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Effect of PCI on Health Status in Ischemic Left Ventricular Dysfunction

Insights From REVIVED-BCIS2

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ABSTRACT

BACKGROUND In the REVIVED-BCIS2 (Revascularization for Ischemic Ventricular Dysfunction) trial, percutaneous coronary intervention (PCI) did not reduce the incidence of death or hospitalization for heart failure (HHF).

OBJECTIVES This prespecified secondary analysis investigated the effect of PCI on health status measured with the Kansas City Cardiomyopathy Questionnaire (KCCQ) combined with the primary outcome in a win ratio.

METHODS Participants with severe ischemic left ventricular dysfunction were randomized to either PCI in addition to optimal medical therapy (OMT) (PCI) or OMT alone (OMT). The primary outcome was a hierarchical composite of all-cause death, HHF, and KCCQ-Overall Summary Score (OSS) at 24 months analyzed using the unmatched win ratio. The key secondary endpoint was a KCCQ-OSS responder analysis.

RESULTS A total of 347 participants were randomized to PCI and 353 to OMT. Median age was 70.0 years (Q1-Q3: 63.3-76.1 years). Mean left ventricular ejection fraction was 27.0 ± 6.7%. PCI did not improve the primary endpoint (win ratio for PCI vs OMT: 1.05; 95% CI: 0.88-1.26; $P = 0.58$). PCI resulted in more KCCQ-OSS responders than OMT at 6 months (54.1% vs 40.7%; OR: 1.96; 95% CI: 1.41-2.71; $P < 0.001$) and fewer deteriorators (25.2% vs 31.4%; OR: 0.69; 95% CI: 0.47-1.00; $P = 0.048$). PCI did not impact KCCQ-OSS responders or deteriorators at 12 or 24 months.

CONCLUSIONS PCI did not improve the hierarchical composite of death, HHF, and health status at 2 years. PCI improved KCCQ-OSS at 6 months, but this benefit was not sustained to 1- or 2-year follow-up. (Revacularization for Ischemic Ventricular Dysfunction [REVIVED-BCIS2]; NCT01920048) (J Am Coll Cardiol HF 2024;■:■-■) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

Treating heart failure has 2 therapeutic aims. The first is to prevent fatal and nonfatal adverse events and the second is to improve health status or quality of life. Though the latter is often included as a secondary outcome in major trials, many patients place greater importance on quality of life than longevity.[1] Patients with heart failure have particularly poor health status or quality of

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ABBREVIATIONS AND ACRONYMS

HHF = hospitalization for heart failure

KCCQ = Kansas City Cardiomyopathy Questionnaire

KCCQ-CSS = Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score

KCCQ-OSS = Kansas City Cardiomyopathy Questionnaire-Overall Summary Score

KCCQ-TSS = Kansas City Cardiomyopathy Questionnaire-Total Symptom Score

OMT = optimal medical therapy

PCI = percutaneous coronary intervention

life.[2] Exertional dyspnea, fatigue, and effort intolerance commonly result in functional limitation, while angina is infrequent in patients with an ischemic etiology. The mechanism of symptoms in people with heart failure are complex and may be attributed to coronary artery disease, left ventricular dysfunction, or the dynamic interplay of both conditions.

In patients with heart failure and significant coronary artery disease, revascularization has the potential to relieve symptoms through relief of ischemia, by improving left ventricular function via reversal of adverse myocardial remodeling, or both.[3] Percutaneous coronary intervention (PCI) is widely used to reduce symptom burden in patients with angina whose symptoms are not controlled with medical therapy, or in those who present with acute coronary syndromes.[4,5] There have been no randomized trials investigating the impact of PCI on health status in ischemic left ventricular dysfunction.[6]

In the REVIVED-BCIS2 (Revascularization for Ischemic Ventricular Dysfunction) trial, patients with ischemic left ventricular dysfunction who received treatment with PCI did not experience improvements in the primary composite outcome of all-cause death or hospitalization for heart failure (HHF) compared with those receiving optimal medical therapy (OMT) alone.[7,8] In the present prespecified analysis, we investigated the effect of PCI vs OMT on health status, accounting for mortality and hospitalizations, with a hypothesis that assignment to PCI improved health status and quality of life.

METHODS

TRIAL DESIGN AND STUDY POPULATION. The REVIVED-BCIS2 trial was a prospective, multicenter, open-label randomized controlled trial, the design and initial results of which were published previously. Participants were recruited from 40 hospitals in the United Kingdom.[7] The trial protocol was approved by the UK Health Research Authority and was registered at ClinicalTrials.gov prior to enrollment of the first patient (NCT01920048). All participants provided fully informed consent prior to randomization. The trial was funded by the National Institute for Health and Care Research, sponsored by King's College London and coordinated by the London School of Hygiene and Tropical Medicine Clinical Trials Unit. Recruitment commenced in August 2013 and completed in March 2020.

