Myocardial Infarct
No One Size Fits All
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Myocardial infarction (MI) connotes an appropriate sense of urgency to both healthcare workers and the lay community. The heightened risk of death in the period immediately after the acute coronary event makes MI a medical emergency in which response times are measured in minutes. Clinical signs, symptoms, and electrocardiographic evaluations currently are supplemented by highly specific cardiac markers that detect even minor amounts of myocardial necrosis: the pathonomia of MI. Indeed, major components of the roots of the subspecialty of cardiology can be traced to the concentration of resources and expertise derived from the establishment of coronary care units and studies of MI.

In many respects, the millions of patients worldwide admitted to coronary care units for suspected acute MI are the fortunate ones, because out-of-hospital sudden death is an all too common heralding event. Those presenting to a hospital have the benefit of 40 solid years of cumulative medical advances. The ability to externally defibrillate what were previously fatal arrhythmias provided tangible immediate proof of the value of coronary care units. Moreover, the development of specialty nursing and the ability of nurses to deliver external defibrillation without awaiting physician directives have saved untold number of lives.

Another major quantum improvement in acute infarct care came from the use of basic physiological principles of understanding and improving the balance between myocardial oxygen supply and demand. In our view, the demonstration by Braunwald and colleagues that the extent of the loss of myocardium after coronary occlusion could be reduced by favorably manipulating this balance between oxygen supply and demand was the discovery that initiated modern acute MI management. This concept of infarct size limitation, or myocardial salvage, then provided the rationale for both β-blockade and prompt reperfusion strategies. These issues of limiting infarct size highlighted the necessity of reducing both the time to presentation and the time to the initiation of lifesaving therapies.

International clinical trials soon translated these concepts into lifesaving alterations in medical practices. Modern acute MI care requires the use of multiple therapies and modalities. The potential improvements in outcomes for a new treatment must be additive to the present accepted practices. The Second International Study of Infarct Survival (ISIS-2) was a rare double-advance study demonstrating 35-day survival benefits of the early use of the thrombolytic streptokinase, as well as the independent benefits of aspirin. Their 2×2 factorial design provided a vivid example that the concomitant use of both therapies was superior to either of the single active agents.

When angiotensin-converting enzyme (ACE) inhibitors were undergoing intensive clinical investigation in MI, β-blockers already had been proved effective, and the lifesaving value of thrombolytics and aspirin were becoming established. As a consequence, there were sufficient data to show that the reduction in risk of death with the use of ACE inhibitors could be demonstrated in the presence or absence of these other proven therapies. This use of an ACE inhibitor was considered of additive value, receiving and sustaining an American College of Cardiology/American Heart Association Class I recommendation that “there is evidence and/or general agreement that [ACE inhibitor treatment] is beneficial, useful and effective” in patients with anterior ST-elevation MI, clinical heart failure, and/or left ventricular ejection fraction ≤ 40% in the absence of known contraindications. A Class IIa recommendation “weight or evidence/opinion in favor of usefulness/efficacy” was provided for all other patients with MI without contraindications.

The cumulative advances in recognition and prompt treatment with multiple therapies have resulted in gratifying temporal trends of reduction in mortality from MI. These outcome improvements have been confirmed from national and international registries. In all of these assessments, it is clear that the risks of death or major recurrent cardiovascular events are not uniformly distributed across patients with MI. This heterogeneity of risk in acute MI has been illustrated in the foundation studies of MI risk assessed by pioneers such as Peel, Norris, and Killip. To characterize risk, key demographic factors such as age and concomitant medical prob-

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DOI: 10.1161/01.CIR.0000020729.75885.39
lems are considered, along with descriptions of the MI (size, electrocardiograph location) and physical signs of adequacy of perfusion and pulmonary congestion. Those patients that manifest with hypotension and pulmonary congestion (cardiogenic shock) continue to have an exceedingly high mortality. Even in the absence of cardiogenic shock, any signs or symptoms of pulmonary congestion during the MI greatly augment the risk of death. More recent clinical trial experiences have continued to confirm the additive importance of age, concomitant medical conditions, and features of the presentation of the infarct in the assessment of overall risk. Additional evidence obtained from a quantitative measure of left ventricular ejection fraction adds mightily to any prognostic index. Ingrained in most cardiologists’ minds is the inverse exponential relationship between low left ventricular ejection fraction and heightened cardiac mortality. In a recent study, a quantitative measure of right ventricular function provided supplemental prognostic information about the risk of death or the development of heart failure.

