SURVIVAL AFTER ACUTE Q-WAVE MYOCARDIAL INFARCTION

Implications for Short- and Long-Term Management After the Acute Event

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During the last decade, the acute management of the patient with an evolving Q-wave myocardial infarction has changed dramatically. Intravenously administered thrombolytic therapy has been shown (a) to restore antegrade flow in the coronary artery occluded by fresh thrombus, (b) to improve left ventricular function in patients receiving it within 3 to 4 hours of the onset of chest pain, and, most importantly, (c) to reduce mortality in those treated within 24 hours of the onset of symptoms [1]. As the 1990s begin, we turn our attention to 3 issues, each of which may exert a marked effect on long-term survival in survivors of Q-wave myocardial infarction: (a) improved methods of giving the available thrombolytic agents and, at the same time, the development of newer -- and better -- agents; (b) administration of thrombolytic agents to patients who previously were not thought to be candidates for them; and (c) therapeutic strategies independent of thrombolytic therapy during the post-infarction period. My purpose today is to review the determinants of survival following acute Q-wave myocardial infarction and to examine the optimal management of survivors of Q-wave infarction -- treated conservatively or with thrombolytic therapy -- during the hours, days, weeks, and months after the acute event.

DETERMINANTS OF SURVIVAL FOLLOWING INFARCTION THAT CANNOT BE ALTERED IN THE POST-INFARCTION PERIOD

1. Functional Class at Hospital Presentation

The treatment of patients with acute myocardial infarction was altered substantially with the inception of the Coronary Care Unit in the 1960s. In this setting, ECG monitoring and the suppression of ventricular tachyarrhythmias led to a marked decline in fatal arrhythmic events. Such monitoring also provided an opportunity to assess the factors that influence prognosis after infarction. Peel et al [2] showed that prognosis for the 4 weeks after infarction was influenced by the patient's age, gender, history of ischemic heart disease, extent of ECG alterations, and the presence of shock, congestive heart failure, or rhythm and conduction disturbances. For each variable a numeric score was calculated, with a higher number signifying a more abnormal value. At the time of hospital admission, a total score was tabulated, from which the subject's mortality at 4 weeks was estimated. Although this so-called Peel index offered useful short-term prognostic information, it was too complicated for the practicing physician to use without referring to a written text.

In a study of 250 patients with acute myocardial infarction, Killip and Kimball [3] showed that the incidence of life-threatening arrhythmias and mortality were related to the extent of left ventricular dysfunction (Table 1, below). Thus, 36% of patients without congestive heart failure had life-threatening arrhythmias, and 6% died in hospital (class I); 46% of those with mild heart failure had arrhythmias, and 17% died (class II); 73% of patients with severe heart failure manifested life-threatening arrhythmias, and 38% died (class III); and 94% of those with cardiogenic shock had arrhythmias, and 81% died (class IV). This classification scheme became very popular, probably in large part because of its simplicity and ease of application.

Table 1

Morbidity and Mortality in Relation to Killip Class

Class	% with Life-Threatening Arrhythmias	% Mortality
I	36	6
II	46	17
III	73	38
IV	94	81

(From reference # 3)

Norris et al [4] used discriminant analysis in 757 patients with acute myocardial infaction to derive a so-called "coronary prognostic index." This index was constructed from numeric weightings of 6 variables: patient age, history of ischemic heart disease, ECG location of infarction, systolic arterial pressure, radiographic heart size, and extent of pulmonary congestion. As with the scheme of Peel et al [2], the Norris index required that each of the variables be given a numeric score, after which the scores were summed. With this index, the 757 patients were divided into several groups, with increasing mortalities from 3% to as high as 78%.

With the advent of thrombolytic therapy, recent attempts have been made to risk stratify patients with acute myocardial infarction in the Emergency Room immediately before the administration of a thrombolytic agent. In Phase II of the Thrombolysis in Myocardial Infarction (TIMI) Trial, 3339 patients with evolving Q wave infarction were treated with intravenous tissue plasminogen activator.

Before the initiation of therapy, the presence of each of the following "risk factors" was noted: (a) pulmonary edema or cardiogenic shock; (b) age ≥ 70 years; (c) female gender; (d) a history of diabetes mellitus; (e) a history of previous infarction; (f) ECG evidence of an evolving anterior infarction; (g) atrial fibrillation; (h) evidence on physical examination of moderate pulmonary congestion (rales heard in more than one-third of the lung fields); and (i) hypotension (systolic arterial pressure < 100 mm Hg) and sinus tachycardia [5].

