The Challenge of Further Reducing Cardiac Mortality in the Thrombolytic Era

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An ever-growing proportion of patients with acute myocardial infarction undergo coronary thrombolysis; recent estimates indicate that in the United States, about 20% of the annual 700,000 patients with myocardial infarctions receive such therapy.¹ Even though thrombolysis reduces short-term mortality by approximately 20–30%,²–⁴ each year a large number of patients leave the hospital with a substantial residual risk of dying. Factors that determine prognosis after myocardial infarction and algorithms for risk stratification have been well established for the prethrombolytic era.⁵–¹⁰ However, it remains to be shown whether these predictors of outcome and risk stratification strategies also apply to the growing proportion of patients who have undergone thrombolysis, and if so, whether high-risk patients selected on the basis of such strategies may benefit from more intense medical or surgical treatment.

Identification of High-Risk Patients After Myocardial Infarction

In patients who do not undergo thrombolysis, many factors related to infarct size and residual left ventricular function have been shown to be major determinants of prognosis.¹¹–¹³ Residual myocardial ischemia, as determined by angina, recurrent infarction, or abnormal exercise testing, and the presence of multivessel coronary artery disease are other important predictors of outcome.¹⁴–¹⁶ Finally, in most studies¹⁷–²⁰ but not all studies,²¹,²² frequent or complex ventricular arrhythmias and occurrence of ventricular tachycardia on 24-hour ambulatory ECG recordings also have been shown by multivariate analysis to be independent predictors of death. The role of other factors such as late potentials, heart rate variability, and inducibility of arrhythmias in improving risk stratification after myocardial infarction is not definitely established. Studies using signal-averaged ECGs found that late potentials, which are thought to arise from areas of slow conduction and thus are a possible marker of the substrate for malignant ventricular arrhythmias, were associated with increased mortality.²³–²⁶ Decreased heart rate variability, reflecting reduced vagal tone and/or enhanced sympathetic activity, is also associated with a poor prognosis after myocardial infarction,²⁷,²⁸ and in some studies, programmed electrical stimulation has been found useful in predicting the occurrence of arrhythmias or arrhythmic death after myocardial infarction.²⁹,³⁰ Risk stratification based on a combination of such clinical criteria in the prethrombolytic era has been increasingly used in the management of patients with myocardial infarction. It allows identification of patients at low risk who may be followed conservatively and patients at high risk who may benefit from more intense therapy.

Effects of Thrombolysis

Information about predictors of outcome after thrombolysis is rapidly accumulating, and not surprisingly, many of the predictors of mortality established in the prethrombolytic era have been found to retain their value. For example, in the Thrombolysis in Myocardial Infarction (TIMI) IIb trial, clinical signs related to pump failure such as cardiogenic shock and pulmonary edema have been found to be major determinants of mortality,³¹ and recurrent ischemia, which may be seen even more commonly after thrombolysis, also remains associated with increased mortality.³² However, there has been little information regarding the value of ventricular arrhythmias as predictors of outcome in patients who have undergone thrombolysis. This was intriguing, since thrombolysis was found to be effective in reducing arrhythmias during the acute phase of myocardial infarction, and preliminary findings suggested that thrombolysis may lead to a decrease in overall frequency of arrhythmias³³,³⁴ and ventricular late potentials³⁵,³⁶ and may impair the inducibility of ventricular arrhythmias by programmed electrical stimulation,³⁷ a finding attributed to improved electrical stability.³⁸

Such beneficial antiarrhythmic effects of thrombolysis have been shown to be associated with patency of the infarct-related artery.³⁵–³⁷ The precise underlying mechanisms by which reperfusion may exert its beneficial effects on arrhythmogenic substrate remain unknown but may include reduced ischemia in the border zone of the infarct, favorable effects on electrophysiological properties of surviving cells and myocardial remodeling,³⁹,⁴⁰ and prevention of nonuniform myocardial responsiveness during sympathetic stimulation.⁴¹

