JACC Vol. 13, No. 5
April 1989:957–68

ACC ANNIVERSARY SEMINAR

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Treatment of Coronary Artery Disease

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As we celebrate the 40th anniversary of the American College of Cardiology, it is fascinating to note the progress that has occurred over the past 40 years in our understanding of the pathophysiology of coronary artery disease as well as its treatment. Appreciation of the extraordinary change in the emphasis and approach to coronary artery disease from 1949 to 1989 is provided by review of the Quarterly Cumulative Index Medicus of 1949. A total of 31 papers are referenced under the topic "angina pectoris and its therapy." Of these, six deal with the use of methylthiouracil or thyroidectomy in treatment of angina (1–6), seven report on surgical resection or local injection therapy of the stellate ganglia or aortic nerve plexus (7–14) and two report on experience with vitamin E (15,16). One additional reference cites what must be one of the earliest placebo-controlled trials in evaluating chest pain (17).

The contrast with today's Index Medicus in terms of volume of studies and approach to coronary disease is readily apparent. The advances have been remarkable and associated with a major decline in coronary heart disease mortality (18). Although the basis for this decline is undoubtedly multifactorial, with fascinating geographic variations (19), there seems little doubt that treatment has played a role (20). The object of this article is to provide a review of current approaches to treatment of specific clinical subsets of patients with coronary artery disease.

Approach to Treatment of Individual Patients

Treatment objectives. As is ideal in all physician-patient interactions that result in diagnostic or therapeutic strategy decisions, a clear objective for each intervention needs to be enunciated. Treatment objectives include 1) symptom relief with a minimum of side effects; 2) enhancement of event-free survival; and 3) risk factor control with the objective of reducing progression in the basic disease process.

Risk stratification. The clinician planning therapy for an individual patient must first establish an accurate clinical profile of the patient in terms of symptoms, functional disability, quality of life and risk for subsequent cardiac events. The most important means to establish such a fundamental clinical profile are the history and physical examination. After these are accomplished, it may be appropriate to proceed with selective noninvasive testing to assess prognosis in mildly symptomatic patients or to proceed directly to coronary arteriography in patients with severe or unstable symptoms. Some patients will not require further testing. The approach selected should be based on a clearly stated objective and a pretest review of how the test result will influence decision making. Fundamental to risk stratification is the recognition that left ventricular function is the most powerful predictor of survival (21,22). Simply acquired clinical and rest electrocardiographic (ECG) variables contain important prognostic infor-

This article is part of a series of articles celebrating the 40th anniversary of the American College of Cardiology. The series attempts to set the stage for the future by describing current state of the art management of selected major cardiovascular problems and the basic knowledge that will provide directions for advances in diagnosis and therapy.

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0735-1097/89/$3.50

mation, in part because they reflect left ventricular function (23–25). The incremental value of any additional testing should be carefully considered before further testing is performed (26).

Stable Angina Pectoris

Once the clinician has established the presence of angina pectoris by history and identified other complicating medical conditions, an assessment of functional impairment and risk for subsequent cardiac events is necessary. It is impossible to include all possible scenarios that might influence decision making. For an elderly patient with no strenuous demands in work or recreation, a trial of medical therapy may be appropriate without other testing. For patients with severe disabling symptoms, particularly those already on medical therapy, coronary arteriography without other testing is necessary to define suitability for coronary revascularization with either coronary angioplasty or coronary artery bypass grafting. Controlled clinical studies have documented 1) the relief of angina pectoris with bypass surgery (27–29), and 2) improvement in objective indexes of functional capacity and myocardial ischemia (30,31). In the large randomized trials, coronary bypass surgery was demonstrated to be more effective than standard medical therapy alone in relief of angina. However, that advantage diminishes after several years as a result of graft occlusion and progression of native coronary artery disease.

Coronary angioplasty. The transluminal approach to treating coronary artery disease was introduced with coronary angioplasty (32). This technique results in sustained improvement in the majority of appropriately selected patients (33), with low morbidity and little time away from work (34). In patients with multivessel disease, event-free outcomes are more frequent in those with "complete" revascularization (35). An American College of Cardiology/American Heart Association Task Force recently emphasized that "the approach to every angioplasty procedure requires a knowledgeable judgment that weighs the likelihood of a successful outcome against the likelihood of failure and the risk of complications" (36). It is important to note the lack of published controlled studies of coronary angioplasty versus other therapies in relief of angina pectoris. Although there are abundant published observational data to support the effectiveness of coronary angioplasty in relief of myocardial ischemia, presumption of applicability of the results of bypass surgery to treatment with angioplasty is unwarranted.

Role of stress testing in assessing prognosis. Stress testing for the purpose of assessing prognosis is appropriate in physically active persons with mild angina and normal ventricular function. Several studies have documented the prognostic value of exercise ECG testing (37,38), radionuclide ventriculography at rest and with exercise (39–41) and stress thallium studies (42,43). Whereas ambulatory monitoring for silent ischemia has been shown to contain important prognostic information in highly selected patients (44–46), its use as a general screening technique in patients at low risk for coronary artery disease in clinical practice has not been established (47). Profound early ischemia with standard stress tests identifies patients at relatively high risk of a subsequent cardiac event and coronary arteriography is indicated. This inference is based on evidence from randomized trials and observational data base studies documenting improved survival of specific angiographic subgroups of patients with stable angina treated with coronary bypass surgery rather than an initial strategy of medical therapy. These studies have emphasized a consistent trend: the higher the risk for subsequent events based on anatomy, left ventricular function and severity of myocardial ischemia, the greater the degree of benefit from coronary artery bypass surgery as compared with medical therapy. Therefore, definition of coronary anatomy and left ventricular global function is necessary in patients with mild symptoms and profound ischemia on stress testing if the patient is a candidate for bypass surgery from a general medical point of view.

Indication for surgery or angioplasty. Patients with angina pectoris associated with >50% luminal diameter narrowing of the left main coronary artery (48) or triple vessel disease and abnormal left ventricular function are generally believed to have better survival with surgery as compared with medical therapy (28,49–53). In the Coronary Artery Surgery Study (CASS) randomized trial, no difference in survival of patients with mild angina and three vessel disease with normal left ventricular function (or single or double vessel disease) was observed in those randomized to an initial strategy of medical therapy compared with those randomized to coronary bypass surgery (54). This observation emphasizes the importance of studies that have documented the value of risk stratification in patients with triple vessel coronary artery disease to define those with a major benefit in survival with bypass surgery (55,56). There are data to support surgical treatment of patients with two vessel disease who have severe angina in association with depressed left ventricular function (57).

Invasive therapy (surgery or angioplasty) is reserved for patients with single vessel disease and disabling symptoms or those with a large area of myocardium at jeopardy with documentation of early profound ischemia on stress testing. Revascularization may be necessary in some patients with single and double vessel disease for control of angina pectoris or protection of large areas of myocardium from subsequent myocardial infarction. However, with the increasing confidence in coronary angioplasty, more patients with single and double vessel disease are coming to angioplasty with less convincing indications. The restenosis rates associated with angioplasty (58,59) should temper enthusi-

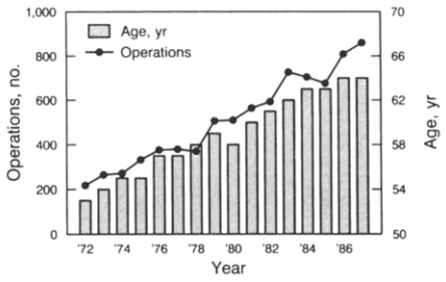


Figure 1. Isolated coronary bypass operations at the Mayo Clinic and average age of patients by year (1972 through 1986 inclusive).

asm for an aggressive approach with angioplasty based solely on anatomic findings in patients at low risk for subsequent events. Most approaches to prevent restenosis have failed (60) and a recent report (61) on the use of fish oil in reducing restenosis needs further study. If the risk for subsequent cardiac events is low in an individual patient, successful accomplishment of angioplasty, while technically satisfying in the short term, may not be in the best interests of the patient. Although criticism from cardiologists regarding surgical treatment of single vessel disease was frequent before angioplasty was available, less is said now that the therapy can be accomplished with coronary angioplasty.

Aggressive invasive treatment of any kind seems doomed to failure if the symptoms are not clearly related to myocardial ischemia (62). Use of angioplasty in patients without definite angina and myocardial ischemia often results in patients with recurrent chest pain, and the multiple subsequent angiographic studies performed to clarify coronary anatomy result in continuing disability and large medical and emotional costs. The same can of course be said of inappropriately applied coronary bypass surgery.

