



# How can we identify patients at high risk of coronary heart disease events?

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*Successful strategies are needed to prevent atherosclerotic plaque development and vessel occlusion and their consequences in terms of cardiac events. "Traditional" risk stratification has used various algorithms based on assessment of standard risk factors and the characteristics and extent of atherosclerotic cardiovascular disease in order to match the intensity of intervention to the level of risk at an acceptable cost. Recent studies have focused on the importance of novel prognostic factors and cardiac markers to predict the risk of future events, including inflammation (C-reactive protein), thrombosis (fibrinogen), direct assessment of the extent of disease (cardiac imaging techniques), predictors of the vulnerable plaque (serum troponin T), as well as cultural, social, and behavioral predictors of outcome such as depression and poor social support.*

**Keywords:** coronary heart disease; angina; myocardial infarction; heart failure; risk factor; risk stratification; quality of life; C-reactive protein; fibrinogen; troponin T

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Given the dramatic progress made in understanding the genesis and consequences of atherosclerotic plaque development and vessel occlusion, it is not surprising that multiple potentially beneficial therapies have been developed to prevent the consequences of plaque progression and rupture. However, as with most medical therapies, our portfolio of treatments is not curative. We have succeeded in developing effective strategies for delaying the progression of the disease and for ameliorating some of its consequences, but not for absolutely preventing it. Furthermore, these approaches to prevention and treatment come at a cost. Given the global nature of the disease and its enormous consequences,<sup>1</sup> we cannot afford to use every possible medical approach. Rather, we must attempt to define the risk to patients over time and then apply the level of intervention that is appropriate to the level of risk.

## RISK STRATIFICATION

Before discussing risk factors, it is important to define what is being predicted by the risk factors. This issue may be considered from the point of view of pathophysiology or clinical outcome. We would like to be able to identify patients at risk of progression of underlying atherosclerosis, of a plaque event (disruption of the plaque causing unstable angina or myocardial

necrosis), of adverse remodeling of the left ventricle causing heart failure, or of sudden ventricular dysrhythmia. While a construct for how these events occur is necessary for devising new risk factors, in the practical application of risk prediction we must keep in mind the primary patient desires: living longer, feeling better, avoiding unpleasant events, and spending less money. From this perspective the major events to predict are death, myocardial infarction, heart failure, sudden death, and symptomatic angina, which are the clinical consequences of the pathophysiologic processes mentioned above. While much progress has been made in predicting clinical events, our efforts to predict quality of life in its multiple dimensions are rudimentary. This perspective on clinical events and quality of life also emphasizes the importance of identifying patients at risk who can be treated preemptively to avoid the cost of expensive procedures such as revascularization.

