Acute Myocardial Infarction*
Then and Now

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Dramatic changes in the management of acute myocardial infarction (AMI) have occurred in the past decade. While previous management strategies were primarily supportive, current strategies focus on achieving and maintaining patency of the infarct-related artery restoring blood flow to jeopardized myocytes, preserving left ventricular function, and preventing recurrences and complications in addition to promoting healing. Restoration of blood flow can be achieved pharmacologically with thrombolytic agents or mechanically with percutaneous transluminal coronary angioplasty (PTCA). Early use of antiplatelet agents and anticoagulants helps maintain patency of the infarct-related arteries and prevents thromboembolic complications. Administration of beta-blockers and angiotensin enzyme inhibitors are more specific means of conserving myocardium and preserving ventricular function. Additionally, several strategies for preventing arrhythmias such as prophylactic lidocaine use and routine long-term suppression of premature ventricular contractions with antiarrhythmic drugs are no longer routinely advocated. Basically, in the era prior to the eighth decade of this century, the primary direction of the therapeutic strategy for AMI was to reduce the oxygen demands in the infarcted myocardiun; whereas in the subsequent years, the emphasis shifts to improvement in oxygen delivery, via thrombolysis, PTCA, and coronary artery bypass graft surgery. These interventional changes, when added to greater sophistication in the use of drugs to reduce oxygen demands, resulted in significant lowering of myocardial mortality.

Over the past decade, improvements in the therapy of acute myocardial infarction (AMI) have contributed to a decrease in early mortality from >20% to <10%. The changes that have taken place are illustrated in a review of the treatment of two patients who presented a decade apart with an AMI.

CASE HISTORY 1985

A 76-year-old man was admitted to the hospital with 7 h of crushing substernal chest pain associated with nausea and diaphoresis. He was in moderate distress with a regular pulse at a rate of 105 beats/min, a blood pressure of 140/80 mm Hg, a temperature of 37°C, and an S4 gallop. The chest radiograph was normal. The electrocardiogram demonstrated sinus tachycardia with 2-mm ST segment elevations in V1-V5 with reciprocal ST segment depressions in the inferior leads.

He was admitted to the cardiac care unit where he received an 8-mg bolus of intravenous morphine, a 75-mg bolus of intravenous lidocaine followed by a 2-mg/min infusion, and heparin 5,000 U subcutaneously every 12 h. He was pain free on the second hospital day. On the third hospital day, a left ventricular heave was palpated and basilar rales were heard. He was treated with 40 mg of furosemide intravenously followed by 20 mg of furosemide orally daily, and 0.125 mg of digoxin daily.

He was transferred to an intermediate unit for monitoring on the fourth hospital day and allowed

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out of bed with meals. Treatment with isosorbide dinitrate, 10 mg every 6 h, was begun. Premature ventricular contractions (35/h) were noted, and he was started on a regimen of quinidine gluconate, 324 mg orally every 8 h. Over the next 5 days he gradually increased his ambulation. A multiple gated acquisition scan showed an ejection fraction of 28%. A low-level exercise treadmill test on the tenth hospital day demonstrated no chest pain, arrhythmias, or ischemic ST segment changes.

He was discharged from the hospital on a regimen of digoxin, quinidine gluconate, isosorbide dinitrate, and furosemide. He was advised to start a cardiac rehabilitation program, avoid intimacy, and not to return to work for a 2-month period.

Six weeks later, he was hospitalized with congestive heart failure. Furosemide dosage was increased to 40 mg orally twice daily, and treatment with hydralazine, 25 mg orally every 6 h, was started. Twelve weeks after his initial hospitalization, he experienced a left hemispheric transient ischemic attack. Two-dimensional echocardiography showed akinesis of the anterior wall and apex with a protruding apical thrombus. Warfarin therapy was begun.

**CASE HISTORY 1995**

A 64-year-old man with a history of hypertension, tobacco use, and hypercholesterolemia presented with the new onset of 2 h of severe, substernal chest pain radiating to the left arm, shortness of breath, and diaphoresis. He appeared to be in moderate distress with a pulse of 104 beats/min, a blood pressure of 170/90 mm Hg, and a temperature of 37.3°C. There was a faint left carotid bruit, bibasilar rales, and an atrial gallop. The chest radiograph was normal.

The electrocardiogram revealed sinus tachycardia, first-degree atrioventricular block, and an evolving acute anterior wall myocardial infarction. Nitroglycerin, 0.4 mg, was given sublingually three times without relief of the chest pain. Tissue plasminogen activator and metoprolol were given intravenously; aspirin was given orally (chewed).

