Early Revascularization and Long-term Survival in Cardiogenic Shock Complicating Acute Myocardial Infarction

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The incidence of cardiogenic shock complicating acute myocardial infarction (MI) has remained constant over 25 years.1-3 Although in-hospital mortality declined for the first time in the mid-1990s, the overall mortality rate is still 60%,1,3 and cardiogenic shock remains the major cause of death for patients hospitalized with acute MI.2-4 We previously reported the initial and 1-year results of the randomized Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock (SHOCK) trial.5,6 This trial demonstrated that a strategy of early revascularization in patients with cardiogenic shock resulted in a nonsignificant reduction in 30-day mortality from 55% to 46% when compared with a strategy of initial medical stabilization, a significant absolute percentage points reduction in 1-year mortality and good functional status at 1 year for the majority of survivors.7-9 We report here the long-term survival for patients with cardiogenic shock complicating acute MI.

Context Cardiogenic shock remains the major cause of death for patients hospitalized with acute myocardial infarction (MI). Although survival in patients with cardiogenic shock complicating acute MI has been shown to be significantly higher at 1 year in those receiving early revascularization vs initial medical stabilization, data demonstrating long-term survival are lacking.

Objective To determine if early revascularization affects long-term survival of patients with cardiogenic shock complicating acute MI.

Design, Setting, and Patients The Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock (SHOCK) trial, an international randomized clinical trial enrolling 302 patients from April 1993 through November 1998 with acute myocardial infarction complicated by cardiogenic shock (mean [SD] age at randomization, 66 [11] years; long-term follow-up of vital status, conducted annually until 2005, ranged from 1 to 11 years (median for survivors, 6 years).

Main Outcome Measures All-cause mortality during long-term follow-up.

Results The group difference in survival of 13 absolute percentage points at 1 year favoring those assigned to early revascularization remained stable at 3 and 6 years (13.1% and 13.2%, respectively; hazard ratio [HR], 0.74; 95% confidence interval [CI], 0.57-0.97; log-rank \( P = .03 \)). At 6 years, overall survival rates were 32.8% and 19.6% in the early revascularization and initial medical stabilization groups, respectively. Among the 143 hospital survivors, a group difference in survival also was observed (HR, 0.59; 95% CI, 0.36-0.95; \( P = .03 \)). The 6-year survival rates for the hospital survivors were 62.4% vs 44.4% for the early revascularization and initial medical stabilization groups, respectively, with annualized death rates of 8.3% vs 14.3% and, for the 1-year survivors, 8.0% vs 10.7%. There was no significant interaction between any subgroup and treatment effect.

Conclusions In this randomized trial, almost two thirds of hospital survivors with cardiogenic shock who were treated with early revascularization were alive 6 years later. A strategy of early revascularization resulted in a 13.2% absolute and a 67% relative improvement in 6-year survival compared with initial medical stabilization. Early revascularization should be used for patients with acute MI complicated by cardiogenic shock due to left ventricular failure.

Trial Registration clinicaltrials.gov Identifier: NCT00000552

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Figure 1. Study Flow

An intra-aortic balloon pump was used in 86% of patients assigned to each group. Median follow-up for 1-year survivors was 4.8 years (range, 1.0-10.7 years) in the initial medical stabilization group and 5.5 years (range, 1.0-11.1 years) in the early revascularization group. Detailed reporting of those not randomized is available elsewhere. The SHOCK trial design has been previously reported. The numbers screened and ineligible differ from those provided in the original report because 1 duplicate ineligible patient was discovered after publication of that report. CABG indicates coronary artery bypass surgery; PCI, percutaneous coronary intervention.

