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The Key to Their Hearts

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The Indispensable Role of the Primary Care Clinician in the Management of Patients Post-MI

The morbidity and mortality associated with acute coronary syndrome (ACS) are significant and, according to CDC, the estimated direct and indirect costs of treating heart disease are ~$165.4 billion this year. The decrease in mortality observed over the last few years, due to increased exercise, smoking cessation, and effective medications, has been partially offset by the increased prevalence of diabetes and increased body mass index (BMI). This newsletter reviews the risk factors that predispose an individual to ACS and describes 4 commonly used risk stratification models that could be very useful in every day practice.

Prevalence, Morbidity, and Mortality in ACS

ACS incidence, morbidity, and mortality are significant[1]:

- An estimated 785,000 new cases of heart attack and 470,000 recurrent attacks will occur this year in the US
- First-time silent myocardial infarction (MI) is estimated in 195,000 individuals
- In 2006, a total of 1.37 million patients diagnosed with ACS were discharged from the hospital
  - Of these, ~518,000 were diagnosed with ST-elevation myocardial infarction (STEMI) and the rest were diagnosed with non-ST segment myocardial infarction (NSTEMI) or unstable angina (UA)
- One coronary event occurs every 25 seconds and 1 MI every 37 seconds, with one death/minute due to these cardiovascular conditions
- The estimated direct and indirect costs of treating heart disease in 2009 are ~$165.4 billion.

Although the comparison of rate of mortality from 1980-2000 revealed a ~47% decrease due to various treatments and a ~44% decrease due to decreases in risk factors (cholesterol, smoking, increased exercise), the recent rise in the prevalence of diabetes and the increase in BMI have at least partially offset these decreases.[2]

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Risk Factors for ACS

The risk factors that predispose a person to cardiovascular disease (CVD) are subdivided into modifiable and nonmodifiable risk factors.

Modifiable Risk Factors

The modifiable risk factors include smoking, hypertension, stress, diabetes, the dyslipidemic triad (high low-density lipoprotein [LDL], high plasma triglycerides, and low high-density lipoprotein [HDL]), obesity, and physical inactivity.

1. SMOKING:

Recent estimates indicate that ~30% of cardiovascular deaths are due to cigarette smoking and that it is the highest risk factor contributing to premature cardiovascular morbidity and mortality.[3] Current evidence also indicates that the prothrombotic state of smokers' blood predisposes them to MI, reinfarction, and other thrombotic events.[4]

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2. HYPERTENSION:

Hypertension (systolic pressure of ≥140 mmHg or diastolic pressure of ≥90 mmHg) leads to ACS through a number of different mechanisms. Increased systolic pressure can lead to myocardial hypertrophy and impaired diastolic function. It can also lead to congestion, which increases left ventricular wall stress and decreases subendocardial perfusion leading to myocardial apoptosis and necrosis.[5] Hypertension can also alter the balance between coagulation and fibrinolysis. It has been shown that the expression of tissue plasminogen activator (TPA) is reduced and plasminogen activator inhibitor (PAI) is increased, resulting in impaired fibrinolysis and increased risk for thrombus formation.[6] Hypertension has also been shown to increase shear force and potentiate endothelial activation and dysfunction.[7]

Risk Factors for Acute Coronary Syndrome

- Diabetes
- Smoking
- Hypertension
- High cholesterol
- Family history of CVD
- Age
- Obestiy
- Socioeconomic status
- Gender (more men with the disease but more women dying)

3. DIABETES AND ATHEROGENIC DYSLIPIDEMIA:

Hyperglycemia has been shown to play a major role in diabetes-associated microvascular complications.[8] Reduced membrane fluidity, increased arachidonic acid metabolism, increased thromboxane (TxA_2) synthesis, decreased prostacyclin and nitric oxide production, decreased antioxidant levels, increased expression of GP IIb/IIIa, P-selectin, and other adhesion molecules, and altered calcium and magnesium homeostasis have all been shown to be contributing factors to the increased platelet reactivity and activation observed in patients with diabetes.[9] The 7-year incidence of recurrent MI in patients with diabetes was determined to be 45% compared to 19% in nondiabetic patients.[10]

