57.8%) achieved FCR (Figure 1). Among the smaller population of patients with functional lesions, 99.8% had anatomic lesions.

Baseline clinical, angiographic, and treatment characteristics of INV patients with vs without ACR and FCR are shown in Table 1 and Supplemental Tables 1 and 2. In univariate analysis, both ACR and FCR patients differed from their ICR counterparts by

being more likely to be women, having better left ventricular function, having a lower BMI, and being less likely to have hypertension. Baseline health status measures were similar between CR and ICR (SAQ Angina Frequency score: anatomic CR vs ICR: 79.5 ± 19.7 vs 79.8 ± 20.8 ; $P = 0.33$; functional CR vs ICR: 79.9 ± 20.2 vs 79.5 ± 20.4 ; $P = 0.84$). On angiography, ACR and FCR patients had less complex coronary disease compared with ICR patients, as measured by the number of diseased vessels, the number of

TABLE 2 Adjusted 12-Month Health Status Outcomes in Invasively Managed and Revascularized Patients				
Baseline Angina	None (n = 521)	Monthly (n = 740)	Daily/Weekly (n = 378)	Interaction P Value
Effect of anatomic CR vs ICR				
SAQ-7 Angina Frequency Score	1.55 (0.85-2.83)	1.04 (0.71-1.53)	2.15 (1.31-3.53)	0.04
SAQ-7 Summary Score	1.15 (0.79-1.67)	0.90 (0.67-1.20)	1.60 (1.05-2.44)	0.05
Quality of life	0.99 (0.66-1.48)	0.78 (0.57-1.07)	1.39 (0.90-2.16)	0.06
Physical function	1.03 (0.64-1.65)	1.08 (0.76-1.53)	1.72 (1.07-2.76)	0.18
Rose Dyspnea Score	1.28 (0.80-2.06)	1.21 (0.84-1.72)	1.79 (1.11-2.89)	0.35
EQ-5D Visual Analog Scale	1.19 (0.83-1.71)	0.89 (0.66-1.19)	1.37 (0.90-2.07)	0.15
Effect of functional CR vs ICR				
SAQ-7 Angina Frequency Score	1.15 (0.64-2.04)	1.14 (0.77-1.67)	2.06 (1.23-3.45)	0.11
SAQ-7 Summary Score	1.13 (0.78-1.63)	1.17 (0.86-1.58)	1.54 (1.03-2.32)	0.43
Quality of life	1.08 (0.73-1.58)	1.09 (0.79-1.49)	1.43 (0.94-2.17)	0.48
Physical function	1.03 (0.66-1.60)	1.32 (0.90-1.93)	1.48 (0.93-2.35)	0.48
Rose Dyspnea Score	1.25 (0.80-1.95)	1.21 (0.85-1.74)	1.63 (0.99-2.70)	0.57
EQ-5D Visual Analog Scale	0.95 (0.67-1.34)	1.00 (0.75-1.35)	1.48 (0.99-2.21)	0.17
Degree of Ischemia	None-Mild (n = 160)	Moderate (n = 575)	Severe (n = 906)	
Effect of anatomic CR vs ICR				
SAQ-7 Angina Frequency Score	0.96 (0.46-2.01)	1.64 (1.04-2.59)	1.31 (0.88-1.96)	0.43
SAQ-7 Summary Score	0.98 (0.52-1.82)	1.51 (1.06-2.15)	0.90 (0.68-1.19)	0.04
Quality of life	0.99 (0.52-1.87)	1.07 (0.74-1.56)	0.92 (0.68-1.23)	0.77
Physical function	0.99 (0.47-2.09)	1.73 (1.14-2.61)	0.97 (0.69-1.36)	0.07
Rose Dyspnea Score	1.79 (0.90-3.55)	1.38 (0.91-2.10)	1.21 (0.85-1.70)	0.55
EQ-5D Visual Analog Scale	1.52 (0.83-2.79)	1.15 (0.81-1.62)	0.98 (0.74-1.30)	0.35
Effect of functional CR vs ICR				
SAQ-7 Summary Score	1.22 (0.62-2.43)	1.66 (1.18-2.33)	1.03 (0.78-1.35)	0.07
SAQ-7 Angina Frequency Score	1.13 (0.50-2.57)	1.47 (0.94-2.29)	1.28 (0.87-1.89)	0.81
Quality of life	1.10 (0.54-2.22)	1.27 (0.88-1.81)	1.14 (0.85-1.52)	0.87
Physical function	1.43 (0.66-3.07)	1.85 (1.24-2.76)	0.96 (0.68-1.35)	0.02
Rose Dyspnea Score	2.32 (1.07-5.02)	1.25 (0.84-1.85)	1.28 (0.90-1.81)	0.33
EQ-5D Visual Analog Scale	1.37 (0.71-2.65)	1.12 (0.81-1.55)	1.02 (0.77-1.34)	0.68
Number of CTOs	0 (n = 976)	1 (n = 560)	≥2 (n = 105)	
Effect of anatomic CR vs ICR				
SAQ-7 Angina Frequency Score	1.22 (0.85-1.76)	1.83 (1.10-3.04)	1.16 (0.32-4.26)	0.38
SAQ-7 Summary Score	1.01 (0.76-1.34)	1.34 (0.93-1.91)	0.58 (0.23-1.49)	0.17
Quality of life	0.90 (0.67-1.21)	1.19 (0.81-1.75)	0.84 (0.31-2.25)	0.45
Physical function	1.17 (0.83-1.62)	1.42 (0.90-2.23)	0.48 (0.17-1.37)	0.17
Rose Dyspnea Score	1.20 (0.84-1.70)	1.63 (1.04-2.54)	0.78 (0.24-2.58)	0.34
EQ-5D Visual Analog Scale	0.94 (0.72-1.23)	1.37 (0.97-1.95)	0.91 (0.30-2.74)	0.19
Effect of functional CR vs ICR				
SAQ-7 Angina Frequency Score	1.05 (0.71-1.54)	1.81 (1.15-2.85)	1.77 (0.48-6.54)	0.16
SAQ-7 Summary Score	1.10 (0.82-1.47)	1.49 (1.07-2.07)	0.91 (0.38-2.14)	0.28
Quality of life	1.06 (0.78-1.42)	1.42 (1.01-1.99)	1.12 (0.46-2.69)	0.40
Physical function	1.21 (0.86-1.70)	1.58 (1.06-2.38)	0.56 (0.20-1.55)	0.15
Rose Dyspnea Score	1.08 (0.76-1.53)	1.82 (1.23-2.71)	1.14 (0.39-3.35)	0.12
EQ-5D Visual Analog Scale	0.87 (0.65-1.16)	1.43 (1.05-1.95)	1.11 (0.44-2.81)	0.06
<p>Values are OR (95% CI) of likelihood of improvement with complete revascularization compared with incomplete revascularization. Results were adjusted for the following covariates: baseline health status score, age, sex, geographic region, hypertension, diabetes, smoking status, prior MI, heart failure, cerebrovascular disease/prior stroke, peripheral arterial disease, prior PCI, left ventricular ejection fraction, body mass index, glomerular filtration rate, NYHA functional class, stress imaging modality, degree of ischemia on stress test, number of diseased vessels, Duke jeopardy score, SYNTAX score, number of chronic total occlusion (CTO) lesions, presence of calcification or tortuosity, use of intravascular ultrasound, fractional flow reserve, total number of anatomic and ischemic lesions, left main disease, proximal left anterior descending artery disease, and the initial mode of revascularization (PCI or CABG).</p> <p>EQ-5D = EuroQoL 5 Dimensions; other abbreviations as in Table 1.</p>				