Statistical Methods
Survival times were calculated as the time from randomization to the time of death or last known follow-up. The Kaplan-Meier product-limit estimator and the log-rank test were used to analyze continuous survival time, and Cox proportional hazards regression modeling was used for testing the interaction of treatment assignment and subgroup factors, as well as for multivariable modeling of risk factors. A clinical model included readily available patient, MI, and shock characteristics, and a second-stage model added left ventricular ejection fraction (LVEF) and right heart catheterization data. When applicable, survival times were censored at the date of heart transplantation. Statistical analyses were conducted using SAS version 9.1 (SAS Institute Inc, Cary, NC) and SPlus version 6.2 (Insightful Corp, Seattle, Wash). P < .05 was considered statistically significant.

RESULTS
Patient Sample
The 302 patients were randomized at 29 international sites; 152 were assigned to early revascularization and 150 to initial medical stabilization (Figure 1). At randomization, patients were a mean (SD) of 66 (11) years old, 97 (32%) were women, and 98 (32%) had a history of MI. Patient characteristics were balanced between the 2 groups, except more patients in the stabilization group had undergone prior CABG surgery. Shock most often developed early after infarct onset (median, 5.5 [interquartile range, 2.3-14.1] hours). The characteristics of patients who did not undergo transplantation and were discharged alive following the shock hospitalization were balanced by treatment group, including with respect to long-term outcome of the SHOCK trial cohort.

METHODS
Trial Design
The SHOCK trial design has been previously reported. Briefly, patients with acute MI who developed cardiogenic shock due to predominant left ventricular failure within 36 hours of MI onset were eligible for the trial if their electrocardiogram showed ST-segment elevation or Q waves, posterior infarction, or new or presumably new left bundle-branch block. Randomization had to be accomplished within 12 hours of shock diagnosis. Strict clinical and hemodynamic criteria for shock were required. The trial enrollment period was April 1993 through November 1998. A long-term study funded by the National Heart, Lung, and Blood Institute in 2000 ascertained long-term vital and functional status, with 3- and 6-year mortality as specified end points. The study was approved by the institutional review board or ethics committee at all participating centers, and written informed consent was obtained from all patients or a surrogate prior to randomization. Patients randomized to a strategy of attempted early revascularization were required to undergo either percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) surgery as soon as possible and within 6 hours of randomization. Those randomized to initial medical stabilization were recommended to receive thrombolytic therapy (used in 63%) and allowed to have PCI or CABG surgery after 54 hours following randomization; revascularization was performed in 25%. Subgroup factors, with prespecified cutoff points for hemodynamic and shock timing variables, were prespecified in the protocol except for creatinine level, for which the upper quartile was compared with all others.

Data Collection Methods
One-year follow-up data were obtained for all patients; an updated vital status was obtained for all patients in 1999-2000 regardless of randomization date, and, for centers participating in the trial continuation, follow-up visits were conducted annually until 2005. Postdischarge vital status was obtained via telephone contact, review of medical records, and search of National Death Registries and the Social Security Death Index for US patients.
prior CABG surgery. Among hospital survivors, patients underwent follow-up for up to 11 years (median, 5.9 [interquartile range, 1.9–8.1] years); 3 patients (1 stabilization, 2 revascularization) underwent follow-up for only 1 year, and 15 additional patients (8 stabilization, 7 revascularization) underwent follow-up for less than 2 years at sites that did not participate in long-term follow-up.

Survival

The Kaplan-Meier curves (Figure 2) showed a significant difference in survival (P = .03), with a 13.1% (95% confidence interval [CI], 2.4% to 28.5%) and 13.2% (95% CI, −1.9% to 28.3%) absolute difference in survival at 3 and 6 years, respectively, favoring early revascularization. The hazard ratio (HR) for death for revascularization vs stabilization was 0.74 (95% CI, 0.57 to 0.97; P = .03). A disproportionate number of deaths occurred in the first year following cardiogenic shock in the stabilization group (26.4 per 100 patient-years) relative to the revascularization group (9.5 deaths per 100 patient-years), with annualized death rates of 8.0 and 10.7 deaths per 100 patient-years for the revascularization and stabilization groups, respectively, after the first year. The survival difference between treatment groups was nearly constant after 2 years.