Cost of surgery. Because of the large volume and expense of coronary bypass operations, the procedure remains under close scrutiny in the era of cost containment. It is estimated that in 1986 well over 200,000 coronary bypass procedures were performed (63). An increasing proportion of operations are performed in elderly patients (Fig. 1) and those requiring reoperation. The appropriateness of bypass surgery has thus been the subject of considerable debate and study. In one study, Winslow et al. (64) studied the appropriateness of surgery in three randomly selected hospitals in the western United States. In this small sample of patients (n = 386), only 56% of patients were considered "appropriate" for coronary bypass surgery by an expert panel. Although this consideration is unfortunate, it demonstrates the need for professional education and guidelines for therapy. When appropriately applied, bypass surgery has been demonstrated to be a highly cost effective therapy (65).

Internal mammary versus vein grafts. Although antiplatelet therapy before and after operation improves aortocoronary vein graft patency (66), there remains a major problem with long-term results of vein graft conduits for relief of myocardial ischemia (67). Loop et al. (68) and others have demonstrated that improved late patency of the internal mammary artery increases patient survival over that in patients who receive only saphenous vein grafts. The clinically documented advantages of internal mammary artery versus vein grafting have a physiologic basis as proposed by Luescher et al. (69). The importance of internal mammary artery grafting is further emphasized by the late follow-up data on surgically treated patients in the early large randomized trials with vein grafts as conduits (70,71), which revealed a decline in survival advantages of surgical therapy after 5 to 8 years. These data emphasize the need for careful yearly surveillance of patients after bypass surgery. Equally important is the yearly follow-up of patients treated medically.

Medical treatment. If medical treatment is deemed appropriate for treatment of angina pectoris, the clinician has three classes of drugs available for control of angina pectoris. These are beta-adrenergic blockers, calcium channel entry blockers and nitrates. The choice of these drugs or their use in combination is based on the individual characteristics of the patient (72). Long-acting nitrates may be effective in patients with mild angina, particularly in those who are relatively inactive. There may be a great cost advantage for nitrates if symptom relief is the only objective. Physicians using nitrates must be aware not only of the pharmacology of the multiple products available but also the cost implications of the various modes of administration. Considering the tolerance issue with long-term administration of nitrates, an oral preparation used two to three times daily may have advantages for most patients. However, in more active patients with coexistent hypertension, drugs that control blood pressure and heart rate may optimize the relation between myocardial oxygen demand and supply. A major advance in our understanding of the pathophysiology of angina pectoris occurred with the observations of Chierchia et al. (73) documenting the importance of vasoactivity of the coronary circulation in patients with coronary artery disease, thus challenging the dogma that myocardial oxygen demand is the most important determinant of myocardial ischemia. This concept provided new approaches for medical therapy (74). The theoretical and objective documentation of beta-blocker efficacy has been indisputably established. Calcium channel blockers have rapidly established their place in the therapeutic armamentarium of angina pectoris. In patients with variant angina, calcium channel blockers and nitrates are the drugs of choice. Enthusiasm for the calcium channel blockers as monotherapy has diminished. However, their synergistic action with beta-blocker drugs may be very helpful, but the increased instance of side effects needs to be borne in mind. The effectiveness of current drugs individually and in combination to provide

relief of angina pectoris has been documented in multiple placebo *controlled* trials (75,76).

Revascularization procedures. For patients in whom revascularization is considered appropriate, we still do not have data from *controlled* studies to help choose between coronary angioplasty or bypass surgery as the initial therapy in patients suitable for either procedure. Fortunately a Veterans Administration trial will provide much needed data for patients with single and double vessel disease. There are other studies comparing angioplasty and surgery in multivessel coronary artery disease, including the Emory Angioplasty Surgery Trial (EAST), Bypass Angioplasty Revascularization Investigation (BARI) and several European studies.

Unstable Angina

It has been known for many years that patients with unstable angina are at high risk for subsequent cardiac events (77–79). Whereas some investigators (80) have considered recent onset angina as an exception to this concept, others (81) have provided evidence to support a high risk of subsequent events in such patients. Other patterns of rest pain with ECG changes seem to identify high risk patients (82,83).

Initial management. The patient who presents with increasingly severe angina including episodes of pain at rest is best treated in the hospital with ECG monitoring. Most would agree with an initial effort to provide pain relief with medical therapy before proceeding to coronary arteriography. Use of all three classes of antianginal drugs may be necessary. Intravenous nitroglycerin combined with a beta-blocker represents the first approach unless there is good evidence for coronary vasospasm as a primary mechanism. In addition to beneficial effects on heart rate and blood pressure, beta-blockers have other advantages (84,85). Calcium channel blockers have also been shown to be effective (86,87) but if nifedipine is used, its combination with beta-blocking treatment is wise (88).

Antithrombotic and antiplatelet therapy. Instability of atherosclerotic plaques with thrombus formation (89–93) has been established as the pathogenesis for this syndrome. Thus, it is not surprising that clinical studies are confirming an important role for the use of heparin and antiplatelet treatment. Fitzgerald et al. (94) demonstrated platelet activation in patients with unstable coronary artery disease, and we now have two well designed trials (95,96) establishing the benefit of aspirin therapy in reducing cardiac mortality and other events in patients with unstable angina. Activation of the intrinsic coagulation cascade occurs in patients with unstable angina and is manifested by elevated fibrinopeptide (97). Theroux et al. (98) have also reported a double-blind, randomized, placebo-controlled trial showing independent beneficial effects of heparin and aspirin in reducing cardiac events in the short term (mean of 6 days) in patients with unstable angina. Given the role of thrombus in pathogenesis of unstable angina, the use of fibrinolytic drugs is receiving attention (99) but will require further study in properly designed trials.

Coronary interventions and revascularization. Whereas the aspirin trials in patients with unstable angina have documented one of the few survival benefits of drug therapy in patients with coronary artery disease, most cardiologists favor proceeding with coronary angiography early, though with a patient in stable condition if possible. Inability to stabilize an unstable condition with drugs may require mechanical support with intraaortic balloon pumping. Once coronary anatomy is defined, a decision on invasive revascularization therapy is necessary. Suitability of lesions for either coronary angioplasty or bypass surgery must be decided (36) and then a decision must be made as to advisability of proceeding with either on the basis of an integration of the likelihood of success, risks and the individual patient profile. Most would base the decision to intervene with bypass surgery on accepted anatomic subsets of patients as previously described while preferring angioplasty for single vessel or less extensive multivessel disease in patients with ongoing symptoms of ischemia who are unresponsive to medical treatment. These judgments are influenced importantly by the Veterans Administration study of bypass surgery in unstable angina (100), which demonstrated a benefit in survival only in patients with a moderate decrease in left ventricular function and triple vessel disease. In our own practice, revascularization is recommended in essentially all clinically and anatomically suitable subsets of patients with unstable angina before hospital discharge. Although many observational studies (101) have documented success rates and problems for coronary angioplasty in unstable angina, the assumption that results from surgical trials apply to angioplasty is not proved. This problem further emphasizes the importance of ongoing clinical trials to compare, directly the benefits and adverse effects of an initial angioplasty versus surgical strategy in patients with unstable angina.