Of the 3339 patients, 78 had pulmonary edema or cardiogenic shock; their mortality at 6 weeks was 33%. Of the remaining 3261 subjects, 864 (26%) had no risk factor ("low risk"). At 6 weeks, only 1.5% had died. In contrast, 2397 (74%) had one or more risk factors ("not low risk"); at 6 weeks, 5.3% had died. The mortality increased in stepwise fashion as the number of risk factors increased (Table 2, below). By logistic regression analysis, the risk factors that were associated most strongly with mortality at 6 weeks were (a) age ≥ 70 years, (b) hypotension and sinus tachycardia, and (c) anterior infarction.

Table 2

Mortality at 6 Weeks According to Number of Risk Factors Present

# Risk Factors	% Mortality at 6 Weeks
0	1.5
1	2.3
2	7.0
3	13.0
≥ 4	17.2

From reference # 5

In contrast to the Peel and Norris indices, these risk factors are easy to remember. One simply determines the presence or absence of each risk factor; it is not necessary to assign a numeric score to each variable. Their presence can be determined during the routine evaluation that precedes thrombolytic therapy within minutes of the patient's presentation. No waiting is required for the results of a chest radiograph or of hemodynamic data available only with invasive monitoring.

2. Patient Age

As noted, Peel et al [2] showed that prognosis for the 4 weeks after myocardial infarction was influenced by a number of factors, among them the patient's age. In formulating their coronary prognostic index, these investigators concluded that survival after infarction began to increase at age 55, steadily rising every 5 years to age 65. Norris et al [4] extended and refined these observations, stating that mortality with infarction began to increase at 50 years and continued to rise steadily with every decade.

More recently, the TIMI investigators demonstrated that patient age was the most important "risk factor" in those about to receive thrombolytic therapy: of the 374 patients in TIMI Phase II who were age 70 or older, the mortality at 6 weeks was 11.2% [5], substantially higher than that for the subjects below age 70. Other large trials have consistently shown that mortality increases substantially with patient age (Table 3, below) in those treated conservatively or with thrombolytic therapy [6,7].

Table 3

Mortality with Myocardial Infarction
According to Patient Age

Age (years)	% Mortality at 1 month	
	Controls	Streptokinase
≤ 65	7.7	5.7
66-75	18.1	16.6
> 75	33.1	28.9

From reference # 6

In short, survival after myocardial infarction is dramatically influenced by the patient's age. As age increases above 65 or 70 years, the mortality of infarction rises markedly.

DETERMINANTS OF SURVIVAL FOLLOWING INFARCTION THAT CAN BE POTENTIALLY ALTERED IN THE POST-INFARCTION PERIOD

1. Left Ventricular Dilatation/Remodeling and Residual Systolic Function

Several studies over the past 10 years have shown that prognosis following myocardial infarction is strongly related to residual left ventricular volumes and ejection fraction. In fact, some authors have argued that left ventricular function after infarction is the most important prognostic factor and that there is a curvilinear relation between ejection fraction and mortality [8]. More recent data offer the hope that the extent of chamber dilatation and systolic dysfunction can be altered favorably by angiotensin-converting enzyme inhibitors, such as captopril.

In a prospective angiographic study, Sanz et al [9] demonstrated that survival after myocardial infarction was most closely related to (a) left ventricular ejection fraction, (b) the extent and severity of coronary artery disease, and (c) the presence of congestive heart failure. In their analysis, the concomitant presence of a depressed ejection fraction and extensive multivessel coronary artery disease portended a very poor prognosis. Similar data concerning left ventricular ejection fraction were provided by Norris et al [10].

More recent angiographic data from over 600 subjects with myocardial infarction [11] have shown that left ventricular

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Table 4

Five Year Survival Following Myocardial Infarction According to Residual Left Ventricular Function

Variable		5 Year Survival
End-Systolic Volume	< 95 ml	94%
	95-130 ml	78%
	> 130 ml	52%
Ejection Fraction	≥ 50%	94%
	40-49%	83%
	< 40%	65%

From reference # 11

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end-systolic volume and, to a lesser extent, end-diastolic volume are even better predictors of long-term prognosis following myocardial infarction than is ejection fraction (Table 4, above). This landmark study was among the first to demonstrate that left ventricular dilatation after infarction identifies those at risk of a subsequent poor outcome, so that the prevention or limitation of dilatation -- accomplished by whatever means possible -- may be beneficial.