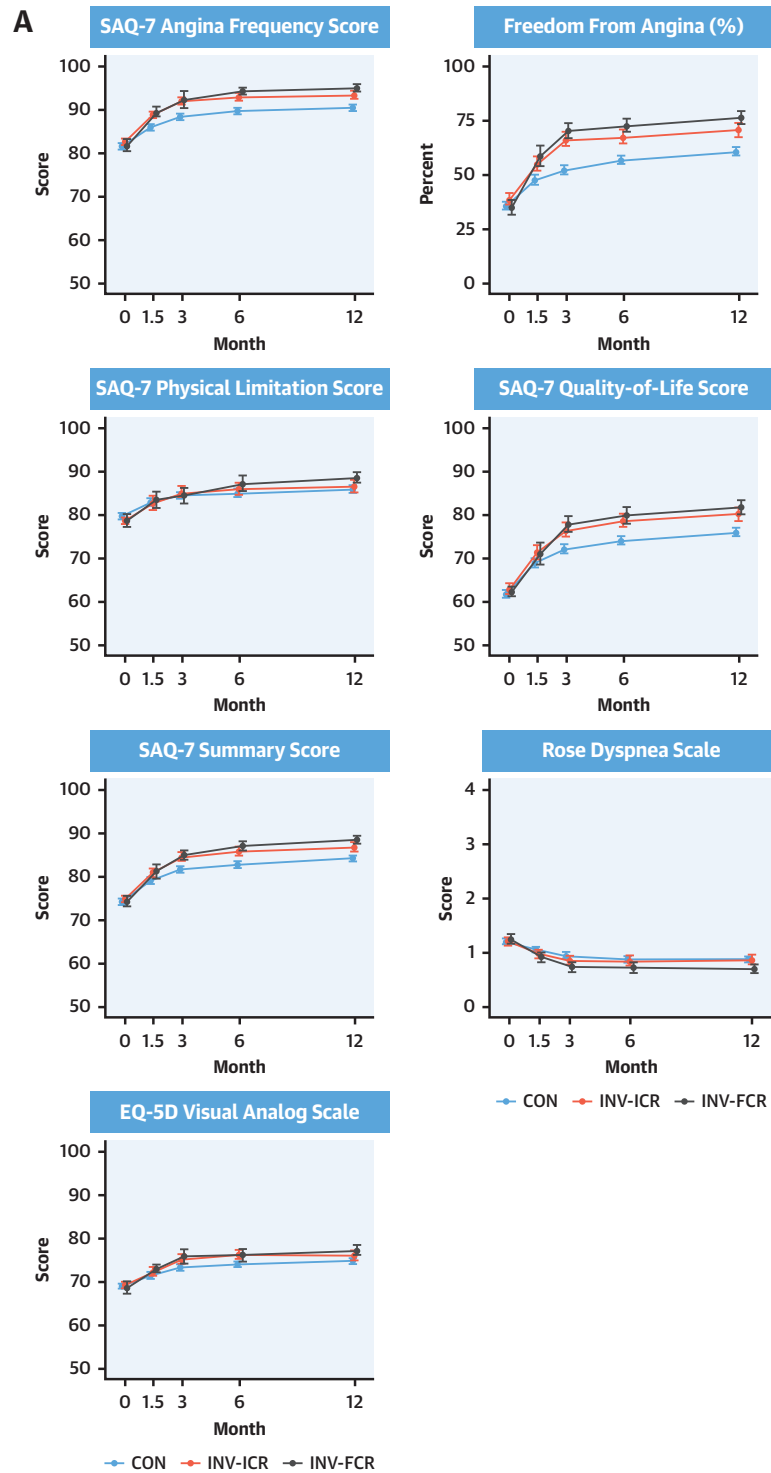
lesions, the Duke Jeopardy Score, the SYNTAX score, and the number of CTOs (Table 1).

After revascularization, unadjusted 12-month QoL scores were similar between CR and ICR patients (Supplemental Tables 3 and 4). However, after adjustment for baseline clinical and angiographic characteristics and initial revascularization method, ORs favored better health status with ACR compared with ICR, particularly for the SAQ Angina Frequency

(SAQ Angina Frequency: OR: 1.37 [95% CI: 1.00-1.86], SAQ Summary Score: OR: 1.08 [95% CI: 0.85-1.36], and Rose Dyspnea Score: OR: 1.30 [95% CI: 0.98-1.73]). FCR had a similar effect (OR: 1.35 [95% CI: 1.00-1.82]), SAQ Summary Score (OR: 1.24 [95% CI: 1.00-1.55]), and Rose Dyspnea Score (OR: 1.34 [95% CI: 1.03-1.74]) (Figure 2).

Stratification by patients' frequency of angina at baseline (daily/weekly angina, monthly angina, or no

FIGURE 4 Adjusted Health Status Outcomes in Patients Randomized to Conservative vs Invasive Management



Adjusted Seattle Angina Questionnaire (SAQ-7) scores, Rose Dyspnea Scale scores, and EuroQoL 5 Dimensions (EQ5D) scores are depicted over time (0, 1.5, 3, 6, and 12 months) for conservatively managed (CON) patients (blue), invasively managed patients achieving incomplete revascularization (ICR) (red), and invasively managed patients achieving complete revascularization (CR) (gray). (A) Functional complete revascularization (FCR). (B) Anatomic complete revascularization (ACR).

