総説 — Review

Early Risk Stratification After Acute Myocardial Infarction: Impact of Newer Treatment Strategies

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Acute myocardial infarct management has changed dramatically in the last decade as the results of major randomized clinical trials have been reported[1-17]. The choice of thrombolytic drug, anti-thrombotic regimen, and role of direct coronary angioplasty are evolving and the subject of an intense research effort. The average reduction in mortality rates for patients treated within 6 and 12 hours of symptom onset is 30% and 20%, respectively. However, approximately 20% of infarct related vessels do not open with thrombolytic regimens and 10-15% of reperfused arteries reclose within 3 or 4 days of reperfusion, adversely affecting left ventricular remodeling and long-term prognosis. The controversies in thrombolytic and anti-thrombotic regimens are partially reviewed elsewhere[9-11, 18].

The open vessel hypothesis has had a major impact on therapeutic regimens and risk stratification of acute infarct patients[19]. Patients who have the best prognosis have an open vessel at 90 minutes with sustained patency to the time of hospital discharge (Figure 1). An open infarct vessel is associated with limited infarct size, improved myocardial healing, limited infarct expansion, reduced aneurysm formation, and results in secondary benefits of diminished arrhythmias, reduced thrombo-embolic rates, decreased episodes of heart failure and a lower mortality rate. The magnitude of benefit is greatest in moderate-to-high risk patients and the goal of risk stratification is to identify these patients so that favorable therapeutic regimens can be applied. Acute myocardial infarct management can be thought of in three phases. Phase Ⅰ is the initial 24 hours from symptom onset, phase Ⅱ from day 2-5, and phase Ⅲ, predischarge management when noninvasive or invasive test procedures are applied to identify prognostic low and high risk patients[20].

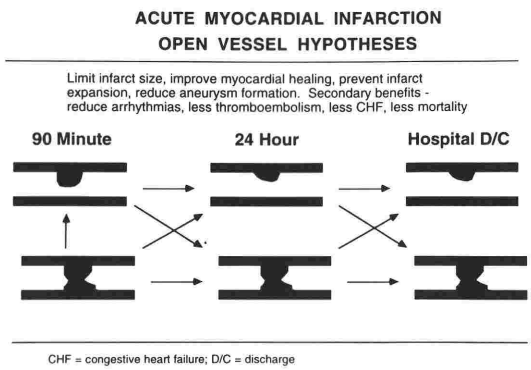

Figure 1 Diagram illustrating the dynamic nature of thrombolysis. Acute myocardial infarct patients with a patent vessel at 90 minutes that remains patent throughout hospital discharge have the best prognosis. In the TAMI I-III trials, in-hospital mortality was 17.2%, 11%, and 4.5% in patients who never reperfused, initially reperfused, but then reoccluded, and who had vessels that were initially patent and remained patent at the time of hospital discharge[11].

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Phase I:

In the TIMI II trial, acute infarct patients who presented with at least 30 minutes of chest pain and ST segment elevation were treated with rt-PA, heparin, and aspirin within four hours of symptom onset. The six week mortality was significantly increased in those who were > 70 years, had a previous history of myocardial infarction, anterior infarction, atrial fibrillation, pulmonary rales, hypotension and sinus tachycardia, female gender and diabetes mellitus[3]. Patients without these risk factors only had a six week mortality of 1.3% from the time of admission compared to a six week mortality rate of 17.2% when ≧4 risk factors were present (Figure 2). The large difference in six week mortality rates illustrate that the therapeutic benefit of reperfusion is likely to be greatest for patients at highest risk. Since the therapeutic benefit diminishes over time, the importance of identifying early on (within hours of the acute occlusion) whether the infarct-related vessel is open, partially open, or occluded is a paramount concern. The difficulty in using clinical parameters alone, such as resolution of chest pain or ST segment elevation, is the relatively poor diagnostic accuracy in identifying the 15% of patients who fail to reperfuse from the 85% of patients who do. Partial reperfusion, which occurs in approximately 20% of patients, is associated with an intermediate benefit compared to no reperfusion or total reperfusion, In the GUSTO angiographic substudy of 2,431 patients, TIMI grade II (partial) and III (complete) flow was observed in 27% and 54% of patients at 90 minutes[13]. Ejection fraction was 55%, 56%, and 62% in patients with TIMI 0-1, 2, and 3 grade flow and the 30 day mortality rate was 8.9%, 7.4%, and 4.4%, respectively ($p<0.001$).

