Long-Term Mortality Data From the Balloon Pump–Assisted Coronary Intervention Study (BCIS-1)

A Randomized, Controlled Trial of Elective Balloon Counterpulsation During High-Risk Percutaneous Coronary Intervention

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***Background*—**There is conflicting evidence on the utility of elective intra-aortic balloon pump (IABP) use during high-risk percutaneous coronary intervention (PCI). Observational series have indicated a reduction in major in-hospital adverse events, although randomized trial evidence does not support this. A recent study has suggested a mortality benefit trend early after PCI, but there are currently no long-term outcome data from randomized trials in this setting.

***Methods and Results*—**Three hundred one patients with left ventricular impairment (ejection fraction <30%) and severe coronary disease (BCIS-1 jeopardy score ≥8; maximum possible score=12) were randomized to receive PCI with elective IABP support (n=151) or without planned IABP support (n=150). Long-term all-cause mortality was assessed by tracking the databases held at the Office of National Statistics (in England and Wales) and the General Register Office (in Scotland). The groups were balanced in terms of baseline characteristics (left ventricular ejection fraction, 23.6%; BCIS-1 jeopardy score, 10.4) and the amount and type of revascularization performed. Mortality data were available for the entire cohort at a median of 51 months (interquartile range, 41–58) from randomization. All-cause mortality at follow-up was 33% in the overall cohort, with significantly fewer deaths occurring in the elective IABP group (n=42) than in the group that underwent PCI without planned IABP support (n=58) (hazard ratio, 0.66; 95% confidence interval, 0.44–0.98; *P*=0.039).

***Conclusions*—**In patients with severe ischemic cardiomyopathy treated with PCI, all-cause mortality was 33% at a median of 51 months. Elective IABP use during PCI was associated with a 34% relative reduction in all-cause mortality compared with unsupported PCI.

***Clinical Trial Registration*—**URL: http://www.isrctn.org. Unique identifier: ISRCTN40553718; and http://www.clinicaltrials.gov. Unique identifier: NCT00910481. **(*Circulation*. 2013;127:207-212.)**

Key Words: high-risk populations ■ intra-aortic balloon pump ■ ischemic cardiomyopathy ■ mortality ■ percutaneous coronary intervention

Intra-aortic balloon counterpulsation ameliorates ischemia by simultaneously augmenting coronary blood flow and reducing myocardial oxygen demand, making it a potentially valuable therapy for providing circulatory support in cardiogenic shock or preventing the occurrence of major complications during high-risk percutaneous coronary intervention (PCI). Single-center observational data had suggested a reduction in mortality and major complications with the use of an elective intra-aortic balloon pump (IABP) during high-risk PCI,[1,2] but the Balloon Pump–Assisted Coronary Intervention Study (BCIS-1) was the first randomized controlled evaluation of the safety and efficacy of counterpulsation during high-risk PCI.[3] Compared with patients who had PCI without planned IABP support, those who received elective IABP insertion were found to have a similar incidence of major adverse cardiac and cerebrovascular events (MACCE) at hospital discharge, which is the primary outcome of the study. However, differences were observed in the major secondary outcomes of BCIS-1: the occurrence of procedural complications and all-cause mortality at 6 months. Procedural complications occurred much less frequently in patients who received elective IABP support, and fewer early deaths were noted in this group, although relatively few deaths had occurred at 6 months, and the difference in mortality was not statistically significant at that stage. Elective IABP use during high-risk PCI has a class IIb recommendation (level of evidence C) in the current American College of Cardiology Foundation/American

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*A list of the BCIS-1 Investigators has been published previously (*Am Heart J*. 2009;158:910–916).

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Heart Association/Society for Cardiovascular Angiography and Interventions guidelines for PCI[4] and is only recommended in the presence of hemodynamic impairment in the current European Society of Cardiology guidelines on revascularization.[5]

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We report here the long-term all-cause mortality rates in those who had elective IABP insertion versus the group that had PCI without planned IABP support in the BCIS-1 trial.