Clinical trials, however, by their very nature cover a more selective group than those in the overall population who suffer an MI. The National Registry of Myocardial Infarction (NRMI), a well-conducted registry used by Spencer et al in their article in this issue of Circulation, offers a more relevant view of the broader MI population presenting to the 1674 participating hospitals. The objective of that article was to define the proportion of patients presenting with acute MI who demonstrated signs and symptoms of pulmonary congestion and to quantify the clinical impact (risk of death) of this complication of MI. Although this often is referred to as heart failure, we believe that there is an important distinction between an MI complicated by pulmonary congestion and the syndrome of chronic heart failure. With a database of >600,000 patients from the late 1990s, Spencer and coworkers further illustrated the heterogeneity of in-hospital survival on the basis of the development of pulmonary congestion. Even with the exclusion of patients with known heart failure before the MI and those presenting in cardiogenic shock, 185,817 of 616,159 patients (30.2%) manifested bibasilar rales or an S3 or pulmonary edema either at the time of presentation or during the hospitalization for the acute MI. The in-hospital case fatality rate for patients with MI in this group was 24.0% compared with 6.2% for patients with MI without acute heart failure features. Even after excluding those with cardiogenic shock and prior heart failure, >60% of all in-hospital deaths from MIs are concentrated in 30% of the population. It can be anticipated that the present results from NRMI, which use only in-hospital mortality, grossly underestimate the long-term morbidity and mortality risk associated with this complication of MI.

The importance of even transient rales as an independent multiplier of risk of death has been consistent across all large MI databases. The Global Registry of Acute Coronary Events (GRACE) enrolled patients with acute coronary syndrome from 94 hospitals across 14 countries. Once again, even after excluding cardiogenic shock or prior heart failure, signs of pulmonary congestion create an ominous complication, increasing the risk of in-hospital death (12% versus 2.9%, Killip 2 or more versus Killip 1, respectively). It is particularly interesting to note in this registry that in >4000 patients with a diagnosis of unstable angina that failed to evolve into a definitive MI by cardiac markers, the development of rales was still associated with a more than 4-fold risk for mortality (6.7% versus 1.6%, Killip 2 or 3 versus Killip 1, respectively).

This consistent information highlights the importance of even transient pulmonary congestion as a readily available bedside means of identifying higher risk patients. With the risk of not only in-hospital mortality but also long-term mortality and morbidity concentrated in these patients, it becomes essential to ensure that proper therapies and resources are allocated to these high event rate patients.

Quality clinical trials have underscored the potential hazards of extrapolating results from the overall population to this higher risk cohort. Quantitative and even directionally different results have been found with the same therapies in MI patients with and without features of pulmonary congestion. As stated, ACE inhibitors have greater relative and absolute life-saving benefits in higher-risk patients with either left ventricular dysfunction or pulmonary congestion. The Multicenter Diltiazem Postinfarction Trial (MDPIT) provided an even more vivid example of the heterogeneity of risk and responses to a therapeutic agent. Overall, the use of the calcium channel blocker diltiazem in the acute and chronic MI setting had a neutral effect on mortality. However, prespecified subgroups that identified the higher risk patients, such as those with transient signs of pulmonary congestion or anterior MI, identified groups that experienced a detrimental influence on survival with randomization to the calcium channel blocker. Although the interpretation of subgroup group analyses requires caution, this study showed a clear statistical interaction and internal consistency supporting the observation that the higher risk patients responded differently, and indeed adversely, to this therapeutic modality.

