The cumulative evidence base informing almost every aspect of myocardial infarction acute coronary syndrome care (ACS) is expansive and has been associated with a decline in the rate of mortality. Within the context of current-era clinical trials of ST-segment elevation myocardial infarction, 30-day mortality rates of 4–5% have now been reported for high-risk individuals with similar rates reported among the non-ST-segment elevation ACS populations. However, large observational studies still report substantially higher rates of in-hospital death than those observed in these studies. Furthermore, recent clinical trials with novel treatment approaches have not provided further reductions in mortality or recurrent ischemic outcomes and have seen a shift in focus toward improved alternate outcomes such as bleeding. Have we reached a ceiling in ischemic outcomes and have seen a shift in focus toward improved approaches? Do we need to look beyond the questions of therapeutic innovation to provide further reductions in mortality from myocardial infarction?

While early clinical studies evaluating the efficacy of aspirin, reperfusion therapy, and angiotensin-converting enzyme inhibition demonstrated the substantial clinical benefits of these agents in terms of mortality, more modest reductions in events observed in recent trials have led to a greater reliance on non-fatal clinical events and composite end-points. For example, placebo-controlled studies of fibrinolysis and percutaneous coronary intervention (PCI) provided approximately 5% absolute risk reductions in 30-day death, while more recent attempts to refine approaches to reperfusion with bolus fibrinolytic agents and improved anti-platelet and anti-thrombin therapies have not led to mortality reductions. Also, attempts to couple a fibrinolytic and emergent PCI within a facilitated PCI strategy have not been associated with further reductions in mortality despite the hope for both earlier and more sustained reperfusion. The ASSENT-4 (Assessment of the Safety and Efficacy of a New Thrombolytic Agent) study randomized 1,667 patients to receive tenecteplase or tenecteplase and emergent PCI. Patients randomized to receive tenecteplase and emergent PCI experienced greater in-hospital mortality than those receiving tenecteplase alone (6% versus 3%; p=0.0105), with associated higher rates of intracerebral bleeding, re-infarction, and urgent revascularization. More novel approaches aimed at reducing mortality following myocardial infarction such as suppressing the inflammatory response via the compliment pathway have also failed to reduce mortality. In the APEX (Assessment of Pexelizumab in Acute Myocardial Infarction) study of 5,745 patients, those randomized to pexelizumab had no benefit for 30-day death (pexelizumab 4.06% versus placebo 3.92%; p=not significant).

Similar observations can be made in the trials in non-ST-elevation ACS. While trials of invasive versus conservative approaches suggest overall benefits of an early invasive approach, these benefits are largely in terms of reducing recurrent ischemia or myocardial infarction, rather than death. Furthermore, these benefits have not been consistently seen in all studies. Attempts to extend the benefit of the invasive strategy to patients with occluded arteries without symptoms of angina in the Open Artery Theory (OAT) study demonstrated no benefit in terms of reduced mortality (four-year mortality: PCI 9.1% versus conservative 9.4%; p=not significant) and a trend for an excess in recurrent myocardial infarction (PCI 6.9% versus 5.0%; p=0.08). Likewise, refinement of percutaneous revascularization in acute infarction with drug-eluting stents has been associated with reduced rates of repeat revascularization, but no reduction in mortality, and more recent registry data suggest an increase in late mortality with the broader implementation of this technology. Consequently, at least in the near-term, it is unlikely that mortality from myocardial infarction will be further substantially reduced by innovations in pharmacological or device therapy.

However, opportunities for the reduction of morbidity and mortality from myocardial infarction remain. Several registries spanning US and European clinical practice have documented the incomplete application of evidence-based therapies among patients presenting with acute coronary syndromes. Observations from these registries demonstrate an association between the application of clinical guidelines-advocated therapies and improved survival. At a hospital level, observations among 64,775 patients
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Abstract Submission
30 May 2007

