MEDICAL GRAND ROUNDS

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MYOCARDIAL INFARCTION 1990
WHAT IS ROUTINE THERAPY?

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INTRODUCTION

It's arbitrary, but I like to think of the history of the development of our concepts of myocardial infarction (MI) and its treatment as occurring in four phases. The first phase began with the first published notions, in 1910-1912, that there was a survivable syndrome of necrosis of part of the myocardium. These reports were met initially with disbelief and disinterest. Application and extension of the new technology of electrocardiography helped greatly in proving the point and widespread treatment of myocardial infarction as a specific diagnosis began in the 1920s. Treatment was principally watchful waiting, prolonged rest, and often life-long and marked reduction in activity. In some ways treatment in this era was worse than the disease. Death from pulmonary embolism probably claimed about one of every seven survivors of the early phase of the infarction. Lifestyles and careers were profoundly disrupted.

The second phase of therapy of MI was initiated by Samuel Levine who popularized "armchair therapy" of these patients in the 1950s. The incidence of deep venous thrombosis and pulmonary embolism plummeted and this work gave birth to the field that we now know as post-MI cardiac rehabilitation.

The third phase was introduction, in the mid-1960s, of coronary intensive care units (CCUs). Recognition that early deaths from MI were usually from severe disturbances of cardiac rate and rhythm and that these dysrhythmias often could be predicted and effectively treated was a giant step forward. Precise figures are not available, but reasonable estimates are that CCUs and the extension of the principles of CCUs to mobile intensive care ambulances and step-down coronary care units reduced the toll of the early phase of MI by 15-30%. By the late 1960s and early 1970s, coronary intensive care pre-hospital and in the hospital became routine in most metropolitan areas in developed nations. Throughout the 1970s and the first part of the 1980s, care for the patient with MI included general supportive care, CCU monitoring and therapy for life-threatening arrhythmias and circulatory compromise, and cardiac rehabilitation. The incidence of left ventricular pump failure and complications occurring after the first few days in the hospital and following hospital discharge were not much changed from previous eras.

The fourth phase, and the one that is the principal topic of discussion today sprung from ideas that began in the early 1970s and have been tested extensively, in the late 1970s and in the 1980s. These ideas revolved around the concept that myocardial infarction is a dynamic event and that aggressive interventions to change factors that influence the eventual outcome of the infarction might well influence the incidence of death and serious morbidity. Death following myocardial infarction is usually the result of ventricular tachycardia or fibrillation, left ventricular pump failure, recurrent myocardial infarction (often called MI extension when it occurs during the initial hospitalization), "remodeling" of the left ventricle after infarction with expansion of the infarct and left ventricular dilation and aneurysm formation, or rupture of the myocardium. The basic approaches that have been tested include the following:

1. Improving the relationship between myocardial oxygen demand and supply:
   By improving myocardial blood flow:
      Thrombolytic agents
      Anti-thrombotic agents
      Nitrates
      Calcium-channel blocking agents
      Coronary reconstruction (angioplasty or surgery)
   By decreasing myocardial oxygen demand:
      Beta-adrenergic blockers

Afterload and/or preload reducing agents
Calcium-channel blocking agents

2. Decreasing the likelihood of life-threatening ventricular rhythm disorders:
   Antiarrhythmic agents
   Beta-adrenergic blockers
3. Preventing recurrent infarction
   Antithrombotic agents
   Beta-adrenergic blockers
   Calcium-channel blocking agents
4. Preventing ventricular remodeling, dilation, and aneurysm formation:
   Afterload and/or preload reducing agents
   Preserving blood supply to the infarcted area (see above)

Some aspects of routine therapy for the patient with MI are well established and will not be covered in this review. They include diagnostic testing, general supportive measures, treatment of early dysrhythmias and heart block, and cardiac rehabilitation. The results that I will review this morning are the results of studies with antithrombotic agents, thrombolytic agents, beta-adrenergic blocking agents, calcium-channel blocking agents, nitrates, anti-arrhythmic agents, angiotensin converting enzyme (ACE) inhibitors, and coronary reconstruction, especially with balloon angioplasty. The chief emphasis will be on the effects of these interventions on mortality, infarction size, and recurrent myocardial infarction.

An unfortunate result of the flurry of clinical trials of the above hypotheses and their interpretations is that the practitioner is apt to be confused. What intervention or sequence of interventions should now be considered routine therapy? What should be considered extraordinary therapy, best reserved for selected cases? What is still considered clinical research? Help in resolving this confusion is my main goal this morning. Whenever possible, I will rely upon the recommendations of consensus panels and regulatory agencies to decide what has become routine therapy. Nevertheless, some of these recommendations will have to be based upon my personal view of where consensus lies. I will often rely upon the results of carefully designed pooling projects (metanalysis, overviews) of some of the treatment modalities in MI. Misused, pooling of data of multiple separate clinical trials is worthless. New, statistically rigorous techniques for metanalysis have developed in recent years, especially under the influence of biostatisticians, epidemiologists, and clinicians at Oxford University in England. These techniques have the respect of most of the biostatistical and epidemiological community. I will be very critical about accepting the results of subgroup analysis of clinical trials. Generally speaking, the results of a clinical trial should be applied to the whole population group. Strictly speaking, the results of subgroup analysis should be considered mainly a stimulus for new hypothesis generation. The results of subgroup analysis should be cautiously and tentatively accepted only if: 1. the rationale for the result is strong and; 2. the results of subgroup analysis are exceptionally strong or the same result has been found consistently in several similar clinical trials. (The Oxford group gives a humorous example of inappropriate subgroup analysis. In the ISIS-2 trial, patients with acute myocardial infarction who were born under one sign of the Zodiac did not benefit from thrombolytic therapy.)

ANTITHROMBOTIC THERAPY

ANTIPLATELET THERAPY

Antiplatelet-Therapy for Acute Myocardial Infarction

Until recently, there were few data regarding a protective effect of antiplatelet therapy given to patients early during acute myocardial infarction. One small study, supported by the MRC, utilized a single 300 mg dose of aspirin given within the first day of admission. (1,2) There was a 7% decrease in mortality at the time of hospital discharge. (NS) The ISIS-2 trial reported its findings in 1988. (3) This trial was a randomized, placebo controlled trial of aspirin (160 mg chewed as soon as possible after entry and then 160 mg daily) and streptokinase given within the first 24 hours after the onset of acute myocardial infarction. A total of 17,189 patients were randomly assigned to receive aspirin alone, aspirin plus streptokinase, streptokinase alone, or both active drugs. The primary end points were vascular and total mortality 5 weeks after the infarct. Aspirin therapy significantly reduced mortality, by 21%, from 11.5% to 9.3%. The effects of aspirin were additive to the effects of thrombolytic therapy. There was a 23% reduction in mortality with aspirin therapy in patients who received active streptokinase (i.e. aspirin plus streptokinase *vs.* streptokinase plus aspirin placebo, $P<0.0003$). This effect was as prominent as the 19% reduction in mortality demonstrated in the patients who received aspirin alone (i.e. aspirin plus streptokinase placebo *vs.* aspirin placebo plus streptokinase placebo, $P<0.0001$). Bolstered by the protective effects that have been demonstrated in patients with unstable angina and in patients who have survived MI a clear consensus favoring routine use of aspirin in the acute phase of MI has developed. The effect presumably is due to prevention of new thrombus and platelet plugging following spontaneous or streptokinase-induced fibrinolysis.

Long-Term Antiplatelet Therapy In Survivors of Acute Myocardial Infarction

Ten large, randomized, placebo-controlled long-term secondary prevention studies have been performed with antiplatelet agents in survivors of myocardial infarction. Eight were carried out with aspirin, either alone (6 studies) or in combination with dipyridamole. Two were carried out with sulfinpyrazone.