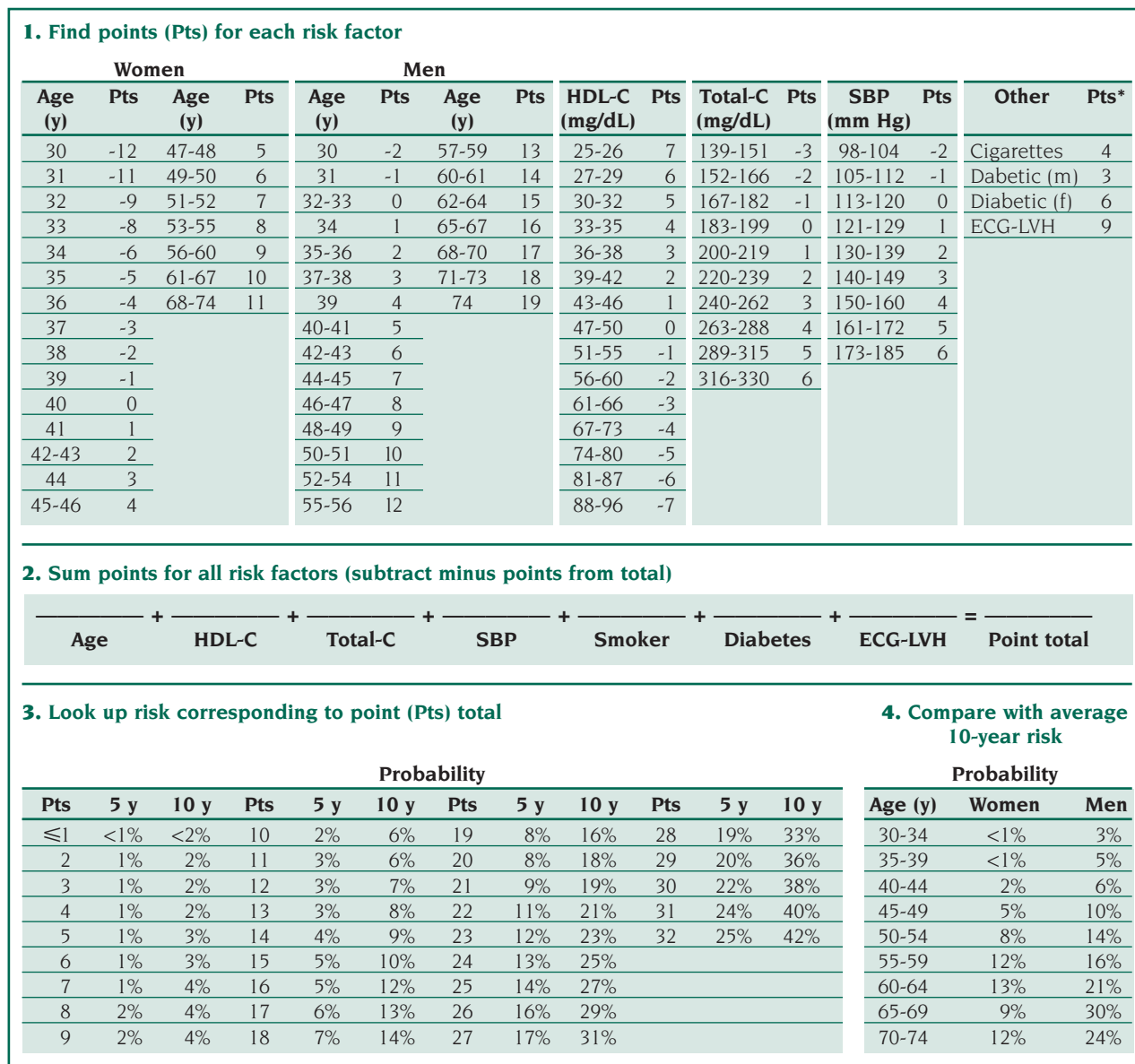
The etiology of atherosclerosis is complex, and epidemiological studies have been unable to identify a single "smoking gun" that can predict risk. Rather, the risk of cardiac events appears to be multifactorial, reflecting multiple ways to reach the same end of a symptomatic cardiac event as a consequence of dynamic alterations of atherosclerotic plaque, the neurohormonal environment, the propensity for thrombosis,

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and inflammation. Because of this complexity, we cannot know in advance if a pair of risk factors will be additive or multiplicative (synergistic), or whether they are simply providing redundant information about risk. Empirical observations are necessary to sort out these complex relationships.

Critical to the modern understanding of risk stratification is the concept of matching the intensity of intervention to the level of risk. In general, effective therapies exert a proportional reduction in the risk of events so that, for the same risk reduction, the therapy will prevent more events per treated patient

in higher-risk patients. Thus, bypass surgery has greater absolute benefit in patients with more severe coronary heart disease (CHD), statins save more lives per 100 patients treated in patients with high low-density lipoprotein (LDL) cholesterol, and angiotensin-converting (ACE) inhibitors save



**Figure 1.** Coronary heart disease risk factor prediction chart: patients without known coronary artery disease.

Abbreviations and symbols: \*, zero points for each “No”; ECG-LVH, electrocardiographic left ventricular hypertrophy; f, female; HDL-C, high-density lipoprotein cholesterol; m, male; Pts, points; SBP, systolic blood pressure; Total-C, total cholesterol.

