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Health Status Outcomes With Percutaneous Coronary Intervention and Coronary Artery Bypass Grafting in ISCHEMIA

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BACKGROUND: In ISCHEMIA (International Study of Comparative Health Effectiveness With Medical and Invasive Approaches), an invasive strategy demonstrated better health status outcomes than a conservative strategy in patients with chronic coronary disease (CCD). Some previous studies have shown greater health status benefits with coronary artery bypass grafting (CABG) than percutaneous coronary intervention (PCI). Whether the health status benefits of invasive management in ISCHEMIA were driven primarily by participants treated with CABG is unknown.

METHODS: The aim of this analysis was to describe the health status outcomes of participants treated with a conservative strategy (n=2232) compared with invasively managed participants treated with PCI (n=1198) or CABG (n=340) in ISCHEMIA. The Seattle Angina Questionnaire–7 summary score (SAQ-SS) and angina frequency score (SAQ-AF) were the primary outcomes, with higher scores indicating better health status. Proportional odds models comparing 1- and 3-year outcomes were fit, adjusting for demographic, clinical, and angiographic characteristics.

RESULTS: SAQ-SS in the conservative, PCI, and CABG groups increased by 9.9±18.1, 15.7±19.3, and 16.1±19.1 points at 1 year and 11.5±20.2, 16.5±21.8, and 15.0±19.4 points at 3 years, respectively. Freedom from angina in the conservative, PCI, and CABG groups was noted in 61.4%, 73.3%, and 82.4% at 1 year and 70.4%, 76.1%, 81.4% at 3 years, respectively. In risk-adjusted analyses, PCI and CABG were each associated with a higher SAQ-SS and SAQ-AF at 1 and 3 years compared with conservative management. SAQ-AF was higher with CABG than PCI at 1 year (odds ratio, 1.54 [95% CI, 1.03, 2.31]), but no differences between CABG and PCI were observed in SAQ-SS (odds ratio, 1.11 [95% CI, 0.78, 1.57]) or SAQ-AF (odds ratio, 0.94 [95% CI, 0.58, 1.54]) at 3 years.

CONCLUSIONS: In ISCHEMIA, both PCI and CABG were associated with better 3-year health status than conservative management. Better angina relief with CABG than PCI was seen at 1, but not 3, years.

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Key Words: coronary artery bypass ■ coronary disease ■ health status ■ myocardial ischemia ■ percutaneous coronary intervention ■ quality of life

Editorial, see p 859

Chronic coronary disease (CCD) affects nearly 200 million people worldwide, with an increasing prevalence over the past 20 years.[1] CCD impairs patients' health status (eg, symptoms, physical functioning, quality of life [QoL]), and improving health status is a primary goal of CCD treatment.[2,3] In the COURAGE

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Clinical Perspective

What Is New?

- In ISCHEMIA (International Study of Comparative Health Effectiveness With Medical and Invasive Approaches), both coronary artery bypass grafting and percutaneous coronary intervention were associated with long-term improvements in health status when compared with conservative chronic coronary disease management.
- An early benefit of better angina relief with coronary artery bypass grafting than percutaneous coronary intervention at 1 year was no longer present at 3 years.

What Are the Clinical Implications?

- Invasive management of chronic coronary disease is associated with long-term health status benefits compared with conservative management, regardless of whether coronary artery bypass grafting or percutaneous coronary intervention is selected as the revascularization approach.
- The decision to pursue an invasive or conservative management approach should result from shared decision-making, but the mode of revascularization is unlikely to affect the health status benefits of invasive treatment.

Nonstandard Abbreviations and Acronyms

BARI-2D	Bypass Angioplasty Revascularization Investigation 2 Diabetes
CABG	coronary artery bypass grafting
CCTA	coronary computed tomography angiography
CCD	chronic coronary disease
CON	conservative strategy
COURAGE	Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation
EQ-5D	European Quality of Life–5 Dimensions
EXCEL	Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization
FAME	Fractional Flow Reserve versus Angiography for Multivessel Evaluation
FREEDOM	Comparison of Two Treatments for Multivessel Coronary Artery Disease in Individuals With Diabetes
ISCHEMIA	International Study of Comparative Health Effectiveness With Medical and Invasive Approaches
ORBITA	Objective Randomised Blinded Investigation With Optimal Medical Therapy of Angioplasty in Stable Angina
PCI	percutaneous coronary intervention
QoL	quality of life
SAQ	Seattle Angina Questionnaire–7
SAQ-AF	Seattle Angina Questionnaire angina frequency score
SAQ-PL	Seattle Angina Questionnaire physical limitation score
SAQ-QoL	Seattle Angina Questionnaire quality of life score
SAQ-SS	Seattle Angina Questionnaire summary score
SYNTAX	Synergy Between PCI With Taxus and Cardiac Surgery

trial (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation), a small but significant health status benefit was observed with percutaneous coronary intervention (PCI) compared with optimal medical therapy through 24 months in patients with CCD, but this difference diminished by 36 months.[4] In contrast, ISCHEMIA (International Study of Comparative Health Effectiveness With Medical and Invasive Approaches) demonstrated a durable and significant health status benefit with invasive versus conservative management through 48 months among patients with CCD with moderate or severe ischemia.[5] The ISCHEMIA protocol for participants randomized to invasive management recommended but did not dictate the mode of revascularization, which could have been either PCI or coronary artery bypass grafting (CABG) based on the recommendations of the local heart team. Some[6–8] but not all[9] previous studies have demonstrated better long-term health status outcomes with CABG than PCI. Thus, assessing the relative benefits of both methods compared with medical management is important to understand the extent to which the overall observed health status benefits of invasive management were driven by the use of CABG in ISCHEMIA. The purpose of this analysis was to describe health status outcomes of patients with CCD who were treated with PCI, CABG, or a conservative approach in ISCHEMIA.

METHODS

Study Design

The design of ISCHEMIA, and the clinical and health status outcomes between its invasive and conservative strategy arms, have been reported previously.[5,10,11] In brief, ISCHEMIA was a multicenter international randomized controlled trial of 5179 patients with CCD and at least moderate ischemia on stress testing comparing an initial invasive management strategy (coronary angiography and revascularization, if possible, plus guideline-directed medical therapy) and an initial conservative strategy (guideline-directed medical therapy alone). Stress

testing was performed at individual study sites, with subsequent review by a core laboratory after randomization. Key trial exclusion criteria included coronary computed tomography angiography (CCTA) results showing left main stenosis >50%, lack of substantial coronary disease, left ventricular ejection fraction <35%, New York Heart Association functional class III or IV heart failure, and unacceptable angina despite maximally tolerated antianginal medical therapy. For this analysis, 481 participants from 5 sites with invalid health status form completion, 81 without baseline or follow-up Seattle Angina Questionnaire–7 (SAQ) data, and 196 with previous CABG were excluded. The population thus comprised 4421 patients randomized in ISCHEMIA with available health status assessments. The trial was approved by the institutional review board at each study site and written informed consent was obtained from all participants. To minimize the possibility of unintentionally sharing information that can re-identify private information, a subset of the data generated for this study is available at BioLINCC (https://biolincc.nhlbi.nih.gov/studies/ischemia).