The first MRC trial was a randomized, double-blind study of aspirin, 300 mg once daily, in 1,239 men who had sustained a myocardial infarction within 10 weeks of enrollment. Follow-up was one year. Mortality was reduced 22%, from 9.8% to 7.6%. (NS). The reduction was much more prominent in men who were enrolled within 6 weeks of infarction. In that case, mortality was reduced from 13.2% to 7.8%. (2-4)

The Coronary Drug Project Research Group (CDP) randomly assigned 1,529 men with MI within 5 years of enrollment to aspirin (324 mg three times daily) or placebo. Total mortality was reduced 30%, from 8.3% to 5.8% (NS). (5,6)

The German-Austrian Trial randomly allocated 946 patients within six weeks of MI to aspirin (500 mg three times a day), placebo, or oral anticoagulation (see above). Follow-up was 2 years. Total mortality was reduced 18%, from 10% to 8.5% (NS). The coronary death rate was reduced more markedly, from 7.1% to 4.1% (NS). (7,8)

The second MRC trial randomly assigned 1,682 patients to aspirin (300 mg three times daily) or placebo within one week of MI. Total mortality was reduced 17%, from 14.8% to 12.3%. The risk of the combined end point of total mortality plus nonfatal MI was reduced from 28% to 22% (NS). (2,3)

The Aspirin Myocardial Infarction Study (AMIS) randomly assigned 4,524 patients with an MI 2-60 months previously and followed them for up to 3 years. Total mortality was increased 11%, from 9.7% to 10.8%. There were fewer nonfatal

MIs in the aspirin group and the combined incidence of coronary heart disease mortality or nonfatal MI was reduced from 14.8% to 14.1%. (100,101) In spite of its size and randomization, the aspirin group received a disproportionately large share of patients with cardiovascular risk factors which may have affected the study outcome. (9)

The first Persantine-Aspirin Reinfarction Study (PARIS) randomly allocated 2,206 patients with MI 2-60 months previously to therapy with aspirin (324mg three times daily), the same aspirin regimen plus dipyridamole (75mg three times daily), or placebo. The average follow-up was 41 months. The active groups had twice as many patients as the placebo group. Total mortality was reduced 18% by aspirin alone, from 12.8% to 10.5%. It was reduced 16% by the combination of aspirin and dipyridamole, from 12.8% to 10.7% (NS). Patients who were entered into the trial within six months of their infarction appeared to have the majority of the beneficial effects of antiplatelet therapy. (102-104)

The results of these six trials were analyzed in an editorial in Lancet in 1980. It was pointed out that a trial of 5,000-10,000 patients would be required to detect with confidence a 10-20% end point reduction. The author of this editorial pooled the data of these six trials and concluded that the risk reduction with aspirin is 16% for cardiovascular death ($P<0.01$) and the combined end point of fatal and nonfatal MI is reduced by aspirin by 21% ($P<0.001$). (10)

The PARIS group carried out a second study, enrolling patients earlier than their first study, 4 weeks to four months after MI. They randomly assigned 3,128 people to the same aspirin plus dipyridamole regimen that they used earlier or to placebo. The groups were of the same size. The follow-up period averaged 23.4 months. At one year, total mortality was reduced 9% and coronary mortality was reduced 20%. (NS) At the conclusion of the study, the differences were much less striking. Nevertheless, the combined end point of coronary mortality plus nonfatal infarction was reduced significantly at one year and at the conclusion of the study. (11)

Based upon these studies, the Food and Drug Administration approved aspirin as an effective treatment following myocardial infarction for reduction of death and reinfarction.

Two randomized, placebo-controlled studies of sulfinpyrazone after myocardial infarction have been performed, one in North America and the other in Italy. Both trials studied the effects of 200 mg of sulfinpyrazone four times daily. The North American trial demonstrated a reduction in mortality of 24%, from 10% to 8% (NS). Total mortality in the Italian study was reduced 26%, from 5% to 4%.(NS). The sulfinpyrazone trials created a lot of controversy about some of the techniques of data analysis. Furthermore, there were some inconsistencies between the two studies in benefits on cardiac death and reinfarction. As a result, the Food and Drug Administration did not approve sulfinpyrazone as effective therapy following MI. (9)

In 1989 results were published, from an enormous reanalysis of the available data from virtually all of the clinical trials of antiplatelet agents in stroke, myocardial infarction, and unstable angina, by the Antiplatelet Trialists Group. (12) They pooled and reanalyzed all of the above 9 trials, plus the Micristin study, a randomized trial in West Germany of aspirin, 1500 mg/day, *vs.* placebo in 1340 people. Pooling these ten antiplatelet trials in survivors of MI, they calculated an odds reduction of 25% for stroke, myocardial infarction, or vascular death ($p<0.0001$), an odds reduction of 31%: for non-fatal myocardial infarction ($p<0.0001$), and an odds reduction for all vascular deaths of 13% ($p<0.005$). A second meeting of the Antiplatelet Trialists group was held earlier this year. More data were available and a repeat analysis confirmed and extended upon the original observations.

Preliminary results of some of the data have been reported at meetings this year and publication is expected in about a year.

The Food and Drug Administration has approved aspirin therapy post MI as effective for prevention of further coronary events. The Antiplatelet Trialists group results strongly suggest that low-dose aspirin should be effective and, therefore, side-effects will be minimized. A strong consensus has developed that survivors of MI should be routinely treated with relatively low-dose aspirin, 162-324 mg per day, for at least 1-2 years following MI.

ANTICOAGULANT THERAPY

Anticoagulant therapy for myocardial infarction has been controversial for several decades. It was embraced enthusiastically as an important part of therapy after publication of the first clinical trial in 1948. (13) By the late 1960s and early 1970s, interest began to wane as doubts grew about the importance of thrombosis in acute myocardial infarction and with the publication of several large randomized studies on this subject. (14-26) An American College of Chest Physicians (ACCP)-National Heart Lung and Blood Institute (NHLBI) consensus panel stated, however, that "critical review of the evidence for the possible value of anticoagulant therapy in acute myocardial infarction suggests that neither the initial enthusiasm nor the subsequent loss of interest is justified by the published reports." (1) Discussion of anticoagulants for myocardial infarction is conveniently divided into four parts: short-term treatment soon after myocardial infarction to prevent death and reinfarction, short-term treatment soon after myocardial infarction to prevent embolism from the left heart, short-term treatment soon after infarction to prevent deep venous thrombosis and pulmonary embolism, and long-term treatment for survivors of myocardial infarction to prevent death and reinfarction.

Short-term Anticoagulant Therapy Soon After Myocardial Infarction to Prevent Death and Reinfarction

More than 30 trials of anticoagulant therapy after MI have been identified (27) Nevertheless, there are only three randomized studies of sufficient size to have a reasonable change of demonstrating a clinically important reduction in death and reinfarction. (14-16)

The Medical Research Council of the United Kingdom (MRC) Trial (14) was a single-blind controlled study in which 1,427 patients with acute MI were randomly allocated to anticoagulation or control therapy for 28 days. Active therapy was intravenous heparin followed by phenindione. The control group received homeopathic doses of phenindione and no heparin. Death was reduced 11%, from 18% in the control group to 16.2% in the active-treatment group (NS). Reinfarction was reduced from 13% in the control group to 9.7% in the anticoagulated group (NS).

The Bronx Municipal Hospital Center Trial (15) was a randomized, placebo-controlled, single-blind trial in 1,136 patients of anticoagulants or placebo within 24 hours of admission. Active therapy was heparin (the first dose was intravenous, the following doses were subcutaneous) followed by phenindione. Control patients received placebos. The duration of therapy was not specified. Death was reduced by 30% from 21.2% in the control group and 14.9% in the anticoagulated group ($P<0.005$). Reinfarction was reduced from 13% in the control group to 11.8% in the actively-treated group (NS).

In a VA Cooperative Trial (16), 999 male patients were randomly allocated to anticoagulant or placebo therapy within 72 hours of the onset of their symptoms. Active therapy was subcutaneous heparin followed by warfarin. They were treated for 28 days. Death was reduced by 14%, from 11.2% in the control group to 9.6% in

the anticoagulated group (NS). Reinfarction was reduced 50%, from 4% in the control group to 2% in the actively-treated group. (NS).