Although higher risk patients may demonstrate greater absolute benefits, they are also more vulnerable to harm. Therefore, we clearly need studies that specifically target the high-risk population. Along these lines, the Carvedilol Post Infarct Survival Control in Left Ventricular Dysfunction (CAPRICORN) study of the β-blocker carvedilol provides comforting data extending the previously proved benefits of β-blockers in patients suffering an MI to the acute heart failure subset. An additional advantage of this more current trial is the confirmation that the clinical benefits of β-blockers were proved with background therapy that included ACE inhibitors. Spencer et al, however, showed that β-blockers are particularly underused in patients with heart failure complicating MI.

The medical community will soon have the advantage of other major trial results from which to make important therapeutic decisions regarding inhibitors of the renin–angiotensin–aldosterone-system in this higher risk MI population. The Optimal Therapy in Myocardial Infarction with the Angiotensin II Antagonist Losartan (OPTIMAAL) study has nearly completed its follow-up evaluation of >5000 patients with MI and transient pulmonary congestion and/or anterior ECG location, to determine whether the previous survival improvement achieved with the ACE inhibitor captopril can
be “bettered” by the angiotensin-receptor blocker (ARB), losartan. This direct head-to-head comparison, which offers patients the prior advances of reperfusion therapies, aspirin, \( \beta \)-blockers, and statins, is determining which mode of inhibition of the renin-angiotensin is most effective. TheValsartan in Myocardial Infarction Trial (VALIANT) has completed enrollment with 14,808 patients with MI who had experienced signs, symptoms, or radiologic evidence of pulmonary congestion and/or a quantitative measure of depressed ejection fraction. This trial also specifically targets this higher risk group for randomization to either the proven ACE inhibitor captopril, the ARB valsartan, or the combination of captopril and valsartan in addition to modern conventional therapy. VALIANT has 2 prespecified, equally weighted comparisons to determine whether the use of an ARB alone or in combination with an ACE inhibitor can improve the survival of patients with a high-risk MI treated with a proven ACE inhibitor. Collectively, these 2 trials will clearly provide important answers regarding the most effective means of inhibiting the renin-angiotensin system in terms of the impact on mortality and major nonfatal cardiovascular events.

Another approach that is currently under investigation in this patient population is the EPVerenone’s neuroHormonal, Efficacy, and SUrVival Study (EPHESUS), which is evaluating a selective antagonist of the aldosterone receptor, eplerenone, in 6000 patients with heart failure complicating their acute MI. This study will test another pharmacological mode of more completely inhibiting the renin-angiotensin–aldosterone system by adding either eplerenone or placebo to standard care, which includes ACE inhibitors. Together, these 3 trials will provide new insights to the care of patients whose MI was complicated by signs and symptoms of pulmonary congestion.

Targeting patients with acute heart failure MI is an important strategy for further progress. As indicated by the registries, the morbidity and mortality is concentrated in this group, and any improvement would have substantial public health implications. These ongoing trials are excellent examples of accepting the challenge of trying to improve patient outcomes in addition to a background of other proven therapies. As trials accept this challenge, it is important for physicians to also accept the challenge of implementing the information that has already been generated from other well-executed clinical trials. All too often, registry and survey information indicates that many patients, especially the high-risk groups, are not receiving the benefits of already proven therapies. To continue the progress that has been made over the last few decades, we need a multiprong approach, new innovative research specifically targeting key populations, and appropriate use of the information that has already been generated. For the impressive progress to continue, there is no room for complacency. We must realize that the MI population is heterogeneous, and we must continue to better define high-risk groups and use appropriate therapies for specifically targeted patients.

References


**Key Words:** Editorials, acute myocardial infarction, coronary disease, trials, heart failure
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Circulation. 2002;105:2577-2579
doi: 10.1161/01.CIR.0000020729.75885.39

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