FIGURE 4 Continued

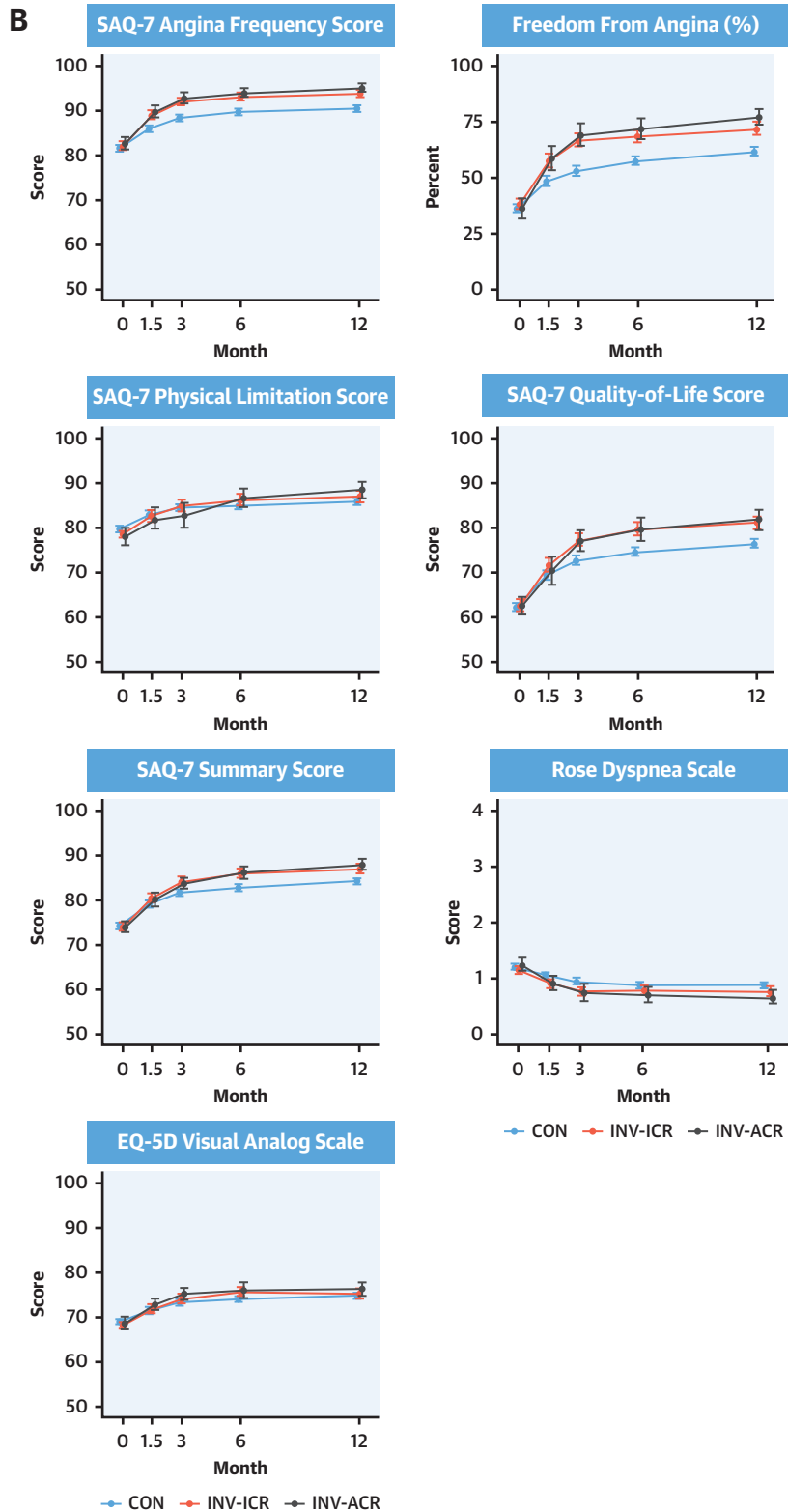


TABLE 3 Difference in Propensity-Weighted 12-Month Health Status Score of Invasively vs Conservatively Managed Patients

	CR vs Conservative Management	ICR vs Conservative Management	CR vs ICR Management
Functional CR			
ΔSAQ-7 Angina Frequency Score	4.5 (3.4, 5.4)	2.8 (1.8, 3.8)	1.7 (0.6, 2.6)
Freedom from angina, OR (95% CI)	2.2 (1.8-2.6)	1.6 (1.3-1.9)	1.4 (1.1-1.7)
ΔSAQ-7 Summary Score	4.6 (3.4, 5.7)	2.4 (1.3, 3.5)	2.2 (0.9, 3.3)
ΔSAQ-7 Quality-of-Life Score	5.9 (4.0, 7.6)	3.8 (2.1, 5.4)	2.1 (0.2, 3.8)
ΔSAQ-7 Physical Limitation Score	3.2 (1.8, 4.7)	0.6 (-1.0, 2.2)	2.6 (0.9, 4.2)
ΔRose Dyspnea Scale	-0.2 (-0.3, -0.1)	0.0 (-0.1, 0.1)	-0.2 (-0.3, -0.1)
ΔEQ-5D Visual Analog Scale	2.7 (0.9, 4.1)	1.6 (0.4, 2.7)	1.1 (-0.8, 2.6)
Anatomic CR			
ΔSAQ-7 Angina Frequency Score	4.1 (3.2, 5.2)	3.3 (2.4, 4.3)	0.9 (0.0, 1.8)
Freedom from angina, OR (95% CI)	2.2 (1.8-2.8)	1.6 (1.4-2.0)	1.4 (1.1-1.7)
ΔSAQ-7 Summary Score	4.8 (3.7, 6.0)	3.6 (2.5, 4.7)	1.2 (0.0, 2.3)
ΔSAQ-7 Quality-of-Life Score	5.7 (3.9, 7.7)	5.1 (3.6, 6.6)	0.6 (-1.4, 2.6)
ΔSAQ-7 Physical Limitation Score	3.6 (2.0, 5.3)	2.4 (1.1, 3.9)	1.2 (-0.4, 3.0)
ΔRose Dyspnea Scale	-0.2 (-0.3, -0.1)	0.0 (-0.1, 0.1)	-0.2 (-0.3, -0.1)
ΔEQ-5D Visual Analog Scale	2.7 (1.2, 4.2)	1.4 (0.4, 2.5)	1.3 (-0.2, 2.7)
Values are median (Q1, Q3) or OR (95% CI). Abbreviations as in Tables 1 and 2 .			

angina) showed that patients with daily/weekly angina had the greatest benefit from ACR compared with ICR, with adjusted ORs of improved SAQ Angina Frequency of 2.15 (95% CI: 1.31-3.53) and SAQ Summary Score of 1.60 (95% CI: 1.05-2.44) ([Table 2](#)). Similar benefits were observed for FCR vs ICR (SAQ Angina Frequency: OR: 2.06 [95% CI: 1.23-3.45], SAQ Summary Score: OR: 1.54 [95% CI: 1.03-2.32]). The benefits associated with CR vs ICR were less and not significant in patients with monthly or no angina ([Table 2](#)). No interaction between CR and the amount of baseline ischemia or number of CTOs was noted ([Table 2](#)).