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more lives in patients with more depressed left ventricular function. Thus, in addition to informing patients about what to expect, a critical goal is to identify patients in whom the benefit of intervening exceeds the risk of intervening at an acceptable cost.

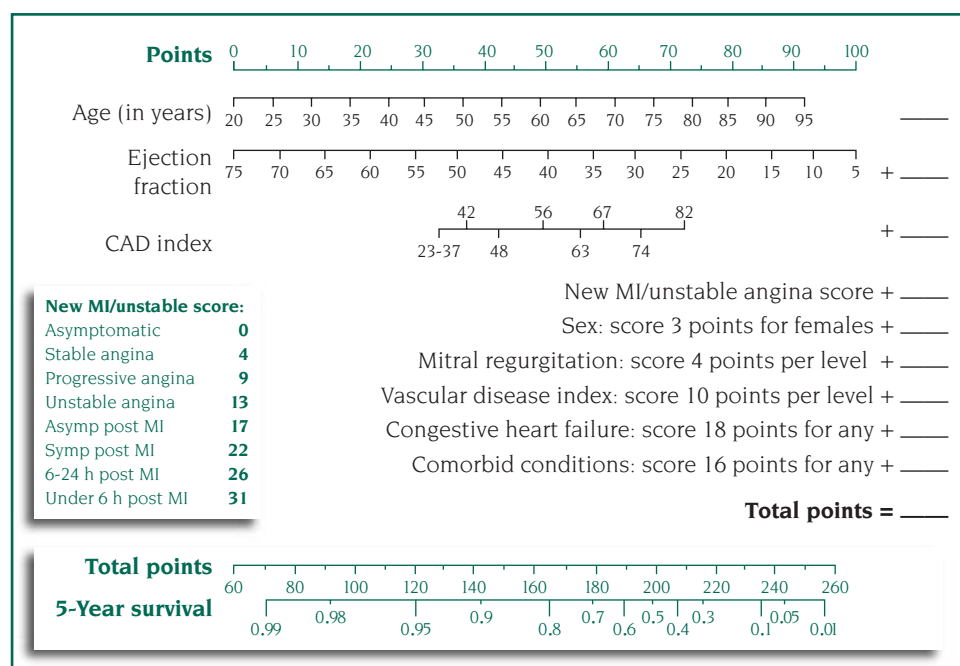
Defining risk of atherosclerotic cardiovascular disease can be considered in several dimensions: stage of disease, time within the stage of disease, and type of risk factor. The quantification of risk must begin with simple measurements that can be made in the course of a routine encounter, but more expensive measures must be used when they can target patients with the most to gain from intervention. Patients who have already experienced a manifestation of atherosclerosis are at much higher risk in general than those with no apparent clinical manifestation of the disease. In defining the risk of individuals in these categories, risk factors may be divided into "traditional" risk factors and novel risk factors, which are in the process of being defined.

### "TRADITIONAL" RISK FACTORS

The most useful information about defining risk in individuals without a previous manifestation of CHD comes from the Framingham Heart Study. Over the course of many years, the Framingham investigators have measured multiple risk factors and quantified their relationship to clinical events during follow-up. *Figure 1* depicts the "classic" Framingham risk model.<sup>2</sup> By knowing the age, sex, high-density lipoprotein (HDL) cholesterol, total cholesterol, systolic blood pressure, smoking status, diabetes status, and whether left ventricular hypertrophy is present on the electrocardiogram, a prediction can be made for the individual person about the risk of a future cardiac event. These equations have been applied in a variety of populations, and they predict outcomes effectively regardless of the culture or geographic location. However, only a portion of the attributable risk is defined by these risk factors, and much more needs to be known.