Methods

Trial Design

The design of the BCIS-1 trial has been described in detail previously[6] (www.isrctn.org. Unique identifier: ISRCTN40553718; and http://www.clinicaltrials.gov. Unique identifier: NCT00910481). In summary, 301 patients with poor left ventricular function (left ventricular ejection fraction <30%) and extensive myocardium at risk (BCIS-1 jeopardy score ≥8; the maximum possible score is 12) were enrolled across 17 centers in the United Kingdom between December 2005 and January 2009. Those in cardiogenic shock, within 48 hours of an acute myocardial infarction, or with contraindications to IABP insertion were excluded. Patients were randomly assigned to receive elective IABP insertion or to have PCI without planned IABP support. Bailout IABP use was allowed in the group assigned to "no planned IABP" only in the event of major hemodynamic compromise after randomization. The primary outcome of the study was the occurrence of MACCE (death, acute myocardial infarction, cerebrovascular event, or urgent further revascularization) at hospital discharge (capped at 28 days). Acute myocardial infarction was defined on the basis of a creatine kinase MB isoform threshold (3 times the upper limit of normal or 1.5 times the baseline value, if the baseline value was elevated) for events occurring within 72 hours of PCI[7] and according to the universal definition[8] for later events. Major secondary outcomes were procedural complications (including ventricular tachycardia/ventricular fibrillation, cardiorespiratory arrest, and sustained hypotension), in-hospital bleeding and vascular complications, and all-cause mortality at 6 months. The study was approved by the Central Office for Research Ethics Committees in the United Kingdom, and all patients provided written consent for participation in the study before randomization.

Data Collection

Randomization, trial conduct, and collection of baseline and 28-day follow-up data were performed by an independent data coordination center with oversight from the trial steering committee. All-cause mortality status was checked via the Office for National Statistics in England and Wales and the General Register Office for Scotland, with data collection completed in October 2011. Approval for extended follow-up was obtained from the National Research Ethics Service in the United Kingdom.

Statistical Methods

Survival duration was calculated as the time from randomization to death or the last known date when patients were known to be alive. Analyses are by intention to treat, unless stated otherwise. A Cox proportional hazards model was used to calculate hazard ratios and 95% confidence intervals (CIs). Kaplan-Meier curves were computed, and the proportional hazards assumption was assessed graphically and also by presenting hazard ratios before and after 1 year together with an interaction test between follow-up time and treatment. As specified in the original trial analysis plan, subgroup analyses were performed according to BCIS-1 jeopardy score, median glomerular filtration rate, diabetes mellitus status, and glycoprotein IIb/IIIa usage. The following post hoc analyses were also performed: comparison of mortality by treatment received (patients assigned to no planned IABP who had PCI without IABP support versus those who were assigned to have IABP before PCI or who required bailout IABP after randomization) and comparison of mortality by treatment assignment in the cohort who did not suffer predefined procedural complications. Hazard ratios and CIs are presented for each level of the subgroup and are formally assessed with an interaction test. Categorical data are presented as percentages, and continuous data are presented as means and SDs unless otherwise stated otherwise. Statistical analyses were performed with the use of Stata 12.1. The authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Results

Baseline Characteristics and Revascularization Details

Three hundred one patients were randomized: 151 to receive elective IABP insertion and 150 to receive PCI without planned IABP support. One patient in each group underwent elective coronary artery bypass graft surgery instead of PCI, and 3 patients in the elective IABP group did not have IABP insertion because of vascular access difficulties. The groups were well balanced in terms of baseline characteristics (Table 1). Mean left ventricular ejection fraction was 23.6%, and the mean BCIS-1 jeopardy score was 10.4, with the maximum jeopardy score of 12 present in 46% of the cohort. Comparable revascularization was performed in both groups (Table 2), with 2.15 (1.04) lesions attempted per patient in the elective IABP group and 2.05 (1.02) lesions in the no planned IABP group and procedural success rates of 94% and 93%, respectively. A total of 51% and 54% of the elective and no planned IABP groups, respectively, underwent revascularization of ≥2 vessels, with similar proportions of left main coronary and proximal left anterior descending coronary artery lesions treated in both groups (Table 2).

In-Hospital Outcomes

In-hospital outcome data were available for the entire cohort and have been published previously. Briefly, the primary composite outcome MACCE occurred in 23 (15.2%) and 24 (16%) of patients in the elective and no planned IABP groups, respectively (odds ratio, 0.94; 95% CI, 0.51–1.76; P=0.85), with acute myocardial infarction occurring in 19 (12.6%) and 20 (13.3%) of each group (odds ratio, 0.93; 95% CI, 0.48–1.83; P=0.85). Two patients (1.3%) in the elective IABP group suffered major procedural complications compared with 16 patients (10.7%) in the no planned IABP group (odds ratio, 0.11; 95% CI, 0.01–0.49; P<0.001). Eighteen patients (12%) assigned to have no planned IABP insertion required bailout IABP therapy.

