The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 13, 2022 VOL. 387 NO. 15

Percutaneous Revascularization for Ischemic Left Ventricular Dysfunction

Divaka Perera, M.D., Tim Clayton, M.Sc., Peter D. O'Kane, M.D., John P. Greenwood, Ph.D., Roshan Weerackody, Ph.D., Matthew Ryan, Ph.D., Holly P. Morgan, M.B., B.Ch., Matthew Dodd, M.Sc., Richard Evans, B.A., Ruth Canter, M.Sc., Sophie Arnold, M.Sc., Lana J. Dixon, Ph.D., Richard J. Edwards, Ph.D., Kalpa De Silva, Ph.D., James C. Spratt, M.D., Dwayne Conway, M.D., James Cotton, M.D., Margaret McEntegart, Ph.D., Amedeo Chiribiri, Ph.D., Pedro Saramago, Ph.D., Anthony Gershlick, M.D., Ajay M. Shah, M.D., Andrew L. Clark, M.D., and Mark C. Petrie, M.D., for the REVIVED-BCIS2 Investigators*

ABSTRACT

BACKGROUND

Whether revascularization by percutaneous coronary intervention (PCI) can improve event-free survival and left ventricular function in patients with severe ischemic left ventricular systolic dysfunction, as compared with optimal medical therapy (i.e., individually adjusted pharmacologic and device therapy for heart failure) alone, is unknown.

METHODS

We randomly assigned patients with a left ventricular ejection fraction of 35% or less, extensive coronary artery disease amenable to PCI, and demonstrable myocardial viability to a strategy of either PCI plus optimal medical therapy (PCI group) or optimal medical therapy alone (optimal-medical-therapy group). The primary composite outcome was death from any cause or hospitalization for heart failure. Major secondary outcomes were left ventricular ejection fraction at 6 and 12 months and quality-of-life scores.

RESULTS

A total of 700 patients underwent randomization — 347 were assigned to the PCI group and 353 to the optimal-medical-therapy group. Over a median of 41 months, a primary-outcome event occurred in 129 patients (37.2%) in the PCI group and in 134 patients (38.0%) in the optimal-medical-therapy group (hazard ratio, 0.99; 95% confidence interval [CI], 0.78 to 1.27; P=0.96). The left ventricular ejection fraction was similar in the two groups at 6 months (mean difference, –1.6 percentage points; 95% CI, –3.7 to 0.5) and at 12 months (mean difference, 0.9 percentage points; 95% CI, –1.7 to 3.4). Quality-of-life scores at 6 and 12 months appeared to favor the PCI group, but the difference had diminished at 24 months.

CONCLUSIONS

Among patients with severe ischemic left ventricular systolic dysfunction who received optimal medical therapy, revascularization by PCI did not result in a lower incidence of death from any cause or hospitalization for heart failure. (Funded by the National Institute for Health and Care Research Health Technology Assessment Program; REVIVED-BCIS2 ClinicalTrials.gov number, NCT01920048.)

The authors' affiliations are listed in the Appendix. Dr. Perera can be contacted at divaka.perera@kcl.ac.uk or at St. Thomas' Hospital, Westminster Bridge Rd., London SE1 7EH, United Kingdom.

*A full list of the REVIVED-BCIS2 investigators is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on August 27, 2022, at NEJM.org.

N Engl J Med 2022;387:1351-60.
DOI: 10.1056/NEJMoa2206606

CME at NEJM.org

A Quick Take is available at NEJM.org

Coronary artery disease is the most common cause of heart failure worldwide. The observation that some patients with severe left ventricular systolic dysfunction had recovery of systolic function after coronary-artery bypass grafting (CABG) first gave rise to the concept of myocardial hibernation, an adaptation to recurrent ischemia that facilitates cardiomyocyte survival in favor of contractile function.[1] Reversal of hibernation by coronary revascularization has been a tantalizing but unproven prospect for decades.[2] In the Surgical Treatment for Ischemic Heart Failure (STICH) trial, the incidence of death from any cause (the primary outcome) at 5 years was similar in the group assigned to undergo CABG and the group assigned to receive medical therapy alone, a finding that was partly due to the early hazard of CABG among these patients.[3] However, a survival benefit emerged over time, with the patients who underwent revascularization with CABG more likely to be alive after 10 years than those receiving medical therapy alone.[4]

Percutaneous coronary intervention (PCI) is an alternative mode of revascularization, but most randomized comparisons between CABG and PCI among patients with chronic coronary syndromes have excluded patients with severe left ventricular systolic dysfunction.[5,6] Whether PCI might allow the benefits of revascularization to be realized without the early hazard associated with CABG in patients with ischemic left ventricular dysfunction is not known. In the Revascularization for Ischemic Ventricular Dysfunction (REVIVED) trial, we hypothesized that revascularization with PCI in addition to optimal medical therapy for heart failure, as compared with optimal medical therapy alone, would improve event-free survival in patients with severe ischemic left ventricular systolic dysfunction and demonstrable myocardial viability. Our main secondary hypothesis was that PCI would ameliorate left ventricular systolic dysfunction.