OBJECTIVE 2: COMPARING PREDICTED OUTCOMES OF INV TREATMENT WITH CR AND ICR AS COMPARED WITH CON TREATMENT STRATEGIES. To better estimate the potential of CR vs ICR as management strategies compared with a CON strategy in patients with CCD, we estimated the effects had all evaluable ISCHEMIA patients undergone: 1) INV with CR; 2) INV with ICR; or 3) CON ([Figure 3](#)). Comparison of baseline, angiographic and treatment characteristics are shown in [Supplemental Table 5](#). After propensity weighted adjustment of the CR and ICR patients to match the overall population, patients achieving both CR and ICR, whether defined anatomically or functionally, had greater improvement in SAQ Angina Frequency Scores at 12 months than those managed conservatively (ACR vs CON: difference = 4.1 [Q1, Q3: 3.2, 5.2]; FCR vs CON: difference = 4.5 [Q1, Q3: 3.4, 5.4];

anatomic ICR vs CON: difference = 3.3 [Q1, Q3: 2.4, 4.3]; functional ICR vs CON: difference = 2.8 [Q1, Q3: 1.8, 3.8]). Similar improvements were present for the SAQ QoL, Physical Function, and Summary Scores, as well as the Rose Dyspnea and EuroQoL-5 Dimensions Visual Analog Scales ([Figure 4](#), [Table 3](#), [Supplemental Figure 1](#)). Improvements compared with CON were greater with CR than with ICR, particularly with regards to freedom from angina: anatomic CR vs ICR OR: 1.36 (95% CI: 1.05-1.70) and functional CR vs ICR OR: 1.37 (95% CI: 1.11-1.68) ([Table 3](#)).

When modeled over the entire population randomized to INV treatment, stratification of patients by baseline angina frequency revealed that the most incremental benefit of CR over ICR occurred in patients with daily/weekly angina ([Figure 5](#), [Table 4](#), [Supplemental Figure 2](#)), particularly with functional revascularization (FCR vs ICR difference in SAQ Angina Frequency = 4.3 [IQR: 1.1-7.4], difference in SAQ Summary Score = 4.2 [IQR: 1.4-7.0]; ACR vs ICR: difference in SAQ Angina Frequency = 3.1 [IQR: -0.1 to 6.2], difference in SAQ Summary Score = 2.0 [IQR: -0.8 to 4.8]) ([Figure 5](#), [Table 4](#), [Supplemental Figure 2](#)). No incremental benefit of CR over ICR was seen in patients with no angina, and little incremental benefit was seen in patients with monthly angina (functional CR vs ICR: difference in SAQ Summary Score = 1.8 [IQR: 0.0-3.7]). No interaction between the benefit from INV-CR and the degree of ischemia was observed.

DISCUSSION

In the ISCHEMIA trial—the largest, most contemporary, randomized controlled strategy trial of patients with CCD and moderate or severe ischemia—an INV management strategy resulted in greater improvement in disease-specific health status (including angina symptoms, physical function and disease specific QoL) than a CON management strategy, but the influence of the completeness of revascularization on these outcomes had not been assessed.⁷ The present prespecified analysis shows that CR was only achieved in ~50% (ACR: 43.3%, FCR: 57.8%) of patients assigned to the INV strategy. After adjustment for differences in baseline, angiographic, and procedural characteristics, CR was associated with greater health status improvement than ICR. When modeled in the entire trial population, INV-assigned patients with both CR and ICR had greater health status gains than CON-assigned patients. For most measures, the health status gains after FCR and ACR were similar. In those patients with daily or weekly angina at baseline, the estimated benefits of CR were greater than

ICR, both of which were better than CON. In contrast, there were no differences in health status between CR or ICR and CON in asymptomatic patients, and little evidence of substantial advantage of CR or ICR, as compared with CON, in those with monthly angina. Collectively, these data suggest little difference between INV and CON strategies on health status at 12 months in patients without angina or with only monthly angina, regardless as to whether CR is achieved. However, in patients with more frequent angina, CR has the potential to confer better health, and efforts to provide more complete revascularization to improve these patients' symptoms, function and quality of life may be important (**Central Illustration**). Finally, these data overall support a patho-mechanistic approach to the treatment of angina in CCD.

Despite the ISCHEMIA protocol's encouragement of the use of CABG and advanced CTO PCI techniques, FCR was achieved in only 57.8% of participants, while ACR was achieved in only 43.3% of participants. Although these CR rates seem similar to the 50.5% CR rate reported in a meta-analysis of 35 older studies of completeness of revascularization, some differences between ISCHEMIA and these prior studies should be noted.¹⁸ The prior studies primarily included patients preselected for their anatomic revascularization potential,¹⁹ whereas in ISCHEMIA, invasive angiography—and therefore feasibility of revascularization—was only determined after randomization. In addition, unlike most prior studies, this ISCHEMIA analysis determined CR by using a very detailed and algorithmic core laboratory-based approach. Notwithstanding the different methodologies used to assess CR and differences in patient populations, the comparison of ISCHEMIA with the prior meta-analysis suggests the rate of achieving CR (~50%) has been relatively stable over time.