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Dyslipidemia, caused by the inability of insulin to suppress enhanced adipose tissue lipolysis, leads to increased plasma free fatty acid (FFA); this induces lipotoxicity, resulting in increased plasma triglycerides and very-low-density lipoprotein (VLDL) secretion from the liver.[11] These changes result in generation of small HDL particles and a low-HDL level.[12] Dyslipidemia has been shown to increase the risk for MI and stroke by 2-fold compared to healthy individuals.[13] In fact, patients with triglyceride (TG) levels >200 mg/dL and an LDL to HDL ratio >5 had a 6-fold higher cardiovascular risk.[14] Analysis of the Pravastatin or Atorvastatin Evaluation and Infection Therapy—Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) trial data revealed that patients with an LDL of <70 mg/dL had significantly lower incidence of cardiovascular disease than those who had an LDL of ≥70mg/dL. A similar trend was seen in patients whose triglycerides were <150 mg/dL compared to those who had a TG of ≥150mg/dL.[15]

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4. OBESITY:

Obesity (defined as a BMI of ≥30 kg/m^2), overweight (BMI of 25-29.9 kg/m^2), and

physical inactivity can predispose an individual to cardiovascular disease, type 2 diabetes, and hypertension, as well as a host of other comorbidities. These risk factors increase the levels of plasma TG and LDL particle numbers and decrease HDL-C and LDL particle size, all of which collectively contribute to atherogenic dyslipidemia.[16]

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5. PHYSICAL INACTIVITY:

According to the Centers for Disease Control and Prevention (CDC), ~60% of Americans do not engage in the recommended 30 minutes/day of exercise, and more disturbingly, 25% of adults do not even participate in leisure-time physical activity.[17] A similar trend of inactivity is seen in young people as well.[12] Physical inactivity increases the risk of cardiovascular disease, whereas increased physical activity has been shown to improve insulin resistance, reduce blood pressure, improve lipid profiles, and decrease cardiovascular risk.[16] In fact, a 500 kcal increase in energy expenditure each week was shown to decrease the risk of developing type 2 diabetes by 6%.[18]

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Nonmodifiable Risk Factors

Nonmodifiable risk factors include gender, age, and family history of cardiovascular disease.

1. AGE AND GENDER:

Advanced age in men and women has been shown to increase the risk of coronary disease due to progressive development of coronary atherosclerosis, and the presence of atherosclerosis itself becomes a major risk factor for cardiovascular disease.[16] Age has also been shown to be significantly associated with the development of insulin resistance.[19]

Advanced age in men and women has been shown to increase the risk of coronary disease due to progressive development of coronary atherosclerosis.

Although the gender differences leading to increased cardiovascular risk in men compared to similar-aged women are not completely understood, it is believed that earlier onset of risk factors such as dyslipidemia and high blood pressure in men play a role.[16] Sixty-nine percent of women present with unstable angina compared to 30% of men[20]; consistently more men are diagnosed with MI than women. A recent comprehensive study of the effects of gender on cardiovascular disease indicates that women are more likely to present with atypical symptoms, resulting in delayed diagnosis and treatment. Also, women admitted to the hospital for ACS were found to have a higher prevalence of heart failure, diabetes, and stroke, potentially accounting for higher short-term mortality observed in women.[21] On the other hand, this analysis also indicates that after percutaneous coronary intervention (PCI), the rates of short-term mortality, restenosis, and target vessel revascularization are the same for women and men.[21]

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2. FAMILY HISTORY OF CARDIOVASCULAR EVENTS:

Family history of cardiovascular disease is an independent risk factor and, in first degree relatives, relative risk for developing a cardiovascular event is 2- to 12-fold higher than in the general population.[16] It has also been shown that the risk of events increases with the number of primary relatives suffering from CVD and the age of onset of disease.[22]