Myocardial Infarction

Extraordinary advances have occurred in treating patients with myocardial infarction; these have been based on redefining the primary pathophysiologic events leading to myocardial infarction. Whereas Herrick (102) suggested that thrombus has a primary role in causing myocardial infarction, others (103) considered most thrombi in the infarct-related artery to be secondary events. However, the work of Davies and Thomas (92) and Falk (93) reemphasizing the role of plaque fissuring leading to acute thrombosis at such sites, and the clinical studies of DeWood et al. (104) documenting acute coronary thrombosis in the earliest phase of acute

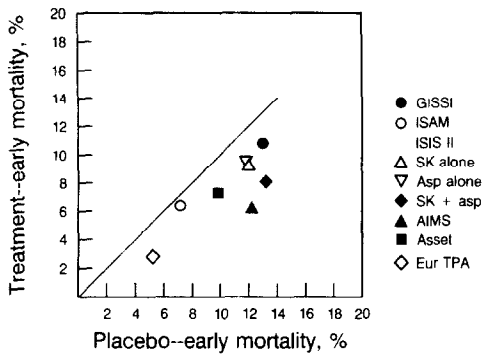


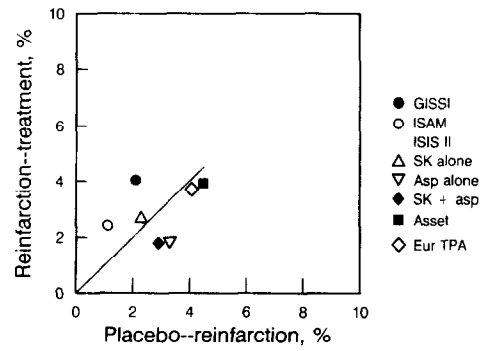
Figure 2. Survival data from randomized trials of intravenous thrombolytic therapy in acute myocardial infarction. The early mortality rate is compared for the treatment group on the vertical axis with the placebo group on the horizontal axis. AIMS = APSAC Intervention Mortality Study; Asp = aspirin; Eur TPA = European TPA; GISSI = Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico; ISAM = Intravenous Streptokinase in Acute Myocardial Infarction trial; ISIS II = Second International Study of Infarct Survival; SK = streptokinase.

myocardial infarction provided a new stimulus for investigation of thrombolytic therapy.

Thrombolytic and antiplatelet therapy. Excellent data from clinical trials have now been published documenting improved survival after intravenous thrombolytic drug therapy (105–110). In Figure 2 early mortality is compared in the placebo versus treatment groups in the large trials of intravenous thrombolytic therapy. There is a consistent trend of enhanced survival in patients receiving thrombolytic therapy as compared with those receiving placebo.

In spite of the survival benefit noted in these trials, a small but definite increase in reinfarction rates followed successful thrombolytic therapy in most trials with use of antiplatelet treatment. Figure 3 summarizes a comparison between placebo and treatment groups for several of the trials of intravenous thrombolytic therapy. Note the reduced

Figure 3. Early reinfarction rates after intravenous thrombolytic therapy in acute myocardial infarction. The treatment group is on the vertical axis and the placebo group on the horizontal axis. Abbreviations as in Figure 2.



reinfarction rates in the Second International Study of Infarct Survival (ISIS-2) subgroups treated with aspirin alone or with combined streptokinase and aspirin. These decreases may be the clinical expression of the important observations of Fitzgerald et al. (111) documenting platelet activation as thrombolysis proceeds after streptokinase. Platelet activation with release not only of thromboxane but also of serotonin has been reported after thrombolysis with tissue plasminogen activator (rt-PA) (112). Activation of coagulation with thrombolysis has also been reported (113). It therefore appears that antiplatelet therapy in conjunction with thrombolytic therapy at the onset of acute myocardial infarction prevents or reduces platelet activation in this setting with a reduction in reinfarction rates. The complex nature of the interaction among platelets, ongoing thrombolysis, the actual clot and underlying arterial disease presents other possible approaches to therapy (114).

Combined thrombolysis and angioplasty. With the observed reinfarction rates (115) and the observed high grade residual obstruction evident after successful thrombolysis, a rationale for combining coronary angioplasty with intravenous thrombolysis was proposed. However, data from several trials (116–118) have consistently shown no advantage in routine early angioplasty in the setting of active thrombolytic therapy. The place of coronary angioplasty as a primary modality to open an infarct-related artery is not settled primarily because, except for a study by O'Neill et al. (119), we have no controlled studies of angioplasty alone versus thrombolytic therapy alone. Angioplasty as primary therapy to open infarct-related arteries needs further study because 20% to 30% of patients presenting with myocardial infarction may have contraindication to thrombolytic therapy (105). Such patients presenting within 4 h of infarction may benefit from mechanical opening of the infarct-related artery. Feasibility of this approach has been demonstrated in observational studies (120,121), as well as by O'Neill et al. (119), with an approximately 85% success rate in opening the infarct-related artery. Additional advantages may include earlier opening of the infarct-related artery with benefit to patients in cardiogenic shock and less risk of bleeding complications.

Decision protocol. The physician considering thrombolytic therapy for a patient with an acute myocardial infarction must make major decisions decisively and early. First, an accurate diagnosis of myocardial ischemic infarction is mandatory. Age of the patient remains a difficult issue. No trial has sufficient numbers of patients over the age of 80 years to conclude that the benefit of thrombolytic therapy justifies the risk; high complication rates have been reported in at least one major study (122). However, mortality rates in elderly patients with myocardial infarction are high and in some patients the potential benefit of thrombolytic treatment may justify the risk. Although most investigators have concluded that the ideal time for intervention and throm-

bolytic treatment is ≤4 h after onset of symptoms, in ISIS-2 benefit was noted through 24 h after symptom onset, thus suggesting an increased time frame for intervention. In ISIS-2, however, a significant proportion of the patients did not meet criteria for acute myocardial infarction at time of randomization and represented patients with unstable myocardial ischemia or a slowly evolving infarction. The choice of a thrombolytic drug is controversial. Increased effectiveness in clot lysis has been documented with rt-PA, but clinical effectiveness in reducing mortality of acute infarction has been proved with both streptokinase and rt-PA. Several large randomized trials have been designed to compare streptokinase versus rt-PA with respect to survival and complications to assess whether the early effects of rt-PA on patency will be associated with better survival.

Other advances in management of acute infarction. Although thrombolysis and angioplasty have attracted a great deal of attention, other extremely important advances in managing patients with acute myocardial infarction have occurred. Hemodynamic monitoring has played an important role in managing a subset of patients with hemodynamic instability (123,124). Intravenous nitroglycerin reduces infarct size (125) and mortality (126), but recognition of the problem of nitrate tolerance in prolonged use of the drug is essential (127). Approaches with vasoactive drugs to help stabilize hemodynamically unstable patients are well established and the recognition of hypovolemia as a cause of hypotension in acute infarction has been a major contribution of hemodynamic monitoring. The role of left ventricular assist devices, as a substitute for intraaortic balloon pumping, is receiving increased attention, and these may serve as a bridge to cardiac transplantation in properly selected patients. Another major advance has occurred in recognition and management of patients with right ventricular infarction (128–130).

Role of beta-adrenergic blockers. Documentation of improved survival and reduced reinfarction rates for patients with myocardial infarction treated with a beta-blocker is one of the most effectively documented effects of drug therapy in cardiology (131–133). Although benefit has been observed even when therapy is started several days after the acute event, recent data (134) support administration of a beta-blocker in the acute phase of infarction unless there are contraindications to its use. The major benefit appears to occur in patients with more complicated myocardial infarction (135). Calcium channel blockers have also been tested in the setting of Q wave infarction with either no benefit or adverse effects (136,137), particularly in patients with a left ventricular ejection fraction <40% (138). In spite of the large volume of published data demonstrating the effectiveness of beta-blockers in reducing subsequent cardiac events, especially sudden death and recurrent infarction, many patients who have no contraindication to these agents are still not receiving them after an acute infarction. Failure to provide this treatment is justified only if the patient is demonstrated to be in a low risk category and its occurrence illustrates a continuing problem of inadequate monitoring of the results of continuing education on the actual practice of physicians.

Non-Q wave infarction. The differentiation of non-Q wave from Q wave infarction is now established as important clinically although the ability of the former to predict absolute transmural distribution of myocardial necrosis is recognized as flawed. The clinical features and subsequent outcome of patients with preservation of QRS integrity but with major repolarization abnormalities and elevated creatine kinase (CK) MB isoenzyme levels have been well described. Most investigators (139) agree that the basic coronary anatomic feature is usually an incomplete occlusion of the infarct-related coronary artery. With a persisting high grade stenosis, it is not surprising there is a high rate of subsequent myocardial infarction (140). Diltiazem has been documented to reduce reinfarction rates (141). However, the continued hemodynamic instability of such patients is reflected in a significant rate of reinfarction even with diltiazem and a high proportion of patients who require early coronary angiography and appropriate revascularization. Few studies have examined the role of stress testing for risk stratification after non-Q wave myocardial infarction and further data are needed. The lack of a direct comparison of outcomes between bypass surgery and angioplasty in controlled studies hampers our conclusions on advisability of an initial strategy of angioplasty or surgery. No direct comparisons of invasive treatment versus medical therapy alone in patients with non-Q wave infarction have been published.