In a series of elegant studies in rats and, more recently, in patients with acute myocardial infarction, Pfeffer et al have characterized the course of left ventricular dilatation in the hours, days, and weeks after the acute event. These investigators have shown that the left ventricle begins to dilate within hours of infarction. In the acute phase, such chamber enlargement is caused primarily by expansion of the infarcted area. Over the ensuing weeks, the noninfarcted portion of the left ventricle dilates in an attempt to maintain forward stroke volume and to normalize diastolic filling pressure. If this dilatation of the noninfarcted left ventricle is sufficient, systemic hemodynamic function -- as reflected by forward stroke volume and diastolic filling pressure -- is restored toward normal. In rats following ligation of a coronary artery, captorpil attenuates this increase in left ventricular size [12] and improves survival 1 year after infarction [13]. In patients following anterior myocardial infarction, captopril, begun 12 to 31 days after the acute event, attenuates the progressive left ventricular dilatation that occurs with standard therapy [14]. As a result, left ventricular filling pressures are reduced, and exercise tolerance is improved.

At present, it is unknown if long-term therapy with captopril improves survival in patients with recent myocardial infarction. Nevertheless, <u>captopril should be given to all survivors of Q wave infarction if (a) the infarction is believed to have been large (anterior, lateral, or inferior with evidence of extensive necrosis) and (b) the patient can tolerate afterload reduction without becoming excessively hypotensive</u>.

2. Recurrent Myocardial Ischemia

Several studies have shown that survival during the year after myocardial infarction is reduced in those with spontaneous or provocable ischemia in the post-infarction period. Theroux et al [15] performed submaximal exercise

testing 1 day before hospital discharge in 210 consecutive patients after myocardial infarction. Of the 146 subjects in whom exercise did not induce ischemic ST segment alterations, only 3 (2%) died within 1 year; in marked contrast, of the 64 patients in whom exercise caused the appearance of ischemic ST segment changes, 17 (27%) died during the next 12 months ($p < 0.001$). Similar results have been reported in which exercise-induced ST segment alterations on a submaximal exercise test in the 1 to 3 weeks after infarction were used to identify patients with an increased risk of subsequent cardiac morbidity and mortality [16,17].

More recent studies have combined radionuclide or echocardiographic imaging with submaximal exercise in the post-infarction period to identify patients whose risk of subsequent cardiac events, including sudden death, is increased. Turner et al [18] demonstrated the utility of thallium-201 scintigraphy in detecting subjects with jeopardized myocardium or multivessel coronary artery disease 3 weeks after infarction, and Corbett et al [19] from this institution showed the superb utility of equilibrium gated blood pool scintigraphy with submaximal exercise in identifying patients at risk of death, recurrent infarction, or medically refractory angina during the 6 months after the acute event. In their analysis, a failure

Table 5

Sensitivity, Specificity, and Predictive Accuracy of Variables in Predicting Subsequent Cardiac Death

Variable	Sensitivity	Specificity	Accuracy
History of previous MI	75%	92%	89%
Anterior MI	50%	83%	79%
LVEF < 50% at rest	50%	96%	89%
ST depression with exercise	25%	92%	82%
Failure of LVEF to rise with exercise	100%	96%	96%
Increase in end-systolic volume with exercise	100%	96%	96%

from reference # 19

of left ventricular ejection fraction to increase or a clear-cut increase in end-systolic volume during submaximal exercise were extremely sensitive and specific in identifying those who sustained a cardiac event over the ensuing 6 months (Table 5, above). Several recent studies have reported similar findings with echocardiography during submaximal exercise [20-22].

All the studies cited above have shown that a "high-risk" subset of patients with recent myocardial infarction can be identified with submaximal exercise without or, preferably, with radionuclide or echocardiographic imaging. These patients are at increased risk of recurrent infarction, unstable angina, and/or sudden death during the months after infarction if they are managed medically. Since their long-term prognosis can be improved with aspirin [7], all survivors of Q wave infarction should receive low-dose (325 mg/day) aspirin, unless contraindicated. Although we assume that their poor prognosis with medical management can be improved with nonmedical intervention (angioplasty or bypass surgery), no controlled study has demonstrated this.

3. Extent of Coronary Artery Disease

Although some studies have found that the extent of coronary artery disease is a predictor of survival after myocardial infarction, others have failed to show that this variable alone influences the long-term outlook. Sanz et al [9] demonstrated that the extent of coronary artery disease was a predictor of survival, though left ventricular ejection fraction was substantially more important in this regard. In fact, the long-term outlook was superb in all patients with left ventricular ejection fractions > 0.50 regardless of the severity of coronary artery disease.

