Circulation

EDITORIAL

Another Nail in the Coffin for Intra-Aortic Balloon Counterpulsion in Acute Myocardial Infarction With Cardiogenic Shock

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Cardiogenic shock occurs in up to 5% to 10% of acute myocardial infarctions (MI) and is associated with high short- and long-term mortality risk. Since its introduction into clinical practice >50 years ago, intra-aortic balloon counterpulsion has been used empirically to provide hemodynamic support in patients undergoing coronary revascularization in the setting of MI and cardiogenic shock. In the landmark SHOCK (Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock) trial, conducted between 1993 and 1998, intra-aortic balloon pumps (IABP) were placed in 86% of participants, irrespective of the assigned management strategy.[1] Although expert opinion supported clinical benefit of IABP use in cardiogenic shock, the first large randomized, multi-center trial of IABP, published in 2012, upended this conventional wisdom. The IABP-SHOCK II (Intra-aortic Balloon Pump in Cardiogenic Shock II) trial randomly assigned 600 participants planned for early revascularization of acute MI complicated by cardiogenic shock to either IABP placement or no IABP placement.[2] The primary end point was 30-day all-cause mortality. At 30 days, all-cause mortality was 40%, with no difference between patients randomized to receive an IABP versus those who were not. There were no differences between treatment groups in secondary outcomes, including bleeding, ischemic complications, stroke, time to hemodynamic stabilization, intensive care unit length of stay, and the dose and duration of catecholamine therapy. A previous intermediate-term report of IABP-SHOCK II trial outcomes demonstrated no difference between treatment groups for all-cause mortality at 12 months.[3]

In this issue of *Circulation*, Thiele et al[4] report the 6-year results of the IABP-SHOCK II randomized trial. At 6 years of follow-up, all-cause mortality was high and did not differ between the IABP and control groups (66.3% versus 67.0%) in intention-to-treat, per-protocol, and as-treated analyses. No signal for benefit associated with IABP use was observed in any prespecified or post hoc subgroups. There were no differences in the frequency of recurrent MI, repeat revascularization, stroke, or cardiovascular rehospitalization between the 2 groups. Quality of life, measured by the EuroQol 5D questionnaire and New York Heart Association classification, was favorable in survivors of cardiogenic shock. Four of 5 survivors had New York Heart Association Class I or II symptoms, with no difference between patients randomly assigned to IABP and no IABP therapy.

The 6-year results of IABP-SHOCK II are consistent with the study findings previously reported at 30 days and 12 months, and confirm lack of benefit associated with IABP placement. In agreement with previous reports from the SHOCK trial, early events account for the majority of fatalities, and the 6-year mortality of the IABP-SHOCK II and immediate revascularization arm of the SHOCK are near-

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ly identical.[4,5] The authors should be commended for their rigorous follow-up of 98.5% of the trial participants through telephone interviews and death registry queries. Outcomes reported at 6 years were clinically relevant and objective, and quality of life metrics were assessed using validated survey instruments.

There are several limitations of the IABP-SHOCK II study. The study was nonblinded, because sham IABP placement is not feasible. An open-label study design may have led to differential use of other therapies between groups; however, the absence of other interventions known to improve outcomes in cardiogenic shock mitigates the impact of this potential limitation. Moreover, there was little risk of ascertainment bias with the primary end point of all-cause mortality. It is notable that the IABP-SHOCK II investigators did not select for a high-risk shock cohort by requiring a minimum lactate threshold, the most potent predictor of long-term mortality after multivariable adjustment, nor was lactate level a prespecified subgroup.[6] Still, the substantial early and late mortality reported in the study population suggests that participants enrolled in IABP-SHOCK II are broadly representative of patients with cardiogenic shock with a sufficient burden of illness to test the effectiveness of IABP support.

The results of IABP-SHOCK II trial had a significant impact on clinical practice guideline recommendations. Based on the 30-day and 12-month outcomes of the IABP-SHOCK II trial, routine placement of IABP in the setting of cardiogenic shock is a Class III (level of evidence B) recommendation in the 2017 European Society of Cardiology Guidelines for ST-segment elevation myocardial infarction.[7] The long-term follow-up from IABP-SHOCK II reinforces this guideline recommendation. Thus, the IABP-SHOCK II follow-up data provide additional evidence to support a limited role for IABP in acute MI with cardiogenic shock in the modern era. The next iteration of North American cardiogenic shock guidelines should also be updated to reflect these randomized clinical trial data and put an end to the clinical inertia that has perpetuated routine use of IABP for cardiogenic shock.

There are a several hypotheses to account for the lack of benefit of IABP therapy on mortality in IABP-SHOCK II. First, balloon counterpulsion provides only a small augmentation of cardiac output in the setting of shock, and the device requires intrinsic left ventricular contractility for optimal benefit. Furthermore, balloon counterpulsion does not directly support right ventricular function, which may contribute to shock in some patients. In this context, IABP use may simply provide insufficient circulatory support to ensure end-organ perfusion. Once irreversible end-organ damage has occurred, outcomes are uniformly poor. Second, although 80% of participants in IABP-SHOCK II had multi-vessel coronary artery disease (CAD), nearly all underwent percutaneous coronary intervention for coronary revascularization. Residual ischemia from nonculprit coronary artery disease may also contribute to the substantial short- and long-term mortality.