The patient was admitted to the coronary care unit where intravenous nitroglycerin and heparin therapy was begun. Ninety minutes later, the patient remarked that his chest discomfort had resolved, but he had begun to experience palpitations. Repeated electrocardiogram revealed almost complete resolution of the previous ST segment elevations; however, frequent multif orm ventricular premature beats, ventricular couplets and triplets, and intermittent episodes of accelerated idioventricular rhythm at 72 beats/min were noted on telemetry. The patient's ventricular ectopy subsequently resolved without further therapy, and on the second hospital day he felt well enough to sit in a chair. He ambulated briefly on the third hospital day; an echocardiogram was done that showed overall normal left ventricular function with anteroapical and septal hypokinesis and a possible apical mural thrombus. Captopril and warfarin therapy was initiated with doses adjusted to therapeutic end points. Intravenous nitroglycerin therapy was discontinued. The patient continued cardiac rehabilitation. On the seventh hospital day, the patient underwent submaximal exercise testing on a modified Bruce protocol ambulating 9 min without chest pain or shortness of breath to a peak heart rate of 122 beats/min. On the eighth hospital day the patient was discharged from the hospital with metoprolol, warfarin, aspirin, and captopril for follow-up lipid and international normalized ratio testing by his local physician.

Regarding the current treatment of AMI:

1. Absolute contraindication to thrombolytic therapy includes which of the following?
   a. suspected aortic dissection
   b. age >70 years
   c. previous hemorrhagic stroke
   d. significant surgery within 2 weeks
   e. uncontrolled hypertension
   f. presentation more than 12 h after the start of infarction
   g. actively bleeding duodenal ulcer
   h. intracranial neoplasm

2. What are some of the potential effects of choosing recombinant human tissue-type plasminogen activator (rt-PA) compared with streptokinase?
   a. a 14% greater relative reduction in mortality compared with streptokinase
   b. an increased incidence of disabling stroke
   c. a higher rate of early patency at 90 min
   d. a higher rate of late infarct-related artery patency at 48 to 72 h
   e. a higher rate of hemorrhagic stroke

3. What is the optimal use of diagnostic cardiac catheterization and percutaneous transluminal coronary angioplasty (PTCA)?
   a. immediate PTCA following thrombolysis
   b. routine angiography with delayed or prophylactic PTCA following thrombolysis
   c. elective PTCA for an ischemic end point following thrombolysis
   d. primary or direct PTCA without thrombolysis

4. What is the optimal loading dose of aspirin?
   a. 30 mg
   b. 80 mg
   c. 160 to 325 mg
   d. 500 mg
   e. 750 mg
5. The consequences of high-dose intravenous heparin include the following:
   a. a decreased incidence of deep vein thrombophlebitis and pulmonary embolism
   b. a decreased incidence of mural left ventricular thrombus and systemic embolization
   c. a decreased incidence of reocclusion of a reperfused infarct-related artery following rt-PA
   d. an improved 90-min thrombolytic reperfusion rate
   e. an increased incidence of hemorrhagic complications

6. In our patient, which of the following statements are true?  
   a. early administration of intravenous beta-blockers will decrease early mortality and reinfarction
   b. early administration of intravenous magnesium will decrease early mortality and reinfarction
   c. administration of angiotensin converting enzyme inhibitors 3 days postinfarction will decrease mortality and reinfarction
   d. administration of low-dose intravenous nitroglycerin will lower left ventricular end-diastolic pressure, increase cardiac output, and offer a trend toward decreased mortality
   e. administration of calcium channel blockers will decrease mortality and reinfarction

7. In our patient, which of the following statements are true?  
   a. early ambulation will decrease the incidence of venous thrombosis and cardiovascular deconditioning
   b. use of exercise thallium myocardial perfusion scanning would be more sensitive for predicting future cardiac events than exercise stress testing alone
   c. a normal postinfarction symptom-limited exercise stress test has a negative predictive value of approximately 90% for future cardiac events
   d. lowering cholesterol level will likely reduce the risk of future cardiac events
   e. continuing therapy with oral beta-blockers after hospital discharge will reduce total mortality, reinfarction, and sudden cardiac death for up to 2 years postinfarction
   f. clinical variables can be identified that would predict those patients who are at little or no risk from early discharge from the hospital
   g. all of the above

Answers

1. a, c, d, e, g, and h

Thrombolytic agents that are essentially plasminogen activators activate the fibrinolytic enzyme system by first converting the inactive endogenous proenzyme plasminogen to the active enzyme plasmin. Free plasmin is very rapidly neutralized by the serine proteinase inhibitor serpin to lyse thrombus in infarct-related coronary arteries. The angiographic demonstration of intracoronary thrombus in close to 90% of patients during the early stages of AMI led to several large randomized trials of intravenous thrombolytic therapy in AMI, including the Gruppo Italiano per lo Studio della Streptochinasi nell’Infarto Miocardico (GISSI-1), the Second International Study of Infarct Survival (ISIS-2), the APSAC Intervention Mortality Study (AIMS), and the Anglo-Scandinavian Study of Early Thrombolysis (ASSET). These trials compared the intravenous thrombolytic agents streptokinase, anisoylated plasminogen streptokinase activator complex (APSAC), and rt-PA with placebo and showed a significant relative reduction in mortality ranging from 18 to 48%. Although these initial trials established the efficacy of these three thrombolytic agents, the trials also raised several important issues. These issues included patient selection criteria for treatment (especially with regard to advanced age and late presentation), use of adjunctive agents to enhance and maintain coronary artery patency, choice of thrombolytic agent, total dose of the agent, and the role of mechanical revascularization.