Among hospital survivors, the annualized death rates for the revascularization and stabilization groups were 8.3 and 14.3 deaths per 100 patient-years, respectively (HR, 0.59; 95% CI, 0.36 to 0.95; P = .03) (Figure 2).

Risk Stratification and Subgroups

Multivariable modeling revealed that older age (HR, 1.23 per 10 years; 95% CI, 1.06 to 1.43; P = .007), shock on admission (HR, 1.68; 95% CI, 1.12 to 2.52; P = .01), creatinine level of 1.9 mg/dL (170 µmol/L) or greater (HR, 2.30; 95% CI, 1.56 to 3.39; P < .001), a history of hypertension (HR, 1.40; 95% CI, 1.03 to 1.91; P = .03), and noninferior wall MI location (HR, 1.50; 95% CI, 1.06 to 2.12; P = .02) were independent risk factors for lower survival rates in a clinical model (n = 230). A model that also incorporated hemodynamic measurements and LVEF (n = 148) demonstrated that only older age (HR, 1.25 per 10 years; 95% CI, 1.02 to 1.52; P = .04), lower LVEF (HR, 1.22 per 5%; 95% CI, 1.10 to 1.32; P < .001), creatinine level of 1.9 mg/dL or greater (HR, 1.96; 95% CI, 1.16 to 3.34; P = .01), and a history of hypertension (HR, 1.56; 95% CI, 1.04 to 2.35; P = .03) were independently associated with death.

Long-term survival analysis of the entire cohort identified no interactions between treatment assignment and any subgroup factor, including age (<75 vs ≥75 years), sex, diabetes, prior MI, hypertension, noninferior wall MI, transfer admission, shock timing (shock on admission vs delayed shock, shock < 6 vs ≥ 6 hours post MI), thrombolytic agent administered, clinical site location, presence or absence of rapid reversal of systemic hypoperfusion with use of an intra-aortic balloon pump, creatinine level (<1.9 vs ≥1.9 mg/dL), pulmonary wedge pressure (<25 vs ≥25 mm Hg), cardiac index (<2.0 vs ≥ 2.0 m/min per L2), ejection fraction (<25% vs ≥25%), presence vs absence of left main artery disease, and single-vessel vs multivessel disease.

Early Revascularization for Cardiogenic Shock

Among hospital survivors who were assigned to receive early revascularization, there was no significant difference (P = .51) in long-term survival between PCI and CABG surgery as the primary emergency mode of revascularization (7.0 and 9.3 deaths per 100 patient-years, respectively), despite differences in coronary anatomy and rates of diabetes.13

The association in the revascularization group between 1-year mortality and timing of revascularization from MI onset was examined as a continuous variable and using timing categories less than 4 hours post MI, in 2-hour increments thereafter, and 10 or more hours...
post MI. No statistically significant association was found due to small strata (11 patients per stratum, except for 99 patients at ≥8 hours), but 1-year mortality estimates increased from 0 to 8 hours and then decreased, presumably due to survivor bias (<4 hours, 36%; 4 to <6 hours, 55%; 6 to <8 hours, 82%; ≥8 hours, 48%).

COMMENT
A strategy of early revascularization resulted in a 67% improvement in 6-year survival in this randomized trial involving patients with MI complicated by cardiogenic shock due to predominant left ventricular failure. The large survival benefit (130 lives saved per 1000 patients treated, or 8 patients needed to be treated to save 1 life) was sustained throughout the follow-up period of up to 11 years. After 1 year, the survival curves remained parallel, with an annualized mortality rate of 8.0 vs 10.7 deaths per 100 patient-years for early revascularization compared with initial medical stabilization. These annual mortality rates are similar to those reported for a comparably aged broad cohort of post-PCI patients and a few percentage points higher than a large cohort of unselected post-MI patients. The overall long-term survival of patients with cardiogenic shock who survived the early period (30 days) in prior studies varies widely, ranging from 32% at 6 years to 55% at 11 years, and is related to the definition of shock, risk profile, and management of the cohort.