Bleeding (major or minor) occurred in 19.2% of the elective IABP group and 11.3% of the no planned IABP group (odds ratio, 1.86; 95% CI, 0.93–3.79; P=0.06).

All-Cause Mortality Data

Long-term mortality status assessment was completed in all 301 patients (100%). The median duration of follow-up was 51 months from randomization (interquartile range, 41–58 months). One hundred deaths (33%) occurred during this

Table 1. Baseline Characteristics of the Study Groups

	Elective IABP	No Planned IABP
Demographics		
Age, mean (SD), y	71 (9)	71 (10)
Men	122 (81)	117 (78)
Medical history		
Diabetes mellitus		
Type 1	3 (2)	6 (4)
Type 2	53 (35)	44 (29)
Smoking		
Current	32 (21)	29 (20)
Former	78 (52)	82 (55)
Hypertension	95 (63)	91 (61)
Prior MI	113 (75)	108 (73)
Prior PCI	17 (11)	14 (9)
Prior CABG	25 (17)	20 (13)
Prior stroke	12 (8)	11 (7)
eGFR, median (IQR), mL/min	58.2 (45.0–78.6)	60.0 (41.9–80.0)
NYHA functional class		
I	8 (5)	11 (7)
II	43 (29)	31 (21)
III	63 (42)	64 (43)
IV	36 (24)	44 (29)
Coronary anatomy and left ventricular function		
LVEF, mean (SD), %	23.6 (5.2)	23.6 (5.5)
BCIS-1 jeopardy score		
6	1 (1)	1 (1)
8	40 (26)	42 (28)
10	39 (26)	39 (26)
12	71 (47)	68 (45)
Left main coronary disease*	41 (27)	44 (29)

Values are number (%) unless indicated otherwise. IABP indicates intra-aortic balloon pump; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; eGFR, estimated glomerular filtration rate (calculated from the Cockroft-Gault formula); IQR, interquartile range; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; and BCIS-1, Balloon Pump–Assisted Coronary Intervention Study.

*>70% diameter stenosis in left main coronary artery.

period in the entire cohort. Forty-two patients in the elective IABP group and 58 patients in the no planned IABP group died during follow-up, corresponding to mortality rates of 7.9 and 12.1 per 100 patient-years, respectively. The Kaplan-Meier curves demonstrate a significant difference in survival, with the hazard ratio for elective IABP versus no planned IABP being 0.66 (95% CI, 0.44–0.98; P=0.039) (Figure 1).

Eighteen deaths occurred in the first 6 months, 16 deaths between 6 months and 1 year, and 66 deaths after 1 year following randomization. Comparison of hazard ratios at different time points demonstrated the hazard ratio to be similar over time (Figure 2). The hazard ratios for events occurring before and after 1 year were 0.68 (95% CI, 0.34–1.35) and 0.65 (95% CI, 0.40–1.06), respectively (P=0.91 on test for interaction).

Table 2. Revascularization in the Study Groups

Variable	Elective IABP (n=151)	No Planned IABP (n=150)	P
Procedural success	142 (94)	140 (93)	0.80
No. of vessels treated			
1 vessel	73 (48)	69 (48)	0.68
2 vessels	64 (42)	64 (43)	0.96
3 vessels	13 (9)	16 (11)	0.55
Coronary segment treated			
Left main stem	35 (23)	41 (27)	0.41
Proximal LAD	73 (48)	71 (47)	0.86
No. of coronary stents, mean±SD	2.56+1.33	2.31+1.54	0.13
Drug-eluting stents	1.75±1.58	1.53±1.64	0.22
Bare metal stents	0.80±1.24	0.78±0.58	0.88
Rotational atherectomy	20 (13)	17 (11)	0.61

Values are number (%) unless indicated otherwise. IABP indicates intra-aortic balloon pump; and LAD, left anterior descending coronary artery.