Treatment Groups

Intensive guideline-directed medical therapy for CCD was recommended for all participants, regardless of assignment to invasive or conservative treatment arms. By protocol, participants randomized to the invasive strategy additionally underwent invasive coronary angiography within 30 days and subsequent revascularization to all feasible ischemic territories. The method of revascularization (PCI, CABG, or none) for each individual participant was determined by the local heart team after diagnostic angiography. The study provided an algorithm for using fractional flow reserve testing to supplement the noninvasive ischemia evaluation to guide PCI.[11]

The current analysis stratified participants on the basis of the mode of revascularization, if any, undertaken within 90 days (Figure 1). Invasively managed participants treated with PCI and CABG were restricted to those who were revascularized within 90 days. For 16 participants in whom both PCI and CABG were performed within 90 days, treatment assignment was based on the intended management strategy documented by the local heart team (most commonly the first procedure performed). Participants in the invasive arm who did not receive revascularization within 90 days (ie, those who did not undergo an invasive angiogram, those with no substantial obstructions, and those with such extensive disease that the risks of revascularization were deemed by the local heart team to exceed its benefits) were described separately. The conservative group included all participants randomized to a conservative strategy, regardless of whether revascularization was ultimately performed. The rate of revascularization within 6 months was <9.0% in this group, with most occurring after suspected clinical events, 1.6% for unacceptable symptoms, and 2.6% for protocol nonadherence.[12]

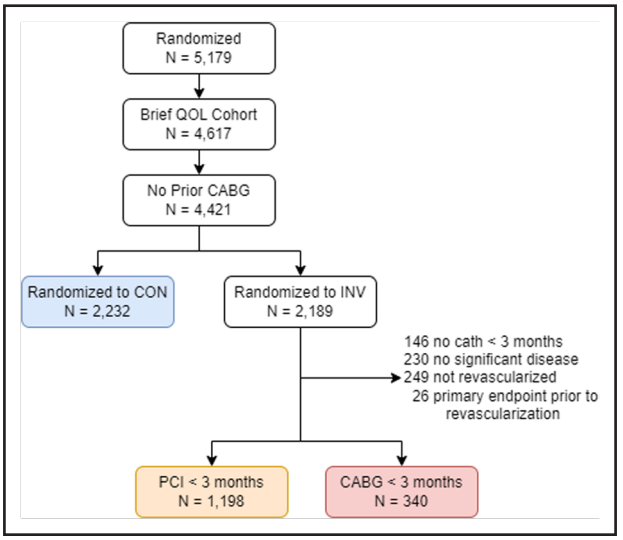

Figure 1. Study groups.
CABG indicates coronary artery bypass grafting; CON, conservative strategy; INV, invasive strategy; PCI, percutaneous coronary intervention; and QoL, quality of life.

Health Status Assessments

Participants' health status was assessed before randomization; at 1.5, 3, and 6 months; and every 6 months thereafter until study completion with the SAQ,[2,8] the Rose Dyspnea Scale,[13] and the European Quality of Life–5 Dimensions (EQ-5D) visual analogue scale.[14]

The SAQ is a disease-specific patient-reported outcome tool to assess angina-related health status in patients with CCD.[2] The shortened 7-item version was the primary health status instrument used in the trial.[15] Validated translations were used in each country (www.cvoutcomes.org). The SAQ provides separate scores for angina frequency (SAQ-AF), physical limitation (SAQ-PL), and QoL (SAQ-QoL). The average of these individual scores generates the SAQ summary score (SAQ-SS). Scores range from 0 to 100, with higher scores indicating better health status. SAQ-AF scores of 0 to 30, 31 to 60, 61 to 99, and 100 correspond to daily, weekly, monthly, and no angina, respectively. For the SAQ-SS, SAQ-PL, and SAQ-QoL scores, values of 0 to 24, 25 to 49, 50 to 74, and 75 to 100 can be interpreted as very poor to poor, poor to fair, fair to good, and good to excellent, respectively. A 5-point change in the SAQ-SS has been suggested as a minimum difference that would be considered clinically important to most patients.[16]

The Rose Dyspnea Scale is a 4-item patient-reported outcome tool assessing the presence or absence of dyspnea under 4 circumstances, yielding a score of 0 to 4.[13] A score of 0 indicates no dyspnea; a score of 4 indicates major limitation due to dyspnea. Although the Rose Dyspnea Scale is not a disease-specific tool for CCD, higher scores on the Rose Dyspnea Scale have been associated with lower QoL in patients with CCD, independent of angina frequency.[17]

The EQ-5D visual analogue scale is a patient-reported outcome tool for general health status assessment. Patients rate their health on a scale from 0 (worst imaginable health status) to 100 (best imaginable health status).[3]

Statistical Analysis

Categorical variables are presented as number (%) and continuous variables as mean±SD. The primary aim of this analysis was to describe health status outcomes, stratified by revascularization method, among ISCHEMIA participants. To achieve this aim, the primary outcome was the unadjusted SAQ-SS. Secondary outcomes were the unadjusted SAQ-AF, SAQ-PL, SAQ-QoL, Rose Dyspnea Scale, and EQ-5D visual analogue

scale. Unadjusted health status scores to 48 months are presented.

A secondary aim of the study was to estimate adjusted differences in 1-year and 3-year health status outcomes among conservative, PCI, and CABG groups. There were 651 participants in the invasive arm who did not undergo PCI or CABG within 3 months or had a primary end point before revascularization. These participants were excluded from risk-adjusted comparisons, leaving a population of 3770 for the risk-adjusted analyses. Given the inherent differences between participants selected for PCI and those selected for CABG, and the high likelihood of selection bias, risk adjustment with a combination of propensity scoring and regression was used. All comparisons included adjustment for age, sex, geographic region, hypertension, diabetes, smoking status, previous myocardial infarction, heart failure, previous stroke, cerebrovascular disease, peripheral arterial disease, previous PCI, left ventricular ejection fraction, body mass index, estimated glomerular filtration rate, New York Heart Association heart failure classification, core laboratory–assessed degree of ischemia, and baseline SAQ, Rose Dyspnea Scale, and EQ-5D scores. For the comparison of PCI and CABG, we additionally included variables obtained from the invasive coronary angiogram: Duke Jeopardy score, SYNTAX score (Synergy Between PCI With Taxus and Cardiac Surgery), left main disease, left anterior descending disease, proximal left anterior descending disease, left circumflex disease, right coronary artery disease, number of chronic total occlusion lesions, number of calcified lesions, and number of tortuous lesions. For comparisons of PCI with conservative management and CABG with conservative management, we repeated the analyses among the 74% of participants for whom CCTA was performed, including additional adjustment for CCTA-derived SYNTAX score and the number of diseased vessels, in addition to the sociodemographic and clinical variables described previously.