Methods

Trial Design and Oversight

The trial design has been described previously.[7] REVIVED was a prospective, multicenter, randomized, open-label trial involving patients with ischemic left ventricular systolic dysfunction. The trial was funded by the National Institute for Health and Care Research Health Technology Assessment Program and sponsored by King's College London. The protocol (available with the full text of this article at NEJM.org) was approved by the U.K. Health Research Authority, and all the patients provided written informed consent. An independent steering committee and a data and safety monitoring committee oversaw the trial. An independent clinical-events committee, the members of which were unaware of the trial-group assignments, adjudicated the key outcomes (see the Supplementary Appendix, available at NEJM.org). The London School of Hygiene and Tropical Medicine Clinical Trials Unit coordinated the trial and performed the statistical analyses. The authors had access to the trial data and vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol. The initial draft of the manuscript was written by the first author.

Patients

Patients were eligible for enrollment if they had a left ventricular ejection fraction of 35% or less (as assessed by echocardiography or cardiovascular magnetic resonance imaging), extensive coronary artery disease (defined as a British Cardiovascular Intervention Society jeopardy score of ≥6, on a scale from 0 to 12, with higher scores indicating greater extent of disease,[8] and demonstrable viability in at least four dysfunctional myocardial segments amenable to revascularization with PCI. Patients were excluded if they had had an acute myocardial infarction in the 4 weeks before randomization or acute decompensated heart failure or sustained ventricular arrhythmias within 72 hours before randomization. The full eligibility criteria, methods of viability testing, and the British Cardiovascular Intervention Society jeopardy score are described in Tables S1 through S3 in the Supplementary Appendix.

Randomization and Treatment

Patients were randomly assigned in a 1:1 ratio to a strategy of PCI plus optimal medical therapy (PCI group) or optimal medical therapy alone (optimal-medical-therapy group). Optimal medical therapy refers to individually adjusted pharmacologic and device therapy for heart failure.

In the PCI group, the protocol required that revascularization be attempted on all diseased proximal coronary vessels subtending areas of viable myocardium. The extent of revascularization was characterized by the British Cardiovascular Intervention Society jeopardy score and anatomical revascularization index, which was calculated as follows: [(the pre-PCI jeopardy score minus the post-PCI jeopardy score) divided by (the pre-PCI jeopardy score)] × 100, with 100% indicating complete revascularization of all angiographically significant coronary disease.[9]

Medical therapy for heart failure was initiated before enrollment and customized according to the patient's individual needs throughout the trial by heart-failure specialists at the recruiting centers. A medical-therapy committee reviewed guidelines periodically and refined recommendations to ensure that the pharmacologic and device therapy given to all patients in the trial remained contemporary. The decision to insert an implantable cardioverter–defibrillator (ICD) or cardiac resynchronization therapy device was at the discretion of treating clinicians but had to be documented before randomization.

OUTCOMES AND FOLLOW-UP

The primary composite outcome was death from any cause or hospitalization for heart failure over a minimum follow-up period of 24 months. The major secondary outcomes were the left ventricular ejection fraction at 6 and 12 months, as measured at the echocardiography core laboratory at Guy's and St. Thomas' NHS Foundation Trust; the Kansas City Cardiomyopathy Questionnaire (KCCQ) overall summary score (range, 0 to 100, with higher scores indicating better quality of life); the score on the EuroQol Group 5-Dimensions 5-Level Questionnaire (EQ-5D-5L), which was converted into an index score ranging from 0 (death) to 1 (full health); and the New York Heart Association functional class.[10,11] Other secondary outcomes were the components of the primary outcome, death from cardiovascular causes, appropriate ICD therapy (antitachycardia pacing or shocks [or both] for either ventricular tachycardia or ventricular fibrillation), acute myocardial infarction,[12] unplanned revascularization, serial N-terminal pro–B-type natriuretic peptide (NT-proBNP) levels, the Canadian Cardiovascular Society angina class, major bleeding, and health resource use, which is not reported here. The definitions of all outcome measures are provided in Table S4.

Patients underwent transthoracic echocardiography at baseline and at the 6-month and 12-month follow-up visit, and the results were analyzed by readers at the core laboratory. The readers were unaware of the trial-group assignments, the temporal sequence of echocardiograms, and all clinical data.

STATISTICAL ANALYSIS

We estimated that a sample of 700 patients, with 300 having a primary-outcome event, would provide the trial with at least 85% power to detect a hazard ratio for a primary-outcome event of 0.70 at a 5% significance level, allowing for a 5% loss to follow-up and increasing recruitment over time.[3,13] For the secondary outcome of the left ventricular ejection fraction, we estimated that a sample of 350 patients (175 patients per trial group) would provide the trial with 90% power to detect a minimum absolute between-group difference of 4 percentage points, assuming a standard deviation of 11 percentage points.