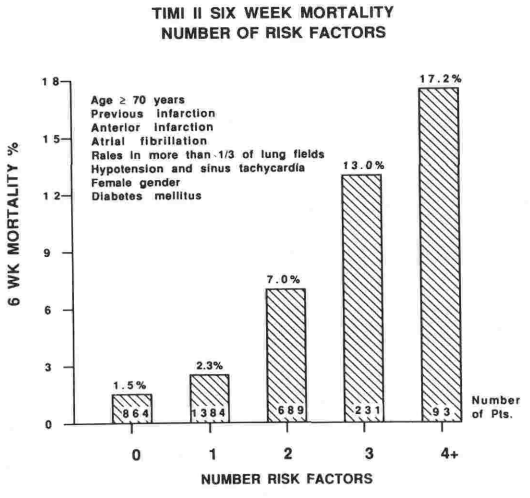

Figure 2 Six week mortality in TIMI II patients according to number of risk factors at entry. Absence of risk factors was associated with a cumulative six week mortality rate of 1.3%, compared to 17.2% in patients with four or more risk factors (3).

These findings have led some physicians to argue that immediate coronary angiography and angioplasty is the preferred routine approach for acute infarct patients to define status of the infarct related vessel, and promptly treat patients who have incomplete or no recanalization. The data from two of three small randomized trials partially support this hypothesis[15-17] (Table 1). Grines et al. randomized 395 patients who presented within 12 hours of symptom onset to I. V. heparin and aspirin and random assignment to immediate PTCA or I. V. rt-PA[17]. In-hospital mortality rates for the tPA and PTCA groups were 6.5 and 2.6%, respectively ($p = 0.06$). However, in high risk patient subsets (elderly, women), mortality was 10.4 and 2%, respectively. After six month follow-up, reinfarction or death occurred in 16.8% of the rt-PA group versus 8.5% of the PTCA group ($p=0.02$). Zijlastra et al. randomized 142 patients with acute infarction to direct coronary angioplasty versus intravenous streptokinase treatment[15]. The direct angioplasty approach was associated with a higher patency rate of the infarct related vessel, a less severe residual stenotic lesion, better left ventricular function (ejection fraction 45% in streptokinase group versus 51% in angioplasty group) and less recurrent myocardial ischemia and infarction compared to the intravenous streptokinase group. In the latter study,

Table 1 Results from Three Randomized Trials of Direct Coronary Angioplasty Versus Thrombolytic Therapy for acute Myocardial Infarction

N	Grines (17) 395		Zijlstra (15) 142		Gibbons (46) 108	
	PTCA	rt-PA	PTCA	rt-PA	PTCA	rt-PA
Mortality (hospital)	2.6	6.5	0	9	4	4
Reinfarction	2.6	6.5	0	13	0	4
LVEF (discharge)	53	53	51	45	53	50
Intracranial bleed	0	2	0	3	NR	NR

LVEF = left ventricular ejection; NR = not reported; PTCA = percutaneous transluminal coronary angioplasty; rt-PA = recombinant tissue plasminogen activator

subgroup analyses were not performed because of small sample size, and streptokinase rather than rt-PA was the thrombolytic regimen used.

The high patency rates seen with rt-PA and newer, more effective antithrombotic regimens to prevent reocclusion may reduce the magnitude of benefit for direct coronary angioplasty as compared to thrombolysis alone to only higher risk patients. The direct PTCA approach is not practical as a routine treatment for acute myocardial infarction in the United States since only 18% of hospitals can perform coronary angioplasty in 1994, and even less can do it on an emergency basis. Therefore, the role of coronary angiography and angioplasty in the acute phase is most commonly reserved for patients where the index of suspicion for failure to reperfuse is high, for clinically high risk patients who are not candidates for thrombolytic therapy but present within 12 hours of symptom onset, for patients who are hemodynamically unstable, or for those who have recurrent sustained ventricular tachyarrhythmias. Optimal management of patients who reperfuse but then reocclude within the hours following treatment remains controversial with a second course of thrombolytic therapy employed in some institutions and coronary angiography and angioplasty employed in others. At the present time, it is unclear if one therapeutic approach is any better than the other.