There was no evidence that the impact of IABP on mortality differed according to the prespecified subgroups (Figure 3). Similarly, the overall treatment effect was minimally changed after adjustment for baseline variables; a model incorporating all baseline variables listed in Table 1 yielded a hazard ratio of 0.64 (95% CI, 0.42–0.98; P=0.038), whereas a model including only the major univariate predictors age (P<0.001), diabetes mellitus (P<0.001), and prior myocardial infarction (P=0.023) yielded a hazard ratio of 0.67 (95% CI, 0.45–1.00; P=0.047).

Eighteen patients assigned to have PCI with no planned IABP required bailout IABP insertion after randomization. Analysis by treatment received showed a hazard ratio of 0.63 (95% CI, 0.43–0.94; P=0.024) for IABP insertion before or during PCI (n=169) versus PCI without IABP support (n=132).

A total of 149 (of 151) patients in the elective IABP group and 134 (of 150) patients in the no planned IABP group underwent PCI without procedural complications. Comparison of long-term mortality in these patients showed a hazard ratio of 0.64 (95% CI, 0.42–0.96; P=0.029) in favor of elective IABP insertion.

Discussion

IABPs have been in clinical use for more than 4 decades,[9] largely on the basis of favorable observational data as well as the beneficial effect of counterpulsation on coronary blood flow and myocardial oxygen demand.[10–12] The widespread use of IABP during high-risk PCI, acute myocardial infarction, and cardiogenic shock[13,14] had been at odds with the paucity of adequately powered randomized controlled trials in these settings. However, the past 2 years have seen publication of randomized trial data on the use of elective IABP support during high-risk PCI[3] and PCI for acute ST-segment elevation myocardial infarction,[15] and the results of the first randomized trial of IABP use in cardiogenic shock were presented earlier this year.[16]

BCIS-1 evaluated the effect of elective IABP use on the incidence of MACCE in patients with severe ischemic cardiomyopathy undergoing PCI. Predefined procedural

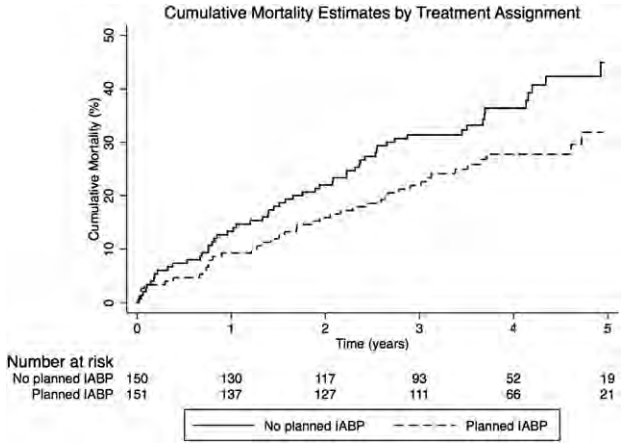

Figure 1. Kaplan-Meier survival curves are shown for patients treated with elective intra-aortic balloon pump (IABP) therapy (solid line) and those who had percutaneous coronary intervention without planned IABP support (dashed line). At median follow-up of 51 months, there were 42 deaths in the elective IABP group and 58 deaths in the no planned IABP group (hazard ratio, 0.66; 95% confidence interval, 0.44–0.98; *P*=0.039).

complications occurred less frequently with elective IABP, and a significant proportion of patients assigned to have PCI without planned IABP support required bailout IABP therapy, but there was no difference in the incidence of MACCE at hospital discharge.[3] Fewer deaths were observed in the elective IABP group at 6 months, and the present study demonstrates that this difference is maintained, with a 34% relative reduction in mortality observed in the elective IABP group at long-term follow-up. One in 3 patients enrolled in BCIS-1 died within a median of 51 months after PCI, a finding that echoes the surgical revascularization data in ischemic cardiomyopathy[17] and confirms the poor prognosis of this population. In this context, a reduction in relative risk by one third would translate to a large, clinically significant treatment