If IABP does not improve survival in MI complicated by cardiogenic shock, which alternative strategies can effectively reduce mortality? Other than early coronary revascularization, no other interventions have been proven to provide clinical benefit. The results of a prespecified analysis of a small subgroup of the SOAP II trial (Sepsis Occurrence in Acutely Ill Patients II) suggest a benefit of norepinephrine over dobutamine in cardiogenic shock, but dedicated robust trials of medical therapy in cardiogenic shock are still needed.[8] Newer mechanical circulatory support technologies have been developed to maintain end-organ perfusion and provide a bridge to left ventricular recovery, wearable ventricular assist device implantation, or cardiac transplantation in the setting of cardiogenic shock. Although promising, the percutaneous left ventricular assist device therapy has not been associated with improved clinical outcomes compared with IABP therapy in small clinical trials.[9] Larger trials of percutaneous left ventricular assist device therapy use in cardiogenic shock are needed. Venoarterial extracorporeal membrane oxygenation can provide complete biventricular mechanical circulatory support, but the optimal methods for catheter placement and unloading of the left ventricle remain uncertain. Randomized trials of extracorporeal membrane oxygenation for cardiogenic shock are currently being implemented, but results of these studies will not be available for years. Thus, the benefits of mechanical circulatory support for cardiogenic shock with percutaneous left ventricular assist device therapy and extracorporeal membrane oxygenation remain uncertain.

Approaches to coronary revascularization in the setting of MI with cardiogenic shock also deserve consideration. Data from the CULPRIT-SHOCK trial (Culprit Lesion Only PCI Versus Multivessel PCI in Cardiogenic Shock) recently demonstrated that multi-vessel percutaneous coronary intervention does not reduce mortality in patients with MI, multi-vessel CAD, and cardiogenic shock.[10]Although the majority of patients in IABP-SHOCK II had multi-vessel CAD, only 3.5% of trial participants underwent coronary artery bypass graft (CABG). In the original SHOCK trial, those who were referred for early CABG had a greater burden of CAD and diabetes mellitus, but had similar survival to trial participants who underwent early percutaneous coronary intervention.[11] Thus, complete revascularization with CABG is a promising path forward. A randomized trial of infarct-only percutaneous coronary intervention versus emergent CABG (with or without balloon angioplasty) in patients with MI, multi-vessel CAD of suitable anatomy, and cardiogenic shock might provide important insights into the optimal treatment of these complex patients. A trial to test whether CABG is superior is in development.[12]

The 6-year follow up of the IABP-SHOCK II trial demonstrates the stubbornly high short- and long-term mortality associated with MI and cardiogenic shock despite advances in cardiovascular care over the past decades. The study also confirms the feasibility of large clinical trials in this critically ill patient population in the modern era. These results should serve as a call to action to identify and test novel approaches to reduce short- and long-term mortality in cardiogenic shock. Large simple multicenter clinical trials are urgently needed to define optimal management strategies to improve outcomes in patients with cardiogenic shock complicating MI. All patients and care providers would ideally contribute to the evidence base.

ARTICLE INFORMATION

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Circulation

ORIGINAL RESEARCH ARTICLE

Intraaortic Balloon Pump in Cardiogenic Shock Complicating Acute Myocardial Infarction

Long-Term 6-Year Outcome of the Randomized IABP-SHOCK II Trial

BACKGROUND: The role of intraaortic balloon counterpulsation (IABP) in cardiogenic shock is still a subject of intense debate despite the neutral results of the IABP-SHOCK II trial (Intraaortic Balloon Pump in Cardiogenic Shock II) with subsequent downgrading in international guidelines. So far, randomized data on the impact of IABP on long-term clinical outcomes in patients with cardiogenic shock complicating acute myocardial infarction are lacking. Furthermore, only limited evidence is available on general long-term outcomes of patients with cardiogenic shock treated by contemporary practice.

METHODS: The IABP-SHOCK II trial is a multicenter, randomized, open-label trial. Between 2009 and 2012, 600 patients with cardiogenic shock complicating acute myocardial infarction undergoing early revascularization were randomized to IABP versus control.

RESULTS: Long-term follow-up was performed 6.2 years (interquartile range 5.6–6.7) after initial randomization. Follow-up was completed for 591 of 600 patients (98.5%). Mortality was not different between the IABP and the control group (66.3% versus 67.0%; relative risk, 0.99; 95% CI, 0.88–1.11; *P*=0.98). There were also no differences in recurrent myocardial infarction, stroke, repeat revascularization, or rehospitalization for cardiac reasons (all *P*>0.05). Survivors' quality of life as assessed by the EuroQol 5D questionnaire and the New York Heart Association class did not differ between groups.