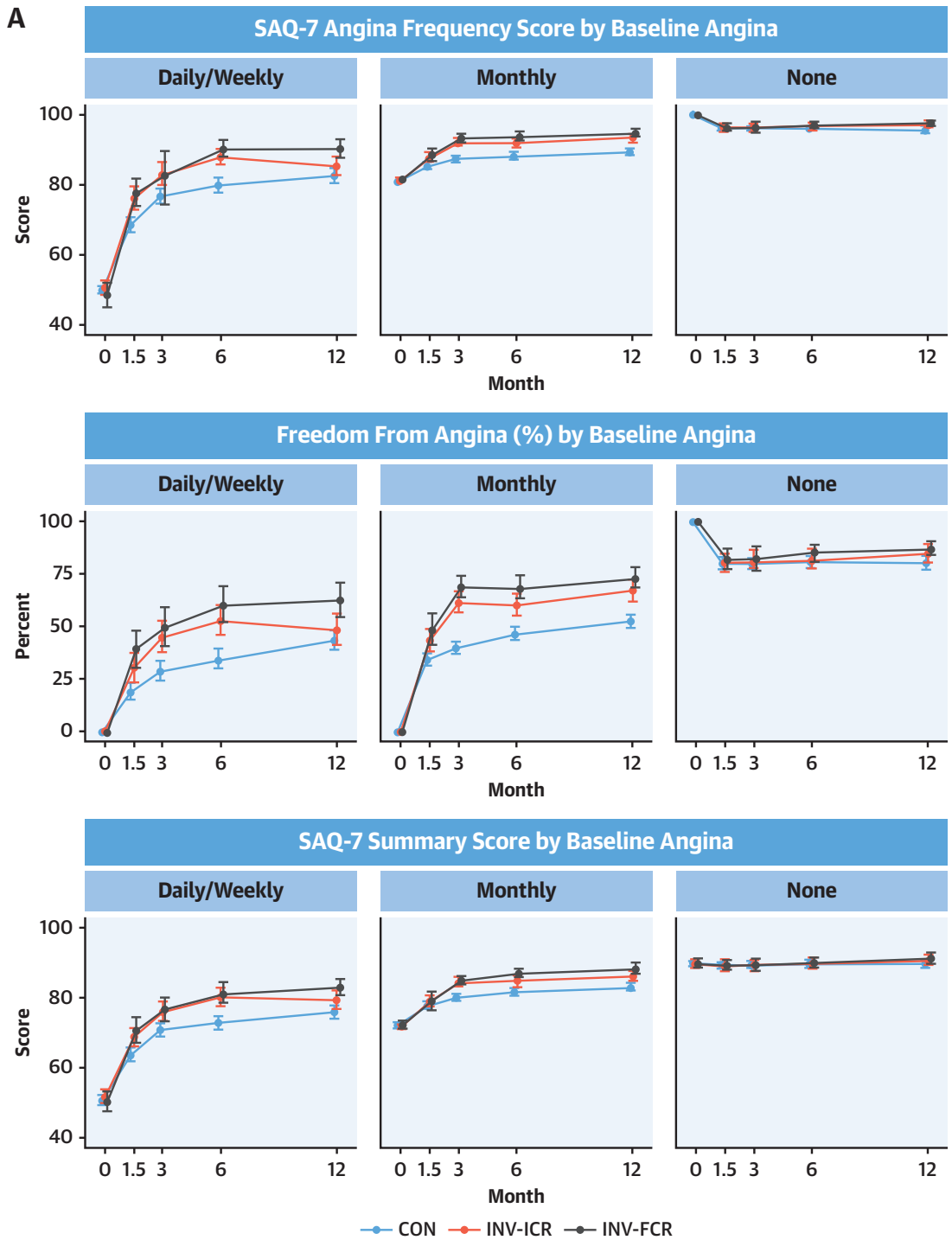
In general terms, functional lesions are a subgroup of anatomic lesions, representing those in whom ischemia has been demonstrated (or is likely). As ischemia underlies angina and anginal-equivalent symptoms in most patients, it is not surprising that CR based on anatomic and functional criteria each resulted in health status improvements at 12 months in our study. However, anatomic CR may provide benefits beyond FCR in providing a greater reduction in cardiovascular death or MI, as separately shown by Stone et al.¹⁰ Presumably, this discordance is caused by the potential for cardiovascular events to arise from nonobstructive plaques that may not be ischemic at baseline.^{20,21}

The reasons that CR is not always achieved in the invasive management of CCD are multifactorial. Independent predictors of ICR in ISCHEMIA included diabetes, BMI, number of diseased vessels and lesions, higher SYNTAX score, and more CTOs, all of which are markers for more complex CAD, and the use of CABG as a revascularization technique (Stone et al¹⁰). These factors suggest that the achievement of CR is dependent on patient comorbidities and coronary artery disease complexity, patient and physician selection for PCI vs CABG (a decision that may reflect local technical expertise, as well as logistical and convenience issues and patient preferences), and the perceived importance of CR vs ICR. Critically, this analysis informs the last factor—and therefore the overall revascularization decision-making process—by providing a deeper understanding of the type and magnitude of benefit of CR with regards to angina-related health status.

Few prior studies have assessed the effect of CR vs ICR on health status. A small single-center study of 210 patients with CR or ICR after CABG showed greater improvement in nondisease-specific SF-36 scores in patients achieving CR, although these results were not adjusted for baseline differences.²² In the COMPLETE (Complete versus Culprit-Only Revascularization Strategies to Treat Multivessel Disease after Early PCI for STEMI) study, patients with ST-segment elevation MI and multivessel disease randomized to CR (PCI of nonculprit lesions as well as the culprit lesion) had greater improvements in SAQ scores at 6 months and 3 years and a 3.2% absolute increase in freedom from angina (87.5% vs 84.3%; $P = 0.01$) compared with patients randomized to intentional ICR (PCI of the culprit lesion only), despite approximately 50% of patients having no baseline angina.²³ The larger ISCHEMIA trial extends these findings to a broader population of patients with CCD, finding a larger improvement in health status with CR in the most symptomatic patients.

The lack of impact of the number of CTOs present on the benefit of CR suggests that revascularization of such lesions has a similar impact on QoL improvement as non-CTO lesions, a fact that should be recognized when developing an overall revascularization plan designed to optimize health status. Successful revascularization of CTOs may be greater with CABG than PCI, although the success rates for CTO PCI are high with advanced techniques at centers of excellence.²⁴ Both registries and randomized controlled trials have shown more angina relief with

FIGURE 5 Adjusted Health Status Outcomes in Patients Stratified by Baseline Angina Level



Adjusted SAQ-7 Angina Frequency scores, Freedom from Angina (Angina Frequency = 100), and Summary Score are depicted over time (0, 1.5, 3, 6, and 12 months) for CON patients (blue), invasively managed patients achieving ICR (red), and invasively managed patients achieving CR (gray). Patients are stratified into groups based on baseline angina levels: daily/weekly, monthly, and none. (A) FCR. (B) ACR. Abbreviations as in Figure 4.

