Cardiogenic shock is still the commonest cause of death in patients with myocardial infarction, and its incidence has remained unchanged for the past 25 years[1]. In the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO-I) Trial, cardiogenic shock occurred in 7.4% of patients treated with fibrinolytic therapy, accounting for 58% of deaths within 30 days[2]. In the Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO)-III Trial, shock occurred in 5.4% of patients.

In the 1960s, successful therapy for cardiogenic shock was defined as recovery from shock and being off pressors for 24 h[4]. In the early 1970s, the definition was changed to survival of sufficient quality that patients were able to leave hospital alive. Now our horizons are shifting towards long-term survival and quality of life.

Prior to 1990, patients with cardiogenic shock had a hospital mortality rate of 70–85%, but a registry from Worcester, Massachusetts (a community of approximately 450,000 people) has recently reported a reduction in hospital mortality from 80% between 1975 and 1990 to 60% in 1995–7[1]. The definition of shock was unchanged over the course of this study. The improvement in survival was associated with increases in the use of fibrinolytic therapy (from 0% to 25%), intra-aortic balloon counterpulsation (from 5% to 42%), percutaneous coronary interventions (from 0% to 42%) and coronary artery bypass surgery (from 0% to 14%). There are no data available as to whether in more recent years these treatments were administered at an earlier stage in the development of cardiogenic shock, and in the absence of randomized trial data, it is not known how much changes in practice might have contributed to the improvement in survival of patients with cardiogenic shock.

Many non-randomized studies have reported that mortality from cardiogenic shock was lower in patients treated with revascularization procedures than in those managed medically[5]. However, the patients selected for revascularization usually had more favourable baseline characteristics than those who did not undergo angiography. For example, in the GUSTO-I Trial, patients with cardiogenic shock who had angiograms had a 30-day mortality rate of 38% compared with 68% in those who did not have angiograms[2]. In addition, patients who died before intervention could be performed were often either excluded from these analyses or included in the conservative-treatment group.

Previous commentators have considered it unlikely that randomized trials could be performed in very sick patients with cardiogenic shock[4], but two such trials have recently been reported.

The Swiss Multicenter Evaluation of Early Angioplasty for Shock Following Myocardial Infarction (SMASH) Trial[6], which randomized patients developing shock within 48 h of the onset of myocardial infarction, was stopped because of recruitment failure after only 55 patients had been enrolled in nine European sites over a period of 4 years. Sixty-nine percent of the 32 patients randomized to percutaneous coronary intervention and 78% of the 25 patients randomized to medical therapy died within 30 days (risk ratio 0.88, 95% confidence interval 0.6–1.2).

The results of the only completed trial, the Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock (SHOCK) Trial, have recently been published[7]. Between 1993 and 1998, 302 patients with cardiogenic shock due to left ventricular dysfunction following acute ST-elevation myocardial infarction (patients with posterior infarcts were also eligible) or new left bundle branch block myocardial infarction were randomized to emergency revascularization (either percutaneous coronary intervention or surgery) or initial medical stabilization. In the latter group, revascularization was permitted if clinically indicated at a minimum of 54 h after randomization. Cardiogenic shock was defined as a systolic blood pressure of ≤90 mmHg lasting 30 min, or a need for vasopressors to maintain the blood pressure above 90 mmHg. Evidence of end-organ hypoperfusion, low cardiac output and elevated filling pressures were also required. Patients with shock due to mechanical causes were excluded. Intra-aortic balloon pumping was recommended for all patients. Fibrinolytic
therapy was recommended for the medical stabilization group, but not for the revascularization group unless angiography was to be delayed. The patients were randomized at a median of 11 h after myocardial infarction. It is noteworthy that percutaneous revascularization was performed at a median time of 54 min after randomization and surgery at 2.7 h.

The number of patients enrolled in the trial was based on a projected, clinically relevant, absolute mortality reduction of 20%. This estimate seemed reasonable given that observational studies had reported possible mortality reductions of 30% with percutaneous coronary interventions. At 30 days, 47% of the revascularization group and 56% of the medical stabilization group had died (an absolute difference of only 9%, \( P = 0.11 \)). However, at 12 months the mortality rates had risen to 53% in the revascularization group and 66% in the medical stabilization group (\( P = 0.025 \)), equivalent to 130 lives saved by revascularization per 1000 patients treated.