CONCLUSIONS: IABP has no effect on all-cause mortality at 6-year long-term follow-up. Mortality is still very high, with two thirds of patients with cardiogenic shock dying despite contemporary treatment with revascularization therapy.

CLINICAL TRIAL REGISTRATION: URL: https://clinicaltrials.gov/. Unique identifier: NCT00491036.

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Key Words: acute myocardial infarction ■ angioplasty ■ assist device ■ cardiogenic shock ■ intraaortic balloon counterpulsation

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ORIGINAL RESEARCH ARTICLE

Clinical Perspective

What Is New?

- The long-term effects of intraaortic balloon pump (IABP) assessed at 6 years in patients with acute myocardial infarction complicated by cardiogenic shock on all-cause mortality have been assessed.
- There were no relevant differences in long-term outcome and other secondary end points between patients randomized to IABP or control.
- Quality of life and functional status were similar at long-term follow-up.

What Are the Clinical Implications?

- The current long-term follow-up of the IABP-SHOCK II trial (Intraaortic Balloon Pump in Cardiogenic Shock II) did not show an effect of IABP on mortality in patients with cardiogenic shock supporting current guideline recommendations to not routinely use IABP.

Short- to midterm mortality in cardiogenic shock complicating acute myocardial infarction remains high at rates between 40% and 60%.[1–6] Intraaortic balloon pumping (IABP) has been the most widely used mechanical hemodynamic support device for ≈5 decades.[6] Experimental and registry trials suggested an augmentation of the diastolic blood pressure, thereby improving coronary perfusion with a small but significant effect on cardiac output.[7] However, in a small randomized trial, these effects on cardiac output were not different to those observed in the control group.[8] Based on the subsequent IABP-SHOCK II trial (Intraaortic Balloon Pump in Cardiogenic Shock II), which did not show a benefit of IABP use versus control on 30-day and 1-year mortality,[9,10] European guidelines downgraded IABP use for cardiogenic shock from a previous class I to a class III B recommendation.[11–13] In the US guidelines, IABP use has been downgraded to a class IIb B recommendation based on registry data.[14,15]

In elective high-risk percutaneous coronary intervention (PCI), IABP showed no benefit at short-term follow-up but suggested a significant mortality reduction at 5-year follow-up.[16,17] So far, randomized data on the impact of IABP on long-term clinical outcomes in patients with cardiogenic shock complicating acute myocardial infarction are lacking. Furthermore, only limited evidence is available on general long-term outcomes of cardiogenic shock patients treated by contemporary practice.[18]

Therefore, we performed a long-term follow-up of the IABP-SHOCK II trial to assess differences in clinical outcome between IABP and control, predictors of cardiogenic shock mortality, effects on quality of life, and functional status.

METHODS

Study Design

The trial design of the randomized, open-label, multicenter IABP-SHOCK II trial and the 30-day and 12-month results, including the primary end point have been previously published.[9,10,19] In brief, this investigator-initiated trial was performed at 37 German centers and coordinated by the Heart Center Leipzig at the University of Leipzig, Germany, and the Institut für Herzinfarktforschung, Ludwigshafen, Germany, a clinical research organization. The main inclusion criterion was cardiogenic shock with planned early revascularization preferably by PCI. Cardiogenic shock was defined by typical criteria with the presence of systemic hypotension, pulmonary congestion, and signs of impaired organ perfusion. Exclusion criteria were resuscitation >30 minutes, no intrinsic heart action, severe cerebral deficit, mechanical causes of cardiogenic shock, onset of shock >12 hours, severe peripheral artery disease precluding IABP insertion, aortic regurgitation >grade 2, >90 years of age, shock of other cause, and other severe concomitant disease with a limited life expectancy of <6 months.

The study was approved by national regulatory authorities and ethics committees of all participating centers. Additional ethical approval was obtained for the extended long-term follow-up. The trial complied with the Declaration of Helsinki and is registered at www.clinicaltrials.gov (ClinicalTrials.gov Identifier: NCT00491036). Informed consent at randomization was obtained using a previously validated and dedicated informed consent process.[10,19] The trial organization included an independent data safety monitoring board and a steering committee responsible for trial conduct. The first and senior authors had full access to all the data in the study and take responsibility for its integrity and data analysis. The data, analytic methods, and study materials cannot be made available to other researchers for purposes of reproducing the results or replicating the procedure because the trial was started long before the general introduction of the data-sharing concept, and informed consent did not incorporate such policy.

Randomization, Treatment, and Long-Term Follow-up

Between June 2009 and March 2012, 600 patients were randomized with a 1:1 ratio in an open-label fashion to IABP (n=301) or control (n=299) using an internet-based program. By protocol, crossover to IABP in controls was only allowed for patients developing a mechanical complication. All other treatment was similar between groups and followed specific guideline recommendations.[20] Thus, the only difference in treatment between groups was IABP support.