FIGURE 5 Continued

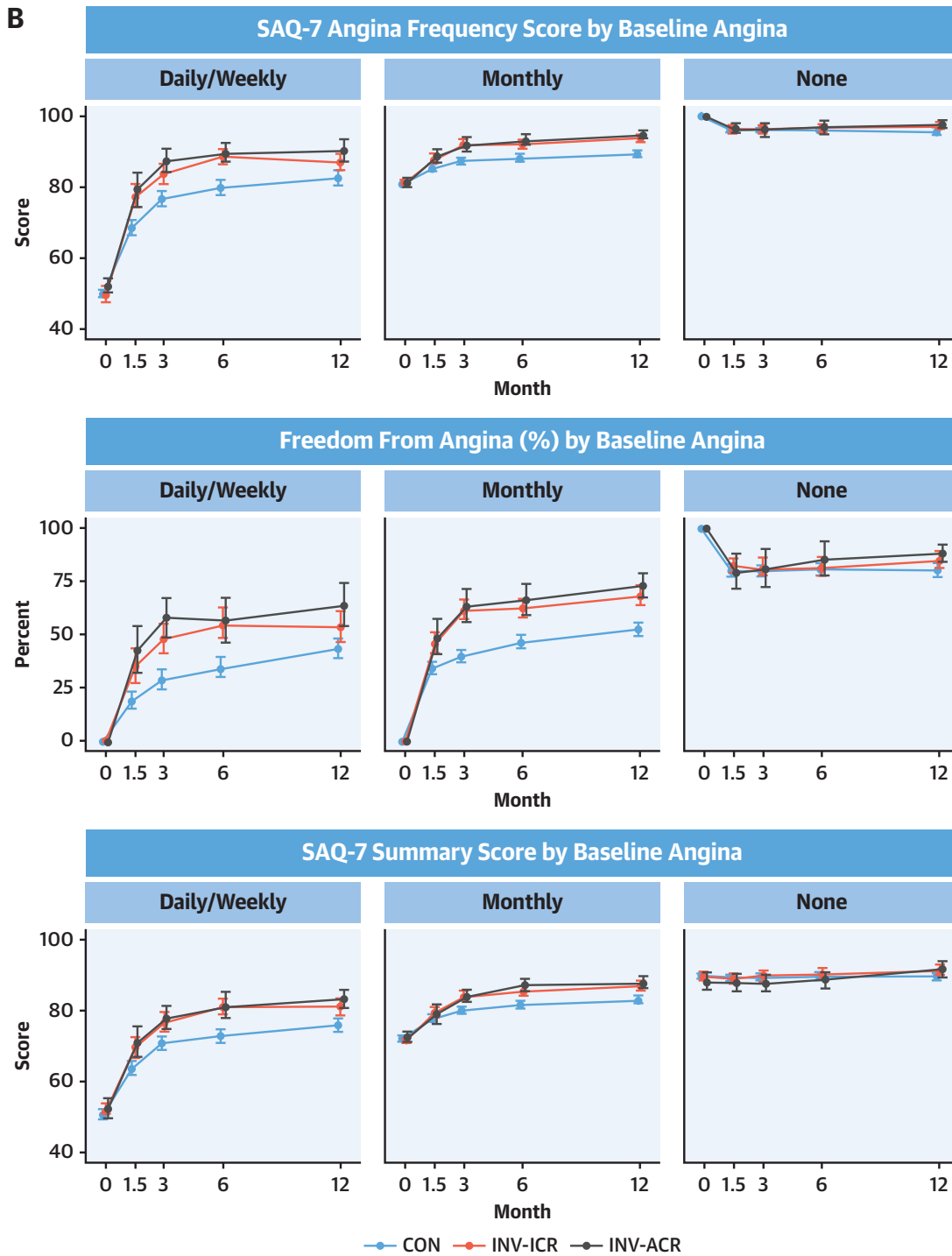


TABLE 4 Difference in Propensity-Weighted 12-Month Health Status Score of Invasively Managed Patients, Stratified by Angina and Ischemia

Baseline Angina	None	Monthly	Daily/Weekly	Interaction P Value
Effect of anatomic CR vs ICR				
SAQ-7 Angina Frequency Score	0.2 (−0.7, 1.0)	1.3 (−0.1, 2.7)	3.1 (−0.1, 6.2)	0.13
Freedom from angina, OR (95% CI)	1.10 (1.63-0.74)	1.25 (1.81-0.87)	1.51 (2.34-0.97)	0.61
SAQ-7 Summary Score	1.6 (−0.4, 3.6)	0.9 (−0.9, 2.8)	2.0 (−0.8, 4.8)	0.80
Quality of life	1.8 (−1.7, 5.3)	−0.2 (−3.2, 2.8)	2.9 (−1.6, 7.3)	0.43
Physical function	1.9 (−0.9, 4.7)	2.0 (−0.3, 4.2)	1.4 (−2.0, 4.8)	0.96
Rose Dyspnea Score	0.0 (−0.2, 0.2)	−0.3 (−0.4, −0.1)	−0.2 (−0.5, 0.1)	0.05
EQ-5D Visual Analog Scale	1.4 (−1.2, 3.9)	0.9 (−1.3, 3.2)	0.4 (−2.2, 3.0)	0.88
Effect of functional CR vs ICR				
SAQ-7 Angina Frequency Score	0.3 (−0.5, 1.1)	1.2 (−0.2, 2.7)	4.3 (1.1, 7.4)	0.03
Freedom from angina, OR (95% CI)	1.12 (1.56-0.80)	1.35 (1.87-0.98)	1.87 (2.84-1.22)	0.15
SAQ-7 Summary Score	0.2 (−1.3, 1.7)	1.8 (0.0, 3.7)	4.2 (1.4, 7.0)	0.03
Quality of life	1.0 (−1.8, 3.8)	2.2 (−0.7, 5.0)	3.0 (−0.8, 6.9)	0.72
Physical function	−0.3 (−2.8, 2.3)	3.8 (1.2, 6.4)	2.8 (−0.5, 6.1)	0.07
Rose Dyspnea Score	−0.1 (−0.2, 0.1)	−0.2 (−0.4, −0.1)	−0.3 (−0.6, −0.1)	0.07
EQ-5D Visual Analog Scale	−0.3 (−2.1, 1.4)	1.8 (−1.2, 4.9)	2.2 (−0.4, 4.8)	0.23
Degree of Ischemia				
	None to Mild	Moderate	Severe	
Effect of anatomic CR vs ICR				
SAQ-7 Angina Frequency Score	0.5 (−2.3, 3.3)	1.8 (0.3, 3.3)	1.2 (−0.1, 2.4)	0.69
Freedom from angina, OR (95% CI)	0.94 (1.59-0.55)	1.49 (2.18-1.02)	1.38 (2.08-0.92)	0.36
SAQ-7 Summary Score	1.8 (−1.2, 4.7)	2.9 (0.9, 5.0)	0.3 (−1.4, 2.0)	0.14
Quality of life	1.6 (−3.2, 6.5)	2.8 (−0.5, 6.1)	−0.2 (−3.1, 2.7)	0.40
Physical function	2.3 (−1.4, 6.0)	4.4 (1.2, 7.6)	0.0 (−2.3, 2.3)	0.10
Rose Dyspnea Score	−0.3 (−0.6, 0.0)	−0.1 (−0.3, 0.0)	−0.2 (−0.3, 0.0)	0.64
EQ-5D Visual Analog Scale	3.3 (−0.6, 7.3)	−0.4 (−3.0, 2.3)	1.4 (−0.4, 3.2)	0.31
Effect of functional CR vs ICR				
SAQ-7 Angina Frequency Score	0.2 (−0.7, 1.0)	1.3 (−0.4, 3.0)	1.9 (0.7, 3.2)	0.47
Freedom from angina, OR (95% CI)	1.10 (1.63-0.74)	1.32 (1.88-0.93)	1.57 (2.20-1.13)	0.52
SAQ-7 Summary Score	1.6 (−0.4, 3.6)	2.1 (0.3, 4.0)	1.5 (−0.3, 3.3)	0.85
Quality of life	1.8 (−1.7, 5.3)	1.1 (−1.8, 4.0)	2.8 (0.0, 5.5)	0.64
Physical function	1.9 (−0.9, 4.7)	3.2 (0.9, 5.6)	0.7 (−1.7, 3.2)	0.20
Rose Dyspnea Score	0.0 (−0.2, 0.2)	−0.1 (−0.3, 0.0)	−0.2 (−0.4, −0.1)	0.66
EQ-5D Visual Analog Scale	1.4 (−1.2, 3.9)	0.3 (−1.8, 2.3)	1.6 (−1.3, 4.5)	0.78