The statistical analysis plan (available with the protocol) was finalized before unblinding of the trial-group assignments. Unadjusted time-to-event analyses were used to evaluate the primary outcome and secondary outcomes; the time to the first event or censoring of the data was measured from randomization on an intention-to-treat basis. The primary analysis included data from each patient up to the date of the outcome event, last follow-up visit, or withdrawal of consent. Hazard ratios with 95% confidence intervals were calculated with the use of a Cox proportional-hazards model; the P value for the difference was calculated with the use of a likelihood ratio test, and proportionality was assessed with the use of Nelson–Aalen plots according to trial group. Cumulative incidence was calculated with the use of Kaplan–Meier estimates.

Serial changes in the continuous outcome measures were estimated by means of a linear mixed-effects model for repeated measures, which was used to calculate the mean values at each time point and the absolute between-group difference.[14] The model, which is described in the statistical analysis plan, assumed that miss-

ing outcome data were missing at random (i.e., that the distributions of missing and observed outcomes were similar among persons with the same values of the covariates). Sensitivity analyses were performed to adjust for the potential competing risk of death.[15] Prespecified subgroup analyses were performed with the use of a Cox proportional-hazards model incorporating tests of interaction. All analyses were conducted with the use of Stata software, version 17.0 (StataCorp). Data are presented as mean values with standard deviations or median values with interquartile ranges. Analyses of secondary outcomes were not adjusted for multiplicity. Results are reported as point estimates with 95% confidence intervals, the widths of which have not been adjusted for multiplicity; hence, these should not be used in place of a hypothesis test.

RESULTS

PATIENTS AND FOLLOW-UP

From August 2013 through March 2020, a total of 700 patients were randomly assigned to the PCI group (347 patients) or the optimal-medical-therapy group (353) across 40 centers in the United Kingdom. The trial groups appeared to be well matched in terms of baseline characteristics, medication use, and heart-failure devices, and the trial population was representative of patients with ischemic heart disease and a low ejection fraction in the United Kingdom (Tables 1 and S5 through S7). Among the patients assigned to the PCI group, 334 (96.3%) underwent PCI at a median of 35 days (interquartile range, 15 to 57) after randomization; further planned staged PCI was carried out in 80 patients. The mean British Cardiovascular Intervention Society jeopardy score was 9.3 before the procedure and 2.7 after the procedure (change, −6.6 points; 95% confidence interval [CI], −6.9 to −6.2), which corresponds with an anatomical revascularization index of 71% (95% CI, 67 to 74). Details of the PCI procedures are provided in Table S8. Follow-up concluded in March 2022; the median duration of follow-up was 41 months (interquartile range, 28 to 60) after randomization in both trial groups. Data on the primary outcome were available for 99.1% of the patients (Fig. S1).

PRIMARY OUTCOME AND COMPONENTS

A primary-outcome event of death from any cause or hospitalization for heart failure occurred in 129 patients (37.2%) in the PCI group and in 134 patients (38.0%) in the optimal-medical-therapy group (hazard ratio, 0.99; 95% CI, 0.78 to 1.27; P=0.96) (Table 2 and Fig. 1). A total of 110 patients (31.7%) in the PCI group and 115 patients (32.6%) in the optimal-medical-therapy group died during follow-up (hazard ratio, 0.98; 95% CI, 0.75 to 1.27) (Fig. S2). At least one hospitalization for heart failure occurred in 51 patients (14.7%) in the PCI group and in 54 patients (15.3%) in the optimal-medical-therapy group (hazard ratio, 0.97; 95% CI, 0.66 to 1.43) (Fig. S3). The treatment effect with respect to the primary outcome was consistent across all prespecified subgroups (Figs. 2 and S4 and Table S9).

MAJOR SECONDARY OUTCOMES

The left ventricular ejection fraction changed from baseline by 1.8 percentage points at 6 months and by 2.0 percentage points at 12 months in the PCI group; the corresponding values at 6 and 12 months in the optimal-medical-therapy group were 3.4 and 1.1 percentage points. The left ventricular ejection fraction was similar in the two groups at 6 months (mean difference, −1.6 percentage points; 95% CI, −3.7 to 0.5) and at 12 months (mean difference, 0.9 percentage points; 95% CI, −1.7 to 3.4) (Fig. 3A and Table S10).

The KCCQ overall summary score appeared to favor the PCI group at 6 months (difference in mean scores, 6.5 points; 95% CI, 3.5 to 9.5) and at 12 months (difference in mean scores, 4.5 points; 95% CI, 1.4 to 7.7). The scores in the optimal-medical-therapy group increased over time, and the between-group difference at 24 months was 2.6 points (95% CI, −0.7 to 5.8). Scores across all component domains of the KCCQ appeared to favor the PCI group at 6 months; at 24 months, the mean between-group difference in the quality-of-life domain score was 4.2 points (95% CI, 0.4 to 8.1). Similarly, the scores on the EQ-5D-5L appeared to favor the PCI group at 6 and 12 months, but the difference had diminished at 24 months (Figs. 3B and S5 and Table S11). The distributions of the New York Heart Association functional class and Canadian Car-