Early Fee Registration
3 October 2007

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7 November 2007

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Heart Failure

drawn from 350 US centers showed that higher rates of adherence to guidelines correlated with lower rates of in-hospital mortality.1 At the patient level, a clear gradient of increasing mortality risk can be observed among patients with acute coronary syndromes discharged on fewer evidence-based secondary prevention therapies. In a study of 1,385 patients, being discharged on all guidelines-advocated therapies was associated with a 10-fold lower risk of mortality by six months compared with the risk in those discharged on none (odds ratio (OR) 0.10, 95% confidence interval (CI) 0.03–0.42; p<0.0001).12

Early non-compliance with evidence-based therapy is also associated with substantial excess in mortality and morbidity. Within a US registry of 1,521 patients with myocardial infarction, discontinuation of beta-blockers, statins, or aspirin occurred in 34% of patients by 30 days. In multivariable modeling, therapy discontinuation of these agents was associated with a hazard ratio of 3.81 (95% CI 1.88–7.72).13 Observations from the same registry showed that among patients undergoing PCI with drug-eluting stents, cessation of clopidogrel by 30 days was associated with a nine-fold increase in late mortality (7.5% versus 0.7%; p<0.0001). These potential gains in survival associated with improved ‘quality of care’ substantially exceed the potential benefits expected from refinements in drug and device therapy for the treatment of myocardial infarction.

Within these inclusive observational registries, a clearer representation of the heterogeneity of the clinical risk of patients presenting with myocardial infarction is evident. Evidence from the Global Registry of Acute Coronary Events (GRACE) study not only demonstrated that the subset of patients enrolled within clinical trials experience a lower risk of mortality compared with eligible but not enrolled patients, but also that those not considered eligible experience an approximately 2-fold excess risk of mortality after adjusting for baseline clinical and treatment differences.14 These findings highlight the fact that there are important under-represented groups within our evidence base. These groups include patients over the age of 75 years, patients with reduced renal function, and racial minorities.15,16 Importantly, not only are these patients associated with increased risk, but several analyses now document that the increased risk is associated with a decrease in the use of proven evidence-based therapies.17,18 Hence, a more complete understanding of the determinants of the ‘high risk/less therapy’ paradox is urgently required.

These observations highlight the need for more objective and effective care systems for the timely and more complete provision of clinical care in the management of patients presenting with myocardial infarction. In contrast to innovations and refinements of pharmacological agents, extending the already robust evidence base of current care to underserved groups and improving compliance with these therapies is more likely to provide substantial gains in survival given the high early and late event rates seen among these patients.

Several initiatives in this regard have been conducted. These include the Guideline Applied in Practice (GAP) and Get with the Guidelines programs.19,20 These programs seek to embed tools designed to increase the application of guidelines within clinical practice, as well as foster local champions for the process. Such programs have been shown to be associated with improvements in the prescription of evidence-based medicines and reductions in mortality. For example, in the GAP program, a standardized discharge tool was associated with a substantial reduction in one-year mortality (OR 0.53; 95% CI 0.36–0.76; p=0.0006).21 While these efforts are encouraging, more widespread application and evidence of efficacy is required. Furthermore, the determinants of poor compliance and evidence application are incompletely characterized, although evidence in this regard continues to emerge.22–24 Clearly, these factors are multifactorial and influenced by patient, physician, and healthcare system characteristics.25–28 Consequently, the capacity to limit missed opportunities in order to maximize the survival gains promised by the current evidence base depends on specific local solutions. Likewise, the resources required to adequately address these issues remains unclear and the cost-effectiveness of such initiatives requires further exploration. The potential improvements in outcome associated with improved systems of care may be large. This highlights the importance of assessing the effectiveness of such programs with the same rigor as that utilized in clinical trials of innovative therapies in order to permit accurate quantification of the incremental costs and benefits. Formal cost-effectiveness evaluation would be of value in order to focus healthcare resource allocation.

Coupled with the need for improved health promotion strategies aimed at encouraging earlier presentation to hospital, specific local programs facilitating implementation and ongoing compliance with life-saving evidence-based therapies offer a substantial capacity to reduce mortality. While current innovations in devices and therapies promise to improve the ease and safety of clinical care, programs that focus on the ‘last mile’ of delivering the evidence to individual patients present a substantial opportunity for mitigating the mortality associated with myocardial infarction.