Initially, elderly patients were excluded from treatment because of the potential adverse effects, in particular, intracerebral hemorrhage. Most studies have shown a twofold increase in intracerebral hemorrhage in patients 70 years of age or older. However, the elderly also experienced a higher early mortality of 20 to 30% from AMI, suggesting that they have the greatest potential to benefit. Pooled data from the four previously mentioned trials showed a relative reduction in mortality of 18%. Therefore, patients experiencing AMI should be considered for thrombolytic therapy without an absolute age cutoff. However, in the 70 years and over age group, angioplasty in skilled hands is a proven alternative (see below).

The time dependency for reperfusion was suggested by experimental models of coronary ligation. In GISSI-1, streptokinase reduced mortality by 47% in patients receiving therapy within 1 h of symptoms onset, by 27% within >5 h, and by 20% between 3 and 6 h. The data strongly suggested a time cutoff where the benefits of thrombolysis would be outweighed by the risks. Nevertheless, in ISIS-2, patients receiving
rt-PA within 12 h of symptom onset had a significant reduction in mortality, and those receiving rt-PA between 12 and 24 h enjoyed a reduction in mortality that approached statistical significance. In the Late Assessment of Thrombolytic Efficacy (LATE) study and the Estudio Multicentrico Estreptoquinasa Republicas de American del Sur (EMERAS) study, rt-PA and streptokinase, respectively, resulted in a trend toward a survival benefit in patients treated between 12 and 24 h and 7 and 12 h after symptom onset, respectively.

Based on this work, any patient, regardless of age, presenting with symptoms suggestive of AMI and 1-mm ST segment elevation in two contiguous electrocardiogram leads who present within 24 h of symptom onset should be considered for thrombolytic therapy. For patients presenting in the 12- to 24-h time frame, a careful individualized analysis of risk-benefit ratio should be made. 

Contraindications to thrombolytic therapy include a history of cerebral vascular accident (especially hemorrhagic), intracranial neoplasm, arteriovenous malformation or aneurysm, bleeding diathesis, recent (within 2 months) intracranial, spinal, or major surgery at a noncompressible site, significant surgery within 2 weeks, uncontrolled hypertension, pericarditis, aortic dissection, and any active bleeding.

The need for adjunctive agents to maintain recanalization achieved by thrombolytic therapy is emphasized by the high (10 to 30%) incidence of reoclusion and by a failure to initially achieve recanalization in 15 to 20% of patients despite the use of the most aggressive protocols. A paradoxical state of thrombogenesis is induced by thrombolytic therapy that appears to be associated with both the activation of platelets and the coagulation cascade by the reexposure of blood to injured endothelium and thrombin in the residual thrombus. Therefore, adjunctive therapy combining antithrombotic agents and antiplatelet agents is rational.

Aspirin inhibits platelet aggregation by irreversibly acetylating cyclo-oxygenase, an enzyme required for the synthesis of thromboxane A2 (a potent stimulus of platelet aggregation, and subsequent thrombosis). In ISIS-2, aspirin alone resulted in a 23% reduction in mortality when compared with placebo. When aspirin was combined with streptokinase, there was a 42% reduction in mortality from AMI compared with placebo. Aspirin should be given early to all patients with AMI; the loading dose of aspirin is at least 160 mg. The role of heparin as an adjunctive therapy is less clear cut. In both GISSI-2 and ISIS-3, delayed subcutaneous heparin therapy did not improve survival and was associated with an increased incidence of bleeding. Both trials have been criticized because the use of heparin was delayed; to our knowledge, no trials of adequate size have demonstrated a mortality benefit of heparin. However, when using rt-PA, intravenous heparin appears important for maintaining early patency. Although the data are incomplete, American College of Cardiology/American Heart Association (ACC/AHA) guidelines recommend the immediate use of intravenous heparin and maintaining the partial thromboplastin time (PTT) at 2 to 2½ times the control for 5 to 7 days. 

2. a, b, c, and f

Fibrin-selective agents, with a relative affinity for fibrin within clots such as rt-PA and prourokinase, were developed. These agents preferentially activate plasminogen within clots, without activating systemic plasminogen with the goal of achieving higher and faster rates of reperfusion while reducing bleeding complications. Studies have demonstrated that rt-PA results in higher early reperfusion rates than streptokinase. However, in GISSI-2, which compared streptokinase and rt-PA, and in ISIS-3, which compared streptokinase, APSAC, and rt-PA, there was no advantage in survival observed among the three fibrinolytic agents. GISSI-2 and ISIS-3 were criticized because of the use of delayed subcutaneous heparin therapy that was believed to favor the nonfibrin-selective agents.