Chalmers and his associates reviewed and reanalyzed the results of all of the adequately-designed, randomized studies of anticoagulant therapy in acute myocardial infarction. (27) They identified more than 30 studies. The results of analysis of the pooled data suggested a reduction in death of 21%. This was one of the first of the modern attempts at metanalysis and some of the statistical techniques used in this study were criticized. (28) Reanalsyses that used more rigorous statistical methods, however, reached similar conclusions showing that anticoagulants reduced mortality about 22% ($P<0.001$). (29-31)

After decades of controversy, based upon the above data, there is now a consensus that short-term anticoagulation soon after myocardial infarction probably produces a reduction of about 20% in early mortality in patients with acute myocardial infarction. Nevertheless, the recent data showing that the majority of patients with acute MI already have an occlusive coronary thrombus at the time of hospital admission make it unlikely that anticoagulant therapy alone would have a major influence on infarction size and, therefore, have a major effect on early mortality after MI that is related to the extent of loss of working ventricular myocardium. The effectiveness of anticoagulants soon after acute MI was probably chiefly a function of maintenance of patency of coronary arteries following spontaneous fibrinolysis and thus prevention of death and reinfarction related to reocclusion of the affected arteries. (9) A few deaths were clearly prevented by prevention of stroke and pulmonary embolism, issues that are discussed below. Therefore, the current consensus is that the roles of short-term anticoagulant therapy soon after myocardial infarction are largely limited to the following: as an adjunct to coronary fibrinolytic therapy, prevention of thromboembolism from the left ventricle, and prevention of deep venous thrombosis and pulmonary embolism. (9,32,33)

Unfortunately, much of the data with short-term anticoagulant therapy predate the current era of thrombolytic therapy. As a result, we do not now have a complete picture of how to best use anticoagulants as adjunctive therapy with thrombolytic agents. Addition of heparin to thrombolytic therapy and aspirin increases the risk of hemorrhage. Nevertheless, several studies and retrospective analyses have suggested a beneficial adjunctive role for anticoagulant therapy, but strong proof is lacking. Two large trials, ISIS-3 and GISSI-2 have this hypothesis as a secondary goal. GISSI-2 and an extension of it that includes centers outside of Italy, the International t-PA/Streptokinase Trial, reported preliminary data in March of this year at the American College of Cardiology meeting. This study, after the primary random assignment to t-PA or streptokinase, randomly assigned patients to low-dose heparin beginning 12 hours later or to a control group. All patients received aspirin. In neither the streptokinase nor the t-PA group did administration of heparin change any of the main study endpoints. These studies have their critics. Use of low-dose heparin,. arbitrary delay in administration of 12 hours, and use of the same adjunctive regimen for both t-PA and streptokinase have been singled out for particular criticism. In my view, the status of heparin as routine adjunctive therapy for thrombolysis is unresolved. Pending further data, a practical approach that is followed by many experts, and one that I find attractive, is to administer heparin concurrently with t-PA and to continue it for 2-3 days or until coronary arteriography, if planned, is performed. Some experts also start heparin concurrently with administration of streptokinase, APSAC, or urokinase. Because these three plasminogen activators are associated with considerable conversion of circulating plasminogen to plasmin and thus creation of an anticoagulated state, other experts recommend delaying heparin administration in this case for 12-24 hours or until there is laboratory evidence (e.g. the thrombin time becomes measurable) of

subsidence of the plasmin-induced anticoagulated state. In this case, heparin--once started--is usually continued as it is with t-PA administration.

Short-term Therapy After Myocardial Infarction to Prevent Systemic Thromboembolism from the Left Heart

Only about 10% of in-hospital deaths after MI are due to systemic embolism and the great majority of those are the result of strokes. (34) In the MRC study (14), the relative risk of stroke was reduced by anticoagulant therapy by 55%, from 2.5% to 1.1%, ($P<0.037$). In the Bronx Municipal Hospital study (66), the relative risk of stroke was reduced 24%, from 2.3% to 1.7% (NS). In the VA study (16), the relative risk of stroke was reduced by 75%, from 3.2% to 0.8% ($p<0.005$).

The risk of systemic embolism is not equally distributed among all patients with acute MI. It is highest in patients with acute anterior wall infarcts associated with wall motion abnormalities. In these patients, the risk is about 30-40%, approximately twice the risk of all patients with MI. This group also has the highest incidence of mural thrombi detected by echocardiography. Nevertheless, about 20% of ventricular thrombi are not detected by echocardiography, Furthermore, it has not been shown clearly that patients with anterior wall infarctions without echocardiographically detectable thrombus are at substantially less risk for thromboembolism than are similar patients with detectable thrombus. Therefore, a strong consensus has developed that patients with anterior wall myocardial infarction should receive heparin therapy followed by oral anticoagulant therapy (prolonging the prothrombin time 1.2 - 1.5 times the control value) for 1-3 months. (9)

Other risk factors for systemic embolism include large infarcts, dilation of the left ventricle, congestive heart failure, atrial fibrillation, and ventricular aneurysms, and history of previous systemic or pulmonary embolism. Therefore, a consensus has also developed that patients with acute myocardial infarction who are at increased risk of systemic embolism because of atrial fibrillation, history of previous systemic or pulmonary embolism, or congestive heart failure should receive heparin therapy followed by oral anticoagulants to prolong the prothrombin time to 1.2-1.5 times the control value for at least three months. (9)

Short-term Anticoagulant Therapy to Prevent Deep Venous Thrombosis and Pulmonary Embolism.

The risk of pulmonary embolism that was diagnosed clinically was reduced in all three of the large anticoagulant trials mentioned above. The relative risk was reduced from 5.6 to 2.2% ($P<0.01$) in the MRC study (14), from 6.1 to 3.8% (NS) in the Bronx Municipal Hospital study (15), and from 2.6% to 0.2% ($P<0.005$) in the VA Cooperative study (16). The clinical diagnosis of pulmonary embolism is often difficult, but two autopsy studies comparing pulmonary embolism in the presence and absence of anticoagulant therapy are supportive of the findings of these three trials. (35,36) Three recent trials that looked for venous thrombosis in the lower extremities with radioisotope scanning techniques are also supportive of a protective effect of anticoagulants. The presence of thrombi in the veins of the leg was reduced significantly in two of the studies (37,38) and reduced, but insignificantly so, in the third (39,40). Modern coronary care emphasizes early ambulation of the patient following MI. The incidence of deep venous thrombosis is reduced as a result. (41) Therefore, pulmonary embolism today probably occurs less frequently than in 5% of patients and is more prevalent in patients at high risk for venous thrombosis, such as patients with heart failure, shock, preexisting venous disease or history of venous thromboembolism, obesity, and patients requiring bed rest for more than 3 days. Nevertheless, there is a strong consensus that patients with acute myocardial infarction should receive anticoagulation, with at least low-dose heparin (5,000 units intravenously or subcutaneously every 12 hours until fully ambulatory). The majority

of the experts appear to favor application to all patients with acute infarction (9,33). Some prefer to restrict it to patients at high risk for venous thrombosis (32).

The hemorrhagic risks of short-term anticoagulation after MI in the groups outlined above appears to be acceptably low enough in light of the demonstrated benefits. The ACCP-NHBLI consensus panel combined the results of the three above-noted randomized trials of short-term anticoagulation after MI. In the 2,348 patients who received anticoagulant therapy, minor bleeding occurred in 7%; major bleeding occurred in 1.5%; and bleeding into the central nervous system occurred in 0.05%. There were no deaths attributed to bleeding. (9)

Long-term Anticoagulation In Survivors of MI to Prevent Reinfarction and Death

The statistical demands of trials to show a beneficial effect on mortality and morbidity in survivors of MI are formidable. (9,42) The death rate and reinfarction rate drop substantially following the hospital phase of MI and continue to drop exponentially for about a year. From a year after MI, the mortality rate returns to a rate identical to patients with stable chronic coronary heart disease without MI. Many trials with oral anticoagulants long-term commencing in the first few weeks after MI have been performed, but only three had an 80% chance to demonstrate a 50% difference in death or reinfarction at the 5% probability level. No such trial has been performed with a power of demonstrating a 20% difference.

The MRC trial was a trial of 383 people who had survived an MI 4-6 weeks before entry into the trial. (43) All of these subjects had been treated with anticoagulant therapy during the hospital phase of their illnesses. They were randomly allocated to receive either full or homeopathic doses of phenindione. The patients were followed for three years. The death rate was decreased 30%, from 21.3% to 14.9% (NS). Recurrent MI was reduced from 39.9% to 20.5% ($P<0.001$).

The VA Cooperative study was a trial of 747 male patients who were enrolled within 21 days of hospital admission for acute MI. (23,24) They were randomly assigned to either placebo or warfarin and were followed for 7 years. At three years of follow-up, mortality was significantly reduced ($P<0.01$), but by the end of the 7-year follow-up, the death rates were virtually identical. Recurrent MI was reduced by 25%.

The German-Austrian Centre Clinical Trial was a trial of placebo vs. aspirin vs. phenprocoumon. (25) (The results with aspirin are discussed below.) Three-hundred and nine patients were randomly allocated to placebo treatment and 320 were assigned treatment with phenprocoumon. They were enrolled 30-42 days after MI and were followed for 2 years. The relative risk of death was increased 18%, from 10% to 12% (NS). There was a non-significant reduction in the rate of recurrent myocardial infarction.