De Feyter et al [23] demonstrated that survivors of myocardial infarction with 3 vessel coronary artery disease were at increased risk of cardiac death during the 3 years after the acute event. Specifically, according to their data, the incidence of cardiac death within 3 years after infarction was 10% for patients with 1 vessel disease, 8% for those with 2 vessel disease, and 36% for those with 3 vessel disease ($p < 0.05$). Similarly, Roubin et al [24] showed that the extent of coronary artery disease predicted survival (Table 6, below), though their data precluded a meaningful analysis beyond 1 year.

Table 6

Survival After Infarction According to the Extent of Coronary Artery Disease

Survival at	1 vessel CAD	2 vessel CAD	3 vessel CAD
1 year	99%	92%	85% *
2 years	96%	92%	+
3 years	96%	92%	+

* $p < 0.005$ in comparison to 1 and 2 vessel CAD.

+ inadequate data available for meaningful analysis

From reference # 24

Other studies have failed to show that the extent of coronary artery disease influences survival after myocardial infarction [11].

In short, although some studies have demonstrated that the extent of coronary artery disease is a predictor of survival after infarction, none has shown this convincingly. Furthermore, no study has shown that the nonmedical treatment of multivessel coronary artery disease improves the long-term outlook in patients who have survived infarction.

4. Patency of the Infarct-Related Coronary Artery

There is growing evidence, much of it emanating from this institution, that the patency of the infarct-related coronary artery exerts a profound influence on survival in the weeks, months, and years after the acute event. It appears that this influence is largely <u>independent</u> of left ventricular function.

<u>Study # 1: In patients with disease of only the infarct-related coronary artery, does the patency of this artery influence long-term survival</u>? To address this question, we identified 179 patients who presented to Parkland Hospital from July, 1978, to December, 1987, with their first myocardial infarction [25]. Over the next 4 to 5 months,

they came to catheterization and were found to have disease of only the infarct-related coronary artery, with it being (a) patent (n = 64) or (b) occluded (n = 115). Only a few of these subjects received thrombolytic therapy, so that patency of the infarct-related artery in most of them was the result of "autolysis" of a presumably occlusive thrombus. The groups were similar in age, gender, risk factors for atherosclerotic cardiovascular disease, maintenance medications, and -- most importantly -- left ventricular volumes and ejection fraction. During long-term medical therapy over a period of follow-up that averaged 4 years, none of the 64 with a patent infarct-related artery died. In marked contrast, 21 (18%) of the 115 with an occluded infarct-related artery died during a follow-up period of similar duration. All 21 experienced sudden cardiac death, strongly suggesting that the mode of death was arrhythmic (Table 7 and Figure 1, below).

Table 7

Comparison of Patients with a Patent or Occluded Infarct-Related Artery (Single Vessel Disease)

	Patent (n=64)	Occluded (n=115)
Age (years)	46 ± 9	47 ± 10
# of men (%)	44 (69%)	88 (77%)
Duration of follow-up (months)	46 ± 29	48 ± 28
LV Ejection Fraction (%)	52 ± 14	52 ± 11
Mortality (%)	0 (0%)	21 (18%) *

* $p < 0.001$ in comparison to those with a patent artery

From reference # 25

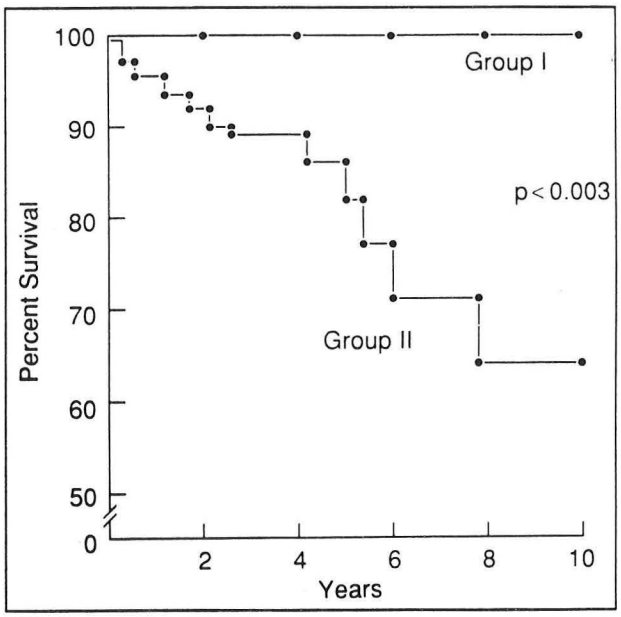


Figure 1
A life-table survivorship analysis for the 2 groups (Group I = antegrade flow; Group II = no antegrade flow). Over the 10 years of observation, Group I had a significantly better survival than Group II. From reference # 25.

