IDENTIFICATION OF HIGH RISK PATIENTS AFTER AN ACUTE MYOCARDIAL INFARCTION. THERAPEUTIC APPROACH FOR SECONDARY PREVENTION

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The high mortality rate associated with coronary heart disease in the western countries has caused increasing concern over the last several decades. The creation of coronary care units in many hospitals has reduced the fatality rate in patients with acute myocardial infarction who reach the hospital. However, this reduction in mortality has had little impact on the overall death rate due to coronary heart disease since many patients never survive to reach the hospital but die very shortly after the onset of their symptoms.

The risk of dying following an acute myocardial infarction (AMI) declines over time. It is highest within the first 24 hours after onset of symptoms and remains high during the first month after infarction. Cardiac mortality is about 9 percent from the second through the sixth month after infarction and then drops sharply from the seventh month to an annual rate of 3 to 4 percent over the next four to five years. Including the first, high-risk month, cardiac mortality rates six months after infarction have been reported as high as 15 percent, almost four times the death rate during the subsequent 6 months. Sixty to 80 percent of these deaths has been attributed to sudden death. Based on these figures, it has been inferred that the risk of mortality associated with acute myocardial infarction is virtually dissipated after 6 months, and that therapeutic interventions, if they are to be effective, should occur early after the onset of the acute event.

Mortality risk after myocardial infarction - demographic and historical factors

Age - The risk of major complications after an acute myocardial infarction is significantly influenced by the age of the patient. The risk relationship to age is not linear, but increases exponentially beginning at age 55.

Hagstrom et al followed, for an extended period of time, 489 patients who survived an AMI. The sudden death rate for this population increased for each decade from 30 to 79 years [1]. Based on the Peel prognostic index using six variables, age 65 or over carried more weight than a prior history of angina, mild hypotension during the acute episode, congestive basilar rales, or S-T and T-wave abnormalities, and was weighted equally with a history of exertion dyspnea or Q-waves on the initial ECG [2]. Norris et al found that increasing age above 70 years at the time of infarction was associated with significantly reduce 3- and 6-year survival rates [3]. Moss et al., using a stepwise discriminate analysis technique for predicting survival after myocardial infarction in an unrestricted age population, found that increasing age was one of the most important factors in identifying patients at increased risk of mortality [4].

Sex - The relatively low incidence of coronary heart disease between women in comparison to men is well known. However, in a detailed report by the Health Insurance Plan group, the 5-year survival among 108 women and 564 men who had survived the first month after infarction was similars. Thus, although the female sex represents a low risk factor for the development of coronary heart disease, women are not protected against secondary complications once a clinical infarction has occurred.

Prior angina pectoris - A clinical history of angina pectoris prior to a myocardial infarction has negative prognostic implications for long-term survival [6].

The more ominous forms of angina, such as those indicating extensive coronary disease, are more likely to be associated with increased mortality and reduced survival in the post-infarction period than the more stable forms of angina.

Prior myocardial infarction - It is a reasonable assumption that patients with a past history of myocardial infarction will have a poorer long-term prognosis after a subsequent infarction than patients suffering from their first coronary event. Since a correlation exists between the extent of cardiac damage and prognosis, patients with one or more prior infarctions probably have less myocardial re-

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serve and therefore are at greater risk of mortality. Research data from a variety of studies support these assumptions [2,3].

The extent, location and type (transmural vs. nontransmural) of the prior myocardial infarction may also be important predictors of outcome. For example, anterior MI's seem to have a worse prognosis when compared to inferior MI's.

Baum et al pointed out in 1794 that prehospital patients with acute myocardial infarction who were resuscitated from ventricular fibrillation did better if an acute transmural infarction evolved than if it did not [7]. Subsequently, Cannom et al found that patients with nontransmural infarcts had a particularly guarded prognosis [8]. These studies suggest that patients with a prior nontransmural or subendocardial myocardial infarction have residual myocardial ischemia, which may contribute to electrical instability. Therefore, factors influencing the prognosis include not only the location of the prior infarct, but also whether or not it was transmural.

Oher preexisting actors - Prior cardiac functional status is an important consideration in the survival rate during and after an acute myocardial infarction. A prior history of hypertension contributes to a pronounced excess mortality. Furthermore [9], the presence of other risk factors such as hypercholesterolemia [10], diabetes mellitus, and cigarette smoking [11] also contributes to the increased mortality after an acute myocardial infarction.