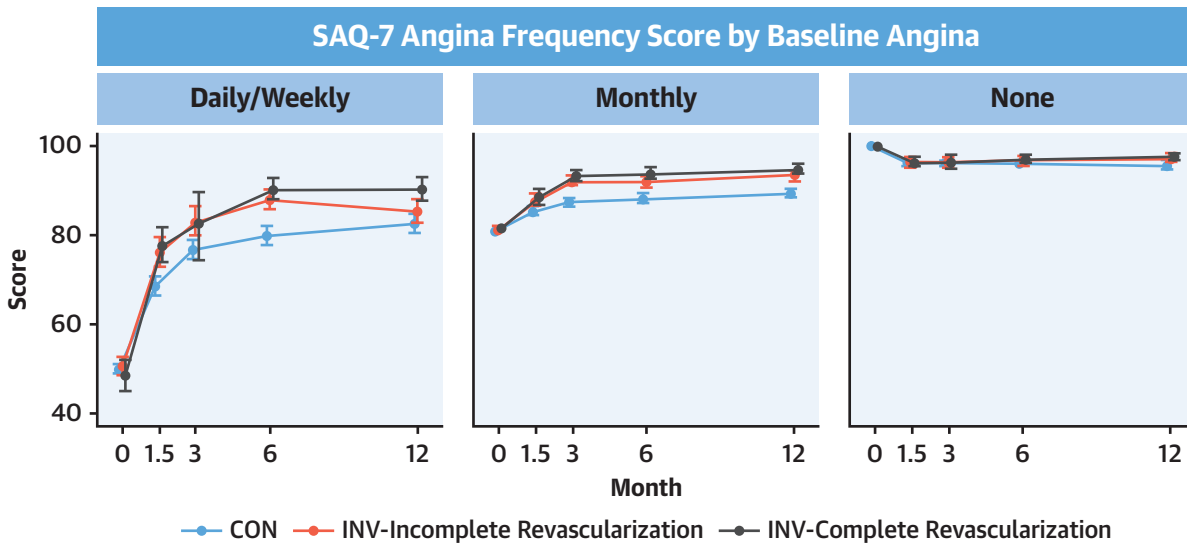
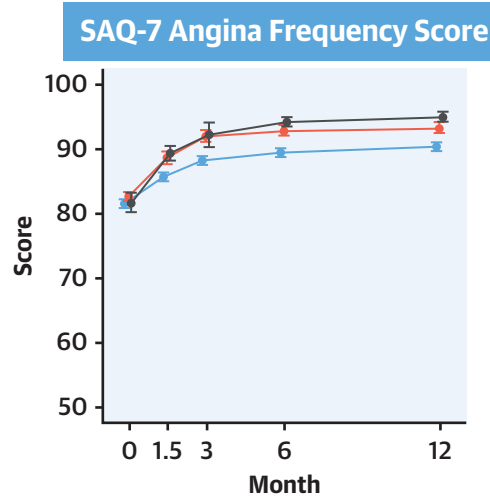
Values are median (Q1, Q3) or OR (95% CI).
Abbreviations as in [Tables 1 and 2](#).

CTO PCI than medical therapy alone.^{21,25,26} The extent to which myocardial viability influences the improvement in health status achieved after revascularization of CTOs (or non-CTOs) after PCI or CABG was not assessed in ISCHEMIA. The benefits of pursuing CR in patients with complex CTO(s) warrant further evaluation.

STUDY LIMITATIONS. The findings from this pre-specified substudy of the ISCHEMIA trial should be interpreted in the context of the following potential limitations. First, it was not possible to randomize

participants to CR vs ICR, and despite the use of multivariable adjustment, the potential for residual confounding remains. Accordingly, causality cannot be assumed. Second, the lack of a sham group in ISCHEMIA introduces the possibility of a placebo effect when comparing CR vs ICR, and the INV and CON groups. However, the impact of a placebo effect is diminished by the following: 1) the fact that this technical issue may not be known by some patients; and 2) the fact that the benefit in health status overall in the ISCHEMIA trial was comparable to that of the sham-controlled ORBITA (Objective Randomised

CENTRAL ILLUSTRATION Health Status Associated With Complete and Incomplete Revascularization in the ISCHEMIA Trial



Mavromatis K, et al. *J Am Coll Cardiol.* 2023;82(4):295-313.

(Top) Adjusted Seattle Angina Questionnaire (SAQ)-7 Angina Frequency scores over time (0, 1.5, 3, 6, and 12 months) in ISCHEMIA patients undergoing conservative management (CON), invasive management (INV) achieving incomplete revascularization, and INV achieving complete revascularization.
(Bottom) Adjusted SAQ-7 Angina Frequency scores over time (0, 1.5, 3, 6, and 12 months) in ISCHEMIA patients stratified for baseline angina levels (daily/weekly, monthly, or no angina) undergoing CON, INV achieving incomplete revascularization, and INV achieving complete revascularization.

Blinded Investigation With Optimal Medical Therapy of Angioplasty in Stable Angina) trial.²⁷ Third, there was no adjustment for multiple testing. Finally, the complex modeling to compare ICR and CR strategies with CON involved a number of assumptions that might account for some of the observed differences, and therefore, definitive

conclusions on treatment effect should not be drawn from this type of analysis.