A fourth trial, the Sixty-Plus Reinfarction Study (44), requires discussion although it does not fit precisely into this section, because the 878 subjects had sustained an MI 6 or more months before entry into the study. In fact, the mean time from infarction was 6 years. All of the patients were over 60 years of age and all had received oral anticoagulant therapy since the time of their infarction. They were randomly assigned to placebo or oral anticoagulant therapy. After two years of follow-up, there was no difference in death rates, but recurrent myocardial infarction was reduced by 55%.

Because of the low statistical power of the available studies, an international pooling group has combined the results of nine studies. (26) The results of this effort suggest that mortality was reduced by 20% in men given long-term anticoagulants, with the benefit limited to patients with prolonged angina or previous MI on admission to the trial.

In 1987, the results of a trial of low-dose, subcutaneous heparin in survivors of MI was reported from Italy. (45) It was a prospective, randomized, controlled trial

of heparin, 12,500 units daily, in 728 patients who had sustained a Q-wave infarction 6-18 months before enrollment. After two years of follow-up, the mortality rate was decreased by 48% ($P<0.05$),(drug efficacy analysis) or 34% (NS),(intention to treat analysis). Recurrent infarctions were decreased by 63%, from 3.56% to 1.32% ($P<0.05$).

Bleeding complications, not unexpectedly, were common in most of these trials. Most of the hemorrhagic episodes were minor, however. In general, the incidence of stroke was reduced, implying a decrease in embolic and thrombotic strokes that outweighed any increase in hemorrhagic strokes.

The risk of bleeding and the practical difficulties associated with long-term oral anticoagulation make this therapy hard to recommend as routine therapy after MI. The reduction in mortality and reinfarction does not appear to be any greater than with anti-platelet therapy, which is simpler, associated with fewer hemorrhagic complications, and presumably has a similar mode of cardiac protection, namely an antithrombotic effect. The incidence of thromboembolism, however, appears to be reduced by oral anticoagulants. [Reviewed in (9)] Therefore, a consensus has developed that oral anticoagulant therapy should not be recommended routinely after MI. (9) A parallel consensus has developed, however, that survivors of MI should be treated long-term with oral anticoagulants if any of the following risk factors for systemic or pulmonary embolism are present: atrial fibrillation, previous systemic embolism, venous thromboembolism, or severe heart failure. (9)

Intravenous Thrombolytic Therapy

The reference standard for successful coronary thrombolysis is the result with intracoronary infusion of streptokinase or urokinase in patients with evolving transmural MI. Reviews of these studies demonstrate that the rate of successful reperfusion, when therapy is employed within 6 hours of the onset of symptoms, is 70-80%. The failure to achieve reperfusion in 20-30% of patients may be due to the presence of older clot. It is well known that coronary thrombosis in unstable angina and MI has layers of varying age. Wide-spread, timely application of intracoronary fibrinolytic therapy is, however, logistically and economically impractical. The delays inherent in administration of thrombolytic agents through intracoronary catheters and the risks of coronary arteriography in patients with an evolving MI may well blunt the effectiveness of coronary thrombolysis on mortality by this route of administration. Trials of early intravenous thrombolytic therapy show that intravenous thrombolytic therapy can approach the patency rate achieved with intracoronary therapy.

The most important end point of fibrinolytic therapy is mortality. The evidence is now overwhelming that mortality is reduced in well-selected patients with acute MI who are treated in a timely way with intravenous thrombolytic agents.

The Netherlands Interuniversity Cardiology Institute study was reported in 1985. (46) Initially this was a trial of intracoronary streptokinase. In the last 117 of the 533 patients, intravenous streptokinase was administered before intracoronary streptokinase. It was a randomized trial of thrombolytic therapy versus no thrombolytic therapy. Mortality was significantly reduced at 28 days. The benefits were maintained at one year follow-up.

The Gruppo Italiano Studio Della Streptochinasi Nell'Infarto Miocardico (GISSI) study was reported in 1986. (47) This trial was an unblinded study of intravenous streptokinase, 1.5 million units in one hour, versus no thrombolytic treatment in 11,806 patients in 76 Italian hospitals. Overall, there was an 18% reduction in mortality at 21 days follow-up, from 13% to 10.7% ($p<0.0002$). The benefit was time dependent. Mortality was reduced 23%, from 12% to 9.2%, when therapy was begun within 3 hours of pain and 47%, from 15.4% to 8.2%, when the infusion was begun within one hour.

The I.S.A.M. study group reported on the results of intravenous streptokinase therapy in 1741 patients in 1986. (48) Patients were treated within 6 hours of onset of symptoms and were randomly assigned to 1.5 million units of streptokinase or placebo. There was reduction in mortality from 7.1% to 5.2% overall (NS). The benefit was greater when therapy was given within 3 hours of symptoms, with reduction in mortality from 6.5% to 5.2% (NS).

The ISIS-2 study mentioned earlier in the discussion of aspirin also showed a highly beneficial effect on mortality with 1.5 million units of intravenous streptokinase administration, given within 24 hours of the onset of symptoms. (3) In the patients who did not receive aspirin, at the 35 day follow-up period there was a 25% reduction in mortality overall, from 12% to 9.2%. ($p<0.00001$) The effect was additive to the effects of aspirin. The combination of streptokinase plus aspirin significantly reduced mortality at 35 days by 42:%. The effects were time dependent. Mortality reduction for streptokinase when given within 4 hours was 37%. ($p<0.0001$).

Yosuf pooled the data from 20 small, early trials of intravenous streptokinase after MI. The analysis included about 5300 patients. Active treatment reduced mortality by 24% ($P<0.001$). (49) In a metanalysis of ISIS-2, GISSI, plus 9 small studies that included about 36,000 more patients who received streptokinase therapy, he found a reduction in early mortality (2-5 weeks) of 24%. (29)

The European Cooperative Study Group for Recombinant Tissue-type Plasminogen Activator presented the mortality results from their randomized trial of rt-PA versus placebo in 1988. (57) A total of 721 patients were enrolled. Active therapy was 100 mg of rt-PA given over 3 hours. All patients received low-dose aspirin and heparin. Patients were treated within 5 hours of onset of symptoms. Overall, mortality was significantly reduced by 51% at 14 days, from 5.7% to 2.8%.

The Thrombolysis in MI (TIMI) Phase I trial was not designed with mortality as a major end point. Nevertheless, this group have reported the mortality experience from that trial of intravenous streptokinase and rt-PA. (50) Patients with patent vessels 90 minutes after thrombolytic drug administration had a significant reduction in mortality compared to patients whose thrombosed coronary arteries were not patent at this interval.

The Anglo Scandinavian Study of Early Thrombolysis (ASSET) was a placebo controlled trial of intravenous t-PA, given within 5 hours of infarction, on mortality in 5,000 patients. Active therapy reduced mortality by 26% ($P<0.001$). (51) Yosuf pooled the data of this study with five other trials with t-PA and found a 26% reduction in death ($P<0.001$) when the agent was given within six hours of the onset of chest pain. (29)

The APSAC in Myocardial Infarctions Study (AIMS) was a placebo controlled trial in the United Kingdom of intravenous APSAC administration within 6 hours of the onset of MI. It was stopped prematurely, after enrolling 1,000 patients, because of a reduction in mortality by 50% ($P<0.001$) with active therapy. (52) Yosuf *et al* presented the pooled the results of all available trials of intravenous APSAC on a total of about 2000 patients and found a 52% reduction in mortality ($P<0.001$). (53)

The surrogate end point of infarct size, assessed by radionuclide perfusion studies, estimates of left ventricular contraction, and enzymatic estimates of infarct size are also valuable as end points for treatment efficacy although less so than mortality. Data supporting preservation of myocardium have come from several sources, including : thallium-201 perfusion studies and left ventricular angiograms from the Western Washington Intravenous Streptokinase Trial [Kennedy, JW , pp 64-70 in reference (42)], left ventricular angiograms from an intravenous streptokinase trial in New Zealand (54), left ventricular angiograms from the I.S.A.M.study (48), a study of rt-PA at Johns Hopkins, and the TIMI-Phase I trial

(56), and enzyme analysis from the I.S.A.M. study and the European Cooperative trial of rt-PA. (57)

In the last two years a consensus has emerged that thrombolytic therapy should be administered to all well-selected patients if therapy can be applied in a timely way. In patients treated within the first six hours, a reduction in mortality of 25-50% can be expected. For patients treated within the first hour, reduction in mortality may approach 80%. The time dependence of the benefit is remarkable. Therefore a parallel consensus has emerged that it is imperative that emergency departments and mobile intensive care unit facilities be sufficiently organized to provide rapid patient assessment and prompt institution of therapy. Selection of patients is still an area of debate as is the duration of the therapeutic window. Sone of these issues are discussed briefly below.