Evaluation and therapy of survivors of myocardial infarction. A major issue in management of patients with myocardial infarction is the risk stratification of those who have survived the initial hospital admission and are being prepared for discharge. The three major determinants of late prognosis after an acute myocardial infarction include 1) the extent of left ventricular dysfunction; 2) the presence and severity of residual myocardial ischemia; and 3) ventricular arrhythmias. Post-infarction residual ischemia carries a poor prognosis but is readily amenable to treatment, usually by coronary revascularization. Experimental data in regard to the ability of afterload-reducing agents to modify left ventricular dysfunction are encouraging and clinical studies (142) have documented this in post-myocardial infarction patients. Additional large clinical trials are evaluating this problem. The adverse impact on prognosis of ventricular arrhythmias is well recognized (143), but the ability of antiarrhythmic therapy to improve survival of symptomatic patients is uncertain and also the subject of current large scale trials.

With this uncertainty in mind, the evaluation of survivors of myocardial infarction should include a measurement of left ventricular function and, in hemodynamically stable patients without angina, noninvasive stress testing before

hospital discharge. It is generally accepted that radionuclide studies enhance the sensitivity and specificity of stress testing, but only when they are performed in centers proficient and experienced in using these complex, quantitative imaging modalities. In patients with postinfarction angina, particularly if it occurs with minimal exertion, prompt angiography with a view toward revascularization is indicated and most physicians would perform this study before stress testing. Signal-averaged ECG studies may be useful in the future to identify those patients at risk for malignant ventricular arrhythmias. Additional tests should be obtained only if the information derived is of incremental value beyond data obtained on review of the bedside clinical profile (144).

The question of coronary angiography before hospital discharge, particularly in patients who have had successful thrombolysis, remains controversial (145). Many investigators would compare these patients to patients previously categorized as having non-Q wave infarction, particularly if myocardial salvage has occurred and there is a residual high grade stenosis remaining with demonstrable ischemia in the distribution of this infarct-related artery. Additional studies will be necessary to establish the role of invasive therapy in these asymptomatic patients with a residual high grade lesion after successful thrombolytic therapy.

Sudden Cardiac Death

Of the almost 1 million deaths that occur each year in the United States, half can be attributed to ischemic heart disease, and almost half of these deaths occur suddenly. Our ability to detect patients at risk of experiencing sudden cardiac death and to effectively treat the underlying ischemic heart disease has increased tremendously since 1949 as described in the preceding sections of this review. The development of cardiac defibrillators and cardiopulmonary resuscitation has permitted us to retrieve from certain death many such patients both in and out of the hospital. The availability of electrophysiologic testing and signal-averaged ECGs help us to better understand and treat survivors of sudden cardiac death (146–148). In 1949 we had only quinidine to medically treat patients with ischemic heart disease who presented with life-threatening ventricular arrhythmias. Today we have an extensive array of effective drugs ranging (in potency and toxicity) from lidocaine to amiodarone. When medical treatment of ventricular arrhythmia proves unsuccessful, surgical options are available that include ablation of ventricular scars or resection of ventricular aneurysm with or without coronary bypass surgery (149,150). Implantation of automatic defibrillators is also occurring and the future of the ultimate defibrillator holds real promise. In short, we have altered an attitude of pessimism and futility in our approach to sudden cardiac death as a manifestation of coronary artery disease in 1949 to a very dynamic process with effective treatment options for many patients in 1989.

Congestive Heart Failure

Patients with coronary artery disease may manifest congestive heart failure because of 1) extensive myocardial necrosis leading to pump failure; 2) mechanical complications of myocardial infarction; and 3) reversible myocardial ischemia. The challenge of the clinician managing the patient with coronary artery disease and congestive heart failure is to determine the relative contribution of these factors to the individual patient's problem. Whereas some cases are obvious clinically, others can be frustrating particularly when components of ischemia are present (angina, reversible perfusion defects) in addition to heart failure. The correct classification is important because revascularization may enhance survival and relieve symptoms of heart failure if there is a concomitant component of reversible ischemia (151).

Early recognition of the mechanical complications of myocardial infarction is critically important in the setting of acute infarction because surgical therapy may dramatically improve the outlook. This possibility is particularly likely for papillary muscle rupture (152), postinfarction ventricular septal defect (153) and, rarely, cardiac perforation (154).

Risk Factor Control

A third category of treatment decisions crucial in the long-term management of patients with coronary artery disease, regardless of the treatment for symptom control or enhanced event-free survival, is control of risk factors and establishing a rational life style. It is important for the patient and family to recognize that such efforts are a life-long process and that coronary surgery and angioplasty are only palliative forms of therapy. Abundant evidence is available to support an aggressive approach to risk factor control, although the strength of evidence for benefit with control of each risk factor varies.

Smoking. Avoidance of tobacco is fundamental to the long-term success of any therapeutic program in patients with coronary artery disease. Enhanced survival after cessation of smoking has been demonstrated in large samples of postmyocardial infarction patients (155), those with angiographyically documented coronary artery disease (156) and others in large population-based studies (157). Behavior modification remains a major challenge in dealing with patients addicted to tobacco use.

Hypertension. Control of hypertension has failed to affect coronary heart disease mortality directly in large trials (158). However, reduced stroke and overall mortality rates emphasize the importance of hypertension control (158,159). In addition to the benefits of systemic arterial pressure treat-

ment, which should initially be non-pharmacologic, some of the drugs utilized (calcium channel and beta-blockers) provide more direct approaches to relief of associated myocardial ischemia.

Hypercholestrolemia. There are data to support aggressive efforts for lipid-lowering programs, particularly in patients with clearly elevated serum levels (>250 mg) and those with documented coronary heart disease. The data presented thus far suggest some reduction in cardiac mortality (160,161) and reduced rates of progression of coronary artery lesions in patients with high pretreatment serum lipid levels after successful lipid reduction is accomplished (162). Details of a systematic approach to lipid lowering have been published by an expert panel of the National Heart, Lung, and Blood Institute (163). The addition of HMG-CoA reductase inhibitors (Lovastatin) for reduction of cholesterol levels is a major advance (164), particularly in those patients not responsive to more simple dietary measures or other drugs. Reduction in cholesterol appears to benefit patients after coronary bypass surgery in terms of enhancing graft patency and reducing progression of disease (165).

Exercise training. Exercise remains an important part of the overall program for all patients with coronary disease, however treated, as well as in general prevention efforts (166). There is documentation (167) of improvement in myocardial performance and reduction in myocardial ischemia associated with achieving certain training levels. Several surveys (168,169) analyzing objectively the benefits of cardiac rehabilitation are available.

Thoughtful critiques of some of the described trials and an overemphasis of application of population-wide risk factor control should be noted (170,171). Those who are engaged in active patient care are aware of the hazards of unrealistic expectations of some patients with risk factor control, and this applies also to society in general.

Conclusions. Extraordinary advances in the management of patients with coronary artery disease have occurred and we can look forward to continued progress. A disturbing note, however, in the accomplishments of the past 40 years is the recognition that the rate of decline in cardiovascular mortality is being maintained only in white men (172). This fact raises important questions for the medical profession as well as for society in general, and consideration of this must be included in our strategy not only for future developments, but for having an equitable distribution of the benefits of medical science to the entire population.

With ever more choices available, the clinician is challenged to identify the safest and most effective treatment for each individual patient. Steps in this process learned today will be valuable in coming years as many more intravascular devices and biologically sophisticated drugs are introduced.