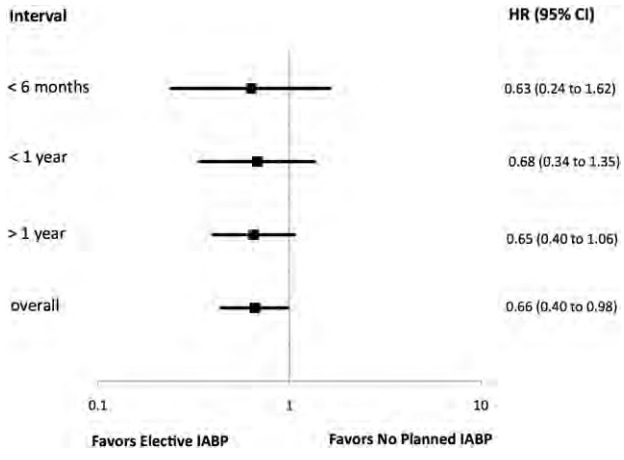

Figure 2. Hazard ratios (HRs) are shown for different follow-up intervals from randomization, 0 to 6 months, 0 to 1 year, and beyond 1 year. The HR for events occurring after 6 months was 0.67 (95% confidence interval [CI], 0.43--1.03). There was no significant difference in mortality rates by treatment assignment before and after 1 year from randomization (*P*=0.91 for interaction). The overall HR is shown for comparison. IABP indicates intra-aortic balloon pump.

effect, although it remains to be established whether these findings will be borne out in larger clinical series.

It should be acknowledged that BCIS-1 was primarily designed to address in-hospital MACCE (capped at 28 days) and therefore was not prospectively powered for all-cause mortality alone in the short term. Nevertheless, the high event rate observed in this cohort over longer-term follow-up provides reasonable power for the comparison of outcomes in the 2 arms. In this context, it is interesting to note that the hazard ratio at 6 months of follow-up is essentially similar to the hazard ratio at long-term follow-up, which would be consistent with an early treatment effect that is subsequently maintained. A similar signal of early mortality benefit with elective IABP use was found in the recently concluded Counterpulsation Reduces Infarct Size Pre-PCI for AMI (CRISP-AMI) trial, a randomized evaluation of elective IABP therapy in acute anterior ST-segment elevation myocardial infarction, although the number of events at 6 months was too low for formal statistical comparison.[15]

One of the strengths of the present study is that all-cause mortality assessment was performed via a central, national database, which allowed robust and complete capture of all deaths. The corollary is that we have no information on the cause of the death in each case, which limits exploration of the possible mechanisms of benefit of counterpulsation in this population. In view of the potent effects of IABP on reducing myocardial ischemia, it is conceivable that the effect on mortality was mediated by a reduction in periprocedural ischemia and infarction. However, there was no difference between the treatment arms in the incidence of in-hospital MACCE, which in turn was largely driven by acute infarction in the periprocedural period. The definition of myocardial infarction in this study depended on the timing of the event in relation to the index PCI, with events within 72 hours being defined by elevation in the serum level of the creatine kinase MB isoform to at least 3-fold the upper limit of the normal range.[7] The relatively high biomarker threshold was chosen to exclusively capture large periprocedural infarctions to ensure clinical equivalence of the components of the composite primary outcome of MACCE. The protocol did not mandate measurement of troponin levels after PCI or coronary artery bypass graft surgery, and, as a consequence, we cannot exclude a difference in the incidence of smaller periprocedural infarctions between the elective IABP and no planned IABP groups. There is a growing body of evidence demonstrating the prognostic importance of any myocardial necrosis in the context of revascularization, even when manifest as troponin elevation with normal creatine kinase MB levels.[18] It is plausible that the impact of such small infarctions would be magnified in patients with severely impaired left ventricular function at the outset and that such events may lead to an increased risk of fatal arrhythmias or adverse ventricular remodeling in the longer term.

A potential confounding factor that should be considered when these mortality data are interpreted is the possible influence of treatment assignment on the nature of revascularization performed in this trial. In particular, is there any evidence that allocation of a patient to an elective IABP strategy may have given the interventional cardiologist