Potential participants were eligible for enrolment if they had a left ventricular ejection fraction ≤35%, extensive coronary artery disease (British Cardiovascular Intervention Society Jeopardy Score ≥6), and at least 4 dysfunctional yet viable myocardial segments that were amenable to treatment with PCI.[9] Key exclusion criteria were myocardial infarction in the 4 weeks prior to randomization, decompensated heart failure or sustained ventricular arrhythmias within 72 hours prior to randomization, or valvular heart disease requiring intervention. Eligible participants were randomized in a 1:1 manner to either PCI plus OMT (PCI) or OMT alone (OMT). Participants allocated to PCI received treatment of all significant coronary artery stenoses that subtended viable myocardium. All participants received OMT, based on recommendation by the trial medical therapy committee, including cardiac implantable electronic devices where indicated. Clinical follow-up was at 6 and 12 months, then annually until 24 months after the final participant was randomized.

OUTCOME MEASURES. The primary outcome was a hierarchical composite of time to all-cause death, the number of HHFs, and a ≥5-point difference in change in Kansas City Cardiomyopathy Questionnaire-Overall Summary Score (KCCQ-OSS). For this primary analysis, KCCQ-OSS was assessed as change from baseline at 24 months, while death and HHF were included across the whole duration of follow-up. The key secondary outcome was a KCCQ-OSS responder analysis defined as a ≥5-point improvement in KCCQ-OSS from baseline to 24 months. Other secondary outcomes included: 1) the primary outcome with the duration of follow-up for death and HHF capped at 24 months; 2) response and deterioration in the Kansas City Cardiomyopathy Questionnaire Clinical Summary Score (KCCQ-CSS) and Kansas City Cardiomyopathy Questionnaire-Total Symptom Score (KCCQ-TSS) domains; and 3) mean between-group difference in KCCQ-OSS scores. Post hoc, an additional secondary analysis was performed, examining the primary win ratio outcome and mean change in KCCQ-OSS stratified by tertiles of baseline scores.

All-cause death and HHF were reported via the trial electronic case report form. An independent Clinical Events Committee adjudicated all reported death and HHF events according to trial definitions. Participant health status was monitored via the Kansas City Cardiomyopathy Questionnaire (KCCQ) at baseline and 6-, 12-, and 24-month follow-up. The KCCQ is a validated self-administered questionnaire used to assess health status in patients with heart failure.[10]

It comprises a 23-item self-administered questionnaire including 7 domains to capture heart failure symptoms, impact on physical and social function, and impact on quality of life. The domains are combined to produce summary measures, the KCCQ-TSS (which captures self-efficacy and the stability, frequency and burden of symptoms), KCCQ-CSS (adding physical limitation scores to the KCCQ-TSS), and KCCQ-OSS (adding social limitation and quality of life scores to the KCCQ-CSS). Results are represented on a 100-point scale, in which higher scores indicate better health status and lower scores indicate worse health status. A change in KCCQ-OSS of ≥5 points is generally considered the minimum clinically important difference in health status, although this is debated.[11]

STATISTICAL ANALYSIS. The current analysis was prespecified in the main trial Statistical Analysis Plan, signed prior to unblinding of treatment assignment, and a Supplemental Analysis plan; both analysis plans are available in the Supplemental Appendix.[8] All analyses were performed on an intention-to-treat basis. Hierarchical composite endpoints were analyzed using the unmatched win ratio method.[12]

Responders were defined as participants who experienced a 5-point increase in score from baseline to the time point of interest. KCCQ-OSS deteriorators were defined as the inverse of responders. Patients who died were considered nonresponders/deteriorators in the respective analyses. In each of the secondary analyses, the odds of response and deterioration were explored using both univariate and mixed effects logistic regression models, including baseline status and treatment allocation as covariates. The latter accounted for the repeated measures at 6, 12, and 24 months using random intercepts, and further included follow-up visit and a treatment-visit interaction as covariates in the model.

The following sensitivity analyses were performed: 1) the win ratio analyses repeated with a 10- and 15-point difference in change in KCCQ-OSS from baseline to 24-month follow-up; 2) the responder analyses repeated with a 10- and 15-point difference in KCCQ-OSS from baseline to 24-month follow-up; 3) using observed scores only, without multiple imputation; and 4) a comparison of KCCQ-OSS scores between patients assigned to OMT who did or did not undergo unplanned revascularization. All analyses were performed with Stata version 17.0 or higher (StataCorp).

MISSING DATA. Missing KCCQ datapoints include those in which participants had not completed the questionnaire and in which they indicated that they do not perform a particular activity.[13] Where domain scores were missing, multiple imputation was used to impute missing scores among all patients who were not known to have died at the respective time points. The win ratio and univariate logistic model analyses were evaluated on the imputed data set, while the mixed-effects logistic model was fit to the observed data set and compared post hoc with an identical model evaluated on the imputed data set. Twenty imputations were performed.

DATA SHARING. The data supporting these findings can be obtained on reasonable request to the corresponding author.

RESULTS

All 700 patients enrolled in the REVIVED-BCIS2 trial were included in the health status and quality-of-life analysis; 347 were assigned to the PCI group and 353 to the OMT group. A total of 334 (96.3%) of the 347 assigned to PCI underwent the procedure at a median of 35 days (Q1-Q3: 15-57 days) after randomization. Baseline characteristics were similar between treatment groups (**Table 1**). The median age of enrolled participants was 70.0 years (Q1-Q3: 63.3-76.1 years), 12% were female, and 91% were White. Mean left ventricular ejection fraction was 27.0 ± 6.7% and median British Cardiovascular Intervention Society Jeopardy Score was 10 (Q1-Q3: 8-12). The majority of patients were classified as NYHA functional class I or II. Diversity information is reported in Supplemental Table 1.