In the United States between 1990-1992, thrombolytic therapy was used in approximately 18-19% of patients presenting with an acute myocardial infarction with thrombolysis used for 31% of patients under age 55 compared to 3% in patients 85 years or over. Women and blacks were less likely to receive throimbolytic therapy than white males[21]. In 1994, the percent of patients treated with thrombolytic therapy is significantly greater with the expanded indications for usage up to 12 hours after symptom onset and greater awareness of the benefit of thrombolytic therapy in a wide range of acute myocardial infarct patient subsets.

Supplemental Medical Therapy in Phase I:

The routine use of intravenous nitroglycerine therapy for acute myocardial infarct patients is recommended, beginning with a 15 mcg bolus injection, and pump controlled infusion of 5-10 mcg per minute, increasing dosage by 5-10 mcg per minute every 5-10 minutes while carefully monitoring hemodynamic and clinical response. If hypotension develops, the nitrate infusion should be stopped, fluids administered, and I. V. nitrate infusion restarted as long as systolic blood pressure is $>$ 90mmHg. The benefits of intravenous nitrate therapy are well established when acute infarction is complicated by congestive heart failure or pulmonary edema, and there is evidence to

show that intravenous nitroglycerine may reduce infarct size in patients with moderateto-large infarctions[22]. In the ISIS-4 trial, 35 day mortality was 6.98% in patients randomized to controlled release oral isosorbide mononitrate versus 7.22% in the placebo treated group (NS). In the GISSI Ⅲ trial, I V nitroglycerine was prescribed for 24 hours after the acute infarct event followed by a 10mg nitroglycerine transdermal patch for six weeks. Mortality was 6.5% in the nitroglycerine treated group versus 6.9% in the control group (NS). The data are consistent with the concept that routine intravenous nitroglycerine therapy followed by oral nitrates has a small beneficial effect compared to no treatment, in that the greatest impact is likely to be in intermediate and higher risk patients without contraindications to nitrate usage.

Between 1988-1992, calcium channel blocker usage during hospitalization for acute infarction decreased from 63% to 47% of patients. There are few data which demonstrate a beneficial effect of calcium channel blocker drugs in the acute treatment phase for myocardial infarction. During the same years, beta blocker usage increased from 29% to 38%[21]. Beta adrenergic blocking drugs are beneficial in appropriately selected patients in the initial phase of infarction, both for patients treated with and without thrombolytic drugs[23]. I. V. magnesium therapy in the initial 24 hours after symptom onset was not shown to be beneficial in the ISIS-4 trial.

Antithrombin, Anticoagulants and Platelet Inhibitory Agents:

One of the main goals of antithrombotic therapy in the initial 24 hours after acute infarction is to prevent early reocclusion and reduce early recurrence or extension of myocardial infarction and death. Systemic heparinization is mandatory in patients who receive rt-PA thrombolysis[24,25]. Failure to use antithrombin drugs is associated with a significant increase risk of reocclusion. The need for systemic heparinization is less for streptokinase therapy. Newer more potent antithrombin drugs such as Hirudin may significantly reduce reocclusion rates over what can be achieved with heparin alone and subsequently reduce reinfarction rates and mortality. In the TIMI V trial, where recombinant hirudin was tested against heparin in acute myocardial infarct patients treated with rt-PA, death or reinfarction occurred in 16.7% of the heparin treated patients versus 6.8% in the hirudin treated patients[26]. The need for coronary revascularization during the index admission was 51% in the heparin treated group versus 34% in the hirudin treated group. There was not a significant increase in hemorrhage risk in the hirudin doses used, although the sample size was relatively small to assess safety in a large patient population, and a large clinical trial (TIMI 9) is currently in progress. Aspirin in a minimum dose of 160mg is important adjunctive therapy and should be used with concomitant antithrombin drugs for a minimum of 24-72 hours with an increase in dose to 220-325mg daily thereafter.

Emergent Versus Delayed PTCA After Thrombolysis:

The role of emergent coronary angioplasty to the infarct related vessel versus delayed or no coronary angioplasty in acute myocardial infarct patients treated with thrombolytic drugs was examined in three relatively large randomized trials[2,27,28]. In each study, urgent coronary angioplasty was no better than thrombolytic therapy alone in reducing in-hospital mortality or reinfarction rates (Table 2). Reocclusion rates were similar regardless of whether an urgent approach was used after thrombolytic drugs and discharge left ventricular ejection fractions were similar. The need for emergency coronary bypass surgery and blood transfusions was greater in patients who underwent the urgent angioplasty approach[2]. In these early studies, front loaded dosing of rt-PA, and newer more potent antithrombotic regimens were not used.