The relatively low mortality rate in the medical stabilization group may have been due to the aggressive treatment used, as 63% received fibrinolytic therapy, 86% intra-aortic balloon pumping, and 25% delayed revascularization, but the contribution of fibrinolytic therapy and intra-aortic balloon pumping in this regard is not clear. Fibrinolytic therapy has not been shown to improve outcomes in patients with cardiogenic shock, although it did improve survival in patients with hypotension in the Fibrinolytic Therapy Trialists’ (FTT) overview. An observational study showed that the availability of intra-aortic balloon pumping increased both hospital survival (46% vs 19%) and 1-year survival (38% vs 10%)[11], and a combined analysis of the GUSTO-I and GUSTO-III Trials showed that the use of intra-aortic balloon pumping in patients with cardiogenic shock was associated with a lower mortality rate (45% vs 58%, \( P = 0.001 \))[12].

In the SHOCK Trial, the percutaneous coronary intervention success rate (defined as \( \leq 50\% \) stenosis and improvement of 20% and Thrombolysis in Myocardial Infarction (TIMI) grade 2 or 3 flow) was 77% in patients randomized to early revascularization, similar to the rates reported from previous observational studies of cardiogenic shock[8]. The mortality rate correlated with the success of the procedure. By 30 days, 46% of all patients undergoing interventions, 38% of those undergoing successful interventions, and 34% of those with TIMI-3 flow after the intervention had died. At 12 months the mortality rate in all patients who had undergone percutaneous intervention was 51%.

The choice of revascularization in the SHOCK Trial was individualized, with percutaneous interven-
life support at 30 days, and assessment at this time-point would not give a good indication of longer-term benefit or quality of life. In addition, the long-term benefits of revascularization are partially offset by the risk of early death associated with the interventions themselves. In patients undergoing percutaneous intervention for single-vessel disease, there may not be much of an increase in early hazard, whereas in patients undergoing surgery there are the added risks of general anaesthesia and cardiopulmonary bypass\(^\text{(16)}\). Mortality at 1 year might have been a more suitable primary end-point for the SHOCK Trial, given the substantial benefits seen in the revascularization group at this timepoint. It will be interesting to see the results of longer term follow-up.

Second, what is the mechanism of benefit? In patients randomized to revascularization in the SHOCK Trial, echocardiography suggested that left ventricular function improved after revascularization\(^\text{(17)}\). In addition to preservation of left ventricular function, there are long-term benefits associated with patency of the infarct-related artery, such as decreased arrhythmogenesis and the potential for provision of collateral blood flow to another infarct zone in the event of reinfarction\(^\text{(18)}\).

It would be helpful to identify patients likely to develop shock so that treatments that might be beneficial could be instituted prior to the downward spiral of end-organ hypoperfusion. An algorithm has been developed to predict the occurrence of shock after the administration of fibrinolytic therapy\(^\text{(19)}\). The major predictive factors are age (the risk of shock increases by almost 50% for every 10 years), heart rate, systolic blood pressure, and Killip class (hazard ratio 2·95 for class III vs class I), with age and physical findings providing >85% of the information. Using this scoring system, patients at greater risk of developing shock (e.g. >30%) can be identified. Other factors which have been shown to increase the risk are female sex, prior angina, prior stroke, peripheral vascular disease\(^\text{(20)}\), diabetes mellitus and larger infarctions\(^\text{(21)}\).

Physical examination is very useful in determining the risk of a poor outcome in patients with cardiogenic shock. Tachycardia, cold clammy skin, altered sensorium and oliguria are better predictors of mortality at 30 days than the baseline systolic blood pressure, which may initially be maintained\(^\text{(22)}\).

Patients with cardiogenic shock may go through a period of pre-shock with non-hypotensive peripheral hypoperfusion\(^\text{(23)}\). These patients have a high 30-day mortality rate (43% in the SHOCK Registry), and need to be identified quickly as the majority will go on to develop hypotension and the full shock syndrome. Early recognition and treatment may therefore lead to better outcomes.