To address these issues, the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) study compared streptokinase administered with subcutaneous heparin, streptokinase administered with intravenous heparin, combined rt-PA and streptokinase administered with intravenous heparin, and an accelerated dosage schedule of rt-PA with intravenous heparin. The latter schedule consisted of a 15-mg bolus of rt-PA, with two thirds of the conventional dose given in the first half hour and the remainder infused over the subsequent hour. This schedule had been shown to attain a remarkable 85% recanalization rate. In GUSTO, rt-PA was demonstrated to have a 14% greater survival benefit compared with the streptokinase regimens. Approximately 50% of the survival benefit was noted at 24 h, implying that early reperfusion was responsible for its advantage. Although an increased incidence of disabling hemorrhagic stroke was noted with rt-PA, for every 1,000 patients presenting with an AMI, there were 9 more survivors without disabling stroke in the rt-PA group. Furthermore, the favorable survival achieved by rt-PA compared with streptokinase was due to a superior 90-min patency rate (81% vs 54%). There were no significant differences in infarct-related artery patency rates among the four thrombolytic regimens after 3 h validating the open artery hypothe-
sis that states that the beneficial effects of thrombolysis are due to myocardial salvage by early reperfusion. Nevertheless, some investigators have questioned the conclusion that rt-PA is the thrombolytic agent of choice because the survival advantage achieved with rt-PA, although significant, was small. Currently, no single thrombolytic protocol is considered to be ideal.\textsuperscript{28,29}

3. c and d

At best, thrombolytic therapy restores the occluded artery to the diseased state that existed prior to intervention, leaving many patients at risk for reocclusion and recurrent ischemic events. Recurrent ischemia or infarction occurring early has been noted in 15 to 20\% of patients after thrombolysis\textsuperscript{15} and may lead to dissipation of an early survival advantage at 1 year of follow-up.\textsuperscript{30} Noninvasive methods have limited effectiveness in predicting clinical status.\textsuperscript{31} Therefore, routine coronary angiography was carried out in many hospitals in the mid 1980s. Despite the logic of this approach, four major studies have failed to show a survival advantage or other clinical benefits of routine coronary angiography. Three of the trials, the European Cooperative Study Group trial, the Thrombolysis in Myocardial Infarction (TIMI) II A substudy, and the Thrombolysis and Angioplasty in Myocardial Infarction trial, found no differences in infarct size or left ventricular ejection fraction between patients undergoing immediate angiography and PTCA after thrombolysis vs a more conservative approach. Additionally, patients in the more invasive arms of the studies tended to have more adverse events, including an increased early mortality, higher rate of recurrent ischemia, and increased requirements for emergency bypass surgery and blood transfusions.\textsuperscript{32-34} In TIMI II, despite a marked anatomic improvement in the infarct-related arteries of the patients who underwent routine delayed PTCA after thrombolysis, there were no differences in mortality, reinfarction, or ejection fraction when compared with patients who underwent PTCA only for an ischemic end point.\textsuperscript{35} In general, patients who have received thrombolytic therapy for AMI are referred for coronary angiography if they have spontaneous ischemia or inducible ischemia with noninvasive testing. Patients with congestive heart failure or significant left ventricular dysfunction due to previous infarction or a large current infarction are considered for coronary angiography on an individual basis.

Direct or primary PTCA without thrombolysis avoids the hemorrhagic complications of thrombolytics, and the severity of the underlying stenosis caused by the atherosclerotic plaque in the infarct-related artery is immediately reduced.\textsuperscript{36} In two trials, primary PTCA produced higher patency rates and less residual stenosis than thrombolysis, as well as reduced mortality, recurrent ischemia and infarction, and was associated with fewer hemorrhagic strokes.\textsuperscript{37,38} In the trial conducted by the Primary Angioplasty in Myocardial Infarction Study Group, benefits were particularly evident in patients older than 70 years, in those with anterior infarctions, and patients presenting with sinus tachycardia. A third trial found equivalent myocardial salvage with direct angioplasty and thrombolytics in AMI.\textsuperscript{39} Primary angioplasty can be applied only in the minority of hospitals in which the cardiac catheterization laboratory and surgical back-up can be rapidly mobilized. Even in these hospitals, primary angioplasty is logistically challenging. However, primary angioplasty is considered for patients who have absolute contraindications to thrombolytics, patients with symptoms suggestive of infarction and nondiagnostic electrocardiograms, patients with AMI and previous coronary artery bypass surgery, patients in cardiogenic shock or with anterior infarction or older than 70 years of age, those with persistent sinus tachycardia, and hospitalized patients with unstable angina who develop AMI. In summary, primary PTCA without antecedent thrombolysis and elective PTCA for an ischemic end-point after thrombolysis have therapeutic roles while immediate and routine delayed PTCA after thrombolysis do not.