CONCLUSIONS

In the ISCHEMIA trial, CR was only achieved in ~50% of patients with CCD undergoing revascularization.

However, the present analysis suggests that the likelihood of safely achieving CR is an important consideration when developing a revascularization plan for patients with CCD, because achieving CR was associated with a greater improvement in QoL, particularly in patients with more frequent angina at baseline.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

This work was supported by National Institutes of Health grants U01HL105907, U01HL105462, U01HL105561, U01HL105565, and T32 HL079896. This project was supported in part by Clinical Translational Science Award Nos. 11UL1 TR001445 and UL1 TR002243 from the National Center for Advancing Translational Sciences and by grants from Arbor Pharmaceuticals LLC and AstraZeneca Pharmaceuticals LP. Devices or medications were provided by Abbott Vascular (previously St Jude Medical, Inc), Medtronic Inc, Phillips (previously Volcano Corporation), and Omron Healthcare Inc; and medications were provided by Amgen Inc, Arbor Pharmaceuticals, LLC, AstraZeneca Pharmaceuticals, LP, Espero Pharmaceuticals, Merck, Sharp and Dohme Corp, and Sunovion Pharmaceuticals. Dr Mavromatis has received grants from the National Heart, Lung, and Blood Institute (CV Inflammation Reduction Trial and GMCSF in PAD-3 Trial), CSL Behring, St Jude Medical, Medtronic, DalCor Pharmaceuticals, AstraZeneca, Novartis, and Regeneron; and is a member of the American College of Cardiology and Society of Cardiovascular Angiography and Interventions. Dr Ali has received institutional grant support from Abbott, Abiomed, Acist Medical, Boston Scientific, Cardiovascular Systems Inc, Medtronic Inc, National Institutes of Health, Opsens Medical, Philips, and Teleflex; has received consulting fees from AstraZeneca, Philips, and Shockwave; and has equity in Elucid, Spectrawave, Shockwave, and VitalConnect. Dr Stone has received speaker honoraria from Medtronic, Pulnovo, Infraredx, Abiomed, and Abbott; has served as a consultant to Valfix, TherOx, Robocath, HeartFlow, Ablative Solutions, Vectorious, Miracor, Neovasc, Ancora, Elucid Bio, Occlutech, CorFlow, Apollo Therapeutics, Impulse Dynamics, Cardiomech, Gore, Amgen, Adona Medical, and Millennia Biopharma; 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 IQVIA; and his employer, Mount Sinai Hospital, receives research support from Abbott, Abiomed, Bioventrix, Cardiovascular Systems Inc, Phillips, Biosense Webster, Shockwave, Vascular Dynamics, Pulnovo, and V-wave. Dr Bangalore has received grants from the National Heart, Lung, and Blood Institute during the conduct of the study; has received grants and personal fees from Abbott Vascular; and has received personal fees from Biotronik, Pfizer, Amgen, and Reata outside of the submitted work. Dr Genreux has served as a consultant for, advisor for, and received speaker fees from Abbott Vascular, Abiomed, BioTrace Medical, and Medtronic; has served as a consultant for Boston Scientific, CARANX Medical, Cardiovascular System Inc (PI Eclipse Trial), GE Healthcare, iRhythm Technologies, Opsens, Siemens Teleflex, and 4C Medical (PI Feasibility study); has served as a consultant for, advisor for, proctor for, and received speaker fees and institutional research grant from Edwards Lifesciences (PI EARLY-TAVR trial, PI PROGRESS trial); has equity in and is a consultant for Pi-Cardia, Puzzle Medical, Saranas, and Soundbite Medical Inc; and has served as a consultant for and received speaker fees from Shockwave. Dr Goodman has received grants and personal fees from the National Heart, Lung, and Blood Institute, during the conduct of the study, Amgen, AstraZeneca, Bayer, Bristol Myers Squibb/Pfizer, CSL Behring/PERFUSE, Daiichi-Sankyo/American Regent/DCRI, Ferring, Novartis, and Regeneron/

Sanofi; and has received personal fees from Esperion/C5, Boehringer Ingelheim/Eli Lilly, GlaxoSmithKline, HLS Therapeutics, Merck, Novo Nordisk, and Servier, outside of the submitted work. Drs Alexander and Chen have received grants from the National Heart, Lung, and Blood Institute during the conduct of the study. Dr Boden has received grants from the National Heart, Lung, and Blood Institute during the conduct of the study; has received grants from Abbvie, Amarin, and Amgen; and has received personal fees from Amgen, Cleveland Clinic Clinical Coordinating Center, and Janssen outside of the submitted work. Dr Reynolds has received grants from the National Heart, Lung, and Blood Institute during the conduct of the study; and has received support from Abbott Vascular (donation of optical coherence tomography catheters for an unrelated research study) and Biotelemetry Inc (donation of telemetry monitors for an unrelated research study). Dr Maron has received grants from the National Heart, Lung, and Blood Institute during the conduct of the study. Dr Hochman is 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 Medtronic, Inc, Abbott Vascular, Inc (formerly St Jude Medical, Inc), Royal Philips NV (formerly Volcano Corporation), Arbor Pharmaceuticals, LLC, AstraZeneca Pharmaceuticals, LP, Merck Sharp and Dohme Corp, Omron Healthcare, Inc, Sunovion Pharmaceuticals, Inc, Espero BioPharma, and Amgen Inc; and financial donations were provided by Arbor Pharmaceuticals LLC and AstraZeneca Pharmaceuticals LP. Dr Spertus has provided consultative services on patient-reported outcomes and evidence valuation to Alnylam, AstraZeneca, Bayer, Merck, Janssen, Bristol Myers Squibb, Edwards, Kineksia, 4DT Medical, Terumo, Imbria, and United Healthcare; holds research grants from Bristol Myers Squibb, Abbott Vascular, and Janssen; owns the copyright to the Seattle Angina Questionnaire, Kansas City Cardiomyopathy Questionnaire, and Peripheral Artery Questionnaire; and serves on the Board of Directors for Blue Cross Blue Shield of Kansas City. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. The contents of this paper are solely the responsibility of the authors and do not necessarily represent official views of the National Center for Advancing Translational Sciences, the National Heart, Lung, and Blood Institute, the National Institutes of Health, or the Department of Health and Human Services.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND

PROCEDURAL SKILLS: Complete coronary revascularization is associated with improved angina-related health status, but in clinical practice is achieved in only one-half of patients.

TRANSLATIONAL OUTLOOK: Randomized trials are needed to confirm the efficacy of CR vs ICR on long-term survival and quality of life.

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KEY WORDS complete revascularization, coronary artery disease, ischemia, quality of life, revascularization

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