Patient Selection for Thrombolytic Therapy

Patients who need thrombolytic therapy the most appear to benefit the most. In the GISSI trial, patients with anterior infarcts and infarcts in multiple locations benefited the most. In a reanalysis of their data, the GISSI group has found that the benefit is greater the more leads of the 12-lead electrocardiogram that have significant ST-segment elevation. Three or more leads with significant ST-segment elevation appeared to be a good dichotomizing variable. Patients with evolving Q-wave infarctions are more apt to have persistent totally occlusive thrombus than are patients with evolving non-Q wave infarcts. The ISIS-2 trial found that the benefit was fairly uniform, regardless of infarct location and a large variety of other cardiac risk factors, but subgroup analysis in this study also showed the greatest benefit in patients with anterior infarcts and those in multiple locations. The least benefit was seen in patients with non-Q-wave infarctions. ISIS-2, GISSI, ASSET, and AIMS found that thrombolytic therapy was particularly beneficial in the elderly, who have a high mortality with MI, and that hemorrhagic side-effects were not unduly prominent. Advanced age, therefore, is no longer generally held to be a relative contraindication to thrombolytic therapy. In the last year or two, a consensus has emerged that all patients with evolving Q-wave MI, documented by significant elevation of ST-segments on 3 or more leads of a 12-lead ECG, should routinely receive thrombolytic therapy if there are no contraindications and if it can be administered within 6 hours of the apparent onset of the infarction. Thrombolytic therapy for patients with an apparent acute MI without significant elevation of ST segments, that is patients with evolving non-Q-wave infarctions, is controversial. Some have argued that the benefits seen generally in the ISIS-2 trial should be applied broadly. Others have argued that the rationale for thrombolytic therapy in an evolving non-Q-wave infarction is weaker than for an evolving Q-wave infarction and that sub-group analyses for the non-Q-wave infarction patients do not yield convincing evidence of efficacy. The TIMI-III study is designed to test the hypothesis that thrombolytic therapy is beneficial for patients with evolving non-Q-wave MI. I believe that there is a consensus that patients with evolving non-Q-wave infarctions should not be treated routinely with thrombolytic agents until more supportive data are available.

Based upon findings in experimental animals that infarction is largely complete and irreversible after 6 hours of total occlusion, one would expect that the window for effective fibrinolytic therapy would be short. The remarkable time dependency of the efficacy of therapy to reduce mortality support that expectation. Until the ISIS-2 trial results were available, a consensus had emerged that the appropriate window was 4-6 hours after the onset of symptoms. The results of the ISIS-2 trial, which showed a beneficial effect of thrombolytic therapy on mortality, even when it was administered 13-24 hours after the onset of symptoms requires a reappraisal of that consensus. This findings also requires development of new

hypotheses to explain them. Two principal hypotheses have been advanced. The first, based upon consistent observations, some provided recently from Parkland, is that it is better after MI to have an open infarct-related vessel than a closed one, regardless of the size or location of the infarct. The incidence of post-MI sudden death appears to be greatly reduced in the present of an open infarct-related vessel. An alternative hypothesis is that late thrombolysis might still achieve myocardial salvage in patients who still have some perfusion in the zone at risk, because of non-persistent or non-totally occlusive thrombus or substantial collateral vessel flow. For now, most physicians will probably wish to limit routine thrombolytic therapy to the first 6 hours pending further confirmation of the ISIS-2 data. Further studies of late thrombolytic therapy are under way and results should be available in the next year or two.

What is the Best Thrombolytic Agent?

There are advantages and disadvantages to all of the thrombolytic agents that are currently available or apt to be available in the near future. (58,59) Compare the effects of different fibrinolytic agents on patency, myocardial salvage, and mortality from different studies with considerable caution. Some or all of the apparent differences may be due to study design, patient characteristics, concomitant medications, etc. The most reliable data derive from direct comparisons in the same study. Currently, we have only limited direct comparisons. In the TIMI-Phase I and the European Cooperative Studies, early patency of the involved vessels was significantly better with rt-PA infusion than with streptokinase. There were no important differences in side-effects, including bleeding and stroke. Direct comparisons of mortality are now underway by the GISSI group and the ISIS group. The GISSI group and its international extension, the International t-PA/Streptokinase Study, presented their data in preliminary form in March of this year at the American College of Cardiology meeting, as noted above.. The report included results from 20,981 patients. There were no differences in the endpoints of death or extensive left ventricular damage. Because t-PA administration was not accompanied by administration of heparin in the way that it is usually given by many physicians, this study may not provide unambiguous answers. ISIS-3 has similar design features. For now, practitioners can give streptokinase, t-PA, or APSAC with full assurance that they are giving highly effective therapy.

Comment is due on the issue of bleeding risk with thrombolytic agents. There is now a consensus among most experts in thrombosis and hemostasis that the principle cause of bleeding with fibrinolytic therapy is lysis of hemostatic plugs and failure to form strong hemostatic plugs, not fibrinogen depletion. The fibrin of hemostatic plugs will be lysed as readily by fibrin-selective agents as the fibrin of thrombus. Furthermore, the fibrin-selective agents cause partial degradation of fibrinogen that results in a fibrin web with less tensile strength than normal. Also, fibrinolytic agents may induce platelet defects. (59) Bleeding complications have been and probably will continue to be as frequent with fibrin-selective as with non-fibrin-selective drugs as long as both are given in doses that lead to equivalent fibrinolysis. Fibrinolytic therapy was given to patients in GISSI and ISIS-2 in a manner very similar to current clinical practice. The bleeding risks were acceptably low. Early trials necessarily had a high bleeding rate at the sites of vascular access. As long as patients are well selected and vascular punctures and surgical incisions are avoided, the incidence of hemorrhage from fibrinolytic therapy for MI will be acceptably low.

BETA-ADRENERGIC BLOCKING AGENTS

Early Therapy to Reduce Infarct Size and Lower In-hospital Mortality

Early therapy with beta-adrenergic blockade was proposed well over a decade ago. These hypotheses were raised based upon several notions: that beta blockers would lower heart rate, blood pressure, and cardiac contractility, and thus lower myocardial oxygen demand and hence reduce ultimate infarction size; that the anti-adrenergic actions might lend an antiarrhythmic effect; and that lowered myocardial wall stress might reduce the incidence of myocardial rupture. Reduction in infarct size, as judged by enzyme release or by ECG scoring system, has been demonstrated in 9 studies. (60,61) Reduction in mortality during the in-hospital phase of MI therapy was difficult to demonstrate conclusively and probably accounts in great part for the slow acceptance of this therapy in the US. Only one trial, the ISIS-1 study, a placebo controlled study of intravenous atenolol in 27,500 patients, achieved statistical significance. In this study, mortality was decreased by approximately 15% during the week of treatment ($P<0.05$). (61) Very similar, but not statistically significant results, were obtained in an international trial of metoprolol vs. placebo, the Metoprolol in Acute Infarction (MIAMI) study. (62) Yosuf, in a metanalysis of 27 randomized trials, including ISIS-1 and MIAMI, has estimated that early beta-blocker therapy reduces early death by 13% ($P<0.02$). (29) He further estimated that the risk of death, nonfatal cardiac arrest, and recurrent MI was reduced by 16% ($P<0.001$). The FDA has accepted the claim of an effective protective effect of acute beta-blocker therapy soon after MI and has approved the early use of intravenous metoprolol and atenolol, followed by oral therapy.