For each pairwise comparison of treatment groups, the following approach was used. First, propensity scores for treatment were generated using logistic regression on the relevant set of covariates. The overlap of propensity score distributions between the 2 groups (plotted visually using nonparametric kernel density estimates; Figure 2 and Figure S1) was then examined and participants whose scores exceeded the 1st or 99th percentile of scores in the alternate treatment group were excluded. For example, when comparing conservative management and PCI, conservative management participants whose probability of PCI was lower than the 1st percentile of scores in the PCI group were excluded, as were PCI participants whose probability of PCI was higher than the 99th percentile of scores in the conservative group. Within the restricted cohort, proportional odds regression models of health status outcomes on treatment group were fit, adjusting for the same variables included in the propensity score as covariates. Whereas the propensity scoring step served to limit inferences to participants who have at least some likelihood of receiving either treatment, covariate adjustment (ie, rather than propensity matching or weighting) produces conditional, or patient-specific, estimates of the effect of treatment, which are generally more relevant to clinicians and patients for health status outcomes than population-average estimates. To examine potential heterogeneity of treatment effects, we re-fit the outcome models including only treatment group, the (logit) propensity score as a linear effect, and a treatment by propensity score interaction. This evaluates

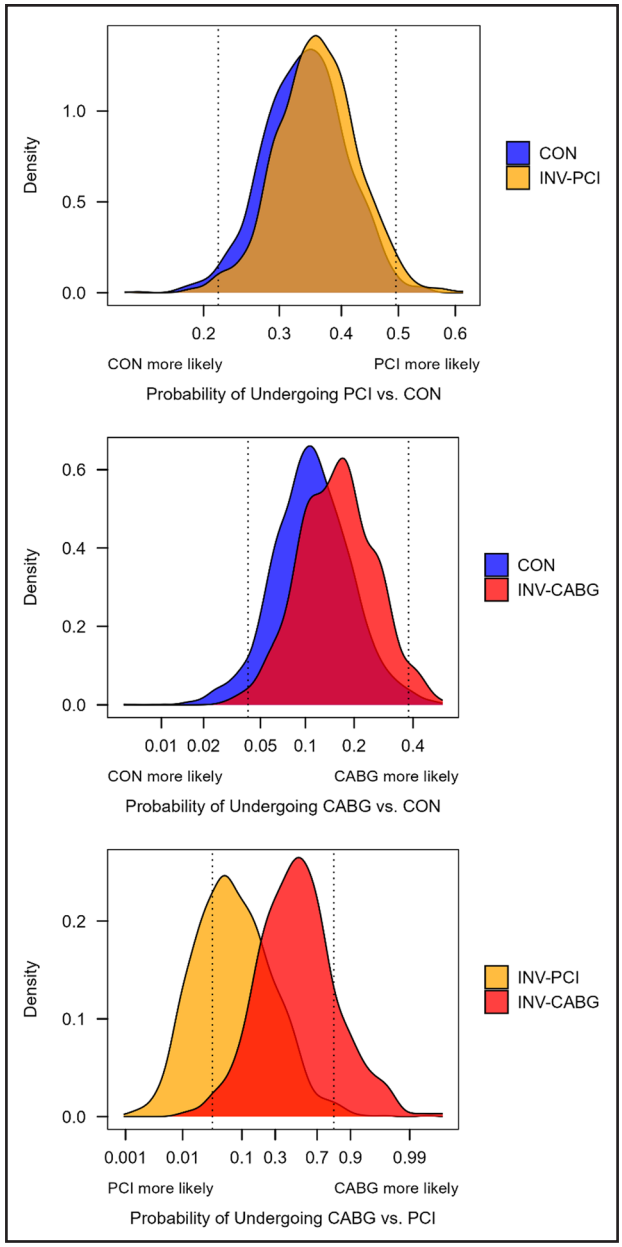

Figure 2. Propensity score distributions.
For each pairwise comparison of treatment groups, propensity score distributions for the probability of undergoing one treatment versus the other is shown, with different colors indicating patients receiving a specific treatment. Propensity scores were constructed using sociodemographics, geographic region, comorbidities, core laboratory–assessed degree of ischemia, and baseline Seattle Angina Questionnaire, Rose Dyspnea Scale, and European Quality of Life–5 Dimensions scores. For the comparison of percutaneous coronary intervention (PCI) versus coronary artery bypass grafting (CABG), we also included variables obtained from the invasive coronary angiogram: Duke Jeopardy score, SYNTAX score (Synergy Between PCI With Taxus and Cardiac Surgery), left main disease, left anterior descending disease, proximal left anterior descending disease, left circumflex disease, right coronary artery disease, number of chronic total occlusion lesions, number of calcified lesions, and number of tortuous lesions. CON indicates conservative strategy; and INV, invasive strategy.

whether the benefit of treatment increases or decreases with the likelihood of receiving the treatment. For both propensity and outcome models, nonlinear effects of continuous covariates were explored by using restricted cubic splines. Treatment effects are reported as estimated odds ratios (ORs) and 95% CIs for better health status with PCI versus conservative management, CABG versus conservative management, and CABG versus PCI. Treatment effects were estimated across all participants and stratified by baseline angina frequency defined by the SAQ-AF score (daily or weekly angina, 0–60; monthly angina, 70–90; no angina, 100).

Of the 3770 participants included in these analyses, 5.4% were missing 1-year health status scores (due to missed assessments [3.1%], loss to follow-up [1.2%], death [0.9%], or study withdrawal [0.2%]) and 45.4% were missing 3-year scores (due to study termination [37.2%], death [3.3%], missed assessments [2.8%], loss to follow-up [1.7%], or study withdrawal [0.4%]). There were no missing covariates, except for angiographic factors and CCTA factors (which we addressed by conducting secondary analyses). For the analyses estimating treatment effects, we imputed missing SAQ domain scores using multiple imputation methods (R package "mice").[18] The imputation model included treatment group, all covariates described previously, and all health status scores between baseline and 1 year. Forty imputed data sets were generated and the results were pooled using the Rubin method to obtain final treatment effect estimates.[19] All analyses were conducted using SAS version 9.4 (SAS Institute) and R version 4.1.3.

RESULTS

Study Cohort

The study population comprised 2232 participants in the conservative management group, 1198 in the PCI group, and 340 in the CABG group. There were 146 participants randomized to the invasive group who did not undergo an invasive angiogram within 90 days, 230 who had no substantial disease identified by invasive angiography, and 249 who had substantial disease not amenable to revascularization.