The difference in survival between those with a patent and those with an occluded infarct-related coronary artery was particularly striking when the infarct-related artery was the left anterior descending or left circumflex. Specifically, as the data in Table 8 (below) indicate, the

Table 8

Comparison of Patients with a Patent or Occluded Left Anterior Descending or Left Circumflex (Single Vessel Disease)

	Patent (n=46)	Occluded (n=58)
Age (years)	47 ± 10	46 ± 11
# of men (%)	31 (67%)	44 (76%)
Duration of follow-up	50 ± 24	45 ± 28
LV Ejection Fraction (%)	50 ± 13	50 ± 12
Mortality (%)	0 (0%)	17 (29%) *

* $p < 0.001$ in comparison to those with a patent artery

From reference # 25

mortality in those with an occluded left anterior descending or left circumflex during 4 years of follow-up was 30%, whereas it was 0% if this artery was patent.

Study # 2: In patients with disease of the infarct-related coronary artery and significant narrowing of 1 or both of the other arteries, does the patency of the infarct-related artery influence long-term survival? To address this question, we retrospectively reviewed our records to identify eligible patients from July, 1978 to December, 1987 [26]. As in Study # 1, these patients were admitted to the Parkland Hospital Coronary Care Unit with their first myocardial infarction, after which they underwent catheterization during the subsequent 4 to 5 months. A total of 110 subjects fulfilled these entry criteria and were treated with long-term medical therapy: 35 with a patent infarct-related coronary artery, 75 with an occluded artery. The groups differed in left ventricular ejection fraction, with the patients whose infarct-related artery was patent having a somewhat higher ejection fraction. Similar to the results of Study # 1, there was a dramatic difference in survival between the groups (Table 9, below). Again, the vast majority of deaths occurred suddenly, suggesting an arrhythmic etiology.

Table 9

Comparison of Patients with a Patent or Occluded Infarct-Related Artery (Multivessel Disease)

	Patent (n=35)	Occluded (n=75)
Age (years)	51 ± 11	53 ± 11
# of men (%)	21 (60%)	49 (65%)
Duration of follow-up (months)	41 ± 26	43 ± 30
LV Ejection Fraction (%)	57 ± 16	47 ± 15 *
Mortality (%)	2 (6%)	24 (32%) *

* $p < 0.02$ in comparison to those with a patent artery

From reference # 26

From Studies 1 and 2, admittedly retrospective, it is clear that long-term survival after myocardial infarction is markedly influenced by the patency of the infarct-related coronary artery in those with single and multivessel

coronary artery disease.

Study # 3: Are survivors of myocardial infarction with an occluded infarct-related coronary artery more likely than those with a patent artery to have late potentials on signal averaged electrocardiography? From Studies 1 and 2, we were impressed that most of the patients with an occluded infarct-related coronary artery who died did so suddenly; it seemed that they died of an electrical event, probably ventricular tachycardia/fibrillation. However, we had no way of proving this suspicion. Signal averaged electrocardiography allows the identification of low-amplitude, high-frequency signals (so-called late potentials) in the terminal portion of the QRS complex. In patients who have had myocardial infarction, they identify those at risk for subsequent arrhythmic events and sudden death [27-29]. We performed signal averaged electrocardiography in 109 survivors of first myocardial infarction with single or multivessel coronary artery disease who were managed on long-term medical therapy: 49 with a patent infarct-related coronary artery and 60 with an occluded artery. As the data in Table 10 (below) indicate, those with an occluded infarct-related artery were much more likely to have late potentials on signal averaged electrocardiography [30].

Table 10

Incidence of Late Potentials in Patients with a Patent or Occluded Infarct-Related Artery

	Patent (n=49)	Occluded (n=60)
Age (years)	50 ± 10	52 ± 11
# of men (%)	30 (61%)	34 (57%)
LV Ejection Fraction (%)	54 ± 19	52 ± 13
# of patients with late potentials (%)	4 (8%)	24 (40%) *

* $p < 0.001$ in comparison to those with a patent artery

From reference # 30

Study # 4: In patients with an occluded infarct-related coronary artery, does the presence of collateral perfusion of the distal artery influence survival? The influence of coronary collateral circulation on mortality in patients with coronary artery disease has been the subject of

controversy for over 5 decades. Some studies [31,32] have suggested that collateral filling of the infarct-related artery is beneficial, whereas others have failed to show that this is true [33,34].

As of December, 1990, we had identified 146 subjects with an occluded infarct-related coronary artery and no disease of the other arteries: 120 with angiogaphic evidence of collateral filling of the infarct-related artery and 26 without collateral filling. As the data in Table 11 (below) indicate, these groups were similar in all respects, including mortality [35].