4. c

Aspirin given during the initial stages of myocardial infarction exerts an independent beneficial effect on early mortality following myocardial infarction in patients whether they do or do not receive thrombolytics. In ISIS-2, 160 mg of aspirin given during the first 24 h of infarction reduced 30-day mortality by 23\% and reinfarction by 49\%. The survival benefits of aspirin as the sole agent were similar in magnitude to that seen with streptokinase alone.\textsuperscript{3} Aspirin may also be effective for secondary prevention in survivors of myocardial infarction; the benefits in secondary prophylaxis are more modest but relevant because of the large number of patients at risk. Of the six large randomized trials that evaluated aspirin in the secondary prevention of recurrent myocardial infarction and death, five studies showed a statistically nonsignificant trend for the reduction of mortality.\textsuperscript{40-44} One study showed aspirin to have a deleterious effect on mortality.\textsuperscript{45} A meta-analysis of antiplatelet therapy trials in secondary prevention after myocardial infarction revealed that aspirin therapy resulted in a 13\% reduction in mortality and a 31\% reduction in reinfarction rate.\textsuperscript{46} The optimal dose of aspirin for treating myocardial infarction remains controversial despite exten-
sive research. As little as 30 mg/d of aspirin may inhibit platelet cyclooxygenase and suppress thromboxane A2 synthesis by 80%.14 Doses ranging from 75 mg to 1,500 mg have been shown to have beneficial clinical effects.45 Since gastrointestinal bleeding is related to dose, there is an advantage to using the smallest effective dose.49 Nevertheless, if small doses are administered, a loading dose of 160 mg to 325 mg is recommended. Despite the efficacy, simplicity, and low cost of aspirin, only 72% of patients with infarction receive aspirin in the United States.30

5. a, b, c, and e

Heparin is also an important pharmacologic agent for the treatment of myocardial infarction in patients who are not candidates for thrombolytic therapy. The incidence of deep vein thrombophlebitis in patients with AMI is 17 to 38%. More than half of these episodes occur within 3 days of initial presentation. Congestive heart failure, shock, prolonged immobilization, and advanced age predispose to a higher incidence of thrombophlebitis. Full-dose heparin therapy was shown to be effective in preventing deep vein thrombophlebitis in the 1970s.51 Low-dose heparin therapy (5,000 U every 12 or every 8 h) acts by minor alterations in the coagulation cascade, and therefore, has the advantage of not increasing bleeding complications. The pooled results of three trials showed that low-dose heparin therapy, when begun early in patients with myocardial infarction, decreased the incidence of deep vein thrombophlebitis from 23 to 4%.51-54 Low-dose heparin therapy (5,000 U subcutaneously every 12 h) is routinely recommended for all patients with AMI for 48 h. High-risk patients with large infarctions, age older than 70 years, hemodynamic instability, obesity, history of venous disease, and prolonged immobilization require low-dose heparin therapy until fully ambulatory. Left ventricular thrombus and systemic arterial embolization are predominantly complications of anterior wall myocardial infarction.55 Most left ventricular thrombi form in the first few days following infarction. High-dose heparin (12,500 U subcutaneously every 12 h) administered early to patients with anterior infarctions reduced the incidence of ventricular thrombus from 32 to 11% in one study,56 and from 37 to 18% in a second study.57 Accordingly, high-dose heparin administered either subcutaneously or intravenously is recommended for all patients with anterior wall Q-wave infarction for the duration of hospitalization. In patients who have left ventricular thrombi or large areas of akinesia in the apical anterior segment showed on two-dimensional echocardiography, warfarin therapy is recommended for the next 3 months. The pathogenesis of non-Q-wave infarction and unstable angina is believed to be similar. Subtotal obstruction of a coronary artery or total occlusion followed by spontaneous recanalization and reperfusion can conceivably lead to both unstable coronary syndromes.58 Since heparin is effective in preventing progression of unstable angina, a role for heparin in preventing recurrent ischemic events in non-Q-wave infarction has been postulated. No large randomized trials have shown a beneficial effect for heparin on ischemic recurrences following myocardial infarction.60 Nevertheless, intravenous heparin is used by many practitioners for non-Q-wave myocardial infarctions.