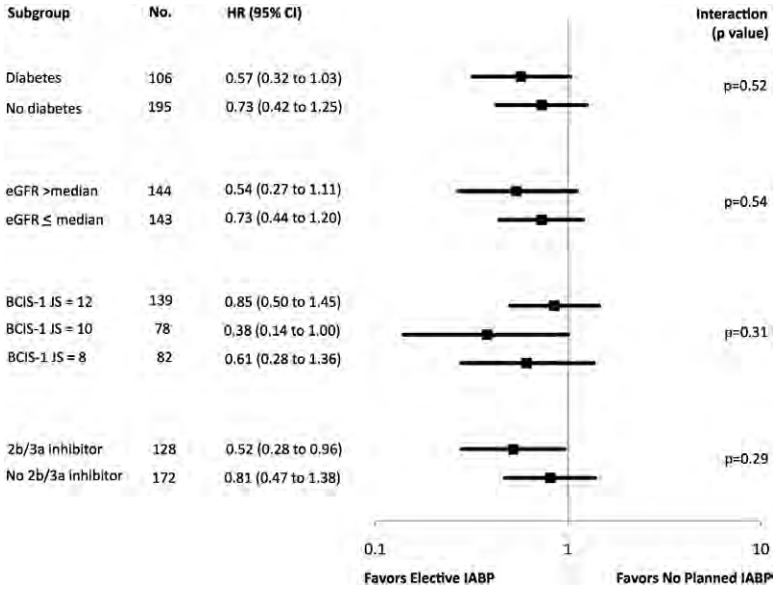

Figure 3. Hazard ratios (HRs) for all-cause mortality in prespecified subgroups. The interaction test results demonstrate that there was no significant impact of stratification by these 4 criteria on the effect of elective intra-aortic balloon pump (IABP) insertion on mortality. The median estimated glomerular filtration rate (eGFR) was 59 mL/min. BCIS-1 JS indicates Balloon Pump–Assisted Coronary Intervention Study Jeopardy Score. Two patients who had a BCIS-1 JS of 6 at baseline were not included in this subgroup analysis. 2b/3a inhibitor indicates the use of glycoprotein IIb/IIIa receptor antagonists. Bivalirudin was considered equivalent to a IIb/IIIa inhibitor according to the analysis plan, and this subgroup (n=128) includes 4 patients who received bivalirudin.

increased confidence with which to undertake more extensive and possibly more complex revascularization? Were it possible to identify differences in the extent of revascularization achieved in the 2 arms of the trial, this may partly explain the observed differences in all-cause mortality because more complete revascularization has previously been associated with improved long-term outcomes in stable coronary disease.[19,20] However, we have not found evidence of any systematic differences in the quality or amount of revascularization achieved with elective IABP therapy compared with a strategy of PCI without planned IABP use. Procedures were attempted in a similar number of vessels, with comparable rates of success, and a similarly high proportion of patients underwent PCI to proximal coronary segments such as the left main stem or proximal left anterior descending coronary artery in both groups. Other indirect markers of the coronary substrate treated, such as the use of adjunctive devices or the frequency of drug-eluting stent deployment, were also comparable in the 2 groups.

Limitations

The study was not prospectively designed to address all-cause mortality. As such, it remains possible that the results may reflect a chance finding, and this should be considered when these data are interpreted. Furthermore, the data do not provide a clear mechanistic explanation for the putative beneficial effect of elective IABP therapy, given the absence of information on the etiology of death in each case and the lack of long-term data on left ventricular function and remodeling. However, this is the largest randomized trial to date of elective IABP use in high-risk PCI and the largest series with long-term outcome data in any clinical setting.

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Disclosures

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CLINICAL PERSPECTIVE

The intra-aortic balloon pump improves myocardial perfusion and decreases myocardial oxygen demand and hence is a valuable adjunct when treating cardiogenic shock. It is also frequently used to prevent complications during high-risk percutaneous coronary intervention (PCI); the only randomized trial to date that addresses this indication is the Balloon Pump–Assisted Coronary Intervention Study (BCIS-1). In BCIS-1, 301 patients with severe ischemic cardiomyopathy were randomly assigned to have elective intra-aortic balloon pump insertion before PCI or to have PCI without planned intra-aortic balloon pump support. The trial failed to show a difference in the occurrence of major cardiovascular events at hospital discharge. The present report documents the long-term survival in patients enrolled in this trial. All-cause mortality at a median of 51 months was 33% in the entire cohort, demonstrating that severe ischemic cardiomyopathy is associated with relatively poor long-term survival. The results also showed that elective intra-aortic balloon pump use is associated with a 34% relative reduction in all-cause mortality compared with PCI without planned balloon pump support. Although the trial was not initially designed to assess long-term mortality and the putative mechanism of benefit is unclear, these data suggest that there may be a role for elective intra-aortic balloon pump therapy during PCI in selected patients with poor left ventricular function and extensive coronary disease.

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Long-Term Mortality Data From the Balloon Pump–Assisted Coronary Intervention Study (BCIS-1): A Randomized, Controlled Trial of Elective Balloon Counterpulsation During High-Risk Percutaneous Coronary Intervention

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