Table 2 Results from Three Randomized Trials of Emergent Versus Delayed or No Coronary Angioplasty After Thrombolysis for Acute Myocardial Infarction

	TAMI (27)		ECSG (28)		TIMI-IIA (2)	
	E	D	E	M	E	D
No. of patients	99	98	183	184	195	194
In-hospital mortality	4	1	7	3	7.2	5.7
Reinfarction	NR	NR	4	7	6.7	4.1
Recocclusion rate	11	13	14	12	17	15
Discharge LVEF	53.2	56.4	51.0	51.0	50.3	49.0

D = delayed; E = emergency; ECSG = European Cooperative Study Group for tissue plasminogen activator; LVEF = left ventricular ejection fraction; M = medical management; M = myocardial infarction; NR = not reported; TAMI = Thrombolysis and Angioplasty in Myocardial Infarction trial; TIMI = Thrombolysis in Myocardial Infarction trial. (From Chaitman BR: More on the saga of routine emergency coronary angioplasty for acute myocardial infarction. *J Am Coll Cardiol* 13 : 1260-1261, 1989; reproduced with permission.)

Phase Ⅱ: Early In-Hospital Course:

The goals of risk stratification after the initial 24 hours are to define the extent of the myocardial infarction and identify continuing myocardial ischemia. The TIMI II trial examined 3,262 patients with acute infarction presenting with ST segment elevation and treated with heparin, aspirin, and recombinant rt-PA within 4 hours of symptom onset[1]. The primary end point (reinfarction or death within 42 days) occurred in 10.9% of the group assigned to the invasive strategy (coronary angiography 18-48 hours after rt-PA followed by prophylactic PTCA if anatomy was suitable) and 9.7% of those assigned to the conservative strategy (arteriography and PTCA performed only in patients with spontaneous or exercise-induced ischemia). Results were similar after one year of follow-up except for patients with a prior history of myocardial infarction where one year mortality was 10.3% in patients in the invasive strategy versus 17% in the conservative strategy ($p = 0.03$)[5]. In contrast, patients with diabetes and no prior infarction had a higher mortality when the invasive strategy was pursued than the conservative strategy (14.8% versus 4.2%; $p < 0.001$) (Figure 3)[4]. Aguirre et al. compared the TIMI II-B results in 841 patients < 50 years of age and 859 patients between 65-75 years of age[29]. In both age groups, there were no

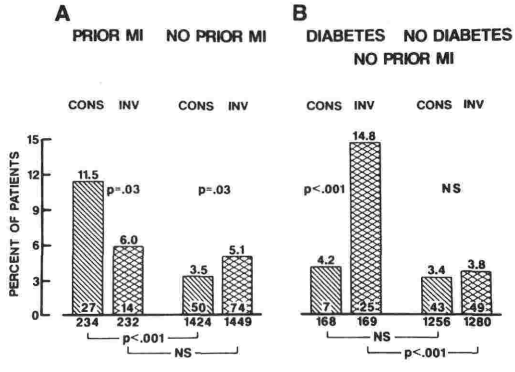

Figure 3 Mortality after 42 days in TIMI II patients according to presence or absence of myocardial infarction (MI) and randomized treatment assignment. In patients with previous myocardial infarction, cardiac events were significantly less in patients assigned to the invasive strategy. In diabetic patients, the invasive strategy was associated with a significant increased risk of cardiac events compared to a conservative strategy (4). (Mueller HS, et al.: Predictors of early morbidity and mortality after thrombolytic therapy of acute myocardial infarction. Analyses of patient subgroups in the Thrombolysis in Myocardial Infarction (TIMI) trial, phase II. *Circulation* 85 : 1254-1264, 1992 ; reproduced with permission.)

significant differences between the two treatment strategies. However, one year mortality was 2.8% versus 13.6% in the young and older patients, respectively. Recurrent ischemic events occurred in a similar percent of patients in the young and older groups (28%).