Warfarin impacts the natural history and prognosis of infarction by preventing four of the thrombosis-related sequelae of infarction: early reinfarction, late recurrent infarction, left ventricular thrombi with systemic arterial embolism, and deep venous thrombosis with pulmonary embolism.21,61 However, the use of anticoagulants in patients with AMI has been controversial.61 After widespread use in the 1940s and 1950s, the use of warfarin declined dramatically during the 1960s and 1970s. Inconclusive trials hampered by inadequate sample size and second- and third-day bedside arm chair treatment in the coronary care unit following an AMI as well as earlier amputation contributed to this decline.62 In 1977, a meta-analysis of six trials showed that the early use of heparin followed by oral anticoagulants resulted in a 21% reduction in early mortality and a 48% reduction in thromboembolic complications.63 Furthermore, in the 60-Plus Reinfarction Study, patients receiving long-term anticoagulants therapy had a 26% reduction in mortality and a 55% reduction in the incidence of reinfarction over a 2-year follow-up.64 In the Warfarin Reinfarction Study, warfarin-treated patients had a 24% reduction in mortality and 34% reduction in reinfarction over a 3-year period.65 Currently, the role of warfarin has been overshadowed by heparin, which is extremely effective in preventing systemic and venous thromboembolic complications and by aspirin, which is effective in preventing early and late reinfarction. Treatment with oral anticoagulants and aspirin appears to produce similar benefits in mortality and reinfarction.66 Oral anticoagulants cause more hemorrhagic complications while aspirin causes more adverse gastrointestinal effects.66 At the present time, aspirin is more widely used than warfarin because of ease of administration, not requiring expensive laboratory monitoring, and lower incidence of bleeding. Nevertheless, warfarin can be used in place of aspirin and may be preferred in patients with large anterior wall myocardial infarction, particularly if complicated by congestive heart failure, left ventricular thrombus, a systemic embolic event, deep vein thrombophlebitis, persistent atrial fibrillation, or dif-
fuse left ventricular dysfunction. With the exception of persistent atrial fibrillation and diffuse left ventricular dysfunction that require long-term anticoagulation, warfarin therapy generally should be continued for 3 months at which time it can be replaced with aspirin.\textsuperscript{61} Currently ongoing investigations evaluate the combined use of aspirin and low-dose warfarin since each block different pathways of the clotting system.

6. \textit{a, c, and d are true}

The Goteburg Metoprolol Trial\textsuperscript{67} examined the use of the \textit{β}-adrenergic blocker, metoprolol, or placebo in suspected myocardial infarction within 48 h of presentation. At 3 months, total mortality was reduced by 36%, fatal and nonfatal reinfarction by 35%, and ventricular fibrillation episodes by 65%. The mortality benefit was sustained at 1 year. The Metoprolol in Acute Myocardial Infarction study\textsuperscript{68} examined intravenous metoprolol vs placebo within 24 h of symptom onset in patients suspected of myocardial infarction. Oral metoprolol therapy was continued for 15 days. Although 15-day total mortality was not statistically different in the two groups, certain subgroup risk factors (including heart failure, advanced age, previous infarction, diabetes, and hypertension) predicted improved survival from metoprolol. The First International Study of Infarct Survival (ISIS-1) trial\textsuperscript{69} showed a benefit of 1 week of atenolol therapy in vascular (cardiac or cerebral) mortality that was evident on day 1 and persisted for 2 weeks. A substudy of the TIMI II trial\textsuperscript{70} that principally examined mortality after thrombolytics in patients with planned or expectant angioplasty showed that early intravenous metoprolol therapy vs deferred (day 6) oral metoprolol therapy resulted in significantly less recurrent ischemia and fewer nonfatal reinfarctions in the first 6 days. The reinfarction benefit continued to 7 weeks.

Magnesium lowers systemic vascular resistance, decreases platelet aggregation, dilates coronary arteries, and protects myocardium from reperfusion injury. A meta-analysis of 930 patients in eight trials showed a 49% reduction in incidence of ventricular tachycardia/fibrillation and a 54% reduction in mortality from myocardial infarction in treated patients.\textsuperscript{71} The Second Leicester Intravenous Magnesium Intervention Trial (LIMIT II) randomized 2,319 patients to intravenous magnesium or placebo therapy within 24 h of suspected AMI. Twenty-eight-day mortality was 7.8% and 10.3% in the treated and placebo groups, respectively, a 24% relative reduction.\textsuperscript{72} However, in ISIS-4 (Fourth International Study of Infarct Survival) with 50,000 patients, magnesium did not show benefit on 35-day mortality.\textsuperscript{73} In view of the disparity in the results of the various trials, the routine use of magnesium within the first 24 h of an AMI is on hold. However, some centers continue using magnesium routinely.