A possible beneficial interaction between the use of intravenous thrombolytic therapy and early intravenous beta-blocker therapy has been proposed based upon analysis of the modes of death in clinical trials with these agents. The ISIS-1 group found, in a retrospective analysis, that the reduction in mortality with beta-blockade was due chiefly to a reduction in myocardial rupture. (63) The MIAMI trial and the earlier Gothenberg metoprolol trial (64) also reported trends toward fewer episodes of myocardial rupture. Yosuf has suggested that the opposite may be the case with intravenous thrombolytic therapy. He has noted that streptokinase therapy, although highly beneficial overall, appears to associated with an excess mortality in the first day. In GISSI, there were 120 deaths in the first 6 hours in the streptokinase group but only 76 deaths in the placebo group. A high fraction were reported to be due to electromechanical dissociation. (65) Although details have not yet been published, the ISIS-2 group have indicated at several meetings that streptokinase was also associated with an excess of deaths in the first day of their trial. It is certainly an interesting hypothesis that the combination of an intravenous thrombolytic agent and intravenous beta-blocker provides additive protection, based in part upon the potential for beta-blockers to protect against a possible deleterious effect of thrombolytic therapy. To date, the combination has been tested in only one trial, the TIMI-IIb study, in which Parkland Hospital participated. (66) Thrombolytic therapy with t-PA was followed by random assignment to intravenous beta-blocker or placebo. This study did not find a difference in mortality at 6 days. There were 17 deaths in both groups. But this absence of a difference, in a relatively small study of 1390 patients, is not outside the confidence limits of an expected 15% protection from death. Furthermore, the study reported that the metoprolol treated group had a reduction in early nonfatal recurrent MI (16/696 vs. 31/694, $P<0.005$) and in episodes of recurrent myocardial ischemia (107/696/696 vs. 147/694, $P<0.005$).

Early therapy with intravenous beta-blocker followed by oral therapy should now be considered routine therapy, as long as there are no contraindications to its use. The probable additive effect to thrombolytic therapy strongly recommends its

use in patients who receive intravenous plasminogen activators. This does raise a logistical problem. Instituting intravenous plasminogen activator therapy, which needs to be started as quickly as possible, is time consuming. Instituting beta-blockers intravenously at the same time is difficult and may make evaluation of deleterious effects confusing. Prudence dictates that plasminogen activator therapy should be started first and that beta-blocker should follow as quickly as feasible. Generally that can be about an hour later.

Long-term Beta-blocker Therapy in Survivors of Infarction

Long-term (1-3 years) therapy of survivors of infarction with beta-blockers has been considered routine therapy for several years and will not be discussed in detail today. Long-term therapy reduces both death and recurrent infarction by about one-fourth. A thorough review is available. (60). In light of the results of the trials with early beta-blocker therapy, patients with acute MI with no contraindications should have beta-blocker therapy started as soon as possible after infarction and continued for 1-3 years. Several European studies with beta-blockers with intrinsic sympathomimetic activity (ISA) did not find as much protective benefit as the studies with beta-blocker without ISA. Accordingly, a beta-blocker without ISA should be used. Metoprolol, timolol, atenolol, and propranolol have been found to be effective in well designed long-term clinical trials. There has been a lot of discussion about how widely to apply long-term beta-blocker therapy after MI. There is general agreement among the trials that the protective effects are seen more or less equally across the spectrum of patients with MI. Therefore, more patients are salvaged among high and moderate risk groups than in low risk groups. Because of this observation and the fairly high incidence of non-cardiac side effects with beta-blockers, some physicians have preferred to restrict beta-blocker therapy to patients who are deemed to be at moderate to high risk for post-MI coronary events.

CALCIUM-CHANNEL BLOCKING AGENTS

Evaluating the data of calcium-channel blockers after MI is a much more difficult task than evaluating the data with beta-blockers. Beta-blockers without ISA tend to have actions on the MI patient that are more alike than different. The available calcium-channel blockers, however, have remarkably different properties on the cardiovascular system. These agents may reduce myocardial oxygen demand, and potentially reduce infarct size, by lowering blood pressure, heart rate, and cardiac contractility. Calcium overload of ischemic cells has been proposed as a mechanism for progression from cell injury to cell death, thus providing another putative mechanism for a protective effect. On the other hand, calcium-channel blockers like nifedipine and nicardipine are powerful arterial vasodilators and have the potential to increase heart rate and cardiac contractility by stimulation of adrenergic tone and to cause a coronary steal phenomenon. (Dilation of more normal coronary vessels lowers blood flow to severely diseased coronary beds where maximal dilation is present in the baseline state.) Held *et al* recently identified 21 randomized trials of calcium-channel blockers after MI, studying a total of almost 18,000 patients. (67) Most of the trials were much too small for detection of the reasonably expected differences in mortality and recurrent infarction. I will discuss six trials this morning. Two fairly large trials with nifedipine have been reported. The Trial of Early Nifedipine in Acute Myocardial Infarction (TRENT) studied 4491 patients with suspected myocardial infarction, They were treated with placebo or nifedipine for treated for one month. Just over two-thirds of the patients received therapy within 8 hours of the apparent onset of MI. The same fraction, 0.64, in each group sustained MI. Mortality was 6.3% in the placebo group and 6.7% in the

nifedipine group. Recurrent infarctions occurred in 2.2% of the nifedipine group and in 1.5% of the control group. None of these differences were statistically significant. (68) The Secondary Prevention Israeli Nifedipine Trial - 2 (SPRINT-2) randomly assigned 1358 patients to nifedipine or placebo and continued treatment for six months. Enrollment into this trial was stopped prematurely because of a trend toward excess mortality in the active treatment group. Death was 15% at 6 months with nifedipine treatment vs. 13% in the control patients. (69) Nifedipine (and presumably similar agents such as nicardipine), at least when unopposed by beta-blockers, therefore appear to be of no benefit or slightly harmful as protective agents after MI.

Two fairly large Danish trials with verapamil have been reported. In the first, which was reported in 1984, patients were randomly assigned to intravenous verapamil or placebo followed by oral therapy for six months. (70) The study had an extremely high withdrawal rate in both groups. At 6 months, mortality was 8.4% in the control group and 8.6% in the active therapy group. Fifty patients who were on active therapy had recurrent MI compared to 60 patients in the control group. A second Danish trial was reported at the American Heart Association meeting in October, 1989, demonstrating a protective effective of verapamil. For now, a protective benefit of verapamil remains speculative.

Two trials with diltiazem have received considerable interest. The first was a placebo controlled, randomized trial of diltiazem, begun within the first 72 hours of non-Q-wave infarction and continued for 14 days. Nine centers enrolled 576 patients. Patients treated with diltiazem had 51:% fewer recurrent infarctions and 50% fewer episodes of refractory postinfarction angina. Whether this is a trend or a proved benefit has been the topic of some debate. The decrease in recurrent MI is statistically significant if a one-sided test of the null hypothesis is used, but not if a more conventional two-sided test of the null hypothesis is employed. Mortality was 3.1% in the placebo group and 3.8% in the diltiazem group. (71)

The second trial, the Multicenter Diltiazem Postinfarction Trial (MDPT) was a randomized, placebo controlled trial of diltiazem, begun 3-15 days after MI, and continued for at least 12 months and up to 52 months. Average follow-up was 25 months. Two thousand four hundred and sixty-six patients were enrolled. Total mortality and cardiac mortality were very similar in the two groups. Nonfatal recurrent MI was less frequent in the diltiazem group so that the coronary event endpoint was 11% lower in the diltiazem group (NS). In a sub-group analysis, the study group found a striking difference in mortality events in patients with and without pulmonary congestion when treated with diltiazem. Patients without pulmonary congestion who were treated with diltiazem had a decreased risk of coronary events (hazard ratio 0.77 with 95% confidence limits of 0.61 and 0.98) but patients with pulmonary congestion had an increased risk of coronary events (hazard ratio 1.41 with 95% confidence limits of 1.01 to 1.96. Similar results were seen when left ventricular dysfunction was dichotomized with left ventricular ejection fraction less than 0.40 vs. 0.40 or above. The study group interpreted their data as being suggestive of a bidirectional effect of diltiazem after MI, negative when considerable left ventricular dysfunction was present, protective in its absence.

It has been proposed that routine diltiazem therapy is appropriate to prevent recurrent infarction following non-Q-wave MI in patients without left ventricular dysfunction. (72) This interpretation is based upon the following reasoning: 1. subgroup analyses of the beta-blocker trials of survivors of MI do not show a benefit for patients with non-Q wave MI; 2. diltiazem reduces recurrent MI after non-Q wave MI; and 3. in a subgroup analysis of MDPT, there was overall reduction of coronary events in patients without left ventricular dysfunction. (72) Because of its heavy reliance on subgroup analysis of several clinical trials and a one-sided test of the hypothesis that diltiazem prevents recurrent infarction following non-Q-wave MI,

this interpretation has not been accepted by some experts. Therapy with diltiazem for prevention of recurrent infarction after non-Q-wave this indication has not yet been approved by the FDA. Nevertheless, diltiazem therapy in this setting has been accepted by many practitioners as suitable routine therapy and is widely employed. The practitioner who adopts diltiazem therapy for this indication, must not forget that it is applicable only for those patients who do not have clinically important left ventricular dysfunction.