The TIMI III-B trial randomized 1,473 patients who presented within 24 hours of ischemic chest discomfort at rest (unstable angina or non-Q wave myocardial infarction) using a similar invasive versus conservative strategy as that employed in TIMI II-B[6]. In the TIMI III-B trial of patients who presented with ST segment depression or T wave inversion, 32% of patients developed a non-Q wave infarct; the remaining patients had unstable angina. After six week follow-up, the mortality rate (2.4%) and myocardial infarct rate (6.3%) were low and similar regardless of whether an early invasive or conservative strategy was used. In the TIMI III-B trial, all patients received heparin and aspirin and half of the patients were randomized to rt-PA or placebo. The group that received rt-PA therapy (in a smaller dose than TIMI II) were not significantly improved compared to those that did not.

Thus, prophylactic coronary angiography followed by coronary angioplasty when feasible is not necessary in the routine management of patients who present with suspected myocardial infarction (ischemic cardiac pain $>$30 minutes) and ST segment elevation, ST depression, or T wave inversion. The use of coronary angiography and revascularization should be reserved for patients who have spontaneous myocardial ischemia after the index event. Patients should be instructed to report anginal symptoms, and telemetry strips should be reviewed each day for silent and symptomatic ischemic episodes. Although medical therapy may reduce the frequency of myocardial ischemic episodes, patients who demonstrate this type of instability have a higher incidence of reinfarction and subsequent death. The risk benefit ratio would favor coronary angiography in this patient subgroup. The need for coronary revascularization can then be assessed and appropriate therapy recommended.

One of the early physiologic responses to acute infarction is left ventricular hypertrophy and remodeling to normalize systolic wall stress and maintain stroke volume. Several large randomized clinical trials report a benefit in reducing left ventricular dysfunction post infarction with ACE inhibitors compared to standard medical therapy[30-32]. Treatment should be started within 3-16 days of the acute infarct event in doses shown to be associated with reduced mortality. In the SAVE trial, all cause mortality was significantly reduced from 25% to 20% after 42 months in the captopril treated group ($p=0.019$)[30]. The benefit was observed in patients who received thrombolytic therapy, aspirin, or beta blockers, as well as those patients that did not.

Predischarge Risk Stratification:

Approximately two-thirds (2/3) of patients with myocardial infarction have a relatively uncomplicated course. The goals of predischarge risk stratification at this point are to identify low risk patients who need no further evaluation and select higher risk patients who might benefit from coronary revascularization[33-40]. The three main determinants of long-term outcome post infarction are: residual post infarct left ventricular function, extent of coronary disease, and electrical instability. Although complex ventricular ectopy is associated with an adverse long-term prognosis, some antiarrhythmic drugs increase mortality compared to placebo and unless cardiac arrhythmias are symptomatic, antiarrhythmic drug therapy is not recommended on a routine basis. This issue is discussed elsewhere in this symposium.

Exercise testing is a relatively inexpensive test that can identify low risk patients. Before the wide spread use of thrombolytic drugs, approximately 20% of patients post infarction would have exercise-induced angina, 30% would have exercise-induced ST segment depression, and 30-50% would have cardiac arrhythmias depending on the

technique used for arrhythmia detection; 10% would have a hypotensive exercise response. In the TIMI II trial, where patients were treated with thrombolytic drugs, one year mortality was 8% in patients who were unable to do the exercise test, 4% in patients who were able to exercise but could not complete 400 kpm of exercise, and 2% in patients who were able to complete 400 kpm of exercise[33]. The patients unable to exercise tended to be older, were more often women, had a previous myocardial infarction, and more often had multivessel disease.