References

1. Frisk AR, Lindgren I. Methylthiouracil (thiourea derivative) in treatment of congestive heart failure and angina pectoris: results of prolonged treatment. Acta Med Scand 1948;132:69–90.
2. Fisher RL, Zukerman M. Propylthiouracil (thiourea derivative): preliminary report. Am Pract 1949;3:318–20.
3. Sniehotta H. Therapy of angina pectoris associated with coronary sclerosis with methylthiouracil (thiourea derivative). Deutsch Med Wochnschr 1949;74:340–2.
4. Raab W. Propylthiouracil (thiourea derivative). Acta Med Scand 1949;135:364–73.
5. Pereira A, Tullio de Assis Fiqueiredo M. Thiouracil (thiourea derivative) with special reference to thyroadrenosympathogenic mechanism. Argent Clin 1949;8:79–100.
6. Bolivar J, Rabina P. Thyroidectomy. Rev Cubana Cardiol 1949;10:145–86.
7. Guillaume J, Mazars G. Posterior radicotomies. Presse Med 1948;56:690–1.
8. Danielopolu D. Present status of surgical therapy: necessary anatomicophysiologic concepts. Cardiologia 1949;14:1–25.
9. Danielopolu D. Present status of surgical therapy: physiologic basis and results of method of suppression of pressor reflex: disadvantages of stellectomy. Cardiologia 1949;14:45–80.
10. Stubinger HG, Busse W. Procaine hydrochloride blocking of stellate ganglion with special regard to electrocardiographic findings. Deutsch Med Wochnschr 1949;74:546–9.
11. Welti H, Oury P, Venet A. Late results of posterior, dorsal radicotomies in therapy: 4 cases. Mem Acad Chir 1949;75:364–70.
12. Lian C. New trends in medical and surgical therapy: procaine hydrochloride infiltrations and resection of preaortic nerve plexus. Sem Med 1949;2:82–4.
13. Lian C, Siguier F, Crosnier L, Crosnier J. Procaine hydrochloride infiltration and resection of preaortic nerve plexus. Arch Mal Coeur 1949;42:215–7. Paris Med 1949;39:305–7.
14. Lian C, Siguier F, Crosnier L, Crosnier J. Resection of preaortic nerve plexus in therapy of angina of coronary origin with frequent and painful crises: 19 cases. Bull Mem Soc Med Hop Paris 1948;65:867–77.
15. Ravin IA, Katz KH. Vitamin E. N Engl J Med 1949;240:331–3.
16. Rush HP. Experience with vitamin E in coronary disease. Calif Med 1949;71:391–3.
17. Travell J, Rinzler SH, Bakst H, Benjamin ZH, Bobb AL. Therapy, comparison of effects of alpha-tocopherol and matching placebo on chest pain in patients with heart disease. Ann NY Acad Sci 1949;52:345–53.
18. Havlick RJ, Feinleit M, eds. Proceedings of the Conference on the Decline in Coronary Heart Disease Mortality. Washington, DC: National Institutes of Health, 1979.
19. Raglund K, Selvin S, Merrill DW. The onset of decline in ischemic heart disease mortality in the United States. Am J Epidemiol 1988;127:516–31.
20. Goldman L, Cook EF. The decline in ischemic heart disease mortality rates in the United States: an analysis of the comparative effects of medical interventions and changes in life style. Ann Intern Med 1984;101:825–36.
21. Vlietstra RE, Assad-Morell JL, Frye RL, et al. Survival predictors in coronary artery disease. Mayo Clin Proc 1977;52:85–90.
22. Nelson GR, Cohn PF, Gorlin R. Prognosis in medically-treated coronary artery disease: influence of ejection fraction compared to other parameters. Circulation 1975;52:408–12.
23. Peduzzi P. Relation of severity of symptoms to prognosis in stable angina pectoris. Am J Cardiol 1984;54:988–93.
24. Califf RM, Mark DB, Harrell FE Jr, et al. Importance of clinical measures of ischemia in the prognosis of patients with documented coronary artery disease. J Am Coll Cardiol 1988;11:20–6.

25. Block WJ Jr, Crumpacker EL, Dry TJ, et al. Prognosis of angina pectoris: observations in 6882 cases. JAMA 1952;150:259–64.

26. Ladenheim ML, Kotler TS, Pollock BH, et al. Incremental prognostic power of clinical history, exercise electrocardiography and myocardial perfusion scintigraphy in suspected coronary artery disease. Am J Cardiol 1987;59:270–7.

27. Peduzzi P, Hultgren HN. Effect of medical vs surgical treatment on symptoms in stable angina pectoris: the Veterans Administration Cooperative Study of surgery for coronary arterial occlusive disease. Circulation 1979;60:888–99.

28. European Coronary Surgery Study Group. Long term results of prospective randomized study of coronary artery bypass surgery in stable angina pectoris. Lancet 1982;2:1173–80.

29. CASS Principal Investigators and their Associates. Coronary Artery Surgery Study (CASS): a randomized trial of coronary artery bypass surgery: quality of life in patients randomly assigned to treatment groups. Circulation 1983;68:951–60.

30. Kloster FE, Kremkau EL, Ritzmann LW, Rahimtoola SH, Rosch J, Hanarek PH. Coronary bypass for stable angina: a prospective randomized study. N Engl J Med 1979;300:149–57.

31. Hultgren HN, Peduzzi P, Detre K, Takaro T and the Study Participants. The five-year effect of bypass surgery on relief of angina and exercise performance. Circulation 1985;72(suppl V):V-79–V-83.

32. Gruntzig HR, Senning A, Seigenthaler WE. Non-operative dilatation of coronary artery stenosis: percutaneous transluminal coronary angioplasty. N Engl J Med 1979;301:61–8.

33. Kent KM, Bentirogio LG, Block PC, et al. Long-term efficacy of percutaneous transluminal coronary angioplasty (PTCA): report from the National Heart, Lung, and Blood Institute PTCA Registry. Am J Cardiol 1984;53:27C–31C.

34. Holmes DR, Van Raden MJ, Reeder GS, et al. Return to work after coronary angioplasty: a report from the National Heart, Lung, and Blood Institute Percutaneous Transluminal Coronary Angioplasty Registry. Am J Cardiol 1984;53:48C–51C.

35. Mabin TA, Holmes DR, Smith HC, et al. Follow-up clinical results in patients undergoing percutaneous transluminal coronary angioplasty. Circulation 1985;71:754–60.

36. ACC/AHA Task Force Report. Guidelines for percutaneous transluminal coronary angioplasty. J Am Coll Cardiol 1988;12:529–45.

37. Mark DB, Hlatky MA, Harrell FE Jr, Lee KL, Califf RM, Pryor DB. Exercise treadmill score for predicting prognosis in coronary artery disease. Ann Intern Med 1987;106:793–800.

38. Rautaharju PM, Prineas RJ, Eifler WJ, et al. Prognostic value of exercise electrocardiogram in men at high risk of future coronary heart disease: multiple risk factor intervention trial experience. J Am Coll Cardiol 1986;8:1–10.

39. Bonow RO, Kent KM, Rosing DR, et al. Exercise-induced ischemia in mildly symptomatic patients with coronary artery disease and preserved left ventricular function: identification of subgroups at risk of death during medical therapy. N Engl J Med 1984;311:1339–45.

40. Pryor DB, Harrell FE Jr., Lee KL, et al. Prognostic indicators from radionuclide angiography in medically treated patients with coronary artery disease. Am J Cardiol 1984;53:18–22.

41. Taliercio CP, Clements IP, Zinsmeister AR, Gibbons RJ. Prognostic value and limitations of exercise radionuclide angiography in medically treated coronary artery disease. Mayo Clin Proc 1988;63:573–82.

42. Kaul S, Lilly DR, Gascho JA, et al. Prognostic utility of the exercise thallium-201 test in ambulatory patients with chest pain: comparison with cardiac catheterization. Circulation 1988;77:745–58.

43. Ladenheim ML, Pollock MPH, Rozanski A, et al. Extent and severity of myocardial hypoperfusion as predictors of prognosis in patients with suspected coronary artery disease. J Am Coll Cardiol 1986;7:464–71.

44. Gottlieb SO, Weisfeldt ML, Ouyang P, Mellits ED, Gerstenblith G. Silent ischemia as a marker for early unfavorable outcomes in patients with unstable angina. N Engl J Med 1986;314:1214–9.

45. Rocco MB, Nabel EG, Campbell S, et al. Prognostic importance of myocardial ischemia detected by ambulatory monitoring in patients with stable coronary artery disease. Circulation 1988;78:877–84.

46. Vaghaiwalla M, Koonlawee N, Intrachot V, et al. Severity of silent myocardial ischemia on ambulatory electrocardiographic monitoring in patients with stable angina pectoris: relation to prognostic determinants during exercise stress testing and coronary angiography. J Am Coll Cardiol 1988;12:1169–76.

47. Berman DS, Roganski A, Knoebel SB. The detection of silent ischemia: cautions and precautions. Circulation 1987;75:101–5.

48. Takaro T, Hultgren HN, Lipton MJ, Detre KM and Participants in the Study Group. The VA cooperative randomized study of surgery for coronary arterial occlusive disease. II. Subgroup with significant left main lesions. Circulation 1976;54(suppl III):III-107–III-16.

49. Takaro T, Hultgren HN, Detre KM, et al. The VA cooperative study on stable angina: current status. Circulation 1982;65(suppl II):II-60–II-67.