Clinical considerations during the coronary care unit phase

The severity of an AMI is a primary determinant of both the in-hospital and posthospital courses. The magnitude of damage to the myocardium and the extent and severity of the underlying obstructive coronary artery disease are reflected in the hemodynamic, ischemic and electrical derangements observed during the acute hospital phase. These functional disorders are intimately related to prognosis after myocardial infarction [2,3].

Left ventricular disfunction - Numerous studies have shown that clinical evaluation of the patient's hemodynamic status in the Coronary Care Unit (CCU) provides valuable information about the posthospital prognosis [12].

There are a number of easily measured clinical parameters that reflect left ventricular dysfunction and are also useful indicators of posthospital prognosis. For example, Norris et al found that qualitative cardiomegaly detected on an admission chest x-ray film was associated with significantly increased mortality at 3 and 6 years after the infarction [13,14].

Infarct size - Extensive myocardial damage at the time of infarction is a permanent liability and a long-term threat to life. The greater the infarct size the more common is the development of cardiogenic shock and ventricular arrhythmias [15].

Conduction disturbances - The development of certain types of conduction disturbances during the CCU phase of an AMI is associated with increased acute, subacute and chronic mortality [16].

Patients at highest risk of mortality are those who had any of the following ECG findings while in the CCU: (1) adjacent fascicular block (left anterior hemiblock and right bundle-branch block or left bundle-branch block) plus P-R interval prolongation; (2) nonadjacent fascicular block (left posterior hemiblock and right bundle-branch block; alternating bundle-branch block) regardless of PR interval; or, (3) transient Mobitz type II complete heart block. In one study, thirteen of 25 (50%) such patients died within one year of hospitalization [16].

Arrhythmias - Newly appearing atrial arrhythmias occurring in patients with AMI in the early CCU phase are frequently associated with signs of congestive heart failure and greater overall early mortality [17]. In all likelihood, atrial arrhythmias per se are not a primary determinant of outcome; rather, they probably reflect a more severe underlying cardiac or pulmonary disease conditions usually associated with increased mortality.

Ventricular arrhythmias recorded in the CCU are unreliable indicators of subsequent prognosis [18]. The only exception is secondary VF and the determinant of outcome is the disordered ventricular function and not, the complicating tachyarrhythmia.

POSTHOSPITAL EVALUATIONS

During the past decade, numerous post-infarction patients have been studied prior to discharge or in the early posthospital period in order to identify those at increased mortality risk. The earlier studies based prognosis on serial ECG findings [9]. With the introduction of Holter ambulatory recordings, research emphasis shifted to the prognostic significant of ventricular arrhythmias [19].

The development of the radionuclide technique for evaluation of the ejection fraction and ventricular wall motion permitted precise, noninvasive evaluation of the important mechanical cardiac factors that relate to outcome [20].

Two-dimensional echocardiography has also been useful in predicting the prognosis [21].

Coronary angiography and left ventriculography have been used to evaluate high-risk post-infarction patients who might be candidates for coronary artery bypass surgery [22].

Because of the relative safety of the angiographic studies reported to date and the valuable information which cannot be obtained in any other way, coronary angiography will probably be used more frequently in post-infarction patients.

Activity and exercise testing using treadmill and bicycle ergometer techniques in post-coronary patients have provided valuable insight into global

cardiac performance as well as ischemic and arrhythmic abnormalities [23].

An electrical stress test, using a temporary transvenous pacing stimulus to evaluate ventricular electrical instability, has also been used as a diagnostic procedure in post-infarction patients.

These studies continue to provide important insights into the electrical, mechanical, ischemic and anatomical factors that influence the clinical course of patients after myocardial infarction.

The posthospital clinical course - The development of angina pectoris or symptoms of left ventricular dysfunction (fatigue, exertional, dyspnea, congestive heart failure) during the posthospital phase of myocardial infarction has significant prognostic implications. Recurrent post-infarction angina almost always indicates multivessel coronary disease, and the long-term survival status of these patients is guarded. The earlier angina occurs after infarction, the more omnious the prognosis. For this reason, many cardiologists are proceeding with exercise testing and coronary angiography in post-infarction patients who develop angina, in order to evaluate more precisely the extent and severity of the coronary disease. Coronary artery bypass graft surgery appears beneficial in those with left main coronary stenosis or proximal triple-vessel coronary disease with good distal runoff.