For the assessment of clinical outcome at 6 years, all-cause mortality was determined based on data of the German national death registry, which is a noncentralized registry run by each German commune. In survivors, a structured telephone interview with interviewers masked to treatment allocation was performed. Any clinical event was verified by hospital or general practitioner records.

End Points

In addition to the primary study end point 30-day all-cause mortality,[10] mortality at 6 and 12 months was assessed by

protocol.[9,19] The current long-term follow-up was added as an amendment to the original study protocol. All-cause mortality, reinfarction using the third universal definition of myocardial infarction definition,[21] revascularization by either PCI or coronary artery bypass grafting, stroke, and implantable cardioverter defibrillator implantation were assessed.

At 6-year follow-up, symptoms of heart failure using the New York Heart Association classification and angina using the Canadian Cardiovascular Society classification were assessed in all survivors in addition to quality of life using the EuroQol (EQ)-5D-3 L (www.euroqol.org) questionnaire. This questionnaire has been described and reported previously at 12-month follow-up.[9] In brief, it is a descriptive system of health-related quality-of-life states consisting of 5 dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression), each of which can take 1 of 3 responses (no problems, some or moderate problems, or extreme problems). In addition, the EQ visual analogue scale was obtained assessing the self-rated health on a scale from 0 to 100. Results are displayed as EQ-5D-3 L index value with 1 indicating best quality of life and the EQ visual analogue scale with 100 indicating the best subjective health status.

The safety end points of bleeding, sepsis, and peripheral ischemic vascular complication were only assessed for the initial hospital phase for ≤30 days. Further safety analyses were only performed for stroke.[10,19]

Statistical Analysis

The initial study was powered to detect a 12% absolute difference for the primary end point of 30-day mortality, assuming a mortality rate of 56% in the control arm and 44% in the IABP arm. Accounting for 2 interim analyses and a 2% dropout rate, 600 patients were recruited.[10,19] There was no formal power analysis for the long-term follow-up. All data were analyzed according to the intention-to-treat principle, with an additional sensitivity analysis according to the per-protocol and as-treated population for the evaluation of data robustness.

Survival times were calculated as time from randomization to time of death or last known follow-up. Log-rank testing was used to analyze continuous survival times, and the χ^2 test was used to compare mortality rates.

Other end points were assessed by Fisher's or χ^2test for binary and Mann–Whitney *U* test for continuous secondary end points to compare both treatment arms.

Cox proportional hazards regression modeling was used to identify independent clinical and laboratory risk factors at baseline associated with mortality. All baseline variables related to mortality on univariable analysis (defined by $P<0.10$) were further analyzed in a stepwise multivariable model. The same previously predefined subgroup analyses were applied for sex, age (<50 years, 50–75 years, >75 years), diabetes mellitus (yes/no), arterial hypertension (yes/no), ST-elevation versus non-ST-elevation myocardial infarction, anterior versus nonanterior myocardial infarction, and previous myocardial infarction (yes/no). Previous post hoc subgroups such as hypothermia versus no hypothermia and baseline blood pressure <80 mm Hg versus ≥80 mm Hg were once again evaluated. The Breslow–Day test was used for analyzing the interaction of treatment assignment and subgroup factors.

A 2-tailed *P* value <0.05 was considered significant. Statistical analyses were performed with SAS statistical package, version 9.4 (SAS Institute).

RESULTS

Patients, Procedures, and Follow-Up

From 790 initially screened cardiogenic shock patients, 600 patients were randomized to IABP (n=301) or control (n=299). Revascularization status, study protocol compliance, and follow-up at 30 days, 6 months, 12 months, and 6 years are displayed in Figure 1. The long-term follow-up was performed a median of 6.2 years (interquartile range, 5.6–6.7) after initial randomization. Follow-up was complete for 591 (98.5%) of the 600 patients. Baseline characteristics were well balanced between treatment groups.[10] The median age at randomization was 70 years (interquartile range, 58–77), and more than two thirds were male. The median duration of IABP support was 3.0 days (interquartile range, 2.0–4.0, with a range of 1–16 days). IABP placement was performed in 86.6% after revascularization.

Clinical Outcome

There was no significant difference in mortality between the IABP group compared with control at 6-year follow-up after randomization (66.3% versus 67.0%; relative risk, 0.99; 95% CI, 0.88–1.11; *P*=0.98) (Table 1). The corresponding Kaplan–Meier curves are shown in Figure 2. For the long-term follow-up, only minor variation occurred in the relative risk estimates when analyses were restricted to the per-protocol (65.2% versus 67.6%; relative risk, 0.96; 95% CI, 0.85–1.08; *P*=0.83) and as-treated (65.8% versus 67.6%; relative risk, 0.97; 95% CI 0.87–1.09; *P*=0.50) (Figure I in the online-only Data Supplement) populations. Subgroup analyses confirmed the consistency of the results among all predefined and post hoc subgroups (Figure 3). For patients in the IABP group, there was no significant difference in long-term mortality between the 13.4% undergoing IABP insertion before revascularization (64.9%) and the 86.6% after revascularization (64.6%; *P*=0.97). For patients with low, intermediate, and high risk based on the IABP-SHOCK II score,[22] long-term mortality was 48.7%, 77.8%, and 90.6%, respectively. There were no differences between the 2 treatment groups based on the risk categories.