50. Kaiser GC, Davis KB, Fisher LD, et al. Survival following coronary artery bypass grafting in patients with severe angina pectoris (CASS): an observational study. J Thorac Cardiovasc Surg 1985;89:513–22.

51. Hlatky MA, Califf RM, Harrell FE, et al. Comparison of predictions based on observational data with the results of randomized controlled clinical trials of coronary artery bypass surgery. J Am Coll Cardiol 1988;11:237–45.

52. DeRouen TA, Hammermeister KE, Dodge HT. Comparisons of the effects on survival after coronary artery surgery in subgroups of patients from the Seattle Heart Watch. Circulation 1981;63:537–45.

53. Passamani E, Davis KB, Gillespie MJ, Killip T and the CASS Principal Investigators and their Associates. A randomized trial of coronary artery bypass surgery: survival of patients with a low ejection fraction. N Engl J Med 1985;312:1665–71.

54. CASS Principal Investigators and Their Associates. Coronary artery surgery study: a randomized trial of coronary artery bypass surgery: survival data. Circulation 1983;68:939–50.

55. Detre K, Peduzzi P, Murphy M, et al. and the Veterans Administration Cooperative Study for Surgery for Coronary Arterial Occlusive Disease. Effect of bypass surgery on survival in patients in low- and high-risk subgroups delineated by the use of simple clinical variables. Circulation 1981;63:1329–37.

56. Weiner DA, Ryan TJ, McCabe CH, et al. Value of exercise testing in determining the risk classification and the response to coronary artery bypass grafting in three-vessel coronary artery disease: a report from the Coronary Artery Surgery Study (CASS) Registry. Am J Cardiol 1987;60: 262–6.

57. Mock MB, Fisher LD, Holmes DR Jr, et al. and Participants in the Coronary Artery Surgery Study: comparison of effects of medical and surgical therapy on survival in severe angina pectoris and two-vessel coronary artery disease with and without left ventricular dysfunction: a Coronary Artery Surgery Study Registry study. Am J Cardiol 1988;61: 1198–1203.

58. Holmes DR Jr, Vlietstra RE, Smith HC, et al. Restenosis after percutaneous transluminal coronary angioplasty (PTCA): a report from the PTCA registry of the National Heart, Lung, and Blood Institute. Am J Cardiol 1984;53(suppl C):C-77–81.

59. Lermgruber PP, Roubin ES, Hollman J, et al. Restenosis after successful coronary angioplasty in patients with single vessel disease. Circulation 1986;73:710–7.

60. Schwartz L, Bourassa MG, Lesperance J, et al. Aspirin and dipyridamole in the prevention of restenosis after percutaneous transluminal coronary angioplasty. N Engl J Med 1988;318:1714–9.

61. Dehmer GJ, Popma JJ, Egerton K, et al. Reduction in the rate of early restenosis after coronary angioplasty by a diet supplemented with n-3 fatty acids. N Engl J Med 1988;319:733–40.

62. Jones RH, Floyd RD, Austin EH, Sabiston DC Jr. The role of radionuclide angiocardiography in the preoperative prediction of pain relief and prolonged survival following coronary artery bypass grafting. Ann Surg 1983;197:743–54.

63. Detailed Diagnosis and Procedures for Patients Discharged from Short Stay Hospitals, U.S. 1986. U.S. Dept. of Health and Human Services publication. National Center for Health Statistics.

64. Winslow CM, Kosecoff JB, Chassin M, Kanouse D, Brook RH. The appropriateness of performing coronary artery bypass surgery. JAMA 1988;260:505–9.

65. Weinstein MC, Stason WB. Cost effectiveness of coronary bypass surgery. Circulation 1982;66(suppl III):III-56–III-66.

66. Chesebro JH, Clements IP, Fuster V, et al. A platelet-inhibitor-drug trial in coronary artery bypass operations: benefit of perioperative dipyridamole and aspirin therapy on early postoperative vein-graft patency. N Engl J Med 1982;307:73–8.

67. Grondin CM, Campeu L, Lesperance J, Enjalbert M, Bourassa MG. Comparison of late changes in internal mammary artery and saphenous vein grafts in two consecutive series of patients 10 years after operation. Circulation 1984;70(suppl I):I-208–I-212.

68. Loop FD, Lytle BW, Cosgrove DM, et al. Influence of the internal-mammary-artery graft on 10-year survival and other cardiac events. N Engl J Med 1986;314:1–6.

69. Luscher TF, Diederich D, Siebermann R, et al. Difference between endothelium-dependent relaxation in arterial and in venous coronary bypass grafts. N Engl J Med 1988;319:462–7.

70. The Veterans Administration Coronary Artery Bypass Surgery Cooperative Study Group. Eleven-year survival in the Veterans Administration randomized trial of coronary bypass surgery for stable angina. N Engl J Med 1984;311:1333–9.

71. Varnauskas E and the European Coronary Surgery Study Group. Twelve-year follow-up of survival in the randomized European Coronary Surgery Study. N Engl J Med 1988;319:332–7.

72. Shub C, Vlietstra RE, McGoon MD. Selection of optimal drug therapy for the patient with angina pectoris. Mayo Clin Proc 1985;60:539–48.

73. Chierchia S, Brunelli C, Simonetti I, et al. Sequence of events in angina at rest: primary reduction in coronary flow. Circulation 1980;61:759–68.

74. Nonogi H, Hess OM, Ritter M, et al. Prevention of coronary vasoconstriction by diltiazem during dynamic exercise in patients with coronary artery disease. J Am Coll Cardiol 1988;12:892–9.

75. de Ponti C, Mauri F, Ciliberto GR, Caru B. Comparative effects of nifedipine, verapamil, isosorbide dinitrate and propranolol on exercise-induced angina pectoris. Eur J Cardiol 1979;10:47–58.

76. Battock DJ, Alvarez H, Chidsey CA. Effects of propranolol and isosorbide dinitrate on exercise performance and adrenergic activity in patients with angina pectoris. Circulation 1969;39:157–69.

77. Russell RO Jr, Moraski RE, Kouchoukos N, et al. Unstable angina pectoris: National Cooperative Study Group to compare surgical and medical therapy. II. In-hospital experience and initial follow-up results in patients with one, two, and three vessel disease. Am J Cardiol 1978;42:839–48.

78. Mulcahy R, Daly L, Graham I, et al. Unstable angina: natural history and determinants of prognosis. Am J Cardiol 1981;48:525–8.

79. Krauss KR, Hutter AM Jr, DeSanctis RW. Acute coronary insufficiency and followup. Arch Intern Med 1972;129:808–13.

80. Duncan B, Fulton M, Morrison SL, et al. Prognosis of new and worsening angina pectoris. Br Med J 1976;1:981–5.

81. Roberts KB, Califf RM, Harrell FE Jr, et al. The prognosis for patients with new-onset angina who have undergone cardiac catheterization. Circulation 1983;68:970–8.

82. Boden WE, Bough EW, Benham I, Shulman RS. Unstable angina with episodic ST segment elevation and minimal creatine kinase release culminating in extensive, recurrent infarction. J Am Coll Cardiol 1983;2:11–20.

83. Blaustein AS, Heller GV, Kolman BS. Adjunctive nifedipine therapy in high-risk, medically refractory, unstable angina pectoris. Am J Cardiol 1983;52:950–4.

84. Campbell WB, Johnson AR, Callahan KS, Graham RM. Anti-platelet activity of beta-adrenergic antagonists: inhibition of thromboxane synthesis and platelet aggretation in patients receiving long-term propranolol treatment. Lancet 1981;2:1382–4.

85. Welman E, Fox KM, Selwyn AP, et al. The effect of established beta-adrenoreceptor blocking therapy on the release of cytoscoloic and lysosomal enzymes after acute myocardial infarction in man. Clin Sci Mol Med 1978;55:549–53.

86. Theroux P, Taeymans Y, Morissette D, Bosch X, Pelletier GB, Waters DD. A randomized study comparing propranolol and diltiazem in the treatment of unstable angina. J Am Coll Cardiol 1985;5:717–22.

87. The Holland Interuniversity Nifedipine/Metroprolol Trial (HINT) Research Group. Early treatment of unstable angina in the coronary care unit: a randomized, double-blind, placebo-controlled comparison of recurrent ischemia in patients treated with nifedipine or metoprolol or both. Br Heart J 1986;56:400–13.