In animal models of myocardial infarction, angiotensin converting enzyme (ACE) inhibitors prevented the progressive acute and chronic changes in ventricular geometry related to infarct size and hemodynamic stresses. Clinical trials showed that ACE inhibitors stopped progressive postinfarction left ventricular dilatation in patients with mildly to moderately depressed left ventricular function.\textsuperscript{74} In the Survival and Ventricular Enlargement trial, patients with a left ventricular ejection fraction of 40% or less, randomized 3 to 16 days postinfarction to receive captopril, showed a 25% risk reduction for all-cause mortality compared with placebo.\textsuperscript{75} The Acute Infarction Ramipril Efficacy study (AIRE) reported a 27% risk reduction in all-cause mortality for patients manifesting heart failure 3 to 10 days postinfarction randomized to ramipril (vs placebo).\textsuperscript{76} However, when intravenous enalapril was administered within the first 24 h of infarction in the Second Cooperative New Scandinavian Enalapril Survival Study (CONSENSUS II) trial, no difference was seen in 6-month mortality; hypotension noted in 25% of treated patients may have confounded the data.\textsuperscript{77} The question of early treatment was reinvestigated in the GISSI-3 trial in which patients were randomized to receive lisinopril, transdermal nitroglycerin, neither, or both within 24 h. Patients allocated to lisinopril therapy had an 11% 6-week mortality reduction (compared with placebo alone).\textsuperscript{78} As was noted in CONSENSUS II, treated patients were significantly more likely to have persistent hypotension and renal dysfunction, but this did not result in a change in overall mortality.

In the setting of AMI, intravenous nitroglycerin lowers left ventricular filling pressure, improves cardiac output, and improves regional myocardial ischemia as measured by precordial ST segment monitoring. The most beneficial hemodynamic effects are seen in patients with the most severe left ventricular failure. Randomized prospective trials of nitroglycerin therapy showed that treated patients evolved smaller infarcts and have a significant improvement in pooled end points of hospital death, infarct extension, and new congestive heart failure.\textsuperscript{79} Low-dose nitroglycerin infusion (without thrombolysis) for at least 48 h initiated within 10 h of myocardial infarction leads to statistically significant improvements in infarct size and ventricular remodeling that result in decreased risk for infarct extension, cardiogenic shock, left ventricular thrombus, and heart failure. Three-month mortality was reduced by 25% in patients with anterior Q-wave infarct.\textsuperscript{80} The GISSI-3
trial examined nitroglycerin given intravenously for 24 h (with thrombolitics), then topically with a 10-h nitrate-free interval. A small statistically insignificant benefit was seen in 6-week mortality. The combination of captopril and nitroglycerin did show a mortality benefit that was better than captopril alone. The ISIS-4 trial randomized 50,000 patients to receive captopril, magnesium, oral nitrates, or placebo within 24 h of confirmed or suspected myocardial infarction. Nitrates demonstrated a trend toward improved 35-day mortality, but this was not statistically significant.

Invariably, tachyphylaxis occurs after 24 h of continuous nitroglycerin administration independent of the route of delivery. Tachyphylaxis can be prevented by providing a 10- to 12-h nitroglycerin-free interval or in the case with continuous intravenous infusion, the dose is progressively increased every 12 h. The increases are regulated by the blood pressure response and headache tolerance.

The Secondary Prevention Reinfarction Trial (SPRINT) evaluated the calcium channel blocking agent nifedipine vs placebo 7 to 21 days after hospitalization. No difference was seen in 10-month mortality or recurrent nonfatal infarction. SPRINT examined higher-risk patients with second or third infarctions randomizing within 3 h to nifedipine or placebo. In the 1,006 patients, 6-day and 6-month mortality was worsened in the nifedipine group. Diltiazem reduced 14-day reinfarction and refractory postinfarction angina rates after non-Q-wave myocardial infarction in patients treated 24 to 72 h after hospital admission. However, diltiazem did not show benefit on total mortality or nonfatal reinfarction in a larger study of patients with non-Q-wave and Q-wave infarctions randomized 3 to 15 days after hospital admission. Subgroup analysis showed that the lack of overall benefit may have been accounted for by the increased cardiac event rate in patients with pulmonary congestion by chest radiograph or left ventricular ejection fraction ≤40% by radionuclide angiogram. On retrospective analysis, patients without either feature benefited from a decreased cardiac event rate. In the Danish Verapamil Infarction Trial (DAVIT) I, a trend toward improved survival and decreased reinfarction rate was seen in patients suspected of having myocardial infarction when randomized early to oral verapamil vs placebo therapy. Patients were excluded if they exhibited heart failure, heart block, or were receiving beta-blockers. DAVIT II examined verapamil use 2 weeks postinfarction and found a trend toward improved 18-month total mortality and reinfarction. Statistically significant improved survival was noted only in patients without heart failure (7.7% vs 11.8% in the verapamil and placebo groups, respectively).

The studied benefits of early ambulation 3 to 5 days postmyocardial infarction became evident in the 1970s. Early ambulated patients clearly developed significantly fewer lower extremity venous thromses even in the presence of heart failure. Other advantages include prevention of cardiovascular deconditioning, enhancement of physical work capacity, and lessening of total disability. The past fears of myocardial rupture and progressive failure were unfounded in that early ambulation has no detrimental effects on heart rate, left ventricular volume (remodeling), ejection fraction, or cardiac output when started 4 to 7 days after myocardial infarction.