Table 11

Influence of Collateral Filling of an Occluded Infarct-Related Coronary Artery

	Collaterals (n=120)	No Collaterals (n=26)
Age (years)	48 ± 11	51 ± 11
# of men (%)	89 (74%)	19 (73%)
Duration of follow-up (months)	42 ± 28	42 ± 28
LV Ejection Fraction	53 ± 11	51 ± 15
Mortality (%)	23 (19%)	5 (19%)

From reference # 35

Thus, the presence of collateral filling of an occluded infarct-related artery exerts no effect -- beneficial or detrimental -- on survival in the months to years following infarction.

<u>Study # 5: In patients with an occluded infarct-related coronary artery and no other coronary artery disease, does the mechanical restoration of antegrade flow (via angioplasty) in the weeks after infarction improve long-term survival</u>? We have recently addressed this question retrospectively. From July, 1978, to June, 1991, we identified 180 subjects with an occluded infarct-related coronary artery and no other coronary artery disease who were treated (a) medically (n = 148) or (b) with angioplasty (n = 32), performed an average of 16 days after infarction. As the data in Table 12 (below) indicate, the patients were similar in all important respects, yet those who had angioplasty had an improved survival when compared to those

treated medically [36].

Table 12

Influence of PTCA of the Occluded Infarct-Related Artery on Survival Following Myocardial Infarction

	Medical Rx (n=148)	PTCA (n=32)
Age (years)	48 ± 11	52 ± 10
# of men (%)	109 (74%)	18 (56%)
Duration of follow-up (months)	41 ± 28	32 ± 26
LV Ejection Fraction (%)	53 ± 12	57 ± 9
Mortality (%)	24 (16%)	0 (0%) *

* p = 0.05 in comparison to those treated medically

From reference # 36

The beneficial influence of elective angioplasty of an occluded infarct-related coronary artery in the days to

Table 13

Influence of PTCA of an Occluded Left Anterior Descending or Left Circumflex on Survival After Myocardial Infarction

	Medical Rx (n=78)	PTCA (n=22)
Age (years)	49 ± 11	53 ± 11
# of men (%)	59 (76%)	14 (64%)
Duration of follow-up (months)	39 ± 27	35 ± 27
LV ejection Fraction (%)	51 ± 13	56 ± 10
Mortality (%)	20 (26%)	0 (0%) *

* p < 0.05 in comparison to those treated medically

From reference # 36

weeks after infarction is particularly evident in those in whom the left anterior descending or left circumflex is the infarct-related artery (Table 13, above).

These retrospective data clearly suggest that the restoration of antegrade flow in an occluded infarct-related artery (accomplished days to weeks after the acute event) exerts a beneficial influence on survival.

Study # 6: In patients identified prospectively 5 to 10 days after infarction in whom late potentials are present on signal averaged electrocardiography, can the mechanical restoration of antegrade flow in the occluded infarct-related coronary artery cause them to disappear? All the previously described studies were performed retrospectively. We are presently involved in our first prospective assessment of the beneficial influence of a patent infarct-related coronary artery in survivors of first myocardial infarction [37]. Patients who are 5 to 10 days post-infarction undergo signal averaged electrocardiography, and those with late potentials are catheterized. If the infarct-related artery is found to be occluded, the patient is assigned to (a) continued observation or (b) angioplasty of the occluded artery in an attempt to restore antegrade flow. Thusfar, 8 patients have been enrolled. Two were assigned to conservative therapy; both still had late potentials 1 to 3 months later. In contrast, angioplasty was performed successfully in the other 6; 1 to 3 months later, the late potentials had disappeared in all 6.

All the above studies offer a growing body of evidence that survival after myocardial infarction is markedly influenced by the presence of antegrade flow in the infarct-related coronary artery independent of left ventricular function. The restoration of antegrade flow -- by whatever means at one's disposal -- may be salutary even if it is accomplished days or weeks after the acute event. Indeed, as mentioned previously, the 32 patients who had angioplasty in Study # 5 underwent the procedure an average of 16 days after infarction. We are presently designing a multicenter, prospective study to test the hypothesis that the routine mechanical restoration of antegrade flow in the infarct-related coronary artery in survivors of myocardial infarction improves survival.