In patients with documented CHD, the risk of future events can be more precisely defined, and much of cardiovascular clinical practice has been dedicated to using technology to estimate this risk. The risk assessment begins with the standard risk factors enumerated above. Unfortunately, once a patient has been identified as having the disease, these "traditional" risk factors are much less important than the extent of the disease at that time point. Once a CHD event has occurred, the patient may be considered to be in one of several disease states: stable CHD, acute coronary syndrome with or without ST-segment elevation, post-coronary revascularization, or heart failure/left ventricular dysfunction. Each of these disease states has its own particular characteristics associated with specific risks of poor outcomes.

Substantial work, as demonstrated in *Figure 2*,<sup>2</sup> has been done to elucidate the prognosis of patients with chronic, stable CHD. The traditional risk factors add only



**Figure 2.** Nomogram for prediction of 1-year survival based on clinical, physical examination, and cardiac catheterization findings.

Abbreviations: Asymp, asymptomatic; CAD, coronary artery disease; MI, myocardial infarction; Symp, symptomatic.

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a modest amount to risk when other aspects of the disease are well characterized. The history is important for characterizing evidence of previous myocardial infarction, severity of angina, and severity of heart failure symptoms, if any. The recent history of the severity and tempo of angina is particularly important in the patient without previous left ventricular dysfunction. Evidence of peripheral vascular disease or cerebral vascular disease also adds to the risk. Of course, the physical examination provides relatively limited information in the typical patient with CHD, but detection of signs of heart failure, valvular dysfunction, or diffuse atherosclerosis can be valuable. Diagnostic and prognostic testing also adds to the prediction of risk. Measures of left ventricular function, provocative tests for ischemia, and measures of exercise capacity provide information that is only partially redundant with information obtained from the history and physical examination. Finally, coronary angiography provides critical prognostic information, albeit at a relatively high cost and risk.

A particularly interesting and large population consists of persons with subclinical atherosclerosis. Because these individuals far outnumber the population with clinically evident atherosclerosis, the opportunity is much greater for intervening effectively to make a major difference. However, because the absolute event rate is low, the cost of intervention for the amount of benefit to the individual may be prohibitive unless effective risk stratification methods are developed.

When patients have an acute plaque event, they may remain asymptomatic (probably the case in most events) or they may develop an

acute coronary syndrome (ACS). When the "culprit" vessel does not occlude, and large platelet emboli do not occur, the symptomatic patient typically has non-ST-segment-elevation ACS. In the presence of vessel occlusion or large platelet emboli, the patient either has non-ST-segment-elevation ACS with positive markers of myocardial necrosis or ST-segment-elevation ACS. Risk stratification should begin in these patients from the moment of first evaluation. Thus, the risk stratification algorithms have much in common, but differences are also apparent.

Patients with non-ST-segment-elevation ACS are a heterogeneous population. The specific configuration of the electrocardiogram is important to estimate their risk.<sup>3</sup> A detailed analysis of the Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrelin Therapy (PURSUIT) data identified a variety of demographic and clinical features available upon admission to the hospital that are important in stratifying risk. Age is a critical factor, while findings reflecting the hemodynamic state (blood pressure, heart rate, rales), whether or not infarction was present, and measures of the extent of atherosclerosis dominate the risk assessment. Additional information is now available indicating that markers of myocardial necrosis (troponin I and troponin T) can add substantially to the clinical information,<sup>4-7</sup> leading to the routine use of these markers in the assessment of patients in the emergency department.