NITRATES

Nitrates might be useful during and after MI by reducing myocardial wall stress by lowering after-load and pre-load. This action might reduce ultimate infarct size and might prevent left ventricular remodeling, dilation, and aneurysm formation. Nitrates might be helpful by diminishing the toll of left ventricular failure. Nitroglycerin might also be useful by preventing abnormal coronary vasoconstriction.

Yosuf and his colleagues have recently provided an overview of the three published trials of intravenous nitroprusside and the six published trials of intravenous nitroglycerin during MI. (73) About 2000 patients were studied in the 9 trials. Overall, death rate was reduced by about 1/3 ($P<0.001$). The death rate was lower with nitrate therapy in 8 of the 9 studies, statistically significantly so in three. Reduction in death was greater (45%), although not statistically significantly so, with nitroglycerin than with nitroprusside (23%). There is now considerable data in experimental animals and humans that nitroglycerin is generally more beneficial than nitroprusside in acute myocardial ischemia, as a result of the greater tendency of nitroprusside to cause reflex augmentation of adrenergic tone and a coronary steal phenomenon. Accordingly, interest in recent years has focused more on nitroglycerin and organic nitrates with similar activities and less on nitroprusside.

Held *et al* have recently provided a metanalysis of of 5 trials with oral nitrates following MI. These studies included 1081 patients. Nitrates were associated with a 21% reduction in death. This reduction is not statistically significantly lower than the reduction seen with intravenous nitroglycerin. Combining oral and intravenous nitrate therapy, they found a statistically significant 31% reduction in the risk of death which was seen across all subgroups analyzed.

In the last year or two, there has been a growing consensus that nitrate therapy, applied immediately and at least for several months-during infarct healing, is appropriate routine therapy for patients with acute MI. The major risks to keep in mind are hypotension, coronary steal phenomenon, and the rare case of profound bradycardia. When used concurrently with intravenous beta-blocker or streptokinase or both, careful attention must be paid to blood pressure. The consensus to use nitrates has occurred more or less concurrently with the consensuses on the immediate use of thrombolytic therapy and intravenous beta-blockers. There are no data currently available regarding interactive effects of nitrates and thrombolytic agents. Immediate use of these three agents concurrently certainly makes careful organization of CCU care necessary. Sub-lingual nitroglycerin is usually given to patients early in their emergency room care so that the effects of nitroglycerin are usually still present when the decisions to use thrombolytic agents and beta-blockers are being made. I find it attractive to continue nitroglycerin in the first few days by either the intravenous or cutaneous route, because of their short half-lives. Oral or cutaneous administration can be planned for intermediate- or long-term administration.

ACE INHIBITORS

Inhibition of angiotensin converting enzyme might be beneficial following myocardial infarction because decreased pre-load and after-load might reduce ultimate infarct size, prevent left ventricular remodeling, and reduce the toll from left ventricular failure.

Pfeffer and his colleagues in Boston have carried out some preliminary investigations with captopril that support the hypothesis that ACE inhibitors may be protective after MI. They found that captopril administration inhibited the time-dependent increase in left ventricular size in rats after experimental myocardial infarction (74), that captopril attenuated the increase in left ventricular volumes and pressures seen in a control group of patients with acute anterior wall infarction and improved exercise performance (75). A clinical trial of about 2200 patients, Survival and Ventricular Enlargement (S.A.V.E.), is now underway to evaluate the effects of captopril therapy in patients with acute myocardial infarction. (75) Death and development of congestive heart failure are the endpoints of the study. This therapy is highly promising but it cannot now be considered routine. It is still clinical research. It will be important in the future to determine if the effects of nitrates and ACE inhibitors are additive.

ANTI-DYSRHYTHMIC THERAPY

Life-threatening ventricular rhythm disorders kill many patients in the first day of myocardial infarction. It is estimated that as many as one-half of all patients with MI die before entry into the health care system and that most of those deaths are due to ventricular tachycardia and ventricular fibrillation. Following hospital admission, some, but not all, episodes of ventricular fibrillation are heralded by warning ventricular premature beats. Following myocardial infarction, the presence of ventricular premature beats more frequent than 10/hour and in complex forms greatly raise the likelihood of cardiac death in the year after the infarction. As a result, there has been strong interest in the use of antidysrhythmic agents to prevent death from ventricular rhythm disturbances. This interest has centered largely around two hypotheses, that prophylactic antidysrhtyhmic therapy in the first day or two after MI and that antidysrhythmic therapy in survivors of MI who have frequent or complex ventricular premature beats will have a beneficial effects on mortality.

MacMahon *et al* recently provided an overview of 14 trials, with a total of 9,155 patients, who received lidocaine in the early phase of MI. (76) These trials include nine trials in 2194 patients of intravenous lidocaine in the first 48 hours of MI and 5 trials in 6961 patients of intramuscular lidocaine in the first few hours of MI. In 7 of these trials, there were fewer episodes of ventricular fibrillation recorded in the lidocaine group. The results were statistically significant in only one trial. In four trials, there were more episodes of ventricular fibrillation recorded in the lidocaine group. In the overview of all 9 trials, lidocaine administration was associated with a 35% reduction in the odds of development of ventricular fibrillation ($P<0.04$), but was not associated with a reduction in mortality. In fact, early death after MI was about 1/3 more frequent with lidocaine administration. (NS). In the overview of these 9 trials, asystole was about twice as common in the lidocaine treated patients as it was in the control patients. It is conceivable that the benefits of prophylactic lidocaine administration that are realized with suppression of ventricular fibrillation are canceled out by stimulation of asystole. (76) Therefore, prophylactic lidocaine administration in the first 24-48 hours after MI, which has become routine in many hospitals and is still recommended as routine therapy by the current Advanced Cardiac Life Support (ACLS) guidelines of the American Heart Association, must now be seriously questioned. Many experts now recommend that lidocaine should not be administered prophylactically to uncomplicated patients in those situations where expert cardiac resuscitation is immediately available. In patients with frequent

and complex ventricular premature beats , the likelihood of ventricular fibrillation is increased and lidocaine administration for 24-48 hours is prudent.

For many years, routine administration of antiarrhythmic agents was employed by many practitioners in the therapy of survivors of MI with frequent (more than 10/hour) or complex ventricular premature beats. The hypothesis was that suppression of the VPBs would suppress the likelihood of sudden cardiac death. It is well established that such patients experience sudden death at least twice as commonly as patients without frequent or complex VPBs. Clinical trials to test this hypothesis have so far been neutral to negative. Two trials of the Ib (lidocaine-like) agent, mexilitene did not find a protective effect. (77,78) In fact, there was a trend towards higher mortality with active therapy. The Cardiac Arrhtyhmia Suppression Trial (CAST) was organized several years ago to test this hypothesis in a large number of patients. A pilot study preceded it to test the feasibility of a large-scale trial and to find agents that markedly suppressed VPBs in post-MI patients. The part of the trial studying two Ic antiarrhythmic agents, encainide and flecainide, was recently stopped prematurely, because mortality was increased from 3:% to 7.7% ($p<0.001$) in patients treated with these two agents. The trial is continuing with drugs with other antiarrhythmic properties. (79) Most arrhythmia experts now strongly discourage routine use of antiarrhythmic agents for asymptomatic survivors of MI with frequent or complex VPBs as their most severe ventricular rhythm disturbance.

ROUTINE CORONARY RECONSTRUCTION AFTER THROMBOLYSIS

Several of the early streptokinase trials suggested that the down side of successful opening of a coronary vessel might be more episodes of recurrent acute myocardial ischemia: unstable angina, myocardial infarction, and sudden death. The notion was that the events in the coronary artery leading to thrombosis would be likely to recur and that routine angioplasty following successful restoration of coronary patency with thrombolytic agents would reduce episodes of recurrent acute myocardial ischemia. While this may be true, routine coronary angioplasty after thrombolytic therapy that was performed relatively early--in the first few days after MI--has uniformly been found to have no benefit and, in fact, probably to be deleterious, with increased early mortality and morbidity. (66,80,81) Therefore, there is now a consensus among the experts that routine coronary angioplasty in the first few days after successful coronary thrombolysis should be avoided.