Multivariable modeling revealed increasing age, history of stroke, baseline arterial lactate, creatinine level, oliguria (<30 mL/h), multivessel coronary artery disease, cold or clammy skin and extremities, and left bundle-branch block at admission as independent risk factors for mortality (Table 2). IABP treatment was not predictive of survival.

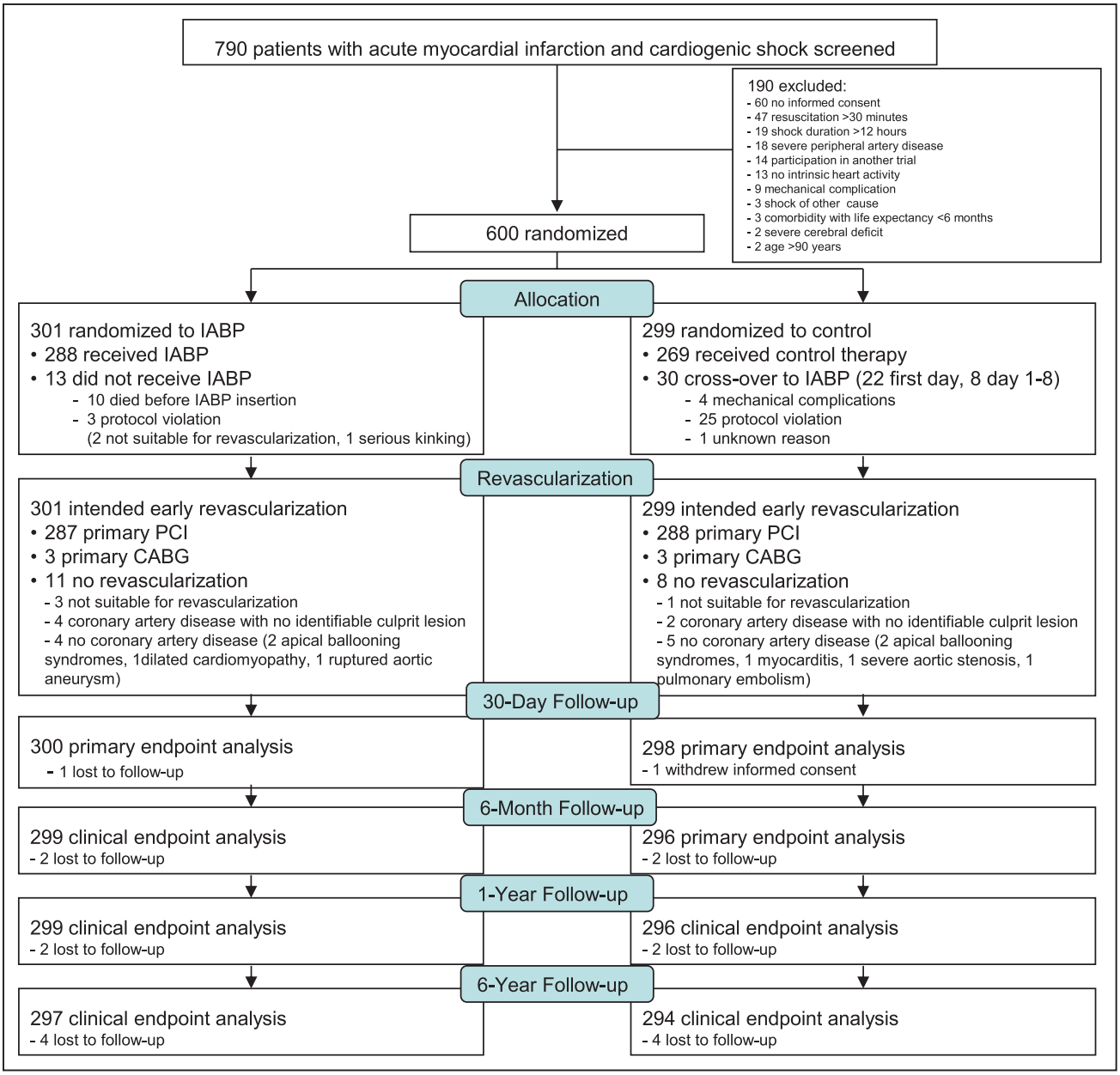

Figure 1. Trial flow.
Screening, randomization, revascularization, management strategy, and follow-up at 30 days, 6 months, 12 months, and 6 years. CABG indicates coronary artery bypass grafting; IABP, intraaortic balloon pump; and PCI, percutaneous coronary intervention.