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	PCI (N=347)	Optimal Medical Therapy (N=353)
Age — yr	70.0±9.0	68.8±9.1
Male sex — no. (%)	302 (87)	312 (88)
Race — no. (%)†		
White	306 (88)	328 (93)
Asian	32 (9)	17 (5)
Black	3 (1)	3 (1)
Mixed, other, or not reported	6 (2)	5 (1)
Body-mass index‡	28.4±5.5	28.7±5.4
Hypertension — no./total no. (%)	184/347 (53)	207/352 (59)
Diabetes — no. (%)	136 (39)	153 (43)
Current or previous smoker — no. (%)	243 (70)	267 (76)
Previous myocardial infarction — no. (%)	175 (50)	197 (56)
Previous PCI — no. (%)	66 (19)	76 (22)
Previous CABG — no. (%)	12 (3)	22 (6)
NYHA functional class — no./total no. (%)§		
I or II	265/345 (77)	248/350 (71)
III or IV	80/345 (23)	102/350 (29)
CCS angina class — no./total no. (%)¶		
No angina	228/346 (66)	236/351 (67)
I or II	111/346 (32)	107/351 (30)
III	7/346 (2)	8/351 (2)
Left ventricular ejection fraction — %‖	27.0±6.6	27.0±6.9
Coronary artery disease characteristic		
Median BCIS jeopardy score (IQR)**	10 (8–12)	10 (8–12)
Left main coronary artery disease — no./total no. (%)	50/346 (14)	45/352 (13)
Three-vessel coronary artery disease — no./total no. (%)	133/346 (38)	148/352 (42)
Two-vessel coronary artery disease — no. (%)	178 (51)	166 (47)
Median NT-proBNP — pg/ml (IQR)	1376 (697–3426)	1461 (712–3365)

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. CABG denotes coronary-artery bypass grafting, IQR interquartile range, NT-proBNP N-terminal pro–B-type natriuretic peptide, and PCI percutaneous coronary intervention.

† Race was reported by the patient.

‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.

§ The New York Heart Association (NYHA) functional class ranges from I (no symptoms) to IV (symptoms at rest or on minimal activity).

¶ In the Canadian Cardiovascular Society (CCS) grading of angina pectoris, grade I denotes symptoms only with strenuous or prolonged exertion; grade II, slight limitation of ordinary activity; and grade III, marked limitation of ordinary physical activity.

‖ The baseline left ventricular ejection fraction was assessed by echocardiography or cardiovascular magnetic resonance imaging; the values were reported by the recruiting center.

** The British Cardiovascular Intervention Society (BCIS) jeopardy score is a quantification of the extent of myocardial jeopardy relating to clinically significant coronary artery stenoses. The score ranges from 0 (no significant coronary disease) to 12 (disease jeopardizing the whole left ventricular myocardium).

Table 2. Primary and Secondary Outcomes.

Outcome	PCI (N=347)	Optimal Medical Therapy (N=353)	Treatment Effect (95% CI)*
Primary outcome			
Death from any cause or hospitalization for heart failure — no. (%)†	129 (37.2)	134 (38.0)	0.99 (0.78–1.27)
Secondary outcomes‡			
Components of the primary outcome			
Death from any cause	110 (31.7)	115 (32.6)	0.98 (0.75–1.27)
Hospitalization for heart failure§	51 (14.7)	54 (15.3)	0.97 (0.66–1.43)
Death from cardiovascular causes — no. (%)¶	76 (21.9)	88 (24.9)	0.88 (0.65–1.20)
Acute myocardial infarction — no. (%)‖	37 (10.7)	38 (10.8)	1.01 (0.64–1.60)
Periprocedural — no. (%)**	14 (37.8)	0	
Spontaneous — no. (%)**	18 (48.7)	33 (86.8)	
Sudden death — no. (%)**††	5 (13.5)	5 (13.2)	
Unplanned revascularization — no. (%)‡‡	10 (2.9)	37 (10.5)	0.27 (0.13–0.53)
PCI — no. (%)§§	9 (90.0)	29 (78.4)	
CABG — no. (%)§§	1 (10.0)	8 (21.6)	
Major bleeding — no. (%)			
At 1 yr	10/319 (3.1)	2/316 (0.6)	4.95 (1.09–22.43)
At 2 yr	10/292 (3.4)	7/290 (2.4)	1.42 (0.55–3.68)