The occurrence of ventricular arrhythmias in the posthospital phase also is associated with a lower survival rate [18,19]. Holter-recorded VPBs 2,3 weeks after infarction have prognostic usefulness in identifying subsequent mortality events.

In patients with symptoms of left ventricular dysfunction, radionuclide assessment of the ejection fraction and regional wall motion provides valuable information [20]. In general this group of patients will have the poorest prognosis. However, the radionuclide study can provide quantitative and qualitative data that are often useful in the clinical management of the individual patient. For example, a surgically correctable aneurysm may be detected by this approach.

SECONDARY PREVENTION

Numerous therapeutic measures are utilized in patients after myocardial infarction including diet, exercise, stress control, and medical. The following section will emphasize pharmacologic intervention.

Antiarrhythmic drugs - There are six controlled studies of the ability of antiarrhythmic drugs administered on a long-term basis to prevent cardiac death in post-MI patients [24-29]. Studies involving beta-blockers are considered separately. The agents that have been evaluated are phenytoin, tocainide, mexiletine, and aprindine.

A total of 1675 post-MI patients were studied in these 6 clinical trials. In four trials in which cardiac rhythm was electrocardiographically monitored, the drugs tested were reported to be effective in reducing the incidence of ventricular arrhythmias. Despite this, there is no evidence that antiarrhythmic therapy reduces cardiovascular mortality in an unselected group of MI patients. The question of whether the subgroup of patients with complex arrhythmias following an MI should be prescribe these drugs in the long-term has not been answered.

Lipid lowering drugs and diet - The association of elevated serum cholesterol levels with an increased risk of developing coronary heart disease is well established. The importance of hyperlipidemia as a risk factor for recurrent myocardial infarction in survivors of a first attack is less certain. A number of randomized controlled clinical trials has been undertaken in the last 30 years in patients with established CHD to determine the effects on morbidity and mortality of diet and/or long-term administration of several lipid-lowering agents [28-34].

In nine well controlled trials, a reduction of serum cholesterol levels between 6.5% and 20% was achieved without any change in mortality. Various adverse effects, ranging from venous thromboembolism to cardiac arrhythmias, gallstones, cancer, and nonfatal MI, were associated with the use of several of the drugs employed. In the case of clofibrate, a toxic effect of long-term usage has also been observed in a large primary prevention study in CHD subjects [35]. It may be that lipid lowering drugs used in patients after an MI do not change the overall risk of death, only the mode. Their use in primary prevention may prove more successful. In fact, in a recent study involving 3806 asymptomatic middle-aged men with primary hypercholesteremia, the group administered cholestyramine had a 24% reduction in coronary heart disease death in a 7.4 year follow-up period when compared to the group that received placebo [36].

Oral anticoagulant drugs - Anticoagulant trials were among the first efforts using drug intervention in patients following an MI [37-44]. In the acute phase, the rationale for their use was based on the expectation that they would not only prevent extension of the responsible thrombus in the coronary vessels, but would also reduce the risk of both systemic arterial embolism from a mural thrombus and pulmonary embolism following deep venous thrombosis in the lower limbs. Their long-term benefit was more uncertain, since it was predicated on the theory of preventing a subsequent coronary thrombus that might, result in reinfarction and possibly death.

The results of five randomized trials, involving a total of 2,327 patients, did not show that long-term anticoagulant therapy lowers mortality in patients who have suffered an MI.

Platelet-active drugs - Since 1970, 7 randomized trials have been completed investigating the usefulness of platelet-active drugs in long-term follow up in patients who have had an MI 45-50. None of the seven studies involving 13,000 patients demonstrated a statistically significant difference between the inter-

vention and control groups for total mortality. The drugs employed in these studies were aspirin, aspirin and dipyridamole and sulfinpyrazone.