Characteristics of the study population stratified by revascularization method are summarized in Table 1. Mean age was between 63 and 67 years, and most participants in each group were White men. Cardiovascular risk factors and comorbidities were common in each group. Moderate or severe ischemia on stress testing, confirmed by the core laboratory, was present in >85% of each group, but was most common in the CABG group (92.4%). Coronary anatomy was also more complex in the CABG group. SYNTAX score <23 was observed in 81.5% in the PCI group versus 33.0% in the CABG group and SYNTAX score >32 was observed in 3.7% in the PCI group versus 30.1% in the CABG group. Left main disease was rare but was observed in a higher proportion of CABG-treated participants. At least 1 chronic total occlusion was found in 38.1% of the PCI group versus 64.1% of the CABG group.

Baseline health status stratified by revascularization groups is summarized in Table 2. Mean baseline SAQ-SS ranged from 72 to 79 points across groups, with the lowest baseline score in the PCI group (72.1). Daily or weekly angina frequency was observed in 12% to 24% of patients; monthly angina (38%–46% of patients) and no angina (30%–43% of patients) were more commonly observed in all groups.

Unadjusted Health Status Outcomes

Unadjusted health status scores through 48 months are provided in Figures 3 and 4 and Table S1. For the SAQ-SS, SAQ-QoL, and SAQ-PL scores, similar patterns were observed in which the PCI group demonstrated the largest early changes from baseline to 3 months. Changes in the CABG group were somewhat delayed, but the highest scores were consistently observed in the CABG groups from 6 through 48 months. SAQ-AF score and freedom from angina rates were highest in the CABG group at all time points from 3 through 48 months. Table 3 provides the proportion of participants with no angina from 3 through 48 months, as assessed by the SAQ-AF category. Rose Dyspnea scores were similar between the PCI and CABG groups at 3 months and lowest (more favorable) in the CABG group from 6 through 48 months. The EQ-5D visual analogue scale score was highest (more favorable) in the PCI group at 3 months and highest in the CABG group from 6 through 48 months.

Among randomized participants in the invasive arm who did not undergo revascularization, there was considerable heterogeneity, but their scores during follow-up were more like those of conservative-managed participants than those managed with PCI or CABG.

Risk-Adjusted Health Status at 1 Year

In risk-adjusted analyses, higher odds of favorable SAQ-SS and SAQ-AF at 1 year were observed for both PCI (SAQ-SS OR, 1.98 [95% CI, 1.73, 2.26] and SAQ-AF OR, 2.10 [95% CI, 1.78, 2.48] versus conservative management) and CABG (SAQ-SS OR, 2.56 [95% CI, 2.04, 3.22] and SAQ-AF OR, 3.46 [95% CI, 2.52, 4.76] versus conservative management) compared with the conservative group (Figure 5). The findings of higher SAQ scores at 1 year with PCI versus conservative management and CABG versus conservative management were confirmed in a sensitivity analysis restricted to participants with baseline CCTA that allowed for further risk adjustment by including CCTA assessments of coronary disease severity (Figure S2). At 1 year, CABG was associated with a higher likelihood of favorable SAQ-AF than PCI (OR, 1.54 [95% CI, 1.03, 2.31]), but no significant difference in SAQ-SS was observed between CABG and PCI at 1 year.

Table 1. Baseline Characteristics by Revascularization Method

Characteristics	Conservative strategy (n=2232)	INV-PCI (n=1198)	INV-CABG (n=340)	INV–no revasc (n=249)	INV–no lesion (n=230)	INV–no cath (n=146)
Age, yrs	64.1±9.6	63.3±9.6	65.0±8.8	66.6±9.2	67.4±9.6	63.3±8.8
Female sex	510 (22.8)	285 (23.8)	64 (18.8)	45 (18.1)	99 (43.0)	35 (24.0)
White race	1606 (72.9)	851 (71.3)	262 (78.2)	188 (76.4)	187 (83.1)	88 (60.7)
Hispanic or Latino ethnicity	375 (16.8)	175 (14.6)	84 (24.7)	37 (14.9)	34 (14.8)	15 (10.3)
Hypertension	1683 (75.7)	907 (75.8)	270 (80.1)	181 (73.0)	172 (75.1)	106 (72.6)
Diabetes	907 (40.6)	460 (38.4)	162 (47.6)	103 (41.4)	82 (35.7)	51 (34.9)
Current or former smoker	1336 (59.9)	692 (57.8)	216 (63.5)	157 (63.1)	134 (58.3)	84 (57.5)
Previous myocardial infarction	429 (19.3)	222 (18.6)	95 (27.9)	52 (21.0)	34 (14.8)	22 (15.1)
Previous PCI	452 (20.3)	253 (21.1)	78 (22.9)	68 (27.4)	59 (25.7)	29 (20.0)
Previous heart failure	84 (3.8)	53 (4.4)	13 (3.8)	9 (3.6)	17 (7.4)	7 (4.8)
Previous stroke	59 (2.6)	35 (2.9)	14 (4.1)	12 (4.8)	7 (3.0)	8 (5.5)
Cerebrovascular disease	159 (7.1)	92 (7.7)	29 (8.5)	26 (10.4)	18 (7.8)	15 (10.3)
Peripheral vascular disease	75 (3.4)	50 (4.2)	18 (5.3)	19 (7.7)	13 (5.7)	4 (2.8)
Body mass index	29.0±5.4	28.6±4.8	28.8±4.7	28.6±4.9	30.1±6.4	28.5±5.3
eGFR, mL·min·1.73 m^2	83.0±22.4	84.3±22.4	82.2±22.3	84.6±24.2	78.8±23.1	81.5±22.3
LVEF, %	60.0±8.3	60.6±8.0	60.2±7.8	59.4±8.7	61.0±7.6	60.3±8.6
History of angina	1965 (88.0)	1085 (90.6)	303 (89.1)	213 (85.5)	196 (85.2)	128 (87.7)
Moderate or greater ischemia	1917 (85.9)	1051 (87.7)	314 (92.4)	223 (90.0)	155 (67.4)	119 (81.5)
SYNTAX score*						
<23		953 (81.5)	111 (33.0)	148 (59.4)	228 (100.0)	38 (74.5)
23 to <33		173 (14.8)	124 (36.9)	60 (24.1)	0 (0.0)	8 (15.7)
≥33		43 (3.7)	101 (30.1)	41 (16.5)	0 (0.0)	5 (9.8)
Left main disease*		12 (1.0)	37 (10.9)	8 (3.2)	0 (0.0)	1 (1.4)
Proximal LAD disease*		238 (19.9)	113 (33.2)	45 (18.1)	0 (0.0)	18 (24.3)
CTO of ≥1 vessel*		456 (38.1)	218 (64.1)	168 (67.5)	0 (0.0)	29 (19.9)
Completeness of anatomic revascularization		549 (47.0)	115 (34.2)	53 (21.3)	166 (72.8)	23 (45.1)
Completeness of functional revascularization		734 (62.8)	167 (49.7)	68 (27.3)	207 (90.8)	32 (62.7)