* Treatment effects are hazard ratios, except for major bleeding, for which the treatment effect is the risk ratio.
† Randomization was stratified according to recruiting center. When recruiting center was taken into account as a covariate, the hazard ratio for a primary-outcome event was 1.00 (95% CI, 0.78 to 1.28; P=0.96).
‡ Because the statistical analysis plan did not include a provision for correcting for multiplicity when conducting tests for secondary or other outcomes, the results are reported as point estimates with 95% confidence intervals. The widths of the confidence intervals have not been adjusted for multiplicity, so the intervals should not be used to infer definitive treatment effects for secondary outcomes.
§ When death from any cause was taken into account as a potential competing risk, the hazard ratio for hospitalization for heart failure was 0.97 (95% CI, 0.66 to 1.42).[15]
¶ When death from noncardiovascular causes was taken into account as a potential competing risk, the hazard ratio for death from cardiovascular causes was 0.87 (95% CI, 0.64 to 1.18).[15]
‖ When death from any cause was taken into account as a potential competing risk, the hazard ratio for acute myocardial infarction was 1.01 (95% CI, 0.64 to 1.59).[15]
** The denominator is the total number of acute myocardial infarctions.
†† Sudden death refers only to the classification of events reported as myocardial infarctions by the recruiting centers.
‡‡ When death from any cause was taken into account as a potential competing risk, the hazard ratio for unplanned revascularization was 0.26 (95% CI, 0.13 to 0.53).[15]
§§ The denominator is the total number of unplanned revascularization procedures.

diovascular Society angina class among the patients were similar in the two groups at baseline and remained similar at 6, 12, and 24 months (Tables S12 and S13).

OTHER SECONDARY OUTCOMES

A total of 250 patients (126 in the PCI group and 124 in the optimal-medical-therapy group) had a heart-failure device implanted before or within 90 days after randomization (Fig. S6). In the PCI group, an ICD was used to terminate ventricular tachycardia or fibrillation at least once in 2 patients (1.8%) at 6 months, in 3 (2.9%) at 12 months, and in 6 (5.9%) at 24 months; the corresponding values in the optimal-medical-therapy group were 4 (3.8%), 7 (6.6%), and 13 (14.0%). The between-group difference in the incidence of appropriate ICD therapy translated to a risk ratio of 0.42 (95% CI, 0.17 to 1.06) at 24 months.

An acute myocardial infarction occurred in

37 patients (10.7%) in the PCI group and in 38 patients (10.8%) in the optimal-medical-therapy group. Although the overall incidence of myocardial infarction was similar in the two groups (hazard ratio, 1.01; 95% CI, 0.64 to 1.60), periprocedural infarction occurred only in the PCI group, and more cases of spontaneous myocardial infarction occurred in the optimal-medical-therapy group. There were fewer unplanned revascularizations in the PCI group than in the optimal-medical-therapy group (10 [2.9%] vs. 37 [10.5%]; hazard ratio, 0.27; 95% CI, 0.13 to 0.53) (Table S14 and Fig. S7). NT-proBNP levels decreased in both groups at 6 months, but there was no appreciable between-group difference in the levels at any time point (Fig. S8).

A major bleeding episode occurred during the first year in 10 patients (3.1%) in the PCI group and in 2 patients (0.6%) in the optimal-medical-therapy group (relative risk, 4.95; 95% CI, 1.09 to 22.43), but there was no substantial difference in the incidence of bleeding at 2 years (relative risk, 1.42; 95% CI, 0.55 to 3.68). A serious adverse event occurred in 102 patients (29.4%) in the PCI group and in 104 patients (29.5%) in the optimal-medical-therapy group (Table S15).

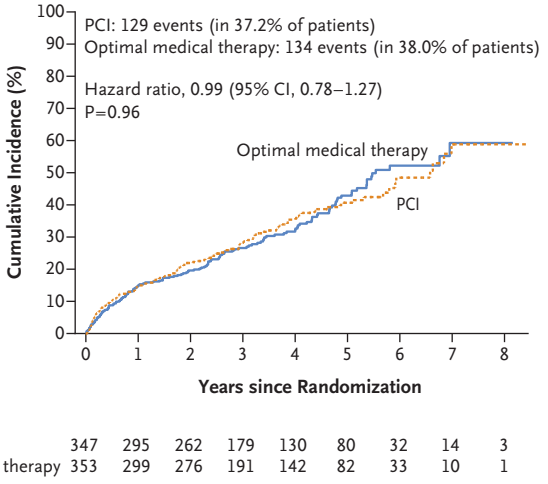

Figure 1. Primary Outcome of Death from Any Cause or Hospitalization for Heart Failure.

Shown are Kaplan–Meier estimates of the cumulative incidence of death from any cause or hospitalization for heart failure in a time-to-first-event analysis. The overall incidence is based on the total number of events in each group in the intention-to-treat population over the entire follow-up period. PCI denotes percutaneous coronary intervention.

DISCUSSION

We performed a randomized comparison of the efficacy and safety of a strategy of PCI plus optimal medical therapy, as compared with strategy of optimal medical therapy alone, among patients with severe left ventricular systolic dysfunction, extensive coronary artery disease, and demonstrable viable myocardium. The incidence of death from any cause or hospitalization for heart failure (the primary outcome) did not differ significantly between the trial groups. An apparent early benefit of PCI was observed with respect to quality of life, but the between-group difference diminished over time owing to the progressive improvement in scores in the optimal-medical-therapy group. Cardiac function appeared to improve in both groups over the course of follow-up, but this change was not affected by the trial-group assignment.