In this issue of Circulation, Maggioni et al⁴² now report that the presence of ventricular arrhythmias on 24-hour ambulatory ECG recordings also retains its value as an independent predictor of mortality and sudden death after thrombolysis, even though the over-
all incidence of arrhythmias in such patients seems to be somewhat reduced compared with historical controls. These findings are in accordance with those of small preliminary studies, suggesting that after thrombolysis, the presence of late potentials on signal-averaged ECGs is a predictor of arrhythmic events and death.\textsuperscript{35,36} Therefore, the study of Maggioni et al adds strong evidence that criteria established in the prethrombolytic era retain their value for risk stratification and selecting a high-risk group of patients who have undergone thrombolysis and who may eventually benefit from aggressive medical or surgical treatment.

**How to Improve Survival After Thrombolysis**

In view of the continuing impact of left ventricular failure and residual ischemia on mortality after thrombolysis, new strategies aimed at further reducing infarct size and improving patency of infarct-related arteries may represent the most important tool to further improve survival in such patients. Trials using either adjuvant pharmacological treatments or early mechanical interventions are ongoing.\textsuperscript{43,44} In this regard, improved early thrombolytic treatment may well turn out to be the most efficient way to further reduce the incidence of postinfarction arrhythmias as well, because such treatment would be expected to result in further reduction of the arrhythmogenic substrate.

Whether treatment of ventricular arrhythmias per se in patients who have undergone thrombolysis will eventually improve survival remains unknown. Results of arrhythmia suppression trials conducted in the prethrombolytic era are disappointing and have cast doubt on the ability of antiarrhythmic treatment to reduce mortality after myocardial infarction.\textsuperscript{45,46} It is possible that these conclusions also will apply to patients who have undergone thrombolysis. One possible explanation for these findings is that ventricular arrhythmias are merely one of the many markers of ventricular damage but not the primary cause of death after infarction. The seemingly independent association between arrhythmias and death found in some clinical studies does not prove a cause-and-effect relation and could be related to the failure to introduce into the multivariate analysis adequate clinical markers of the extent of coexistent ventricular damage.\textsuperscript{45}

It is also possible, however, that in these trials, antiarrhythmic therapy has been useful to a few patients but deleterious to most others, leading to an overall negative result. If this hypothesis is true, the selective use of antiarrhythmic agents in a subgroup of high-risk patients who may truly benefit from such treatment might improve overall survival by avoiding exposure of patients with a good initial prognosis to potentially lethal proarrhythmic effects. Risk stratification strategies based on clinical criteria are therefore essential, and it is reassuring that predictors of arrhythmic events established in the prethrombolytic era retain their value in patients who have undergone thrombolysis.\textsuperscript{42} Whether invasive methods, such as programmed electrical stimulation, will help to further improve risk stratification in this setting remains to be established.

Finally, the efficacy of antiarrhythmic interventions in such a high-risk population of patients after myocardial infarction needs to be assessed in prospective trials. Are automatic implantable cardioverter defibrillators a safe and cost-effective alternative to drug therapy? Two prospective trials, the Multicenter Automatic Defibrillator Implantation Trial (MADIT) and the Multicenter Unsustained Tachycardia Trial (MUSTT), are currently under way to address this question. What is the potential role of class III antiarrhythmic agents for further reducing mortality? Based on recent observations of a potentially favorable effect of amiodarone in patients with persistent asymptomatic complex arrhythmias after myocardial infarction,\textsuperscript{47,48} large prospective studies with this agent in such patients are actually ongoing in Europe (European Myocardial Infarct Amiodarone Trial, EMIAT) and in Canada (Canadian Amiodarone Myocardial Infarction Trial, CAMIAT).

In the meantime, clinicians will still have to rely on β-blockers and anti thrombotic agents, the efficacy of which has been demonstrated in treating coronary patients with and without arrhythmias.

**References**


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