Median baseline KCCQ-OSS, KCCQ-CSS, and KCCQ-TSS were 62.0 (Q1-Q3: 41.1-81.8), 69.8 (Q1-Q3: 50.4-88.1), and 77.1 (Q1-Q3: 54.2-93.8), respectively. Completeness of KCCQ-OSS data was 91% at baseline and 85%, 86%, and 82% at 6, 12, and 24 months, respectively. The median duration of follow-up was 3.4 years (Q1-Q3: 2.3-5.0 years), at which point 155 patients had died.

PRIMARY OUTCOME. PCI did not improve the primary hierarchical outcome (win ratio: 1.05; 95% CI: 0.88-1.26; $P = 0.58$) (**Figure 1**). Of the 122,491 pairwise comparisons, 43% were untied on time to death, 9% on HHF count, and 42% on KCCQ-OSS; 7% failed to untie.

KEY SECONDARY OUTCOME. Responder analysis. PCI increased the number of KCCQ-OSS responders at 6 months (54.1% in the PCI group vs 40.7% in the OMT group; OR: 1.96; 95% CI: 1.41-2.71; $P < 0.001$) but not at 12 and 24 months (49.5% vs 41.1%; OR: 1.36; 95% CI: 0.97-1.89; $P = 0.072$; and 45.1% vs 39.9%; OR: 1.23; 95% CI: 0.89-1.71; $P = 0.21$, respectively) (**Figure 2**, Supplemental Tables 2 and 3).

TABLE 1 Baseline Characteristics According to Treatment Assignment

	PCI (n = 347)	OMT (n = 353)
Age, y	70.0 ± 9.0	68.7 ± 9.1
Male	302 (87)	312 (88)
Body mass index, kg/m^2	28.4 ± 5.5	28.7 ± 5.4
Race/ethnicity		
Asian	32 (9)	17 (5)
Black	3 (1)	3 (1)
White	306 (88)	328 (92.9)
Other	5 (1)	5 (1)
Hypertension	184/347 (53.0)	207/352 (58.8)
Hypercholesterolemia	193 (55.6)	189 (53.5)
Diabetes	136 (39)	153 (43)
On insulin	42/135 (31)	44/153 (29)
Smoking history		
Current	61 (18)	75 (21)
Former	182 (52)	192 (54)
Never	104 (30)	86 (24)
Hospitalization for heart failure in previous 2 y	112 (32)	121 (34)
Previous myocardial infarction	175 (50)	197 (56)
Peripheral vascular disease	48 (14)	46 (13)
Cerebrovascular disease	38 (11)	46 (13)
History of atrial fibrillation	54 (17)	60 (18)
NT-proBNP, pg/mL	1,376 (697-3,426)	1,461 (712-3,365)
Left ventricular ejection fraction, %	28 (23-32)	29 (22-33)
BCIS Jeopardy Score	10 (8-12)	10 (8-12)
Left main coronary artery disease	50/346 (14)	45/352 (13)
NYHA functional class I/II	265/345 (77)	248/350 (71)

Values are mean ± SD, n (%), n/N (%), or median (Q1-Q3).

BCIS = British Cardiovascular Intervention Society; NT-proBNP = N-terminal pro-B-type natriuretic peptide; OMT = optimal medical therapy; PCI = percutaneous coronary intervention.

Deteriorator analysis. The proportion of patients reporting a 5-point or more deterioration in KCCQ-OSS at 6 months was lower in the PCI group (25.2% vs 31.4%; OR: 0.69; 95% CI: 0.47-1.00; $P = 0.048$). There was no between-group difference at 12 and 24 months (**Figure 2**, Supplemental Tables 2 and 3).

OTHER SECONDARY OUTCOMES. Win ratio capped at 24-month follow-up. PCI did not improve the win ratio hierarchical analysis when the duration of follow-up for all-cause death and HHF were limited to 24 months (win ratio: 1.04; 95% CI: 0.85-1.26; $P = 0.72$) (Supplemental Figure 1).

Responder analysis for KCCQ-CSS and KCCQ-TSS. PCI improved the proportion of KCCQ-CSS responders at 6 months (45.0% vs 35.3%; OR: 1.70; 95% CI: 1.19-2.42; $P = 0.004$), with no difference observed at 12- or 24-month follow-up (40.9% vs 38.1%; OR: 1.20; 95% CI: 0.86-1.67; $P = 0.28$; and 36.6% vs 37.1%; OR: 1.01; 95% CI: 0.72-1.42; $P = 0.94$, respectively) (**Figure 2**, Supplemental Figure 2). PCI did not increase the proportion of KCCQ-TSS responders at any time point (6 months: 42.1% vs 38.1%; OR: 1.33; 95% CI: 0.94-1.88; $P = 0.34$; 12 months: 37.7% vs 36.0%; OR: 1.18; 95% CI: 0.84-1.65; $P = 0.34$; 24 months: 34.0% vs 40.0%; OR: 0.82; 95% CI: 0.58-1.17; $P = 0.27$). Lower rates of deterioration were observed with PCI for both KCCQ-CSS and KCCQ-TSS at 6 months (28.9% vs 36.6%; OR: 0.71; 95% CI: 0.51-0.99; $P = 0.046$; and 25.4% vs 34.9%; OR: 0.64 (95% 0.45-0.90; $P = 0.011$, respectively) (**Figure 2**, Supplemental Figure 3). The difference was no longer significant at 12 months and neutral at 24 months for both scores.