With the stipulation of a minimum number of dysfunctional segments that were viable and amenable to revascularization, our trial was designed to enroll an enriched cohort of patients who were most likely to show reverse remodeling after revascularization. However, PCI failed to produce recovery of global left ventricular function that was incremental to the improvement with optimal medical therapy alone. These findings challenge the paradigm of myocardial hibernation, which is classically defined according to improvement in left ventricular volumes and function after revascularization. Our observations mirror those in the STICH trial, in which revascularization by CABG did not affect left ventricular function, a finding that was consistent across the whole trial cohort, including the subgroup who underwent discretionary viability testing.[16] We have not yet determined the concordance between the coronary arteries revascularized by PCI and the viable myocardial segments; hence, we cannot determine whether viability tests predict changes in segmental contractile function after medical therapy or revascularization or whether such changes are linked to clinical outcomes.[17]

In our trial, the incidences of death from any cause and the composite of death or hospitalization for heart failure were similar to the annualized rates observed in the medical-therapy groups

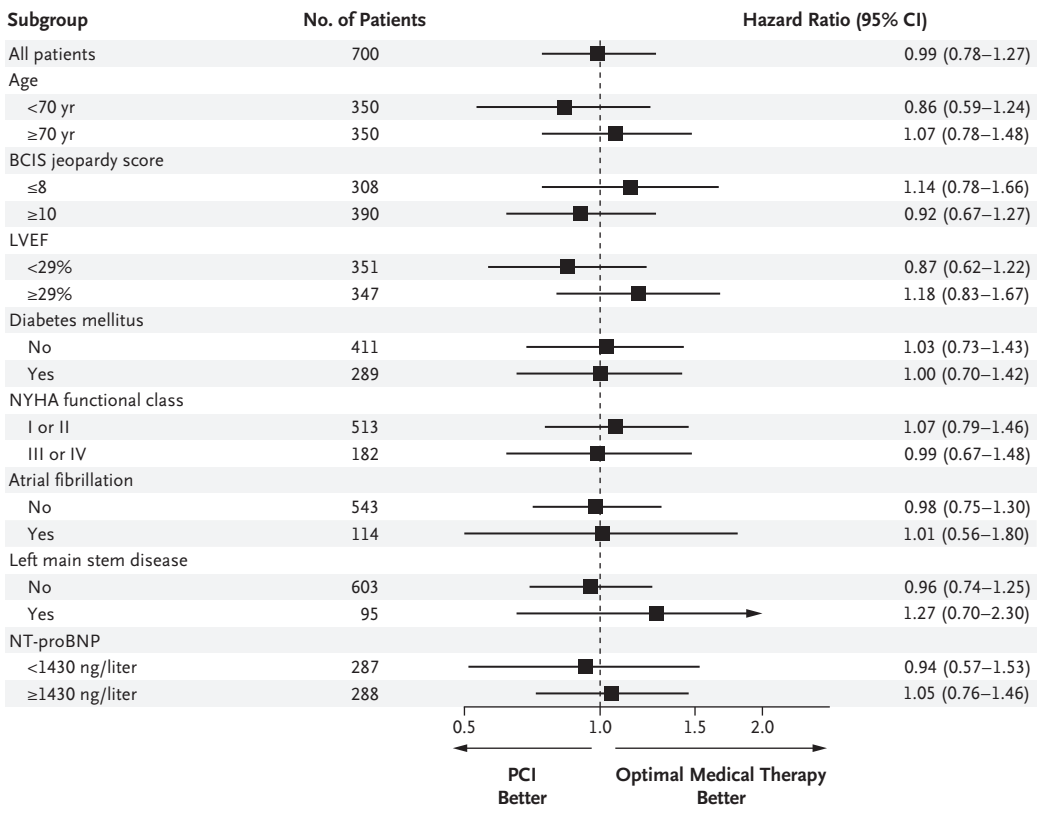

Figure 2. Subgroup Analyses of the Primary Outcome.

Shown is a forest plot of hazard ratios for a primary-outcome event according to prespecified subgroups. The British Cardiovascular Intervention Society (BCIS) jeopardy score ranges from 0 to 12, with higher scores indicating greater extent of disease. The dashed vertical line represents the null hypothesis of no treatment effect. LVEF denotes left ventricular ejection fraction, NT-proBNP N-terminal pro–B-type natriuretic peptide, and NYHA New York Heart Association.

of STICH and contemporary trials involving patients with left ventricular systolic dysfunction (Fig. S9), despite enrollment of a population with a more adverse risk profile. We enrolled older patients (mean age, 70 years) with a greater burden of coronary disease and included patients with left main coronary disease, a group that has traditionally been excluded from trials of revascularization as compared with medical therapy.[18,19] The percentage of patients with ICD or cardiac resynchronization devices in our trial may be one reason why the clinical outcomes were similar despite higher baseline risk, and the serial improvement in left ventricular systolic function and reduction in NT-proBNP concentrations in both groups in our trial are objective markers of effective medical and device therapy.