Beta-Blocking agents - The role of sympathetic nervous system activity in precipitating sudden death after myocardial infarction is well recognized clinically. The first indication that the prototype beta-blocker, propranolol, might be useful in myocardial infarction was a study completed by Snow in 1965 [51]. Although the number of patients was small (91 patients) and the trial was neither randomized nor double-blind, it showed that propranolol reduced mortality by 54 percent in the first month after myocardial infarction. However, these encouraging results could not be confirmed in two randomized double-blind trials reported subsequently [52-53].

In a landmark study published in 1974, Wilhelmsen reported a decreased incidence of sudden death following infarction in patients treated with alprenolol [54]. Later, Green found that post-infarction mortality was reduced with chronic practolol therapy, but the effect was limited to patients with anterior infarcts [55]. This particular beta-blocker was later found to have unacceptable side effects. It has also been reported that oral therapy with alprenolol for one year following infarction produced a significant reduction in mortality56. However, this effect was limited to patients less than 66years of age. In older patients, the drug appeared to exert an adverse effect on survival.

Clarification of the value of post-infarction beta-blocker therapy was obtained in 1981 with the completion of three major studies (timolol, metoprolol and propranolol). In 1992, two other beta-blocker trials (sotalol and oxprenolol) were also completed. In the Beta-Blocker Heart Attack Trial (BHAT), 3.837 patients were randomly assigned to placebo or propranolol therapy at 5-21 days post infarction [57]. The dose of propranolol was 180-240 mg per day, depending on serum drug levels. Total mortality during the 25 month follow-up period was 7.2 percent in the propranolol and 9.8 percent in the placebo group, a reduction in total mortality of 26.5 percent. In the metoprolol study, 1,395 patients were randomized either to active drug or placebo. This study differs from the timolol (discussed below) and propranolol studies in that therapy was started acutely (first day), and maintained for 3 months. Patients received either placebo or 15 mg of metoprolol intravenously followed by 100 orally twice daily. During a 90 day follow-up period, the death rate was 8.9 percent in the placebo group versus 5.7 percent in the metoprolol group, a reduction of 36 percent in mortality [58].

In the timolol study [59] 1,884 patients were randomly assigned to timolol (10 mg twice daily) or placebo starting 7 to 28 days post infarction. During a mean follow up period of 17 months, the cumulative sudden death rate was 13.9 percent in the placebo group and 7.7 percent in the timolol group - a reduction of 44.6 percent. The cumulative total mortality rate was 21.9 percent in the placebo group and 13.3 percent in the timolol group, a reduction of 39.4 percent. Furthermore, reinfarction rates were assessed and found to be reduced in the timolol group by 28 percent. Of interest also was the report that patients who were taking the drug and were withdrawn because of unacceptable side effects did not display any apparent "rebound" increase in the rate of reinfarction and mortality.

In the sotalol study, 1,456 patients were randomly assigned to either sotalol (320 mg daily) or placebo beginning five to 14 days post infarction. During a follow-up period of 12 months, the cumulative mortality was 18 percent lower in the treated group but without statistical significance [60].

In the oxprenolol study [6l], 1,103 patients were randomly assigned to either oxprenolol (40 mg twice daily) or placebo starting 1-90 months post infarction. During a follow-up period of six years, the total cumulative survival rate was similar in both groups. However, if the study is arbitrarily divided into three categories: 1) patients entering in the study up to five months post-infarction; 2) patients entering in the study five to 12 months post-infarction and; 3) patients entering the study later than 12 months post infarction, the results are as follows: beneficial for group 1, no changes for group 2 and deleterious or group 3. It is important to bear in mind that the results from this trial can not be extrapolated to any other beta-blocker, and the theoretical possibility of accelerated atherogenesis due to long term beta-blockade cannot be ignored.

The design, conduct and data analysis of these studies was of high quality by clinical trial standards. There is, however, an absence of information about the mechanism of beneficial effects. The reduction in mortality and/or reinfarction may be due to the prevention of primary arrhythmic death, protection of the myocardium during subsequent ischemia, prevention of recurrent coronary occlusion, or some combination of these actions. These aspects warrant further study.

Although a total of 43.000 patients has been evaluated using 25 different interventions, the opportunities for secondary prevention in a post-MI population are not exhausted. Benefit in particular sub-groups may have been concealed by equivocal results in the majority of patients. In the future, interventions would probably best be evaluated in selected high risk patient populations.

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