88. Gottlieb SO, Weisfeldt ML, Ouyang P, et al. Effect of the addition of propranolol to therapy with nifedipine for unstable angina pectoris: a randomized, double-blind, placebo-controlled trial. Circulation 1986;73:331–7.

89. Holmes DR Jr, Hartzler GO, Smith HC, Fuster V. Coronary artery thrombosis in patients with unstable angina. Br Heart J 1981;45:411–6.

90. Ambrose JA, Winters SL, Stern A, et al. Angiographic morphology and the pathogenesis of unstable angina pectoris. J Am Coll Cardiol 1985;5:609–16.

91. Sherman CT, Litvack F, Grundfest W, et al. Coronary angioscopy in patients with unstable angina pectoris. N Engl J Med 1986;315:913–9.

92. Falk E. Unstable angina with fatal outcome: dynamic coronary thrombosis leading to infarction and/or sudden death: autopsy evidence of recurrent mural thrombosis with peripheral embolization culminating in total vascular occlusion. Circulation 1985;71:699–708.

93. Davies MJ, Thomas AC. Plaque fissuring—the cause of acute myocardial infarction, sudden ischaemic death, and crescendo angina. Br Heart J 1985;53:363–73.

94. Fitzgerald DJ, Roy L, Catella F, FitzGerald GA. Platelet activation in unstable coronary disease. N Engl J Med 1986;315:983–9.

95. Lewis HD Jr, Davis JW, Archibald DG, et al. Protective effects of aspirin against acute myocardial infarction and death in men with unstable angina: results of a Veterans Administration Cooperative Study. N Engl J Med 1983;309:396–403.

96. Cairns JA, Gent M, Singer J, et al. Aspirin, sulfinpyrazone, or both in unstable angina: results of a Canadian multicenter trial. N Engl J Med 1985;313:1369–75.

97. Theroux P, Latour JG, Leger-Gauthier C, De Lara J. Fibrinopeptide A and platelet factor levels in unstable angina pectoris. Circulation 1987;75:156–62.

98. Theroux P, Ouimet H, McCans J, et al. Aspirin, heparin, or both to treat unstable angina. N Engl J Med 1988;319:1105–11.

99. de Zwaan C, Bar FW, Janssen JHA, et al. Effects of thrombolytic therapy in unstable angina: clinical and angiographic results. J Am Coll Cardiol 1988;12:301–9.

100. Luchi RJ, Scott SM, Deupree RH, Principal Investigators and Their Associates of Veterans Administration Cooperative Study No. 28. Comparison of medical and surgical treatment for unstable angina pectoris: results of a Veterans Administration Cooperative Study. N Engl J Med 1987;316:977–84.

101. de Feyter PJ, Suryapranata H, Serruys PW, et al. Coronary angioplasty for unstable angina: immediate and late results in 200 consecutive patients with identification of risk factors for unfavorable early and late outcome. J Am Coll Cardiol 1988;12:324–33.

102. Herrick JB. Clinical features of sudden obstruction of the coronary arteries. JAMA 1912;59:2015.

103. Roberts WC. Coronary arteries in fatal acute myocardial infarction. Circulation 1972;45:215–30.

104. DeWood MA, Spores J, Notske R, et al. Prevalence of total coronary occlusion during the early hours of transmural myocardial infarction. N Engl J Med 1980:303:897–902.

105. Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI). Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. Lancet 1986;1:397–402.

106. Wilcox RG, von der Lippe G, Olsson CG, et al. Trial of tissue plasminogen activator for mortality reduction in acute myocardial infarction. Anglo-Scandinavian Study of Early Thrombolysis (ASSET). Lancet 1988;2:525–30.

107. AIMS Trial Study Group. Effect of intravenous APSAC on mortality after acute myocardial infarction: preliminary report of a placebo-controlled clinical trial. Lancet 1988;1:546–9.

108. Van de Werf F, Arnold AER, and the European Cooperative Study Group for Recombinant Tissue-Type Plasminogen Activator (rt-PA). Intravenous tissue plasminogen activator and size of infarct, left ventricular function, and survival in acute myocardial infarction. Br Med J 1988;297:2374–9.

109. ISIS-2 Collaborative Group. Randomized trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected myocardial infarction. Lancet 1988;2:349–60.

110. Simoons ML, van der Brand M, de Zwabb C, et al. Improved survival after early thrombolysis in acute myocardial infarction. Lancet 1985;2: 578–81.

111. Fitzgerald DJ, Catella F, Roy L, Fitzerald GD. Marked platelet activation in vivo after intravenous streptokinase in patients with acute myocardial infarction. Circulation 1988;77:142–50.

112. Golino P, Ashton JH, Glas-Greenwalt P, et al. Mediation of reocclusion by thromboxane A2 and serotonin after thrombolysis with tissue-type plasminogen activator in a canine preparation of coronary thrombosis. Circulation 1988;77:678–84.

113. Owen J, Friedman KD, Grossman BA, et al. Thrombolytic therapy with tissue plasminogen activator or streptokinase induces transient thrombin activity. Blood 1988;72:616–20.

114. Gold HK, Coller BS, Yasuda T, et al. Rapid and sustained coronary artery recanalization with combined bolus injection of recombinant tissue-type plasminogen activator and monoclonal antiplatelet GPIIb/IIIa antibody in a canine preparation. Circulation 1988;77:670–7.

115. Schroder R, Neuhaus KL, Leizorovicz A, et al. A prospective placebo-controlled double-blind multicenter trial of Intravenous streptokinase in acute myocardial infarction (ISAM): long-term mortality and morbidity. J Am Coll Cardiol 1987;9:197–203.

116. Simoons ML, Betriu A, Col J, et al. Thrombolysis with tissue plasminogen activator in acute myocardial infarction: no additional benefit from immediate coronary angioplasty. Lancet 1988;1:197–203.

117. Topol EJ, Califf RM, George BS, et al. A randomized trial of immediate versus delayed elective angioplasty after intravenous tissue plasminogen activator in acute myocardial infarction. N Engl J Med 1987;317:581–8.

118. TIMI Research Group. Immediate vs. delayed catheterization and angioplasty following thrombolytic therapy for acute myocardial infarction. JAMA 1988;260:2849–58.

119. O'Neill W, Timmis GC, Bourdillon PD, et al. A prospective randomized clinical trial of intracoronary streptokinase versus coronary angioplasty for acute myocardial infarction. N Engl J Med 1986;314:812–8.

120. Hartzler GO, Rutherford BD, McConahay MD. Percutaneous transluminal coronary angioplasty: application for acute myocardial infarction. Am J Cardiol 1984;53:117C–21C.

121. Rothbaum DA, Linnemeier TJ, Landin RJ, et al. Emergency percutaneous transluminal coronary angioplasty in acute myocardial infarction: a 3 year experience. J Am Coll Cardiol 1987;10:264–72.

122. Lew AS, Hod H, Cerrek B, Ghah P, Ganz W. Mortality and morbidity rates of patients older than 75 years with acute myocardial infarction treated with intravenous streptokinase. Am J Cardiol 1987;59:1–5.

123. Forrester JS, Diamond G, Chatterjee K, Swan HJC. Medical therapy of acute myocardial infarction by application of hemodynamic subsets. N Engl J Med 1976;295:1356–62.

124. Forrester JS, Diamond G, Chatterjee K, Swan HJC. Medical therapy of acute myocardial infarction by application of hemodynamic subsets. N Engl J Med 1976;295:1404–13.

125. Jugdutt BI, Warnica JW. Intravenous nitroglycerin therapy to limit myocardial infarct size, expansion, and complications: effect of timing, dosage, and infarct location. Circulation 1988;78:906–19.

126. Yusuf S, MacMahon S, Collins R, Peto R. Effect of intravenous nitrates on mortality in acute myocardial infarction: an overview of the randomized trials. Lancet 1988;1:1088–1092.

127. May DC, Popma JJ, Black WH, et al. In vivo induction and reversal of nitroglycerin tolerance in human coronary arteries. N Engl J Med 1987;317:805–9.

128. Cohn JN, Guiha NH, Broder MI, et al. Right ventricular infarction. Am J Cardiol 1974;33:209–14.

129. Lorell B, Leinbach RC, Pohost GM, et al. Right ventricular infarction: clinical diagnosis and differentiation from cardiac tamponade and pericardial constriction. Am J Cardiol 1979;43:465–71.