Although the differences in the baseline characteristics of the patients enrolled in the STICH and REVIVED trials hamper direct comparison, the beneficial effect of CABG observed in the STICH trial was not seen with PCI in our trial.[3] Incomplete revascularization by PCI has historically been a confounder in comparisons between PCI and CABG among patients with stable coronary disease.[20] This factor is unlikely to be a consideration in the REVIVED trial, because the median percentage of completeness of revascularization was 71% in the PCI group, as measured by a coronary anatomical index, and the percentage of functional completeness of revascularization would be even higher, given that the protocol recommended revascularization for only coronary disease subtending viable myocardium.

Our trial has some limitations. First, we cannot rule out the possibility that the open-label design affected patient-reported outcomes. Any effect on the primary outcome was mitigated by ensuring that all hospitalizations for heart failure were adjudicated in a blinded fashion by an independent events committee, and the determination of death was robust to such bias; the left ventricular ejection fraction was assessed in a blinded fashion at the core laboratory. Second, most patients had little or no angina at enrollment, so the findings cannot be extrapolated to patients with angina that limits their quality of life or patients presenting with acute coronary syndromes. Third, there were 37 fewer primary-outcome events than what we estimated for the trial to have at least 85% power to address the primary hypothesis. Although this lower number of events had some effect on the prospective statistical power (263 events would provide the trial with 82% power if the other variables in our power calculation remained constant), the hazard ratio of 0.99 and the 95% confidence intervals observed with respect to the primary outcome suggest that the risk of a type II error was low.

In our trial involving patients with severe left ventricular systolic dysfunction, extensive coronary disease, and dysfunctional but viable myocardium who received optimal medical therapy, the addition of revascularization by PCI did not result in a lower incidence of death from any cause or hospitalization for heart failure, incremental improvement in the left ventricular ejection fraction, or a sustained difference in quality of life at a median of 3.4 years.

The views expressed are those of the authors and not necessarily those of the National Institute for Health and Care Research (NIHR) or the Department of Health and Social Care.

Supported by the NIHR Health Technology Assessment Program (award 10/57/67).

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

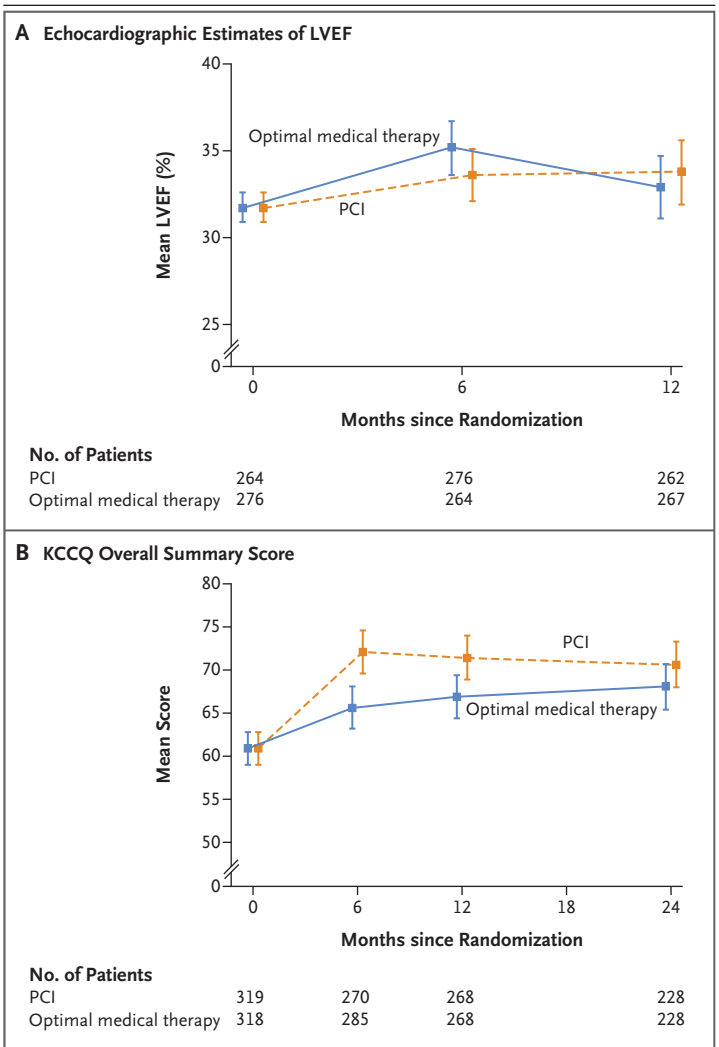

Figure 3. Major Secondary Outcomes.

Panel A shows the echocardiographic estimates of the LVEF at baseline, 6 months, and 12 months, as quantified in a blinded fashion at the core laboratory. The LVEF was imputed as 0% for the patients who died. Panel B shows the Kansas City Cardiomyopathy Questionnaire (KCCQ) overall summary scores at baseline, 6 months, 12 months, and 24 months. The KCCQ overall summary score ranges from 0 to 100, with higher scores indicating better quality of life. In both panels, data are mean values derived from a linear mixed-effects model; I bars indicate 95% confidence intervals.