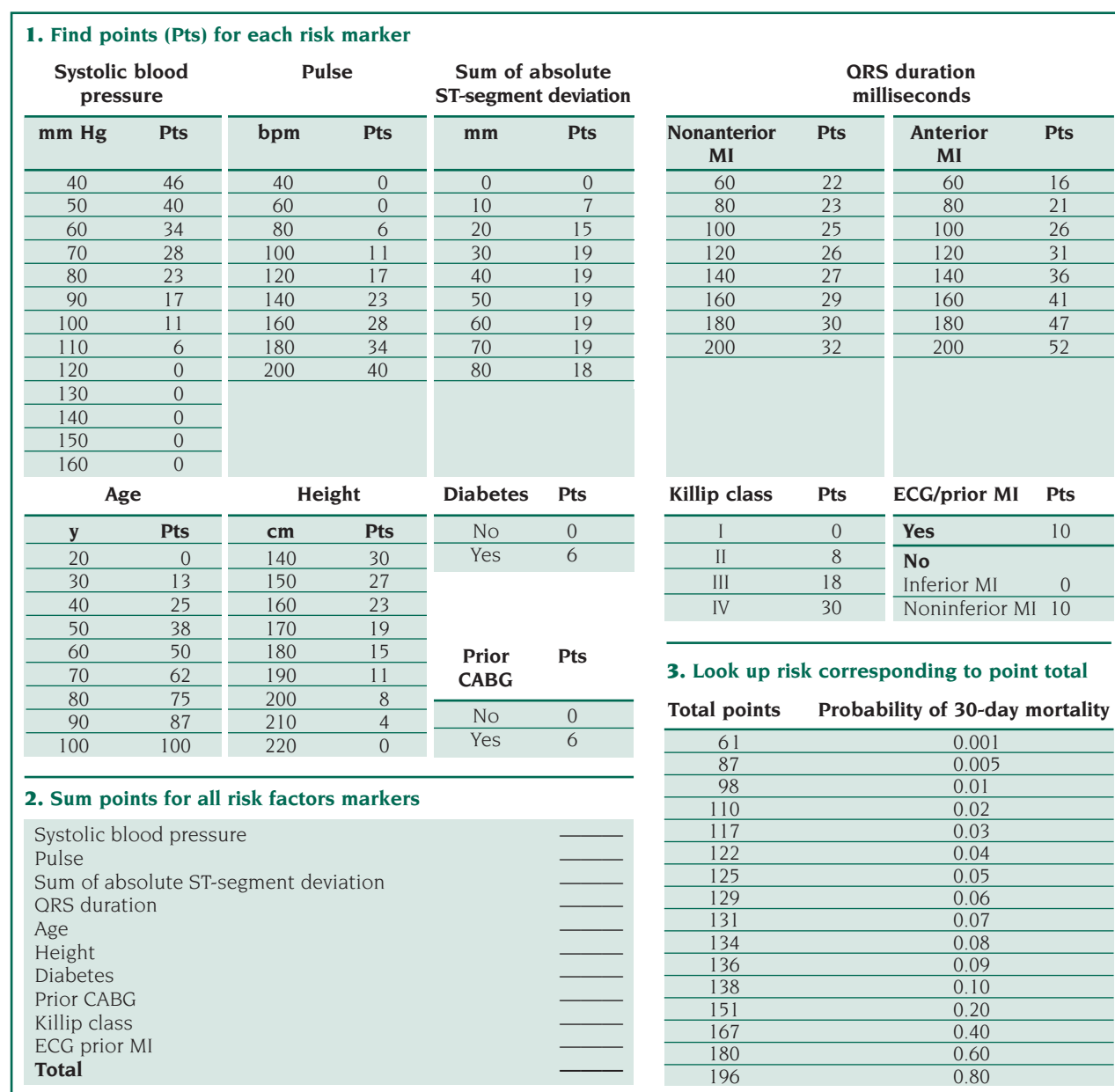
Extensive risk stratification has been done in patients with ST-segment-elevation ACS. The key factors are age, the hemodynamic state of the patient, the extent of myocardial necrosis, the extent

of atherosclerosis, and the degree of electrical instability. Lee and colleagues have developed a risk stratification model based on over 40 000 patients in the Global Use of Strategies To Open occluded coronary arteries (GUSTO)-I trial,<sup>8</sup> and this model has been extended to include a detailed evaluation of the electrocardiogram.<sup>9</sup> A nomogram depicting these elements of risk is displayed in *Figure 3*.<sup>9</sup>

The assessment of risk in a patient with ACS should continue throughout the hospitalization as depicted in *Figure 4 (page 144)*.<sup>10</sup> The patient with ACS has an increased risk of death that persists for several months after diagnosis; after that time the risk reverts to that of the patient with chronic, stable angina.

