The intersection between acute coronary syndrome and heart failure

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There is a tremendous spectrum of disease severity within the diagnosis of myocardial infarction. The risk of major cardiovascular outcomes is highly related to age and concomitant medical conditions, as well as factors that characterize the extent of the myocardial infarction. Patients that develop pulmonary congestion with transient signs of heart failure and/or left ventricular dysfunction as measured by a reduced ejection fraction are generally at the high end of risk stratification. Prior studies have demonstrated that these patients derive particular benefit with the use of angiotensin-converting enzyme (ACE) inhibitors. The development of angiotensin-receptor blockers (ARBs) raises the question of whether this mode of inhibiting the renin–angiotensin system will be as good as or potentially even better than the ACE inhibitors. Unfortunately, the first major test of this concept in the Optimal Therapy in Myocardial Infarction with the Angiotensin II Antagonist Losartan (OPTIMAAL) study did not show a favourable trend for the ARB. The Valsartan in Acute Myocardial Infarction Trial (VALIANT) study is in its final phases of completion and is testing whether the use of the ARB valsartan either alone or in combination with captopril can improve survival over and above what is already achievable with the ARB. Since this patient population is at particularly high risk, even small relative improvements in clinical outcomes will have major public health implications.

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Introduction

The term ‘myocardial infarction’ (MI) represents a spectrum of severities. In some cases the abrupt loss of myocytes is so profound that the patient dies in overt cardiogenic shock either before or shortly after presentation, whereas in other instances even the diagnosis of MI is uncertain, requiring clinical suspicion and use of the most modern sophisticated biomarkers to confirm that some myocyte death has occurred. In the early days of the development of coronary care units, pioneering observations by Killip, Peel, Norris and others clearly distinguished outcome groups based on key clinical characteristics, including the degree of signs of acute heart failure. In their respective risk stratification systems, each underscored the adverse prognostic importance of the development of pulmonary congestion during MI. Haemodynamic monitoring using quadrants defined by combinations of low or normal cardiac index and normal or high pulmonary capillary wedge pressures clearly distinguished acute mortality risk profiles and demonstrated that an elevated pulmonary capillary wedge is a relatively common and worrisome complication of MI.

Although pulmonary congestion is generally associated with more extensive infarctions with acutely depressed ejection fractions, this relationship is far from consistent. Experienced clinicians anticipate problems with large MIs and maintain vigilance for complications from what...
appear to be smaller MIs, as assessed by biomarkers. Beyond the event of the acute infarction, patient characteristics that existed before the MI occurred contribute to the risk for experiencing pulmonary congestion. Clearly, the presence of a prior MI, previous heart failure and advanced age all contribute to a greater likelihood of manifesting pulmonary congestion or acute heart failure during MI. Other patient demographic factors, such as a history or presence of hypertension, diabetes or renal insufficiency, each independently and collectively enhance the risk for pulmonary congestion complicating acute MI. The extent and nature of coexistent coronary disease also plays a major role in the likelihood of manifesting pulmonary congestion.

Regional and discrete loss of myocytes resulting from an acute MI imposes increased stress on the remaining myocardium as it attempts to maintain adequate systemic perfusion. The presence of left main or multivessel coronary disease greatly compromises the compensatory reserve capacity of the non-infarcted regions. Other mechanical complications of MI, such as papillary muscle dysfunction leading to mitral regurgitation and ventricular rupture, are obvious multipliers of risk for developing acute heart failure and death. Although the extent of myocardial necrosis produced by MI is the most important modifiable feature of the MI that leads to acute heart failure, prior patient demographic factors, the magnitude of the coexistent coronary disease and other features of the MI all interact with the extent of myocyte necrosis to best define an individual's risk.

Current prognostic models for short-term survival consider patient demographic factors obtained from the history, such as age, sex, presence of a prior MI, diabetes, hypertension, smoking and prior cerebral vascular events. Physical findings at the time of presentation or during the infarct such as relative hypotension, presence of acute failure and increased heart rate are major contributors to this risk assessment. Characteristics of the infarct itself, such as the location as determined by ECG and the magnitude of abnormalities in biomarkers, factor importantly in modern scoring systems. These risk scores nicely illustrate the spectrum of risk for an acute MI. Indeed, using the Thrombolysis in Myocardial Infarction (TIMI) risk score for ST-segment elevation MI in a population of over 80,000 patients, 30-day mortality ranged from 1.1% to 30%. As indicated, these risks are not uniformly distributed across the MI population, and the use of these historical and demographic infarct features indicate that most deaths and, for that matter, other MI complications are concentrated in a minority of higher risk MI patients. Utilizing the National Registry of Myocardial Infarction database of over 185,000 patients from 1674 participating hospitals, it is possible to demonstrate that the in-hospital mortality is sixfold greater in the 30% of patients who manifest acute heart failure. Indeed, most in-hospital deaths in MI occurred in this important minority group manifesting heart failure.