The frequency of exercise-induced ischemic ST segment depression in TIMI II was 20% in patients with a nonanterior infarct, but only 10% in patients who had an anterior infarct. The reason why exercise-induced ST segment depression is seen less frequently in patients who receive thrombolytic drugs is related to the patient selection criteria for thrombolytic drugs. Three-vessel coronary disease tends to be less frequent in patients who receive thrombolytic drugs compared to a consecutive post infarct series. The less extensive the coronary disease, the less frequent exercise-induced ST segment depression is observed. In TIMI II, patients were enrolled within four hours of symptom onset, whereas the current recommendations include treatment for up to 12 hours after symptom onset. Expansion of entry criteria for thrombolytic therapy are likely to permit higher risk patients to be treated, and it may be that the frequency of exercise-induced myocardial ischemia will increase as higher risk patients are entered. There are no data at the present time to confirm this hypothesis. In the TIMI II patients assigned to the conservative treatment where exercise testing was used to determine if a patient required cardiac angiography, the relative risk of dying was reduced to < 1 in patients with exercise-induced ST depression (i.e. if exercise-inducesd ST depression was present, mortality rates were lower than absence of exercise-induced ST depression). Thus, patients who are able to exercise are a low risk patient subset; after selecting patients with exercise-induced ST depression for coronary angiography, angiographic high risk patients received coronary revascularization. The remaining patients are a lower risk group in whom exercise-induced ST depression is not associated with an increased likelihood of subsequent cardiac events compared to the larger group of patients who do not have exercise-induced ST segment depression and in whom coronary angiography was not used to select out prognostic angiographic higher risk patients. In GISSI II, the prognostic significance of maximal symptom limited exercise testing four weeks post infarction was examined in 10, 219 patients. Exercise testing was not predictive of reinfarction events: six month mortality rates were significantly increased only in the patient subgroup with a submaximal positive test[34].

The use of exercise myocardial perfusion imaging can be quite useful in evaluating myocardial viability in patients with large infarcts, and to identify continuing myocardial ischemia in patients with a noninterpretable electrocardiogram. In the subgroup of patients who cannot exercise post infarction, pharmacologic stressors such as I. V. dipyridamole or adenosine with myocardial perfusion imaging or dobutamine echocardiography can be used to further risk stratify this higher risk patient group.

Patients with left main, left main equivalent, and three-vessel disease with ejection fraction $<$ 50% are prognostic high risk patients in whom coronary revascularization has been shown to be of benefit. In patients with multivessel coronary disease (excluding left main), in whom coronary angioplasty or coronary bypass grafting are feasible, it is not yet clear which revascularization procedure is optimal for individual patients. In the RITA trial, where patients were randomly allocated to coronary bypass grafting or coronary angioplasty, two year death or reinfarction rates were similar in both groups[41]. However, patients assigned to the coronary angioplasty group had a very high likelihood of returning for a second coronary angiogram or revascularization proce-

dure. In the NIH sponsored Bypass Angioplasty Revascularization Investigation (BARI) trial which randomized the largest number of patients with multivessel to either coronary angioplasty or bypass grafting, patients are followed for a minimum five year follow-up. This trial which will be reported within the next year should provide important information as to the best choice of coronary revascularization procedure for selected patient groups[42].

The risks and benefit of coronary revascularization in moderate-to-high risk post infarct patients needs to be carefully evaluated. Patients with severe left ventricular dysfunction and diffuse coronary disease where the degree of attempt at revascularization will be minimal, are not candidates for the procedure, regardless of their poor long-term outcome with medical therapy. Similarly, patients with concomitant medical illness that limit life expectancy to less than can be achieved with coronary revascularization are not candidates for revascularization. The risks and benefits of coronary revascularization procedures vary from patient-to-patient, and the decision as to which type of revascularization procedure will be an empiric one which should be enhanced once the long-term results of large scale multicenter clinical trials comparing the two procedures are reported.

Conclusions

The United States health care system is expensive (in 1994) and the cost benefit ratio of the direct coronary angioplasty approach, multiple noninvasive testing, and routine prophylactic coronary angiography at the time of hospital discharge needs to be critically examined. In the Survival and Ventricular Enlargement (SAVE) study, Rouleau et al. studied treatment patterns for patients with acute myocardial infarction in 19 Canadian and 93 U.S. hospitals[43]. Although baseline characteristics of the 1,573 American and 658 Canadian patients were similar, the American patients more frequently had undergone coronary angiography prior to randomization (68% versus 35%) and coronary revascularization procedures had been more frequently performed in the American patients (31% versus 12%). Coronary angiography and revascularization were also more frequently performed after randomization in the American patients. Nevertheless, after 42 month follow-up, there was no difference in mortality (23% versus 22% in the U.S. and Canada) or rate of reinfarction (13% versus 14%).

The dramatic reduction in mortality after acute myocardial infarction with improved quality of life is a wonderful achievement. The challenge to physicians caring for patients with acute myocardial infarction is to select the most cost effective approach for individual patients, yet still achieve maximum therapeutic benefit[44]. Vigorous efforts to reduce risk factors which lead to atherosclerotic disease progression are mandatory to achieve sustained benefit.

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