5. Propensity for Arrhythmic Events

Among the factors that are most strongly related to mortality after myocardial infarction, recurrent myocardial ischemia, left ventricular dilatation and dysfunction, and ventricular tachyarrhythmias appear to be important. An elevation of plasma catecholamines, with enhanced and sustained sympathetic drive, may contribute to the occurrence and severity of arrhythmias. Thus, beta-adrenergic blockade may favorably influence survival after infarction. Indeed, over the past 15 to 20 years, a number of studies have convincingly shown that beta adrenergic blockers reduce mortality by about 20% in the months to years after infarction.

In Table 14 (below) are listed the specific beta adrenergic blockers that are of proven long-term efficacy in patients following myocardial infarction and that are presently available for use in the United States.

Table 14

Beta Adrenergic Blockers Shown to Reduce Mortality After Acute Myocardial Infarction

Agent	Reference	% Reduction in Mortality
Metoprolol	38	36
Propranolol	39	26
Timolol	40	45

In Figure 2 (below) is a pictoral display of the mortality of patients treated with placebo or propranolol in the Beta Blocker Heart Attack Trial [39].

Recent data from our laboratory [41] have shown that beta blockade is especially beneficial in patients whose infarct-related coronary artery is persistently occluded. Of those with disease of only the infarct-related artery, survival was superb if the artery was patent regardless of whether the patient received long-term beta blockade. In contrast, as noted previously, those with an occluded infarct-related artery frequently had sudden death. Interestingly, almost all those who died were not, for some reason, treated with beta blockers. Specifically, of the 113 patients with an occluded infarct-related coronary artery, 21 died, and 20 of these were not receiving long-term beta blockade (Table 15 and Figure 3, below).

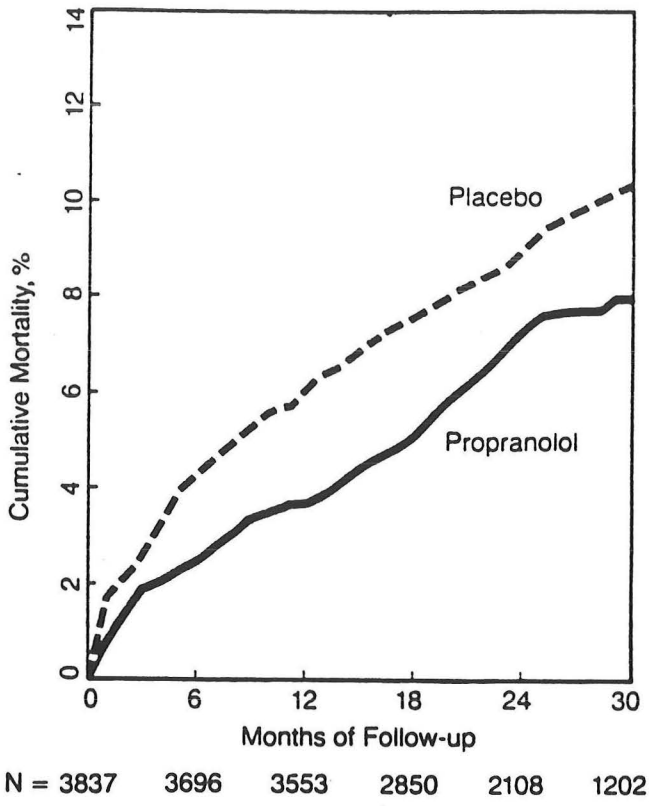


Figure 2
Life table cumulative mortality curves for the 2 groups. N denotes the number of patients followed through each time period. From reference # 39.

Table 15

Comparison of Patients with an Occluded Infarct-Related Artery With or Without Beta Blockade

	B-Blockade (n=46)	No B-Blockade (n=67)
Age (years)	45 ± 10	47 ± 11
# of men (%)	36 (78%)	51 (76%)
Duration of follow-up (months)	54 ± 27	43 ± 29
LV Ejection Fraction (%)	55 ± 10	50 ± 12
Cardiac mortality (%)	1 (2%)	20 (30%) *

* $p < 0.01$ in comparison to B-blocker
From reference # 41

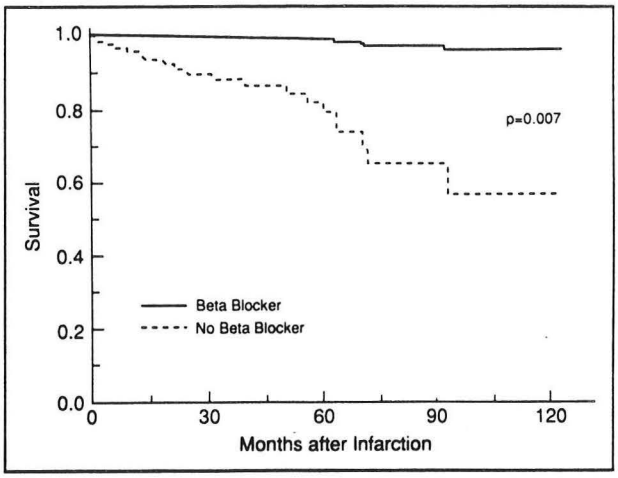


Figure 3
A life-table survivorship analysis for the 2 groups. Those receiving beta blockers had a significantly better survival than those not receiving them. From reference # 41.