Continuous variables are presented as mean±SD and categorical variables as n (%). CTO indicates chronic total occlusion; eGFR, estimated glomerular filtration rate; INV-CABG, invasive strategy with coronary artery bypass grafting within 3 months; INV–no cath, invasive strategy without invasive catheterization within 3 months; INV–no lesion, invasive strategy with invasive catheterization, but no substantial coronary artery lesion identified; INV–no revasc, invasive strategy with invasive catheterization, but no subsequent coronary revascularization procedure within 3 months; INV-PCI, invasive strategy with percutaneous coronary intervention within 3 months; LAD, left anterior descending; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; and SYNTAX, Synergy Between PCI With Taxus and Cardiac Surgery.

*Assessed by invasive angiography.

Risk-Adjusted Health Status at 3 Years

At 3 years, a higher odds of favorable SAQ-SS and SAQ-AF scores were observed with both PCI (SAQ-SS OR, 1.55 [95% CI, 1.32, 1.83] and SAQ-AF OR, 1.44 [95% CI, 1.17, 1.77] versus conservative management) and CABG (SAQ-SS OR, 1.78 [95% CI, 1.33, 2.38] and SAQ-AF OR, 1.58 [95% CI, 1.11, 2.26] versus conservative management; Figure 6). The sensitivity analysis of patients with inclusion of baseline CCTA for risk adjustment showed similar findings (Figure S3). By 3 years, there was no difference in the odds of a higher SAQ-SS or SAQ-AF score between CABG and PCI.

Health Status Outcomes by Baseline Angina Frequency

In a secondary analysis of health status outcomes stratified by baseline angina frequency, PCI and CABG both showed higher risk-adjusted odds of favorable 1-year SAQ-SS and SAQ-AF compared with conservative management, regardless of baseline angina frequency (Figure S4). Among participants with daily or weekly baseline angina, CABG was associated with higher odds of a more favorable SAQ-SS than PCI at 1 year (OR, 2.09 [95% CI, 1.05, 4.15]).

At 3 years, the odds of a more favorable SAQ-SS were generally higher in both CABG and PCI compared

Table 2. Baseline Health Status by Revascularization Method

Score	Conservative strategy (n=2232)	INV-PCI (n=1198)	INV-CABG (n=340)	INV–no revasc (n=249)	INV–no lesion (n=230)	INV–no cath (n=146)
SAQ-7 summary score	75.0±18.6	72.1±19.1	73.7±17.9	75.7±19.5	75.8±19.3	78.6±17.2
SAQ-7 angina frequency score	82.2±19.1	79.3±20.4	80.2±20.1	82.9±19.8	85.1±17.2	85.3±16.1
SAQ-7 angina frequency category						
Daily or weekly	418 (18.7)	281 (23.5)	74 (21.8)	52 (21.0)	35 (15.2)	18 (12.3)
Monthly	994 (44.6)	545 (45.6)	154 (45.3)	96 (38.7)	96 (41.7)	67 (45.9)
None	818 (36.7)	370 (30.9)	112 (32.9)	100 (40.3)	99 (43.0)	61 (41.8)
SAQ-7 physical limitation score	80.5±23.0	77.9±23.9	81.2±21.4	81.1±22.5	76.2±26.2	81.5±22.8
SAQ-7 quality of life score	62.7±26.2	59.1±26.5	59.8±25.6	64.0±27.5	65.5±26.7	68.6±25.2
Rose Dyspnea Scale	1.2±1.3	1.2±1.3	1.1±1.3	1.1±1.3	1.4±1.4	1.1±1.3
EQ-5D visual analogue scale	69.4±16.5	68.4±17.3	70.5±16.4	69.5±16.7	68.1±16.6	69.5±15.6

Continuous variables are presented as mean±SD and categorical variables as n (%). EQ-5D indicates European Quality of Life–5 Dimensions; INV-CABG, invasive strategy with coronary artery bypass grafting within 3 months; INV–no cath, invasive strategy without invasive catheterization within 3 months; INV–no lesion, invasive strategy with invasive catheterization, but no substantial coronary artery lesion identified; INV–no revasc, invasive strategy with invasive catheterization, but no subsequent coronary revascularization procedure within 3 months; INV-PCI, invasive strategy with percutaneous coronary intervention within 3 months; and SAQ, Seattle Angina Questionnaire.

with conservative management, regardless of baseline angina severity (Figure S5). However, benefits in terms of SAQ-AF score among CABG- and PCI-treated participants compared with conservative management were generally restricted to those with daily or weekly angina at baseline. Findings of the 1- and 3-year models of PCI versus conservative management and CABG versus conservative management among patients with baseline CCTA for risk adjustment, stratified by baseline angina frequency, are provided in Figures S6 and S7.

DISCUSSION

After the initial recovery period from CABG, some, but not all, previous studies have demonstrated greater late health status benefits with CABG compared with PCI. This secondary analysis of ISCHEMIA explored whether the sustained health status benefits of an invasive strategy were primarily driven by CABG. Significant health status benefits among participants managed with both PCI and CABG compared with conservative management were found. Durable improvements in health status were observed in both groups, and these improvements with both PCI and CABG were greater than those observed in the conservative group based on risk-adjusted comparisons through 3 years of follow-up. When directly comparing CABG with PCI, CABG was observed to result in better angina control at 1 year, but not at 3 years.

Health Status Benefits of PCI, CABG, and Medical Therapy

Nearly all previous trials have demonstrated better early symptom relief after PCI than CABG during the postoperative recovery period of 1 to 6 months. After this period, some previous studies have suggested that CABG is associated with better intermediate-term health status compared with PCI, but long-term differences in health status after these procedures appear to be minimal.[6,7,20,21] In the FREEDOM trial (Comparison of Two Treatments for Multivessel Coronary Artery Disease in Individuals With Diabetes) of patients with CCD, diabetes, and multivessel coronary disease randomized to PCI or CABG, the CABG arm showed better health status through 2 years, but not later.[7] Data from a large Canadian registry of diabetic patients with multivessel CCD treated with PCI and CABG demonstrated higher (better) SAQ scores across multiple domains with CABG at 1 year, with attenuated differences by 3 years.[21] The 5-year outcomes of the SYNTAX trial, which compared PCI with drug-eluting stents versus CABG for the treatment of left main or 3-vessel CCD, reported a small but significant improvement in SAQ-AF with CABG over PCI that persisted out to 5 years.[6] However, in EXCEL (Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization), which evaluated left main disease revascularization, health status outcomes were better with PCI compared with CABG at 1 month, but similar at 1 and 3 years.[20] In a recently published systematic meta-analysis of all 5 randomized trials of PCI versus CABG in which QoL was formally assessed in 10 760 patients, the mean differences in SAQ-AF scores were similar between procedures at 1 month, favored CABG at 1 year, and were similar between procedures between 36 and 60 months.[9]