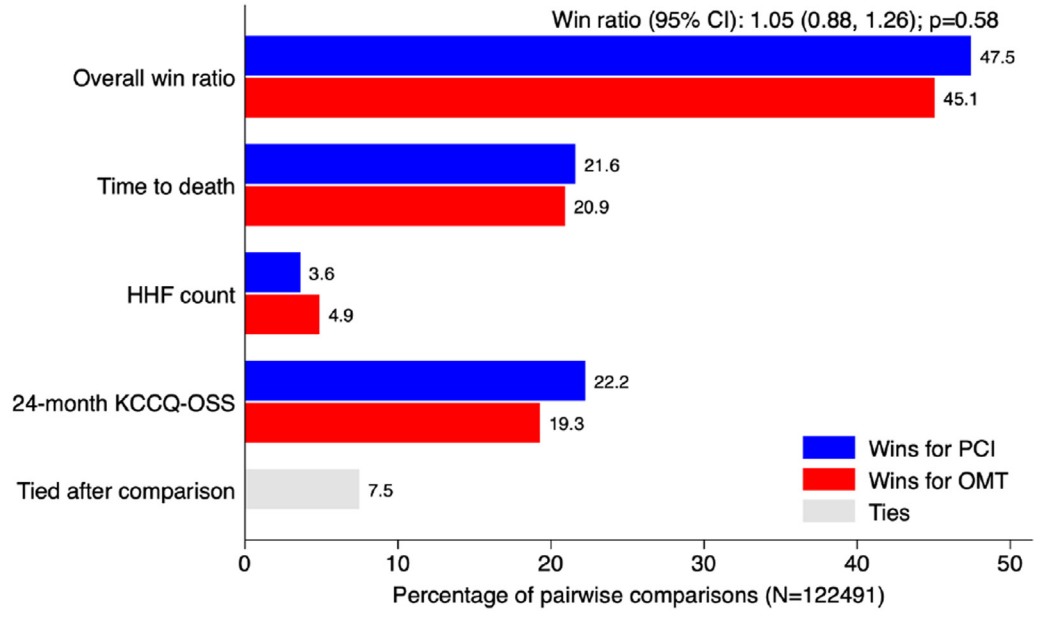
The proportion of 6-month KCCQ-OSS responders with a ≥10 or ≥15-point change was higher in the PCI group (43.7% vs 29.6%; OR: 2.20; 95% CI: 1.56-3.11; $P < 0.001$; and 31.9% vs 22.9%; OR: 1.99; 95% CI: 1.35-2.92; $P < 0.001$, respectively) (Supplemental Figure 4). PCI increased the proportion of 10-point responders at 12-month follow-up (41.6% vs 30.5%; OR: 1.51; 95% CI: 1.07-2.12; $P = 0.018$) (Supplemental Figure 5). At 24 months, PCI did not improve the KCCQ-OSS at any threshold.

Between-group difference in KCCQ-OSS, KCCQ-CSS, and KCCQ-TSS. At 6 months, participants assigned to PCI had markedly higher KCCQ-OSS, KCCQ-TSS, and KCCQ-CSS than those assigned to OMT (mean between-group difference 7.09 ± 2.11, 6.27 ± 1.89, and 6.49 ± 1.98, respectively) (**Figure 3**, Supplemental Table 4). At 12 months, these between-group differences had attenuated slightly (mean between-group differences 4.73 ± 2.14, 3.08 ± 1.92, and 4.23 ± 2.00, respectively). At 24 months, no meaningful between-group differences were observed. Analysis of between-group differences in KCCQ-OSS stratified by baseline score tertiles suggested a sustained between-group difference in the middle tertile across all time points but not in the upper or lower tertiles (Supplemental Figure 6).

Stratified win ratio. The win ratios were similar across the lower, middle, and upper tertiles of the baseline KCCQ-OSS (win ratio: 1.10; 95% CI: 0.81-1.51; $P = 0.53$; win ratio: 1.10; 95% CI: 0.81-1.51; $P = 0.55$; and win ratio: 0.97; 95% CI: 0.67-1.40; $P = 0.87$, respectively). The overall, stratified win ratio estimate was consistent with the findings of the primary analysis.