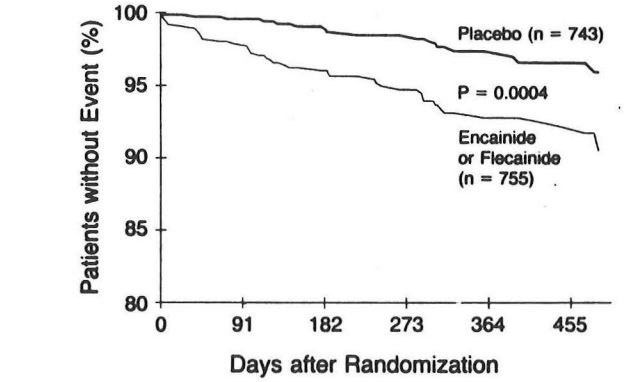
The prognosis of survivors of myocardial infarction who have an occluded left anterior descending or left circumflex coronary artery and who do not receive long-term beta blockade is particularly guarded. Of the 36 subjects who formed this subgroup, the cardiac mortality during a follow-up period of 3 to 4 years was 50% even though these individuals had only disease of the infarct-related coronary artery.

Thus, in survivors of myocardial infarction with antegrade flow in the infarct-related artery, survival is extremely good, and long-term beta blockade may be superfluous, costly, and unnecessary. On the other hand, if antegrade flow is absent and cannot be restored, long-term beta blockade may profoundly improve survival, particularly in those whose left ventricular function is impaired. Therefore, long-term beta blockade -- with 1 of the agents listed above -- should be given to all survivors of myocardial infarction, especially those (a) with an occluded infarct-related artery and (b) with compromised left ventricular function.

The Cardiac Arrhythmia Suppression Trial (CAST) was performed to test the hypothesis that the suppression of ventricular ectopy after myocardial infarction would reduce the incidence of sudden death. The pharmacologic agents used in this study were flecainide, encainide, and moricizine. In comparison to placebo, the administration of

encainide and flecainide was associated with a worse outcome (Figure 4, below). The adverse outcome in patients treated with flecainide or encainide was attributed primarily to unforeseen death or cardiac arrest due to arrhythmia [42]. Specifically, of 1498 patients, 743 were assigned to receive placebo, whereas the other 755 received flecainide or encainide. After an average follow-up of 10 months, 89 patients had died: 59 of arrhythmia (16 receiving placebo, 43 receiving active drug; p = 0.0004), 22 of nonarrhythmic cardiac causes (5 receiving placebo, 17 receiving active drug; p = 0.01), and 8 of noncardiac causes (5 receiving placebo, 3 receiving active drug). Thus, in patients with ventricular ectopy in the post-infarction period, flecainide and encainide appear to exert a deleterious influence on morbidity and mortality.

Figure 4
Actuarial probability of freedom from death or cardiac arrest due to arrhythmia in 1498 patients receiving encainide, flecainide, or placebo. From reference 42.



Placebo	743	632	516	412	292	201
Active drug	755	631	507	392	286	198

CONCLUSIONS

From the data presented above, it appears that the major determinants of survival after myocardial infarction are (a) age, (b) the extent of left ventricular dilatation and dysfunction and (c) the patency of the infarct-related coronary artery. Therefore, the optimal management of the patient with infarction should include agents or maneuvers to accomplish several goals. First, if the infarction is sizable, the patient should receive captopril in an attempt to minimize the extent of left ventricular dilatation in the weeks to months after the event. Second, the patient should receive low-dose aspirin to reduce the incidence of recurrent ischemia, infarction, or cardiac death. Third, if the infarct-related coronary artery is known to be occluded or has not been evaluated angiographically, the patient should receive a beta blocker -- propranolol, metoprolol, or timolol. The patient should not receive encainide or flecainide. Fourth, if prospective assessments confirm our retrospective observations concerning the beneficial influence of patency of the infarct-related artery, serious consideration should be given to restoring antegrade flow mechanically in the weeks following infarction. This final possibility awaits confirmation in a properly performed prospective trial.

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