Stress testing can assist in the evaluation of patients following AMI. ST segment depression on limited stress testing was shown to predict subsequent cardiac events. However, ST segment shifts in leads representing the potential electrical variations of the epicardial surface of areas that were not involved in the process of infarction are more predictive of future cardiac events. Exercise thallium 201 myocardial perfusion scanning is suggested in cases where the electrocardiogram is uninterpretable for ischemia. Thallium redistribution, thallium defects in more than one vascular territory, and lung uptake are more sensitive for predicting cardiac events (death, recurrent infarction, or severe angina) than angiography or stress testing alone. Failure of the left ventricular ejection fraction to increase by 5% on radionuclide ventriculography is 95% sensitive (compared with 54% for electrocardiographic changes) for cardiac events. More recently, reversible thallium defects post-Q-wave myocardial infarction have been shown to be 75% sensitive and 51% specific for future cardiac events, whereas angina or ST depression was 40% sensitive and had a positive predictive value of only 17%. Importantly, the negative predictive value for thallium scintigraphy was 89%. Despite this, other recent reports have suggested that stress testing after thrombolysis is less sensitive in predicting future adverse cardiac events. A symptom-limited modified Bruce protocol used 7 to 21 days after infarction, with over 10 months of follow-up, showed that only ST depression at <7 METS or inability to perform >7 METS discriminated for future cardiac events. ST depression at >7 METS or angina was not predictive. Combining all abnormal exercise tests, sensitivity for future cardiac events was 83% but specificity was 25%. Again the negative predictive value of a normal stress test was 89%.

Studies conducted in the 1960s and 1970s confirmed the premise that cholesterol was an important risk factor for coronary heart disease events after myocardial infarction. The Coronary Drug Project...
examined in a double-blind, randomized, placebo-controlled fashion the effect of lipid-lowering therapy of men surviving myocardial infarction. In 5 years of follow-up, elevated cholesterol level was positively associated with worsened total and cardiac mortality and recurrent nonfatal infarction; triglycerides were not specifically correlated. A meta-analysis of secondary prevention trials showed that serum cholesterol level lowering (via drug or diet) by 10% was associated with a 19% reduction in recurrent nonfatal infarction and a 12% reduction in fatal infarction. Angiographic studies have demonstrated over a 1- to 2-year period nonprogression and even regression of coronary lesions (although of a minor absolute degree) with currently available aggressive cholesterol level-lowering agents. Most marked in these studies was a decrease in acute event rates.

Most Q-wave myocardial infarctions and sudden cardiac deaths have been related to rupture of the fibrous cap of a susceptible plaque leading to overlying thrombus formation. These susceptible plaques are more lipid laden and are paradoxically minimally or moderately occlusive. It therefore follows that lipid depletion of cholesterol plaques reduces susceptibility to acute rupture and hence, acute ischemic events. Furthermore, elevated plasma cholesterol level correlates with both impaired endothelial function measured as a lack of acetylcholine-dependent vasodilatation and increased monocyte adhesion that may initiate accumulation of subendothelial lipid-laden macrophages prior to the development of angiographically visible lesions.

The efficacy of \( \beta \)-adrenergic blocking agents in secondary prevention was examined in the Beta-Blocker Heart Attack Trial (BHAT) that randomized patients to propranolol or placebo therapy 5 to 21 days postmyocardial infarction. Over a 2-year follow-up, total mortality of treated patients was reduced by 26%, cardiac mortality by 27%, sudden cardiac death by 28%, and reinfarction by 15% compared with placebo. The Norwegian timolol study randomized patients to timolol or placebo therapy 7 to 28 days postmyocardial infarction with a mean follow-up of 17 months. Total deaths in the treatment group were reduced by 36% and reinfarction was reduced by 28%. The benefit did not segregate to a particular age group or radiographic cardiac size. Similar benefits have been seen for studies up to 3 years postmyocardial infarction.

The rapid rise of health-care costs in the last 15 years has spawned research in risk stratification postmyocardial infarction with special attention to length of hospital stay and appropriate guidelines for \textit{early discharge} from the hospital. Risk factors such as ventricular tachycardia or fibrillation, supraventricular tachycardia, postinfarct angina, infarct extension, pulmonary edema, or cardiogenic shock have identified a poorer prognosis, the need for more invasive investigation, and a longer hospital stay. In a risk assessment model, the risk of death, cardiogenic shock, or cardiac arrest was assessed during the 2-week period following proposed hospital discharge. By this model, 47% of the patients could be discharged from the hospital after 5 days with \(<2\%\) risk of adverse outcome. A group of patients with uncomplicated (no angina, heart failure, or arrhythmia) infarction without provokable ischemia on exercise testing discharged from the hospital on day 3 (vs day 7 to 10) showed no difference in readmission, reinfarction, or angina and the total hospital bill was approximately $5,000 less. Nearly all of the patients had received thrombolytics, angioplasty, or both. However, only 15% of screened patients qualified for randomization. Therefore, simple clinical variables can identify a proportion of patients suitable for early hospital discharge (day 3 to 5); however, this proportion appears to be low.

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