In this report, the clinical and MI factors that were independently associated with a higher long-term mortality rate, regardless of treatment assignment, are similar to those associated with death at 30 days in the SHOCK Trial and Registry. In a model that also incorporated hemodynamics and LVEF, the latter was strongly independently associated with both short-term and long-term outcome. However, hemodynamic variables measured close to shock onset that are highly predictive at 30 days (eg, cardiac index, cardiac power, stroke work, and systolic blood pressure while receiving support) were not associated with long-term outcomes. In general, variables we observed to be independently associated with long-term outcome after shock (age, LVEF, and serum creatinine level) have been consistently demonstrated to be similarly associated with long-term outcome in patients with a variety of cardiovascular disease presentations.

The better long-term survival with early revascularization was remarkably consistent among multiple subgroups. The previously reported differential treatment effect at 1 year for the elderly patients (≥75 years) was no longer statistically significant. The findings at 1 year appear to be due to an imbalance that occurred by chance; ie, the elderly patients assigned to medical stabilization had a higher baseline ejection fraction than those assigned to early revascularization, and they also had an associated high survival rate, similar to patients younger than 75 years who were assigned to medical stabilization, despite the powerful prognostic importance of age. Furthermore, the larger nonrandomized SHOCK Registry demonstrated a markedly lower adjusted risk of in-hospital mortality for those aged 75 years or older (n=257) who were clinically selected to undergo early revascularization. Other large registries have shown similar results. The revised American College of Cardiology/American Heart Association ST Elevation MI guidelines indicate that primary or rescue PCI or CABG surgery is reasonable for selected patients aged 75 years or older with cardiogenic shock (class IIa recommendation).

The survival benefit of urgent revascularization is similar for patients who develop shock late after MI and those with early shock. Furthermore, there was benefit of revascularization throughout the SHOCK trial enrollment time window, which included up to 48 hours post MI and 18 hours post-shock onset. The current data are consistent with prior studies of time to reperfusion in acute MI with or without shock, which demonstrate a strong survival advantage for earlier reperfusion, although we did not observe a statistically significant relationship. This is likely due to inherent selection bias, with the limited cohort size and more stable patients surviving to undergo later revascularization.

Our data demonstrate that the substantial survival benefit for early revascularization of patients with cardiogenic shock is maintained over long-term follow-up. These data therefore lend further support to the need to identify quickly all patients with cardiogenic shock who are candidates for early revascularization, as recommended in the guidelines. Early revascularization has been increasingly used in recent years in tertiary care centers, but only approximately 60% of those younger than 75 years received it in these select US centers in 2004. Furthermore, the rate of transfer of patients with cardiogenic shock out of hospitals that cannot perform revascularization is 38% and did not change from 1998-2001. The rate of revascularization for shock in Global Registry of Acute Coronary Events hospitals was only 43% from 1999-2001. These rates of revascularization are too low in light of the current study's finding of the striking durability of treatment effect.

Limitations
One limitation of this analysis is the shorter follow-up period of patients from SHOCK centers that did not participate in the long-term follow-up component conducted from 2000 to 2005. However, all but 2 centers (3 patients) completed a vital status confirmation in 1999 regardless of randomization date, and only 18 patients had follow-up less than 2 years. The use of the Social Security Death Index may have led to overestimation of the long-term event rate, since patients lost to follow-up who did not appear in the index were recorded as alive only as of the date last seen at or contacted by the SHOCK center. We have limited information on the use of very late (ie, after hospital discharge) revascularization and implantable cardioverter-defibrillators.
CONCLUSIONS
Patients with cardiogenic shock complicating ST-segment elevation MI undergoing early revascularization with PCI or CABG surgery have substantially improved long-term survival compared with patients undergoing initial intensive medical therapy followed by no or late in-hospital revascularization. These data further underscore the need for direct admission or early transfer of patients in cardiogenic shock to designated tertiary care shock centers with demonstrated expertise in acute revascularization and advanced intensive care of these high-risk patients.

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