Risk Stratification

Outcomes of ACS are heterogeneous in terms of risk of cardiac death and nonfatal ischemic events; therefore, assessment of the prognosis should guide the initial treatment.[23,24] Stratification of patients into low-, medium-, and high-risk groups has been shown to provide prognostic information and help to determine the level of intervention required for a patient with a specific risk.[25] A number of risk stratification models

have been described and some are developed using large claims databases whereas other models have used STEMI patients treated with fibrinolytic therapy. Due to their severe limitations, these models are not used commonly. Three major risk stratification models, Global Registry of Acute Coronary Events (GRACE), Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT), and TIMI, have been developed that are either based on data from clinical trials or from large registries and are widely used to determine short-term outcomes.[26-28]

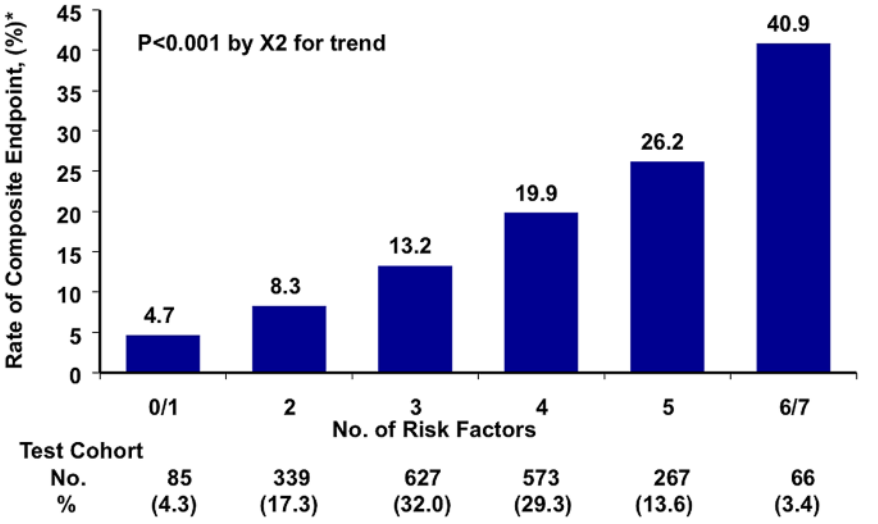

Figure 1. TIMI UA/NSTEMI Risk Score Correlates with Outcomes

GRACE Score Determination:

This model was developed from a multinational registry consisting of an unselected population of patients with ACS to enable practical and accurate prediction of in-hospital mortality.[28] This model is based on 8 variables: Killip class (a classification of the severity of heart failure with MI), age, systolic blood pressure, ST-segment deviation, cardiac arrest during hospital admission, heart rate, creatinine level, and elevated serum cardiac markers. The total of the individual scores for each variable assigned, based on the specific value of each variable, is calculated and compared against a standard nomogram to predict the risk of the patient.[28]

PURSUIT Score Determination:

This model was developed based on the data from NSTEMI patients enrolled in the PURSUIT trial and is based on 7 variables: age, gender, heart rate, systolic blood pressure, Canadian Cardiovascular Society-defined angina grading scale class in the previous 6 weeks, signs of heart failure, and ST depression at presentation. Similar to the GRACE model, the total score is obtained after adding the individual scores and the risk is estimated based on a nomogram.[27]

TIMI Score Determination:

There are 2 TIMI score calculation models: one for use in STEMI patients and the other for use in UA/NSTEMI and high TIMI scores have been shown to correlate well with worse outcomes.[26,29] The TIMI score for UA/NSTEMI use is based on 7 easily assessed variables that include age, 3 or more risk factors for coronary artery disease, use of aspirin in the last 7 days, ST-segment deviation, elevated cardiac serum markers (CK-MB or troponin), 2 or more anginal events in the last 24 hours, and prior coronary stenosis of ≥50%. Correlation of this risk score with outcomes is shown in Figure 1.[26] The score for use in STEMI patients is based on 8 variables: age, systolic blood pressure, heart rate, Killip class, anterior ST elevation or left bundle branch block, diabetes or history of hypertension or angina, weight, and time to therapy.[29]