SENSITIVITY ANALYSES. The results of the sensitivity analysis were consistent with the findings of the primary and secondary analyses (Supplemental Table 5, Supplemental Figure 7). The post hoc examination of the mixed-effects model fit to the imputed data set yielded consistent results to those from the

FIGURE 1 Primary Outcome: Comparison of PCI and OMT on the Hierarchical Composite Outcome



The first set of horizontal bars denote the overall mean percentage of wins across the 20 imputed datasets in the PCI (blue) and OMT (red) arms relative to the total number of pairwise comparisons. The grouped bars below denote the percentage of wins in the 2 groups at each component of the hierarchy. The grey bar denotes the percentage of comparisons that remained tied after comparison. Time to death and hospitalization for heart failure (HHF) count were included across all follow-up time points. Change from baseline Kansas City Cardiomyopathy Questionnaire-Overall Summary Score (KCCQ-OSS) was measured at 24 months. Reported percentages are an average across the 20 imputed data sets. OMT = optimal medical therapy; PCI = percutaneous coronary intervention.

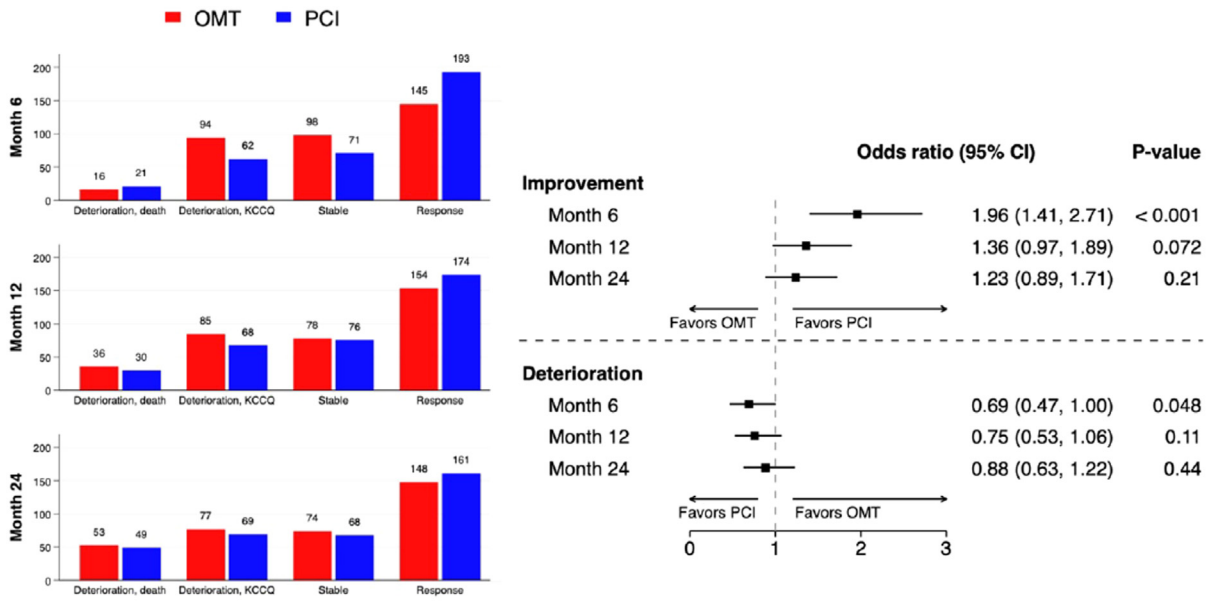
observed data set (Supplemental Table 6). In patients assigned to OMT, those who underwent unplanned revascularization had lower KCCQ-ISS at baseline compared with those who did not (Supplemental Table 7). Unplanned revascularization was associated with a significantly greater improvement in KCCQ-OSS from baseline at 6 and 12 months but not at 24 months.

DISCUSSION

In this prespecified secondary analysis of the REVIVED-BCIS2 trial, treatment with PCI was not associated with improved outcomes compared with OMT, when death, HHF, and health status were combined in a win ratio analysis at 2 years. Participants assigned to PCI had a short-term improvement in health status (at 6 months), which did not persist over extended follow-up of 1 and 2 years (**Central Illustration**). This early improvement in health status was driven primarily by improvements in the physical limitation, quality of life, and social limitation domains, while symptom scores were unchanged between treatment groups at all time points.

The results of our analysis should be viewed in context of open-label randomized trials investigating the health status and/or symptomatic benefit of revascularization in patients with stable coronary artery disease with or without left ventricular dysfunction receiving OMT. In a secondary analysis of the COURAGE trial, treatment with PCI was associated with an improvement in angina score (measured with the Seattle Angina Questionnaire) in the first 2 years but was not sustained at 36-month follow-up.[14] In a responder analysis of the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial, higher rates of treatment response for physical function, angina frequency, and quality of life were only observed in the first 6 months, and were no longer significant from 1 year onward. In the ISCHEMIA (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches) trial, angina-related health status was improved in patients who had daily,

FIGURE 2 Key Secondary Outcome: Comparison of PCI and OMT on KCCQ-OSS Response and Deterioration at Each Time Point