There were no significant differences in recurrent infarction, stroke, requirement for internal cardioverter defibrillator, or additional revascularization procedures at 6-year follow-up (Table 1).

Functional Status and Quality of Life

Among 6-year survivors (n=197), 82% were in New York Heart Association class I or II (82% in the IABP and 82% in the control group; *P*=1.00). The overall rate of angina was low. In total, 13% in the IABP group versus 25% in the control group were in Canadian Cardiovascular Society class I or II (*P*=0.06). The EQ-5D-3 L index value was assessed for 173 survivors (88%), with 0.8 indicating moderate to good quality of life. There were no differences in quality-of-life assessment between both treatment groups with respect to the 5 quality-of-life dimensions and the EQ visual analogue scale (Figure IIA and IIB in the online-only Data Supplement).

DISCUSSION

In this randomized trial of patients with cardiogenic shock complicating acute myocardial infarction, IABP support did not result in a 6-year survival benefit compared with control, supporting the short-term 30-day

Table 1. Clinical Outcomes at 6 Years

Variable	Intraaortic Balloon Pump (n=297)	Control (n=294)	Relative Risk (95% CI)	*P* Value
All-cause mortality	197/297 (66.3)	197/294 (67.0)	0.99 (0.88–1.11)	0.98
Events in 6-year survivors				
Reinfarction	9/100 (9.0)	7/97 (7.2)	1.25 (0.48–3.22)	0.65
Stroke	1/100 (1.0)	6/97 (6.2)	0.16 (0.02–1.32)	0.06
Recurrent revascularization	26/100 (26.0)	31/97 (32.0)	0.81 (0.52–1.26)	0.36
Repeat percutaneous coronary intervention	18/100 (18.0)	26/97 (26.8)	0.67 (0.39–1.14)	0.14
Additional coronary artery bypass grafting	8/100 (8.0)	7/97 (7.2)	1.11 (0.42–2.94)	0.84
Implantable cardioverter defibrillator implantation	13/100 (13.0)	15/97 (15.5)	0.84 (0.42–1.67)	0.62

Values indicate n/total (%).

and midterm 1-year data. In addition to mortality, there were also no benefits of IABP on other secondary outcome variables. Despite early revascularization in all patients and optimal guideline-adherent medical therapy, mortality remains high, with more than two thirds of patients dying at 6-year follow-up. However, a relevant portion of survivors report no or mild symptoms with respect to New York Heart Association and Canadian Cardiovascular Society class with a moderate to good quality of life.

IABP has been in clinical use for ≈5 decades,[23] largely on the basis of observational data as well as the belief in a beneficial effect on coronary blood flow, myocardial oxygen demand, and afterload reduction.[7] The widespread use of IABP in cardiogenic shock had been at odds with the paucity of adequately powered randomized controlled trials in this setting. After publication of the IABP-SHOCK II trial, IABP use has been downgraded in guidelines with a parallel decline in clinical practice.[11,13,24–26] Similar to cardiogenic shock, data are sparse for IABP in elective high-risk PCI, with only 1 randomized trial in this setting, which also showed no benefit of IABP on major adverse cardiac and cardiovascular events at 28 days in patients with severe left ventricular dysfunction and extensive coronary disease.[16] In this trial, there was a mortality benefit at longer 5-year follow-up.[17] However, there was a lack of information on possible mechanisms supporting this observed mortality reduction with IABP support in this population, given the absence of death etiology and lack of data on left ventricular function and remodeling. As such, the finding of a mortality benefit may be a play of chance in this trial. In the current long-term follow-up of IABP-SHOCK II, results were consistent with respect to a lack of benefit at short-, mid, and long-term follow-up.

There are multiple possible explanations for this lack of benefit. In the IABP-SHOCK I randomized pilot trial, no differences between IABP and control were observed