APPENDIX

The authors' affiliations are as follows: the National Institute for Health and Care Research Biomedical Research Centre and the British Heart Foundation Centre of Research Excellence, School of Cardiovascular and Metabolic Medicine and Sciences, King's College London (D.P., M.R., H.P.M., A.C., A.M.S.), Guy's and St. Thomas' NHS Foundation Trust (D.P., S.A., K.D.S.), the London School of Hygiene and Tropical Medicine (T.C., M.D., R.E., R.C.), Barts Health NHS Trust (R.W.), St. George's University Hospitals NHS Foundation Trust (J.C.S.), and King's College Hospital NHS Foundation Trust (A.M.S.), London, University Hospitals Dorset NHS Foundation Trust, Bournemouth (P.D.O.), Leeds Teaching Hospitals NHS Trust, Leeds (J.P.G.), Belfast Health and Social Care NHS Trust, Belfast (L.J.D.), Newcastle Hospitals NHS Foundation Trust, Newcastle (R.J.E.), University Hospitals Bristol NHS Foundation Trust, Bristol (K.D.S.), Mid Yorkshire Hospitals NHS Trust, Wakefield (D.C.), Royal Wolverhampton NHS Trust, Wolverhampton (J.C.), the Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow (M.M., M.C.P.), the University of York, York (P.S.), University Hospitals of Leicester NHS Trust, Leicester (A.G.), and Hull University Teaching Hospitals NHS Trust, Hull (A.L.C.) — all in the United Kingdom.

REFERENCES

1. Rahimtoola SH. The hibernating myocardium. Am Heart J 1989;117:211-21.
2. Allman KC, Shaw LJ, Hachamovitch R, Udelson JE. Myocardial viability testing and impact of revascularization on prognosis in patients with coronary artery disease and left ventricular dysfunction: a meta-analysis. J Am Coll Cardiol 2002;39:1151-8.
3. Velazquez EJ, Lee KL, Deja MA, et al. Coronary-artery bypass surgery in patients with left ventricular dysfunction. N Engl J Med 2011;364:1607-16.
4. Velazquez EJ, Lee KL, Jones RH, et al. Coronary-artery bypass surgery in patients with ischemic cardiomyopathy. N Engl J Med 2016;374:1511-20.
5. Serruys PW, Morice M-C, Kappetein AP, et al. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. N Engl J Med 2009;360:961-72.
6. Stone GW, Sabik JF, Serruys PW, et al. Everolimus-eluting stents or bypass surgery for left main coronary artery disease. N Engl J Med 2016;375:2223-35.
7. Perera D, Clayton T, Petrie MC, et al. Percutaneous revascularization for ischemic ventricular dysfunction: rationale and design of the REVIVED-BCIS2 trial: percutaneous coronary intervention for ischemic cardiomyopathy. JACC Heart Fail 2018;6:517-26.
8. Perera D, Stables R, Booth J, Thomas M, Redwood S. The balloon pump-assisted coronary intervention study (BCIS-1): rationale and design. Am Heart J 2009;158(6):910.e2-916.e2.
9. De Silva K, Morton G, Sicard P, et al. Prognostic utility of BCIS myocardial jeopardy score for classification of coronary disease burden and completeness of revascularization. Am J Cardiol 2013;111:172-7.
10. Green CP, Porter CB, Bresnahan DR, Spertus JA. Development and evaluation of the Kansas City Cardiomyopathy Questionnaire: a new health status measure for heart failure. J Am Coll Cardiol 2000;35:1245-55.
11. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res 2011;20:1727-36.
12. Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. Eur Heart J 2012;33:2551-67.
13. Maggioni AP, Dahlström U, Filippatos G, et al. EURObservational Research Programme: regional differences and 1-year follow-up results of the Heart Failure Pilot Survey (ESC-HF Pilot). Eur J Heart Fail 2013;15:808-17.
14. Frost C, Kenward MG, Fox NC. Optimizing the design of clinical trials where the outcome is a rate: can estimating a baseline rate in a run-in period increase efficiency? Stat Med 2008;27:3717-31.
15. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc 1999;94:496-509.
16. Panza JA, Ellis AM, Al-Khalidi HR, et al. Myocardial viability and long-term outcomes in ischemic cardiomyopathy. N Engl J Med 2019;381:739-48.
17. Ryan M, Morgan H, Chiribiri A, Nagel E, Cleland J, Perera D. Myocardial viability testing: all STICHed up, or about to be REVIVED? Eur Heart J 2022;43:118-26.
18. Boden WE, O'Rourke RA, Teo KK, et al. Optimal medical therapy with or without PCI for stable coronary disease. N Engl J Med 2007;356:1503-16.
19. Maron DJ, Hochman JS, Reynolds HR, et al. Initial invasive or conservative strategy for stable coronary disease. N Engl J Med 2020;382:1395-407.
20. Gössl M, Faxon DP, Bell MR, Holmes DR, Gersh BJ. Complete versus incomplete revascularization with coronary artery bypass graft or percutaneous intervention in stable coronary artery disease. Circ Cardiovasc Interv 2012;5:597-604.