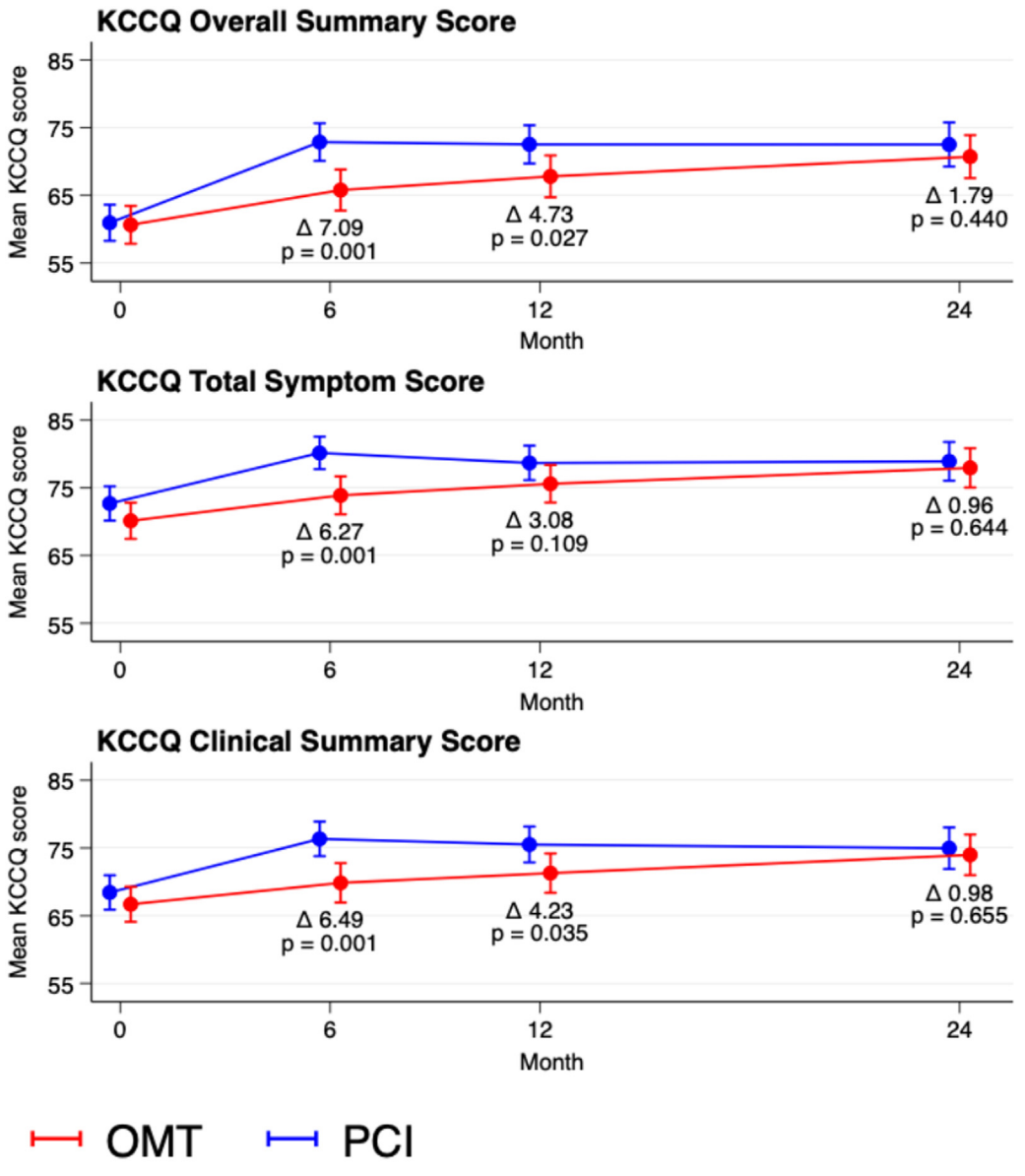
The bars on the left side denote the mean number (across the 20 imputed datasets) of patients that were classified as having deteriorated on account of death or KCCQ-OSS, the number that remained stable, and the number that were responsive to treatment. Forest plot of the odds ratio for KCCQ-OSS responders and deteriorators, at a 5-point threshold, across all time points. Abbreviations as in Figure 1.

weekly, or monthly angina at baseline but not in patients who had no angina at baseline.[15] The between-group difference in quality of life attenuated over time but remained statistically significant due to the large sample size of over 5,000 participants. In the STICH (Surgical Treatment for Ischemic Heart Failure) trial, the only other randomized trial of revascularization in patients with ischemic left ventricular dysfunction, coronary artery bypass grafting was associated with a sustained improvement in KCCQ-OSS over 36 months, though the peak difference was observed at 12 months (likely due to initial deterioration in quality of life while recovering from major surgery), though the difference again attenuated over time.[16]

While the current study is therefore consistent with prior observations of an initial effect of PCI, which is attenuated throughout follow-up, the duration of effect was shorter in the REVIVED-BCIS2 trial. Several hypotheses are likely to explain this observation. The most prominent is a placebo effect, which is unavoidable in an open-label trial. The second could be a treatment effect of PCI on health status, due to improved epicardial perfusion. We have previously reported that PCI did not improve left ventricular ejection fraction in REVIVED-BCIS2. Patients in REVIVED-BCIS2 were not mandated to have optimized therapies at baseline, but there was a major effort to establish patients randomized to both PCI and OMT onto heart failure therapies (working to REVIVED-BCIS2 heart failure medical therapy guidance). So, patients in both the PCI and OMT arms were subject to prompt optimization of OMT, and this is reflected in the improvements in both arms early in the trial. Patients in REVIVED-BCIS2 were older than those recruited to other trials (and consequently more representative of the population of patients with heart failure), and this may have led to other competing conditions placing a ceiling on quality of life and limiting the possible response to PCI.