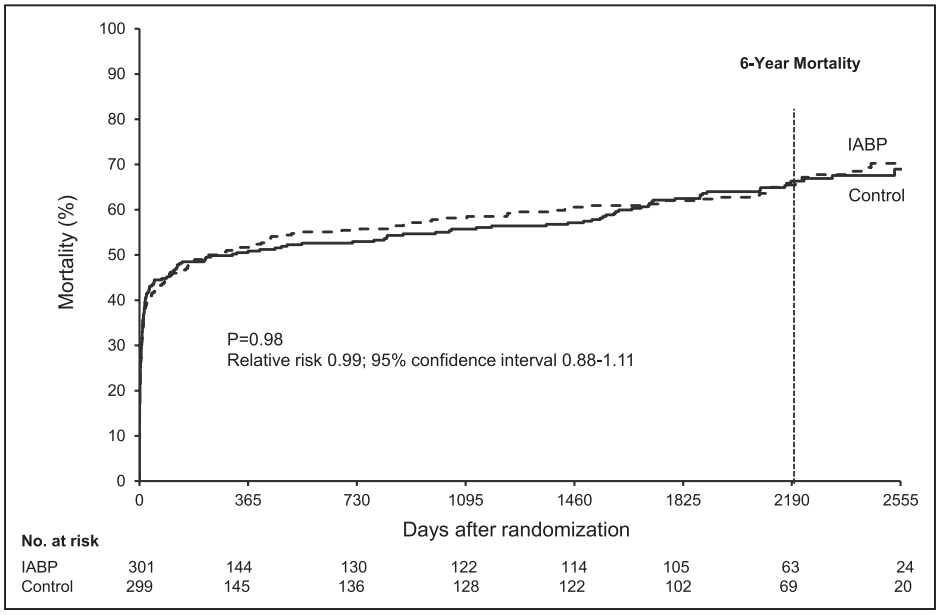

Figure 2. Time-to-event curves through 6 years.
Time-to-event curves through 6 years for all-cause mortality. *P* value is based on the log-rank test. Event rates represent Kaplan–Meier estimates. IABP indicates intraaortic balloon pump.

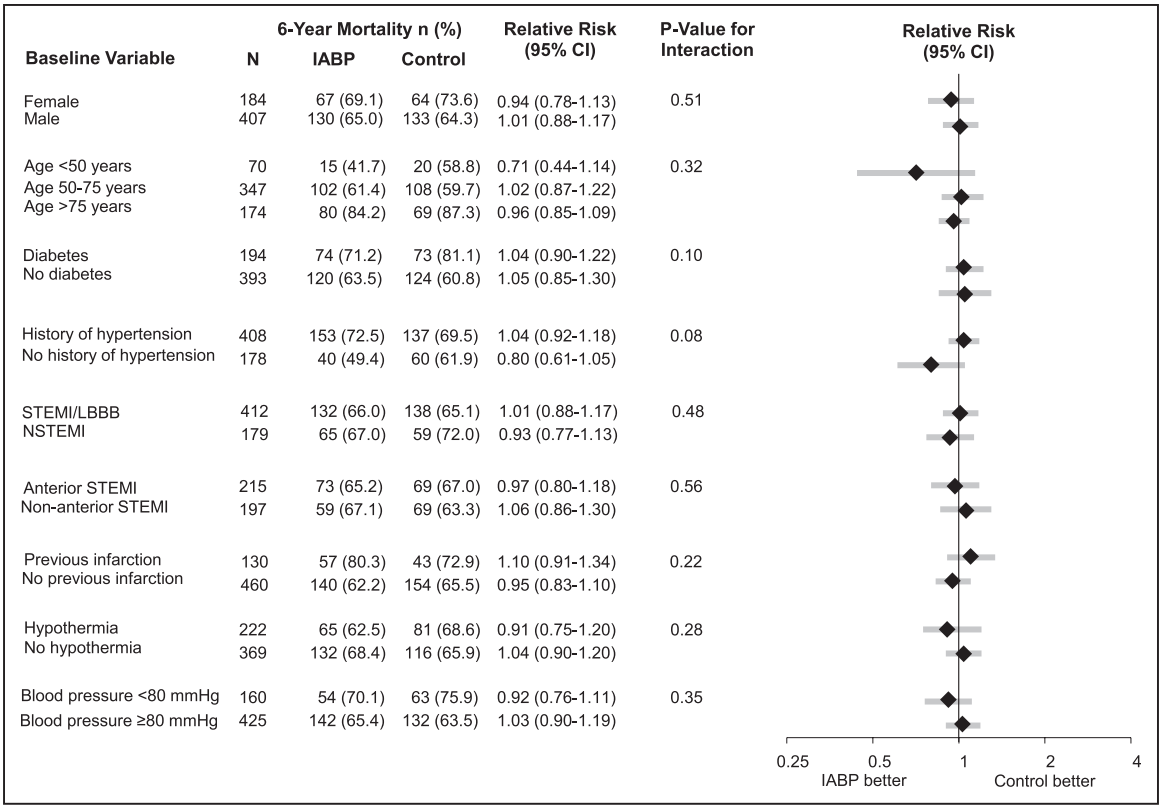

Figure 3. Forest plot subgroup analyses for all patients with 6-year follow-up.
The forest plots indicate relative risk and 95% CIs for predefined subgroups and the post hoc subgroups hypothermia versus no hypothermia and baseline systolic blood pressure <80 mm Hg versus ≥80 mm Hg. IABP indicates intraaortic balloon pump; LBBB, left bundle-branch block; NSTEMI, non-ST-elevation myocardial infarction; and STEMI, ST-elevation myocardial infarction.

in any of the measured hemodynamic parameters.[8] In the subsequent large IABP-SHOCK II trial, there were no effects on markers of systemic inflammation, arterial lactate, renal function, mean arterial blood pressure, intensive care unit scores, or doses of catecholamines, thereby providing supportive pathophysiological explanations for any lack of mortality benefit.[10] The results were also remarkably consistent for all subgroups studied in the shorter and current long-term follow-up. Furthermore, the results with this long-term follow-up are in line with previous registry data and 2 small randomized trials using fibrinolysis or PCI, which were all negative.[8,15,27]