Patients with CHD and heart failure are subject to the same risk factors as patients with chronic CHD without heart failure but, in addition, the specific characterization of the heart failure adds important information. This information may be considered in the categories of severity of symptoms of heart failure, measures of exercise capacity,<sup>11</sup> and measures of neurohormonal activation.

Once a patient has experienced a symptomatic ventricular arrhythmia or a resuscitated sudden death event, it intuitively makes sense that a new set of prognostic features would be of value. While ambulatory monitoring, signal-averaged electrocardiography, and heart rate variability measures have been found to provide prognostic information, these measures have not been demonstrated to be useful in selecting patients for intervention. Given the efficacy and the cost of the implantable cardioverter/defibrillator, better risk stratification measures are urgently needed.



**Figure 3.** Nomogram for estimating 30-day mortality from initial clinical and electrocardiographic variables. This reduced version of the full multivariable model yielded a C-index statistic of 0.830.

Abbreviations: bpm, beats/min; MI, myocardial infarction; ECG, electrocardiogram; CABG, coronary artery bypass graft.

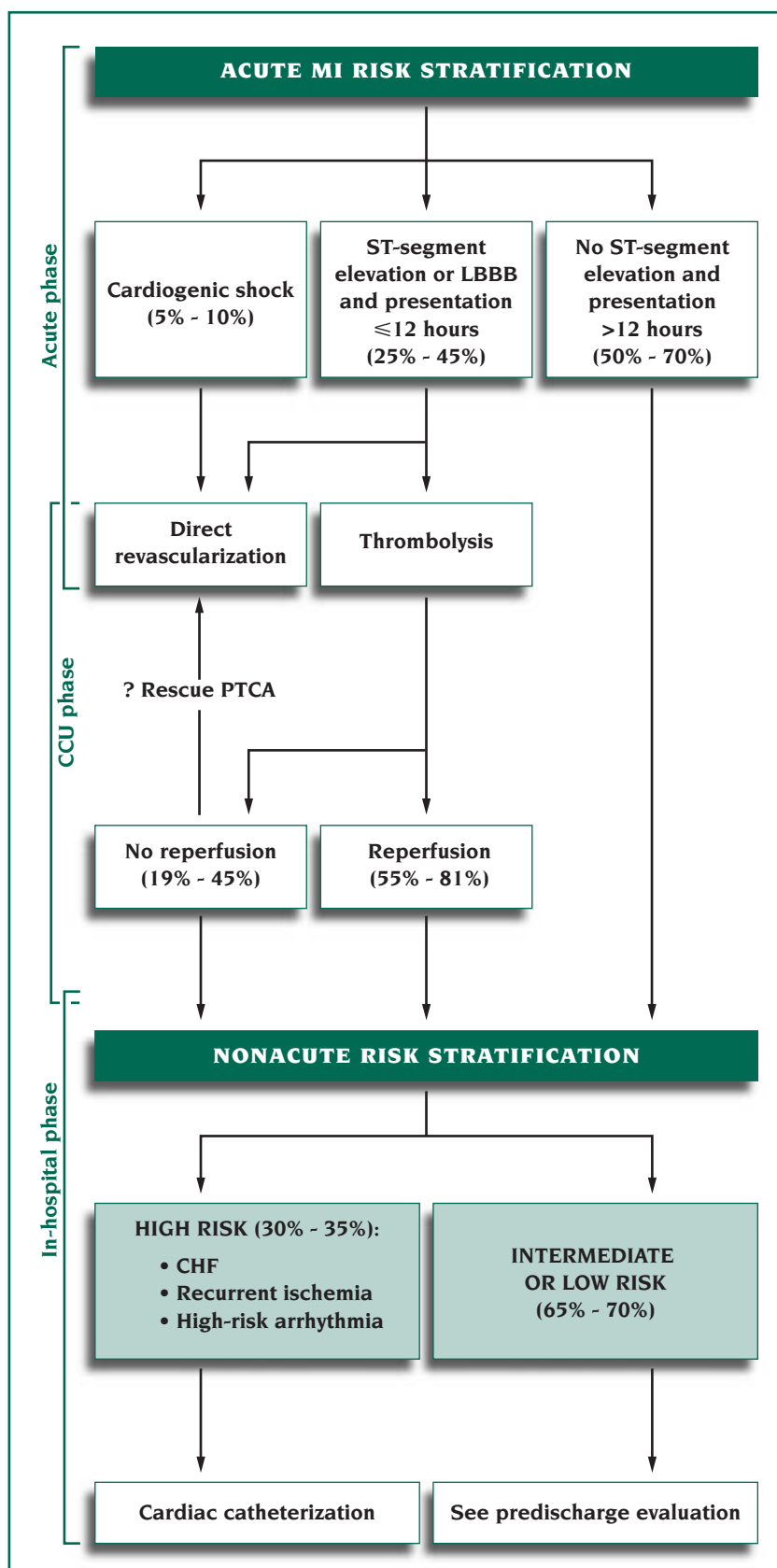
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### NOVEL PROGNOSTIC FACTORS