Notwithstanding the lack of a significant persistent treatment effect, the early improvement in quality of life with PCI in REVIVED-BCIS2 was greater than that observed in other contemporary trials in heart failure with reduced ejection fraction. In the DAPA-HF (Dapagliflozin and Prevention of Adverse-Outcomes in Heart Failure) trial, the mean between-group difference in the change in KCCQ-OSS was 1.7 points at 4 months and 2.3 points at 8 months. In PARADIGM-HF (Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure), the between-group difference in

FIGURE 3 Crude Mean KCCQ Profiles, by KCCQ Domain

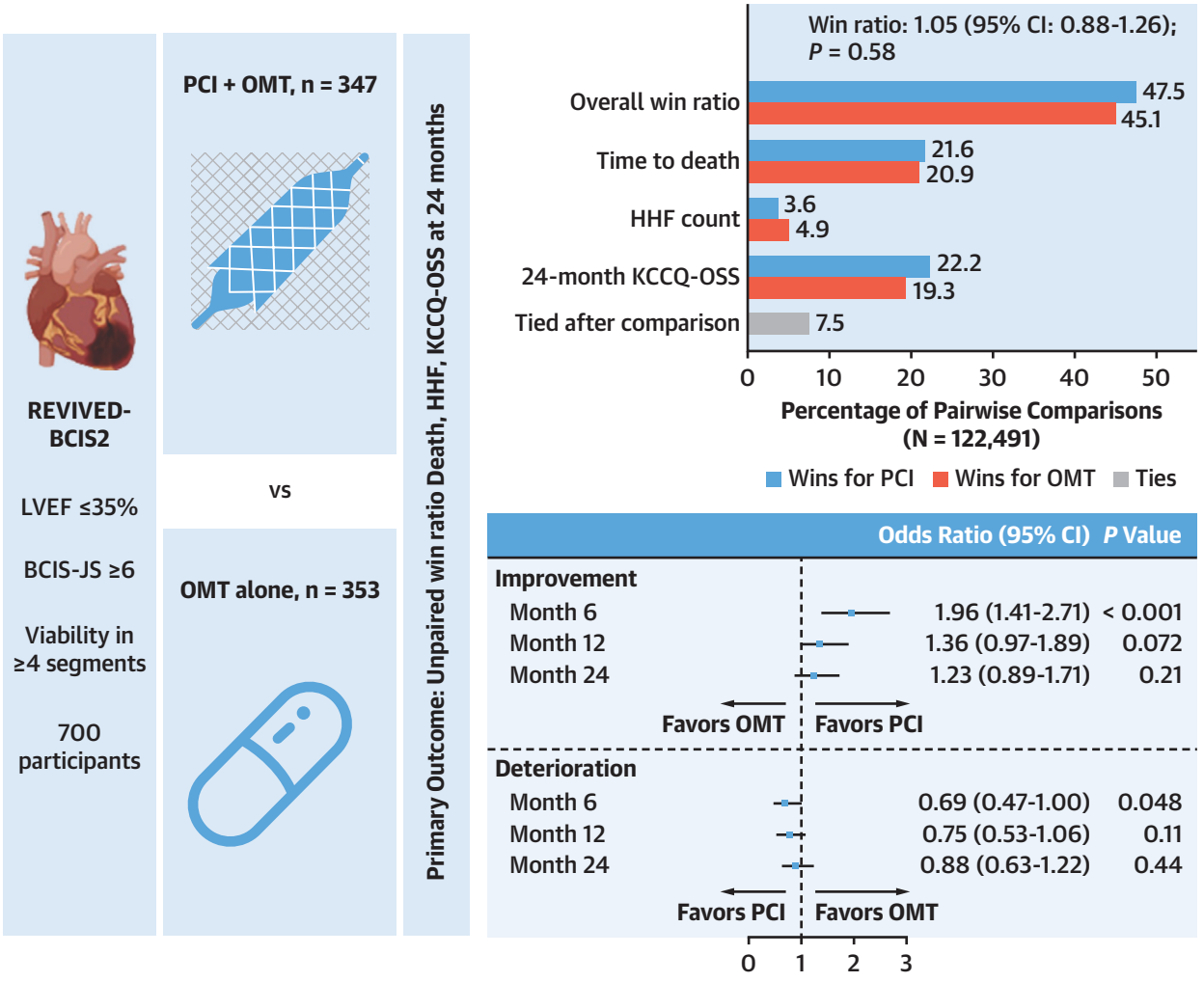


The *P* values presented are from simple Student's *t*-tests and are provided for illustration only. Mean values at each time point are plotted with normally approximated 95% CIs. KCCQ = Kansas City Cardiomyopathy Questionnaire; other abbreviations as in Figure 1.