The health status outcomes of PCI versus medical therapy have also been evaluated in multiple previous trials, with mixed findings. The COURAGE trial, which randomized patients with CCD by coronary angiography to PCI or medical therapy, identified a small but significant health status benefit early (SAQ-QoL 73±22 with PCI

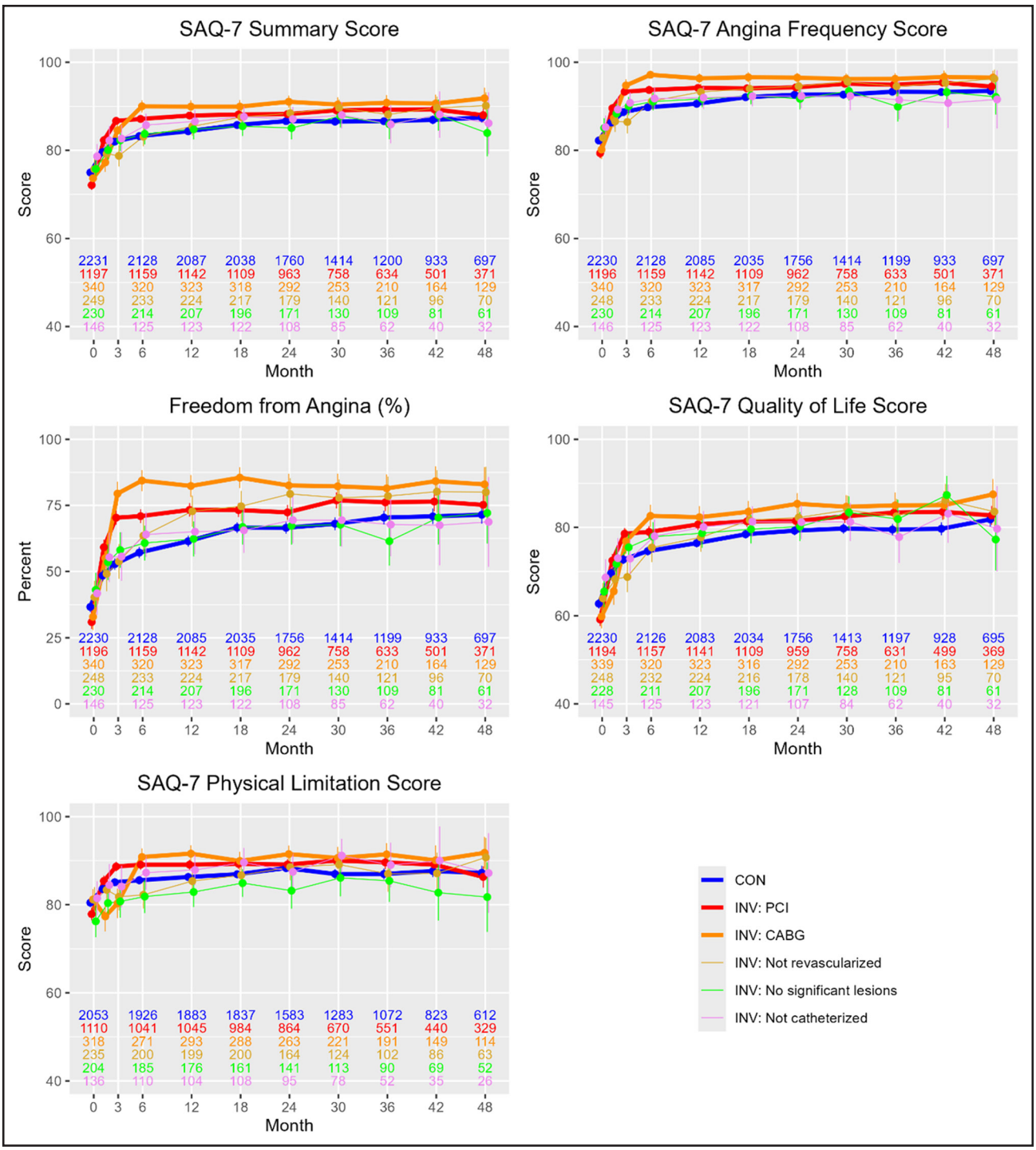

Figure 3. Seattle Angina Questionnaire scores by revascularization method.
CABG indicates coronary artery bypass grafting; CON, conservative strategy; INV, invasive strategy; PCI, percutaneous coronary intervention; and SAQ, Seattle Angina Questionnaire.

versus 68±23 with medical therapy at 3 months), which dissipated by 3 years of follow-up.[4] Patients with more severe angina had greater health status benefit with PCI in that analysis, similar to the findings in ISCHEMIA.[5] Of note, however, most patients undergoing PCI in COURAGE were treated with bare metal stents rather than drug-eluting stents. The substantially high restenosis rates with bare metal stents, coupled with performance of PCI in the optimal medical therapy arm during follow-up in nearly one-third of patients, may explain the modest QoL benefits at 1 year and loss of a durable effect of PCI over time. BARI-2D (Bypass Angioplasty Revascularization Investigation 2 Diabetes) was a randomized trial of revascularization (with stratum for CABG and PCI)

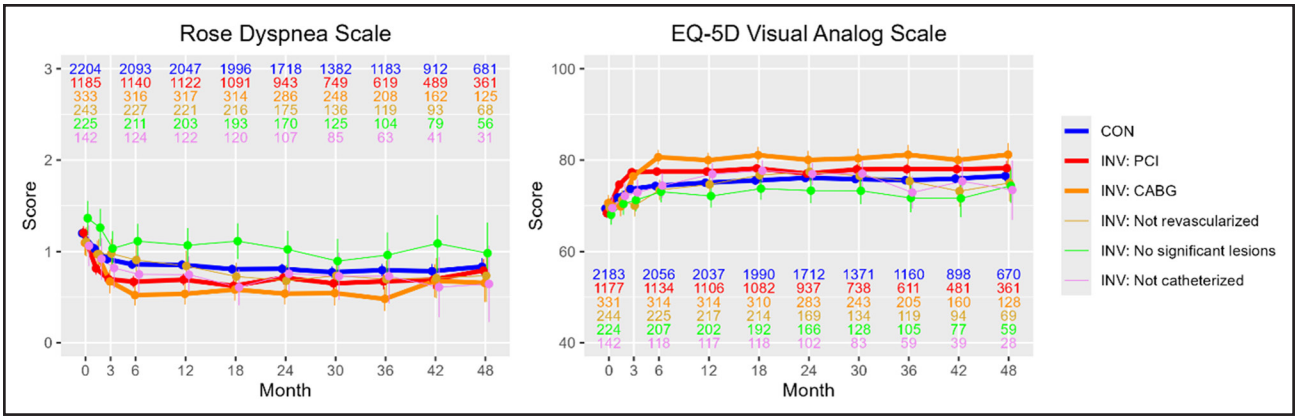

Figure 4. Rose Dyspnea Scale and EQ-5D scores by revascularization method.
CABG indicates coronary artery bypass grafting; CON, conservative strategy; EQ-5D, European Quality of Life–5 Dimensions; INV, invasive strategy; and PCI, percutaneous coronary intervention.