**Angiotensin-converting enzyme inhibition**

Based on the findings of a series of international studies on use of angiotensin-converting enzyme (ACE) inhibition therapy in MI these agents were proven to confer survival benefits across a broad range of patients. However, the greatest relative and absolute reductions in mortality rates were observed in patients selected for heightened risk, such as those with left ventricular dysfunction and/or signs or symptoms of pulmonary congestion. In these patients, long-term ACE inhibitor therapy resulted in an approximate 50–70 lives saved per 1000 treated (Fig. 1). These improvements in outcome were found in the presence or absence of concomitant therapy with a beta-blocker, which was previously established as a therapy that improves survival in MI. However, most of the pioneering studies of beta-blockers in MI patients excluded this higher risk heart failure group with left ventricular dysfunction.
the use of beta-blockers in chronic heart failure,21,22 that a more definitive trial of high-risk MI patients was undertaken with a beta-blocker. The recent demonstration of clinical benefits in an acute MI heart failure population among those randomly assigned to a beta-blocker with concurrent ACE inhibition therapy solidifies the importance of using both classes of drug.23 Therefore, a practical conclusion is that both of these therapies are associated with a survival benefit and that concomitant use of both is preferred. For both of these therapies, the greatest relative and absolute survival benefits were achieved with long-term use in the higher risk patients.

Angiotensin receptor blockers

The development of a new mode of inhibiting the renin–angiotensin system at the angiotensin II receptor subtype 1 (AT₁) level provides an opportunity and, indeed, an obligation to evaluate the relative merits of this inhibitor compared with what can be achieved with a proven ACE inhibitor. From a theoretical point of view, use of an AT₁ inhibitor or angiotensin receptor blocker (ARB) offers an opportunity to provide more complete inhibition of the deleterious effects of angiotensin II.24 It is now well established that angiotensin II can be generated by non-converting enzyme pathways, and therefore blockade at this specific receptor could potentially provide more complete inhibition.25 The increasing evidence that the active angiotensin II can bind to other receptors such as AT₂ has led to the hypothesis that blocking the AT₁ receptor would result in more of the angiotensin II being available to stimulate the AT₂ receptor, which would add to the punitive actions and lead to cardiovascular benefit.26 Practically speaking, the available ARBs are effective antihypertensive agents and are well tolerated.27,28 It remains to be seen whether they will be comparable to ACE inhibitors in terms of the clinical benefits that can be achieved.29 In the MI field, two major trials have been undertaken to determine the relative merits of ACE inhibitors and ARBs. The first of these, the Optimal Therapy with Angiotensin II Antagonist Losartan (OPTIMAAL) was recently completed and reported.30 OPTIMAAL randomly assigned 5477 high-risk MI patients to receive either the proven ACE inhibitor captopril (titrated to a target dose of 50 mg three times daily) or the ARB losartan (titrated to a target dose of 50 mg day⁻¹). With over 900 deaths, that study provided an adequate test of the investigators’ major hypothesis, namely that treatment with losartan in selected, high-risk patients after acute MI will reduce all-cause mortality in comparison with captopril.31 There was no risk reduction achieved with losartan as compared with captopril, and indeed the relative risk for death was 1.13 (95% confidence interval 0.99—1.28; P=0.07) in favour of captopril.30 Losartan was well tolerated and other cardiovascular non-fatal events were similar between the two groups. It must be underscored that this was not a placebo-controlled trial and that all patients received active therapy (either ACE inhibitor or ARB). However, with the trend in survival favouring captopril, in the OPTIMAAL trial it is not possible to say that the outcomes of the losartan group were ‘as good as’ those of the captopril group and therefore presumably better than placebo. Although this outcome is disappointing in that it does not advance the care of our patients, many believe that the dose of losartan (i.e. 50 mg day⁻¹) was not sufficient to fully test the relative merits of ARB and ACE inhibitors.

The Valsartan in Acute Myocardial Infarction Trial (VALIANT) trial. Adapted from Pfeffer et al.32 CHF= congestive heart failure; LVD=left ventricular dysfuction; MI= myocardial infarction.
to be superior to captopril, then VALIANT is prospectively designed with a non-inferiority comparison to test whether the use of valsartan can be considered comparable to that of captopril and, therefore, superior to placebo.\textsuperscript{32}

As in OPTIMAAL, all VALIANT patients are on an active inhibitor of the renin–angiotensin system and no other limitations on concurrent medical therapy are imposed on treating physicians. Therefore, the overall intent is to determine whether the use of valsartan either in addition to captopril or as a replacement for captopril can lead to improvements in clinical outcomes. Although the trial was designed to address all-cause mortality, a concerted effort was made to determine the number of non-fatal major cardiovascular events in order to fully evaluate the influence of the ARB valsartan on cardiovascular outcomes in these high-risk patients.

Conclusion

The intersection of acute heart failure in the setting of MI defines a high-risk group that experiences a disproportionate number of fatal and non-fatal cardiovascular events. The OPTIMAAL and VALIANT studies were designed to determine whether an ARB could lead to an incremental improvement in prognosis among MI patients with heart failure or left ventricular dysfunction. The objectives of those studies are important in that any reduction in adverse cardiovascular events in these patients at the dangerous intersection of MI and heart failure would have major public health implications.

References