KCCQ-OSS increased from 0.66 at 4 months to 1.27 at 8 months and 2.28 at 36 months. The DAPA-trial HF and PARADIGM-HF were, of course, placebo-controlled and double-blind trials. In most heart failure trials, KCCQ is measured between 6 and 9 months, as this is generally where the greatest effect is observed. Issues such as increasing missing data and events such as hospitalizations and deaths tend to complicate assessment of efficacy as the duration of follow-up lengthens.

Although the symptoms reported by most patients were classified by clinicians into NYHA functional class I or II, this does not mirror the self-reported KCCQ data, which demonstrates that this was a highly symptomatic population. The median KCCQ-OSS scores observed in the REVIVED-BCIS2 trial

CENTRAL ILLUSTRATION **Effect of PCI on Health Status in the REVIVED-BCIS2 Trial**



Ryan M, et al. J Am Coll Cardiol HF. 2024;■(■):■-■.

Treatment with percutaneous coronary intervention (PCI) did not improve overall health status; there was a greater number of Kansas City Cardiomyopathy Questionnaire Overall Summary Score (KCCQ-OSS) responders at 6-month follow-up but not at 12- or 24-month follow-up. BCIS-JS = British Cardiovascular Intervention Society Jeopardy Score; HHF = hospitalization for heart failure; LVEF = left ventricular ejection fraction; OMT = optimal medical therapy; REVIVED-BCIS2 = Revascularization for Ischemic Ventricular Dysfunction.

were similar to those of patients in the STICH trial, and reflect worse health status than patients enrolled in the DAPA-HF trial and PARADIGM-HF.[17-19] This reflects the low fidelity of physician-reported NYHA functional class in accurately quantifying symptoms.[20]

A proportion of participants assigned to OMT received PCI during follow-up, in accordance with protocol-approved criteria including worsening angina or myocardial infarction; while not crossovers (as the patients had developed guideline-indicated indications for revascularization due to new events). Our post hoc analysis demonstrated significantly greater improvements in KCCQ-OSS at 6 and 12 months in patients assigned to OMT who underwent unplanned revascularization; however, no difference was observed at 24 months. These findings suggest that unplanned revascularization was unlikely to have influenced the primary outcome.

Finally, the improvement in KCCQ-OSS was not seen in all KCCQ domains. PCI improved physical function, quality of life, and social function at

6 months, but these improvements were not sustained, while symptom severity and frequency were similar between arms across all follow-up. This may reflect differences in health priority and perception of functional limitation in patients with ischemic left ventricular dysfunction, in which improvements in fatigue and effort intolerance are experienced more in their functional consequences than in a manner directly attributable to symptom domains. It may also suggest that in patients with heart failure and significant coronary artery disease that ischemia is not the predominant driver of symptoms.

STUDY LIMITATIONS. As an open-label trial, it is likely that some of the observed early differences in health status are due to a placebo effect. Sham- or placebo-controlled randomized controlled trials of PCI vs OMT would be of value in populations with heart failure. The prescription of medical therapy was at the discretion of treating clinicians, who were aware of treatment assignment, and we cannot exclude differential dose prescribing of heart failure therapy between arms (though the proportion of participants receiving each class of drugs over follow-up was the same in each treatment group). We do not know whether the recent addition of sodium glucose cotransporter 2 inhibitors as a fourth pillar of pharmacological therapy for heart failure would influence the results, as REVIVED-BCIS2 completed follow-up before the publication of the relevant trials. KCCQ data completion was imperfect, particularly at later follow-up; however, the proportion of missing data was similar to other randomized trials of coronary revascularization, and it should be remembered that the final 2 years of follow-up covered the COVID pandemic. Follow-up for KCCQ was limited to 2 years, and while EQ-5D-5L data were collected over all follow-up, these are primarily designed for health economic analysis, and are not disease-specific measures for heart failure or suitable for responder analysis.[21] We did not collect data to allow us to conduct a KCCQ anchor-based analysis, which has been recommended by the Food and Drug Administration. Finally, the relatively small sample size means that we do not have the power to exclude a smaller difference in health status between groups, though these smaller differences are unlikely to be clinically meaningful or cost-effective.

CONCLUSIONS

For patients with ischemic left ventricular dysfunction, the addition of PCI to standard care did not improve the hierarchical composite outcome of death, HHF, and quality of life at 2 years. When quality of life was considered in isolation, treatment with PCI led to a short-term improvement in health status. In patients with left ventricular dysfunction, PCI should not be recommended to improve health status beyond the short term.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: PCI provides short-term but not sustained improvement in health status in patients with ischemic left ventricular dysfunction treated with OMT.

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: In patients with ischemic left ventricular dysfunction, PCI should be not be recommended to improve health status beyond 6 months.

TRANSLATIONAL OUTLOOK: Identifying subgroups of people with heart failure in which PCI results in improvements in health status should be the focus of future (preferably blinded and placebo-controlled) trials.

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KEY WORDS coronary artery disease, left ventricular dysfunction, percutaneous coronary intervention, quality of life, randomized trial, win ratio

APPENDIX For an expanded Methods section as well as supplemental tables and figures, please see the online version of this paper.