compared with medical therapy in patients with CCD. In that study, improved health status was observed in the revascularization group, but this effect was primarily driven by patients treated with CABG. Patients treated with PCI had similar health status to medically treated patients.[8] However, the PCI and CABG arms were not randomized in BARI-2D, and a substantially greater amount of myocardium was at risk and was revascularized in the CABG strata. More recently, the ORBITA study (Objective Randomised Blinded Investigation With Optimal Medical Therapy of Angioplasty in Stable Angina) of medically optimized patients with CCD demonstrated no improvement in 6-week exercise time with PCI compared with a sham PCI procedure,[22] whereas the ORBITA-2 study of patients with CCD on no anti-anginal medical therapy demonstrated reduced angina with PCI compared with sham PCI.[23]

Given the better health status observed with CABG over PCI in FREEDOM and SYNTAX, and the questionable long-term effects of PCI on health status observed in COURAGE, BARI-2D, and ORBITA, one might have hypothesized that the health status benefits achieved with an invasive strategy in ISCHEMIA was driven primarily by CABG. However, the current analysis demonstrates that both PCI and CABG, when selected in the context of a multidisciplinary heart team guided by evidence-based study recommendations, were associated with improved angina-related health status through 3-year follow-up. These findings are congruent with the 3-year outcomes of the FAME 2 trial (Fractional Flow Reserve versus Angiography for Multivessel Evaluation), which randomized patients with CCD and documented ischemia by fractional flow reserve assessment to PCI versus medical therapy and demonstrated a significant reduction in angina severity with PCI out to 3 years.[24] More recently, the FAME 3 trial, which randomized patients to fractional flow reserve–guided PCI versus CABG for multivessel CCD, demonstrated no difference in EQ-5D scores at 1 year between PCI and CABG.[25] In this regard, only the EXCEL and FAME trials used second-generation contemporary drug-eluting stents, which may have contributed to similar QoL improvements with PCI compared with CABG, and more durable effects of PCI demonstrated in this analysis of ISCHEMIA.

Table 3. Freedom from Angina Among Revascularization Groups

Month	Conservative strategy (n=2232)	INV-PCI (n=1198)	INV-CABG (n=340)
3	52.8	70.3	79.4
6	57.1	70.9	84.4
12	61.4	73.3	82.4
24	66.5	72.3	82.5
36	70.4	76.1	81.4
48	71.4	75.2	82.9

The proportions of participants with no angina at each time point, based on the Seattle Angina Questionnaire Angina Frequency category, are shown. INV-CABG indicates invasive strategy with coronary artery bypass grafting within 3 months; and INV-PCI, invasive strategy with percutaneous coronary intervention within 3 months.

Other potential explanations may have contributed to the durable health status benefits of PCI versus conservative management and the similar long-term health status of CABG versus PCI observed in this study. First, revascularization methods in ISCHEMIA were nonrandomized and guided by evidence-based protocol recommendations and local heart team decisions. This may have improved selection of patients treated with PCI based on their providers' belief in the success and sustainability of percutaneous revascularization. Second, in ISCHEMIA, revascularization was performed with the goal of relieving all substantial areas of ischemia. Although most participants in the study did not have complete anatomic revascularization, the rates of both anatomic and functional complete revascularization were ≈13% higher in the invasive management with PCI group compared with the invasive management with CABG group, supporting providers' judgments in recommending PCI. We have

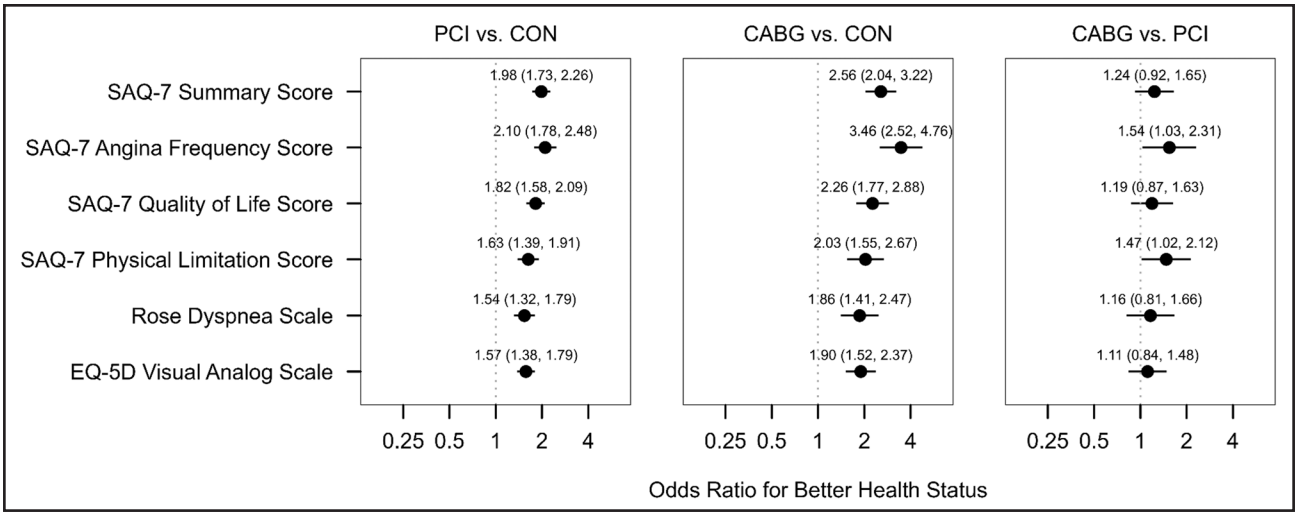

Figure 5. Adjusted odds ratios for health status at 1 year by revascularization method.
CABG indicates coronary artery bypass grafting; CON, conservative strategy; EQ-5D, European Quality of Life–5 Dimensions; PCI, percutaneous coronary intervention; and SAQ, Seattle Angina Questionnaire.

previously demonstrated from ISCHEMIA that complete ischemic revascularization may optimize clinical and health status benefits.[26,27] These results, when taken in the context of the previous results of FAME 2 and FAME 3, suggest that PCI targeting complete relief of objective ischemia may achieve better long-term health status improvements than PCI based only on anatomic assessments of coronary stenoses.