130. Dell'Italia LJ, Starling MR, O'Rourke RA. Physical examination for exclusion of hemodynamically important right ventricular infarction. Ann Intern Med 1983;99:608–11.

131. The Norwegian Multicenter Study Group. Timolol after myocardial infarction. N Engl J Med 1981;304:801–7.

132. Beta-Blocker Heart Attack Trial Research Group. A randomized trial of propranolol in patients with acute myocardial infarction. I. Mortality results. JAMA 1982;247:1707–14.

133. The MIAMI Trial Research Group. Metoprolol in acute myocardial infarction (MIAMI): a randomized placebo-controlled international trial. Eur Heart J 1986;6:199–226.

134. The International Collaboration Study Group. Reduction of infarct size with the early use of timolol in acute myocardial infarction. N Engl J Med 1984;310:9.

135. Furberg CD, Hawkins CM, Lichstein E. Effect of propranolol in postinfarction patients with mechanical or electrical complications. Circulation 1984;69:761–5.

136. Muller JE, Morrison J, Stone PH, et al. Nifedipine therapy for patients with threatened and acute myocardial infarction: a randomized, double-blind, placebo-controlled comparison. Circulation 1984;69:740–7.

137. Sirnes PA, Overskeid K, Pedersen TR, et al. Evolution of infarct size during the early use of nifedipine in patients with acute myocardial infarction: the Norwegian Nifedipine Multicenter Trial. Circulation 1984;70:859–65.

138. The Multicenter Diltiazem Postinfarction Trial Research Group. The effect of diltiazem on mortality and reinfarction after myocardial infarction. N Engl J Med 1988;319:385–92.

139. Madigan NP, Rutherford BD, Frye RL. The clinical course, early prognosis and coronary anatomy of subendocardial infarction. Am J Med 1976;60:634–41.

140. Hutter AM, DeSanctis RW, Flynn T, Yeatman LA. Nontransmural infarction: a comparison of hospital and late clinical course of patients with that of matched patients with transmural anterior and transmural inferior myocardial infarction. Am J Cardiol 1981;48:595–602.

141. The Diltiazem Reinfarction Study Group. Diltiazem and reinfarction in patients with non-Q-wave myocardial infarction. N Engl J Med 1986;315: 423–9.

142. Sharpe N, Murphy J, Smith H, Hannan S. Treatment of patients with symptomless left ventricular dysfunction after myocardial infarction. Lancet 1988;1:255–9.

143. Bigger JT Jr, Fleiss JL, Kleiger R, Miller JP, Rolnitzky LM. The Multicenter Post-infarction Research Group. The relationships among ventricular arrhythmias, left ventricular dysfunction, and mortality in the 2 years after myocardial infarction. Circulation 1984;69:250–8.

144. Tibbits PH, Evaul JE, Goldstein RE, and the Multicenter Post-infarction Research Group. Serial Acquisition of Data to Predict One-Year Mortality Rate After Acute Myocardial Infarction. Am J Cardiol 1987;60: 451–5.

145. Dittus RS, Roberts SD, Adolph RJ. Cost-effectiveness analysis of patient management alternatives after uncomplicated myocardial infarction: a model. J Am Coll Cardiol 1987;10:869–78.

146. Roy D, Waxman RD, Kienzle MG, Buxton AE, Marchlinski FE, Josephson ME. Clinical characteristics and long-term follow-up in 199 survivors of out-of-hospital cardiac arrest: relation to inducibility at electrophysiologic testing. Am J Cardiol 1983;52:969–74.

147. Wilber DJ, Garan H, Finkelstein D, Kelly E, et al. Out-of-hospital cardiac arrest: use of electrophysiologic testing in the prediction of long-term outcome. N Engl J Med 1988;318:19–24.

148. Vatterott PJ, Hammill SC, Bailey KR, Berbari EJ, Matheson SJ. Signal-averaged electrocardiography: a new noninvasive test to identify patients at risk of ventricular arrhythmias. Mayo Clin Proc 1988;63:931–42.

149. Swerdlow CD, Mason JW, Stinson EB, Oyer PE, Winkle RA, Derby GC. Results of operations for ventricular tachycardia in 105 patients. J Thorac Cardiovasc Surg 1986;92:105–13.

150. Ostermeyer J, Borggrefe M, Breithardt G, et al. Direct operations for the management of life-threatening ischemic ventricular tachycardia. J Thorac Cardiovasc Surg 1987;94:848–65.

151. Alderman ED, Fisher LD, Litwin P. Results of coronary artery surgery in patients with poor left ventricular function (CASS). Circulation 1983;68:785–95.

152. Nishimura RA, Schaff HV, Shub C, Gersh BJ, Edwards WD, Tajik AJ. Papillary muscle rupture complicating acute myocardial infarction: analysis of 17 patients. Am J Cardiol 1983;51:373–7.

153. Held AC, Cole PL, Lipton B, Gore JM, et al. Rupture of the interventricular septum complicating acute myocardial infarction: a multicenter analysis of clinical findings and outcome. Am Heart J 1988;116:1330–6.

154. Cobbs BW Jr, Hatcher CR Jr, Robinson PS. Cardiac rupture: 3 operations with 2 long-term survivals. JAMA 1973;223:532.

155. Rosenberg L, Kaufman DW, Helmrich SP, Shapiro S. The risk of myocardial infarction after quitting smoking in men under 55 years of age. N Engl J Med 1985;313:1511–4.

156. Vlietstra RE, Kronmal RA, Oberman A, Frye RL, Killip T. Effect of cigarette smoking on survival of patients with angiographically documented coronary artery disease. JAMA 1986;255:1023–7.

157. Gordon T, Kannel WB, McGee D. Death and coronary attacks in men after giving up cigarette smoking: a report from the Framingham Study. Lancet 1974;2:1345–8.

158. Management Committee. The Australian trial in mild hypertension. Lancet 1980;1:1261–7.

159. Hypertension Detection and Follow-up Program Cooperative Group. The effect of treatment on mortality in 'mild' hypertension. N Engl J Med 1982;307:976–80.

160. Lipid Research Clinics Program, National Heart, Lung, and Blood Institute. The Lipid Research Clinics coronary primary prevention trial results: reduction in incidence of coronary heart disease. JAMA 1984;251:351–64.

161. Manninen V, Elo MO, Frick MH, et al. Lipid alterations and decline in the incidence of coronary heart disease in the Helsinki heart study. JAMA 1988;260:641–51.

162. Brensike JF, Levy RI, Kelsey SF, et al. Effects of therapy with cholestyramine on progression of coronary arteriosclerosis: results of the NHLBI Type II Coronary Intervention Study. Circulation 1984;69: 313–24.

163. Report of the National Cholesterol Education Program Expert Panel on detection, evaluation, and treatment of high blood cholesterol in adults. Arch Intern Med 1988;148:36–48.

164. The Lovastatin Study Group III. A multicenter comparison of lovastatin and cholestyramine therapy for severe primary hypercholesterolemia. JAMA 1988;260:359–66.

165. Blankenhorn DH, Nessim SA, Johnson RL, et al. Beneficial effects of combined colestipol-niacin therapy on coronary atherosclerosis and coronary venous bypass grafts. JAMA 1987;257:3233–40.

166. Hatziandreu EI, Koplan JP, Weinstein MC, Caspersen CJ, Warner KE. A cost-effectiveness analysis of exercise as a health promotion activity. Am J Public Health 1988;78:1417–21.

167. Ehsani AA, Biello DR, Schultz J, et al. Improvement of left ventricular contractile function by exercise training in patients with coronary artery disease. Circulation 1986;74:350–8.

168. Oldridge NB, Guyatt GH, Fischer ME, Rimm AA. Cardiac rehabilitation after myocardial infarction. JAMA 1988;260:945–50.

169. Dennis C, Houston-Miller N, Schwartz RG, et al. Early return to work after uncomplicated myocardial infarction: results of a randomized trial. JAMA 1988;260:214–20.

170. Oliver MF. Reducing cholesterol does not reduce mortality. J Am Coll Cardiol 1988;12:814–7.

171. Kronmal R. Commentary on the published results of the Lipid Research Clinics Coronary Primary Prevention Trial. JAMA 1985;253:2091–3.

172. Sempos C, Cooper R, Kovar MG, McMillen M. Divergence of the recent trends in coronary mortality for the four major race-sex groups in the United States. Am J Public Health 1988;78:1422–7.