When hypotension develops, tissue perfusion is impaired. This causes left ventricular dysfunction, which impairs tissue perfusion even more, and a vicious cycle is thus induced. As tissue perfusion falls, local tissue metabolites accumulate, and hypoxia ensues. Stunned myocardium after reperfusion is responsive to inotropic stimulation with dopamine\(^\text{(24)}\), and the vicious cycle can be interrupted by increasing the systolic blood pressure.

Seventy percent of the patients randomized to angioplasty during the last 2 years of the SHOCK Trial had stents deployed, and 59% received adjunctive abciximab, both of which may increment the benefits of revascularization\(^\text{(25)}\). Platelet glycoprotein IIb/IIa antagonists may increase microvascular flow\(^\text{(26,27)}\), and their use during angioplasty has been shown to improve clinical outcomes in patients with shock\(^\text{(28,29)}\). In the Platelet Glycoprotein IIb/IIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) Trial of patients with non-ST-elevation acute coronary syndromes, epifibatide treatment did not affect the incidence of shock, but did reduce the mortality of patients with shock from 73·5% to 58·5%\(^\text{(30)}\). Another study of patients with cardiogenic shock undergoing primary angioplasty found that the use of stenting and abciximab reduced the incidence of death, myocardial infarction or target vessel revascularization\(^\text{(59)}\).

What is perhaps not well appreciated is that most cardiogenic shock patients who survive the first few days are still alive with a reasonable quality of life at 1 year. In GUSTO-I, 88% of 30-day survivors with cardiogenic shock were alive at 1 year\(^\text{(42)}\). In the SHOCK Trial, 81% of 30-day survivors were alive at 1 year, and 87% of 1-year survivors were in New York Heart Association class I or II\(^\text{(31)}\). The SHOCK Trial data should encourage a more aggressive approach to the management of patients with cardiogenic shock. The SHOCK Registry shows that the patients randomized in the trial were representative of the broad population of patients with cardiogenic shock. The standards of surgery and angioplasty were high in this trial, and these results can therefore be extrapolated to experienced centres.

On the basis of the SHOCK Trial, the 1999 American College of Cardiology/American Heart Association Guidelines for the management of acute myocardial infarction rate percutaneous coronary intervention as a Class I recommendation for the treatment of cardiogenic shock (evidence for effective treatment), and surgery as Class IIa (weight of evidence is in favour of efficacy)\(^\text{(32)}\).

Although the outcomes of patients with shock have improved, the early signs of shock too often go
unrecognized. Efforts must be made to encourage early presentation of patients with symptoms of infarction, and the door-to-needle or door-to-balloon time must be minimized. The earlier treatment is obtained, the better the outcome. Several studies have reported that the incidence of shock was reduced by fibrinolytic therapy[33,34], but it is disappointing that the outcome of patients with shock has not been improved by the newer fibrinolytic agents[3]. However, more effective fibrinolytic strategies incorporating adjunctive IIb/IIIa antagonists[35] or antithrombin agents[36] may reduce the incidence of shock and improve the outcome of shock patients. Surprisingly, angioplasty has not reduced the incidence of shock compared with administration of accelerated tissue plasminogen activator[37].

The management of shock patients should include a combined, fast-acting strategy to raise blood pressure, improve haemodynamics, and rapidly restore blood flow, which is crucial to the preservation of myocyte function and survival. Future approaches may involve metabolic support with fluosol, glucose, insulin or potassium, reduction of the infarct size and/or reperfusion damage with magnesium, LNMA (a nitric oxide synthase inhibitor), N-acetylcysteine, Na/H+ pump inhibitors, or treatments limiting the inflammatory response with anti-CD-18 monoclonal antibodies or P-selectin antibodies, and improved mechanical support, perhaps with a view to cardiac transplantation in the longer term.

Cardiogenic shock remains a major problem worldwide. Many resources are consumed in caring for patients with cardiogenic shock, and aggressive treatment is expensive. There are some patients for whom such measures are futile, and clinicians must continue to judge when it is better to opt for conservative management with compassionate care. The SHOCK Trial provides strong support for the incorporation of early revascularization into the treatment of most other shock patients.

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References