In the current long-term follow-up trial, there was an additional absolute mortality increase of ≈28% at 6 years compared with the 30-day results. This difference is slightly higher, but overall mortality rates are nearly identical compared with the SHOCK trial (Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock), the only other large randomized cardiogenic shock trial reporting a 6-year long-term follow-up, which had mortality rates of 46.7% at 30 days and 67.2% at 6 years in the early revascularization strategy.[18,28,29] These data confirm once again, as also shown recently in the CULPRIT-SHOCK trial (Culprit Lesion Only PCI versus Multivessel PCI in Cardiogenic Shock),[4,5] that mortality or differences in mortality in cardiogenic shock are determined to a greater extent by the first 30 days. However, the risk of death is still substantial after the acute phase. Any possible improvement in mortality over time may be counterbalanced by increasing patient age and also more patients experiencing resuscitation before hospital admission. For these survivors, additional intensified medical and possibly interventional therapy may be required.

Quality of life and the functional status for survivors were relatively good. Similar to the SHOCK trial and the 1-year data of the CULPRIT-SHOCK trial, ≈90% of survivors were in New York Heart Association class I or II.[4,28] The more detailed quality-of-life assessment in the current trial using a standardized questionnaire showed health-related quality-of-life states being comparable to a general population survey.[30]

There is wide range in the risk of death for patients with cardiogenic shock complicating myocardial infarction.[22] An objective score to assess the mortality risk for individual patients has been derived from the IABP-SHOCK II population, which has been validated internally and externally.[22] The current results confirm that the readily available baseline arterial lactate, indicating the severity of end organ perfusion abnor-

Table 2. Predictors of 6-Year Mortality in Univariable and Stepwise Multivariable Cox Regression Analysis

Variable	Univariable		Stepwise Multivariable	
	Hazard Ratio (95% CI)	*P* Value	Hazard Ratio (95% CI)	*P* Value
Altered mental status	1.37 (1.08–1.74)	0.009	–	–
Mechanical ventilation	1.00 (0.82–1.22)	0.99	–	–
Current smoking	0.68 (0.54–0.84)	<0.001	–	–
History of arterial hypertension	1.41 (1.12–1.77)	0.003	–	–
Hemoglobin, mmol/l	0.87 (0.81–0.93)	<0.001	–	–
Hematocrit, %	0.11 (0.03–0.42)	0.001	–	–
Sinus rhythm	0.72 (0.57–0.90)	0.005	–	–
ST-elevation myocardial infarction	0.76 (0.62–0.94)	0.01	–	–
pH <7.36 at admission	1.37 (1.11–1.69)	0.004	–	–
Age, per 10 y	1.39 (1.27–1.52)	<0.001	1.33 (1.20–1.47)	<0.001
History of stroke	1.99 (1.41–2.80)	<0.001	1.52 (1.06–2.05)	0.02
Baseline arterial lactate, per 10 mmol/l	2.79 (2.22–3.51)	<0.001	2.68 (2.06–3.49)	<0.001
Baseline creatinine, per 100 µmol/l	1.03 (1.02–1.04)	<0.001	1.02 (1.00–1.03)	0.004
Oliguria (<30 mL/h)	1.68 (1.36–2.06)	<0.001	1.28 (1.01–1.62)	0.04
Multivessel coronary artery disease	1.37 (1.17–1.52)	<0.001	1.28 (1.05–1.46)	0.02
Cold, clammy skin and extremities	1.49 (1.11–2.00)	0.008	1.48 (1.06–2.05)	0.02
Left bundle-branch block	1.99 (1.53–2.60)	<0.001	1.52 (1.13–2.03)	0.005

Baseline patient variables related to mortality on univariable analysis defined by a *P* value <0.10. The first 9 variables initially entered into the model were not independently associated with mortality in the stepwise multivariable model.

malities, is 1 of the strongest predictors of long-term mortality. Baseline arterial lactate, together with age and oliguria, should therefore be integrated in mortality risk assessment in clinical practice and may also guide decision management for mechanical circulatory support.[6]

This long-term follow-up study has some strengths, including its size, multicenter design, recruitment of a high-risk real-world cardiogenic shock population, and near complete clinical follow-up. There are also some limitations, such as the lack of blinding, which is because of the nature of the intervention. Given the low number of surgically treated patients, the IABP effects might not be generalizable to patients undergoing immediate bypass surgery.

In conclusion, this randomized, multicenter trial confirmed that in patients with cardiogenic shock complicating myocardial infarction undergoing early revascularization, IABP support does not reduce 6-year long-term mortality. Cardiogenic shock mortality has virtually not changed since the introduction of early revascularization >2 decades ago. For the one third of survivors at 6 years functional outcome as well as quality of life is good.

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Disclosures

None.

APPENDIX

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