The Importance of Health Status in CCD

Medical therapy is the cornerstone of cardiovascular risk reduction in patients with CCD,[28–30] and revascularization does not further reduce the risk of mortality or myocardial infarction in the absence of high-risk coronary anatomy.[31–33] Therefore, the decision to revascularize a patient with CCD should be based largely on the health status benefits of treatment and the incorporation of patients' preferences. In this study, it was observed that 61.4% of participants in the conservative group were angina-free at 1 year and 70.4% were angina-free at 3 years, highlighting the potential benefits of medical therapy in managing patients with CCD. ISCHEMIA demonstrated that participants with CCD managed invasively had better health status through 4 years than participants managed conservatively, and this analysis expands upon those results, demonstrating that both PCI and CABG were associated with durable improvements in health status. This approach is consistent with the American College of Cardiology/American Heart Association guidelines on coronary revascularization, which give a class 1A indication for revascularization in patients with CCD and refractory

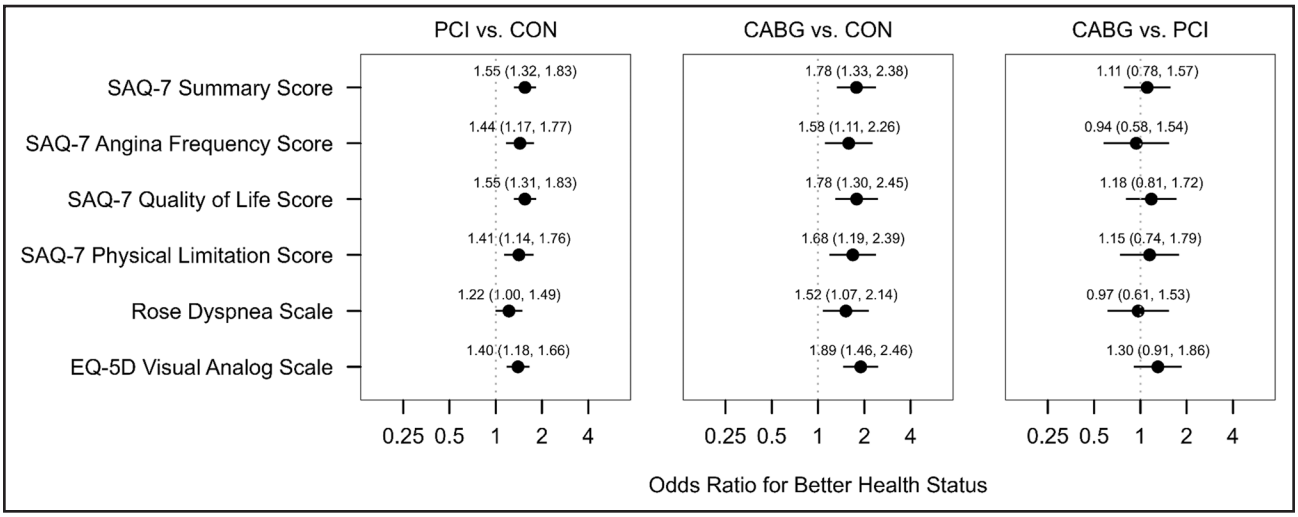

Figure 6. Adjusted odds ratios for health status at 3 years by revascularization method.
CABG indicates coronary artery bypass grafting; CON, conservative strategy; EQ-5D, European Quality of Life–5 Dimensions; PCI, percutaneous coronary intervention; and SAQ, Seattle Angina Questionnaire.

symptoms despite medical therapy.[32] To aid in the selection of invasive and conservative options for CCD management, a shared decision-making tool for patients and physicians was developed using data from ISCHEMIA to estimate an individual patient's 1-year health status and 4-year survival with invasive and conservative approaches to manage their CCD (https://myhealthoutcomes.org/tools/shared-decision-making-tool).[34,35]

Heart Team Approach to Revascularization

This was an observational study of health status changes over time among patients treated with PCI or CABG in a nonrandomized fashion, compared with patients who were managed conservatively. The treatment groups in this study were clearly different in terms of baseline characteristics and coronary anatomy, with the CABG group showing higher anatomic complexity than the PCI group. This highlights that the decision to perform PCI versus CABG was greatly influenced by coronary anatomy. The findings of this analysis support that this approach is effective in achieving long-term health status improvements regardless of the revascularization method ultimately selected, when guided by a multidisciplinary heart team, with the goal of complete revascularization. Our group has previously reported that complete revascularization in ISCHEMIA was associated with better health status than incomplete revascularization in symptomatic patients.[26] The use of a multidisciplinary heart team for patients with coronary disease is now supported with a class IB recommendation in the 2021 American College of Cardiology/American Heart Association coronary revascularization guidelines.[32]

Limitations

The study results should be interpreted within the context of the following limitations. First, as highlighted previously, CABG and PCI revascularization strategies were not randomly assigned, and there were clear differences in baseline characteristics and coronary anatomy, which cannot be fully accounted for despite extensive risk adjustment. For example, factors such as anxiety, depression, chronic pain, frailty, and functional limitations were not included in the risk adjustment, and these may have influenced treatment allocation and response to intervention. Therefore, this study is a descriptive summary of the health status outcomes of these procedures when selected within the framework of a multidisciplinary heart team and not representative of a randomized comparison of these strategies. An advantage of this approach, however, is that the study findings may more closely represent real-world clinical practice in which patients are selected for revascularization strategies in a nonrandomized fashion. Second, ISCHEMIA did not use sham control procedures when comparing invasive and conservative arms. Furthermore, the comparison of PCI and CABG was adjusted for both clinical and angiographic variables, but the comparison of each revascularization strategy with conservative management could not be adjusted for angiographic variables, as conservatively managed participants did not undergo a diagnostic angiogram. To account for this limitation, a sensitivity analysis was conducted among participants with baseline CCTA studies performed. CCTA findings were used to adjust comparisons of PCI versus conservative management and CABG versus conservative management for anatomic severity of baseline coronary disease. However, baseline CCTA data were not available in all participants and are not equivalent to invasive angiography adjudicated by a core laboratory, although there was a high correlation between these techniques in ISCHEMIA.[36] Third, the cohort that underwent CABG was small (n=340) compared with the cohort that underwent PCI (n=1198).

CONCLUSION

Among participants with CCD in ISCHEMIA, both PCI and CABG were associated with better angina-related health status than conservative management through 3 years when these procedures were selected within the context of a multidisciplinary heart team. Angina relief was better with CABG than PCI at 1 year, but no difference was observed between CABG and PCI at 3 years.

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Supplemental Material

Table S1
Figures S1–S7
Appendices S1–S2

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