What if coronary reconstruction with angioplasty or surgery is delayed, when a routine procedure can be performed more safely? The recently completed TIMI IIB study did not find improved long-term survival after MI when routine coronary reconstruction was applied later in the hospital course. (66) These observations have been confirmed recently by a multicenter British study in 800 patients that was reported in the fall of 1989 at the Congress of the European Society of Cardiology by deBono, *et al.* Nevertheless, these findings are still the topic of spirited debate. Much of the debate revolves around the problem that in these studies some of the patients assigned to conventional therapy eventually came to coronary revascularization because of post-MI myocardial ischemia and some of the patients assigned to coronary reconstruction did not get it as a result of choice or technical problems. I do not sense a consensus on this issue developing across the country yet. At Parkland and the VA, we have generally accepted the findings of these studies and are not routinely recommending post-MI coronary reconstruction in the absence of post-MI myocardial ischemia.

ROUTINE THERAPY--A SUMMARY

Based on the above, I think that the following can be considered reasonable routine plans for pharmacological and procedural therapies of the patient with acute MI in 1990. The patient should receive standard CCU care and be placed into one of the following groups as quickly as possible, based upon history, physical exam, ECG, and laboratory evaluation: 1. evolving Q-wave anterior, antero-septal, or antero-lateral MI; 2. evolving Q-wave inferior, posterior, or lateral MI; 3. evolving non-Q-wave MI. Routine therapy for these groups might then include the following:

(* Indicates that this therapy is recommended if there are no contraindications to its use and administration is not associated with side-effects that would warrant its discontinuation.)

Evolving Q-wave anterior, antero-septal, or antero-lateral MI

1. Immediate aspirin, 162 mg [preferably chewed or given as in a soluble form such as Alka-Seltzer (R)], and 162-324 mg per day for at least 1-2 years.*
2. Intravenous thrombolytic therapy if the patient presents within 6 hours of the apparent onset of MI.*
3. Intravenous or cutaneous nitroglycerin for 2-3 days followed by cutaneous or oral nitrates for 3-4 months.*
4. Intravenous metoprolol or atenolol, according to published and approved protocols, begun as soon as feasible after thrombolytic therapy is instituted, if the patient presents within 12 hours of the apparent onset of the infarct. Follow intravenous therapy with oral metoprolol or atenolol. If the patient presents more than 12 hours after onset of infarction, commence oral beta-blocker as early as possible. In either case treat with oral metoprolol, atenolol, timolol, or propranolol for 1-3 years. Beta-blocking doses must be given.*
5. Intravenous heparin administration to achieve full anticoagulation. Begin concurrently with t-PA. Delay 12-24 hours or until the thrombin time becomes measurable with streptokinase or APSAC (or urokinase if it receives FDA approval for intravenous use). Full anticoagulation with heparin, followed by warfarin, for 3 months. Long-term full anticoagulation may be indicated if the patient has a history of atrial fibrillation, thromboembolism, advanced heart failure, need for prolonged bedrest, etc.*
6. Observe carefully for myocardial ischemia and other major complications that would put the patient in a high-risk category. Note that many if not most of these patients will be found to be in a high-risk category based upon bedside observations. Plan risk stratification if the patient is a potential candidate for coronary revascularization and high-risk status is not obvious from observation. Patients found to be in a high-risk category should undergo coronary arteriography late in their hospital course. Plan coronary revascularization if coronary anatomy, functional testing, and clinical judgment indicate probable benefit.
7. Intravenous lidocaine only if warning VPBs are present or if immediate expert cardiac resuscitation may not be available. Long-term antidysrhythmic therapy only for symptomatic VPBs, atrial dysrhythmias, or for life-threatening ventricular rhythm disturbances (sustained ventricular tachycardia or ventricular fibrillation) that occur later than the first 48 hours post-MI.

Evolving Q-wave Inferior, Posterior, or Lateral MI (with at least 3 ECG leads showing significant ST-segment elevation).

1. Immediate aspirin, 162 mg [preferably chewed or given as in a soluble form such as Alka-Seltzer (R)], and 162-324 mg per day for at least 1-2 years.*
2. Intravenous thrombolytic therapy if the patient presents within 6 hours of the apparent onset of MI.*
3. Intravenous or cutaneous nitroglycerin for 2-3 days followed by cutaneous or oral nitrates for 3-4 months.*
4. Intravenous metoprolol or atenolol, according to published and approved protocols, begun as soon as feasible after thrombolytic therapy instituted, if the patient presents within 12 hours of the apparent onset of the infarct. Follow intravenous therapy with oral metoprolol or atenolol. If the patient presents more than 12 hours after onset of infarction, commence oral beta-blocker as early as possible. In either case, treat with oral metoprolol, atenolol, timolol, or propranolol for 1-3 years. Beta-blocking doses must be given.*
5. If thrombolytic therapy is administered, commence intravenous heparin administration to achieve full anticoagulation. Begin concurrently with t-PA. Delay 12-24 hours or until the thrombin time becomes measurable with streptokinase or APSAC (or urokinase if it receives FDA approval for intravenous use). Continue for 2-3 days or until coronary arteriography, if planned. Replace with low-dose sub-cutaneous heparin until the patient is ambulatory. If thrombolytic therapy is not administered, low-dose sub-cutaneous heparin should be begun as soon as possible and continued until the patient is ambulatory. In both cases, long-term full anticoagulation may be indicated if the patient has a history of atrial fibrillation, thromboembolism, advanced heart failure, need for prolonged bedrest, etc.*
6. Observe carefully for myocardial ischemia and other major complications, that would place the patient in a high-risk category. Plan risk stratification testing if the patient is a candidate for coronary revascularization and high-risk status is not already obvious from observation. Patients stratified to high risk should undergo coronary arteriography late in the hospital course. Plan coronary revascularization if coronary anatomy, functional testing, and clinical judgment indicate probable benefit.
7. Intravenous lidocaine only if warning VPBs present or if immediate expert cardiac resuscitation may not be available. Long-term antidysrhythmic therapy only for symptomatic VPBs, atrial dysrhythmias, or for life-threatening ventricular rhythm disturbances (sustained ventricular tachycardia or ventricular fibrillation) that occur later than the first 48 hours post-MI.

Evolving Non-Q-Wave MI

1. Immediate aspirin, 162 mg [preferably chewed or given as in a soluble form such as Alka-Seltzer (R)], and 162-324 mg per day for at least 1-2 years.*
2. Intravenous or cutaneous nitroglycerin for 2-3 days followed by cutaneous or oral nitrates for 3-4 months.*
3. Intravenous metoprolol or atenolol, according to published and approved protocols, begun as soon as feasible if the patient presents within 12 hours of the apparent onset of the infarct. Follow intravenous therapy with oral metoprolol or atenolol. If the patient presents more than 12 hours after onset of infarction, commence oral beta-blocker as early as possible. In either case treat with oral metoprolol, atenolol, timolol, or propranolol for 1-3 years. Beta-blocking doses must be given. An alternate regimen, for the patient with no pulmonary congestion or other evidence of clinically important left ventricular dysfunction, may be to initiate

diltiazem therapy within 24-72 hours with 90 mg every six hours and to continue it for 1-2 years.*
4. Low-dose sub-cutaneous heparin should be begun as soon as possible and continued until the patient is ambulatory. Long-term full anticoagulation may be indicated if the patient has a history of atrial fibrillation, thromboembolism, advanced heart failure, need for prolonged bedrest, etc.*
5. Observe carefully for myocardial ischemia and other major complications, that would place the patient in a high-risk category. Plan risk stratification testing if the patient is a candidate for coronary revascularization and high-risk status is not already obvious from observation. Patients stratified to high risk should undergo coronary arteriography late in the hospital course. Plan coronary revascularization if coronary anatomy, functional testing, and clinical judgment indicate probable benefit.
6. Intravenous lidocaine only if warning VPBs present or if immediate expert cardiac resuscitation may not be available. Long-term antidysrhythmic therapy only for symptomatic VPBs, atrial dysrhythmias, or for life-threatening ventricular rhythm disturbances (sustained ventricular tachycardia or ventricular fibrillation) that occur later than the first 48 hours post-MI.

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