Recent studies have focused on the importance of markers of inflammation in predicting the risk of future events. Initial studies looked at patients with acute coronary syndromes and found a concentration of events in those with elevated levels of C-reactive protein, a general marker of inflammation.<sup>12</sup> These early observations were

followed by long-term observations in the chronic setting<sup>13</sup> and evaluations of other markers of inflammation,<sup>14</sup> all leading to the same conclusion: inflammation is a major issue in atherosclerosis. Still unsolved is the question of whether the inflammation is a causative factor or a result of the atherosclerotic process.

Since the consequences of plaque disruption are largely mediated by



the degree to which thrombotic occlusion obstructs the vessel lumen, a logical conclusion is that elevated markers of thrombosis should predict which patients are likely to have events. Despite the demonstration that there is a relationship between outcome and thrombotic markers, the relationships have not been strong enough to incorporate measuring these markers to stratify risk into clinical practice. Fibrinogen has emerged as a major predictor across a large number of studies; it may become the first thrombotic marker to be used in routine risk prediction.

The field of cardiac imaging is progressing at a rapid pace, bringing about the possibility of directly measuring the extent of disease and following it as a marker of prognosis. Rapid electron beam computed tomography (CT) scanning has developed as a method of detecting and following coronary calcification in a semiquantitative fashion.<sup>15</sup> Similarly, positron emission tomography (PET) provides vivid semiquantitative information about ischemia and viability. While these technologies have great promise, they have not yet accumulated enough evidence to determine their place in clinical practice.

We also cannot forget about cultural, social, and behavioral issues in risk stratification. Recent studies

**Figure 4.** Flow diagram of risk stratification after myocardial infarction.

Abbreviations: CCU, coronary care unit; CHF, congestive heart failure; LBBB, left bundle-branch block; MI, myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty; ST, ST-segment.

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have implicated depression<sup>16,17</sup> and poor social support<sup>18</sup> as major predictors of poor outcome. Whether these differences in outcome result from physiological manifestations of the underlying disorders or whether depression and social isolation lead to lower compliance and less medical care remains to be resolved.

Perhaps the most intriguing target for risk prediction is the vulnerable plaque. Most of our efforts to predict the risk of events are limited because angiographic and physiologic measures characterize the state of the arteries, the myocardium, or the hemodynamic state in a static situation. Yet we know that a person with normal left ventricular function, normal neurohormones, and no ischemia on provocative testing can be transformed into a victim of acute myocardial infarction almost instantaneously when a vulnerable plaque becomes disrupted. The troponins may be giving us insight into the degree to which a "hot" plaque is shedding platelet emboli and markers of inflammation may provide indirect insight into weakening of the plaque by inflammatory infiltrates, but we do not yet have direct measures that can discern a vulnerable plaque.

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