The above described risk stratification models have all been validated in a number of clinical trials and have been shown to be relevant for routine clinical use.[26-32] Correlation of this risk score with outcomes is shown in Figure 2.[29]

Road Blocks to Everyday Use of Risk Stratification:

Recent evidence indicates that physicians could stratify patients as low, medium, or high risk according to the ACC/AHA guidelines; however, at least 30% of patients who were stratified as high risk did not undergo the recommended cardiac catheterization, indicating that implementation of ACC/AHA guidelines in everyday practice still lags very much behind the recommendations of the guidelines.[33] Some of the hurdles to everyday use include:

1. LACK OF CLEAR PATHS IN CASES OF PATIENTS WITH NONOBSTRUCTIVE LESIONS

Some clinicians believe that lesions <50%, discovered during angiography, do not adequately explain coronary events and therefore do not warrant secondary prevention.[34] Adding to this complication, the risk scores are not capable of showing a clear distinction

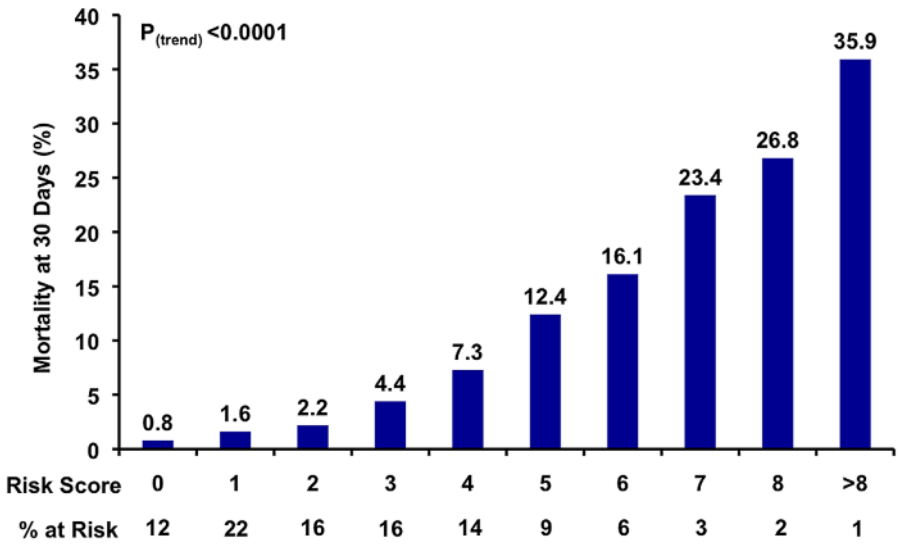

Figure 2. TIMI Risk Score for Patients with STEMI Correlates with Outcomes

Physicians could stratify patients as low, medium, or high risk according to the ACC/AHA guidelines; however, at least 30% of patients who were stratified as high risk did not undergo the recommended cardiac catheterization.

between patients with obstructive or nonobstructive coronary disease as these models have been derived using data from all ACS patients without any distinction between the severity of the lesion.[35] This might explain the routine under treatment of women, as they more frequently show nonobstructive lesions.[35]

2. LACK OF INCLUSION OF FINDINGS FROM ANGIOGRAPHY IN CALCULATING RISK SCORE

Most of the risk stratification models do not include angiographic findings as one of the variables to calculate the risk score, which leads to the possibility of ignoring either the risk score or the angiographic severity.[35]

3. LACK OF CLEAR PATHS FOR ASYMPTOMATIC PATIENTS WITHOUT OBSTRUCTIVE LESIONS

The 1-year death and MI rate of patients with ACS but without obstructive coronary artery disease is 2.1%, a rate that is higher than that of the general population of low-risk asymptomatic subjects (0.6%) and lower than that of ACS patients with obstructive lesions and a TIMI risk score of 4 or more.[36] However, for patients without obstructive lesions, in spite of displaying a wide spectrum of cardiac risk, the existing models do not provide a basis for their risk stratification.

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