The best determinants for predicting cardiometabolic risk continue to be controversial.

The guidelines of the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) recommend using traditional cardiovascular risk factors. These factors include:

- men 45 years and older
- women 55 years and older
- hypertension
- cigarette smoking
- low level of high-density lipoprotein cholesterol (HDL-C)
- family history of premature cardiovascular disease
- use of the Framingham Risk Score as the basis to determine cardiac risk.

The ATP III guidelines identify specific treatment goals for low-density lipoprotein cholesterol (LDL-C) for patients in the various cardiovascular risk categories.

In addition, the guidelines allow for a secondary goal in those who meet the LDL-C goal but still have triglyceride (TG) levels greater than 200 mg/dl. The ATP III guidelines recognize metabolic syndrome as an additional cardiometabolic risk that warrants both attention and treatment. The criteria for diagnosing metabolic syndrome include:

- low HDL-C
- blood pressure measurements greater or equal to 130/85 mmHg
- TG greater than or equal to 150 mg/dl
- fasting blood glucose (FBG) level greater than or equal to 100 mg/dl
- waist circumference greater than 40 inches in men or greater than 35 inches in women.

The diagnosis of metabolic syndrome requires three of these five criteria to be present. However, this method for predicting cardiometabolic risk remains controversial. The following case exemplifies many of the issues that contribute to this controversy.

**Case history**

LM is a 59-year-old woman who experienced an acute myocardial infarction (MI) three weeks after being evaluated in an outpatient setting.

At LM’s initial outpatient visit, she denied any history of chest pain and cardiovascular disease, as well as any history of hypertension, diabetes mellitus, dyslipidemia and smoking. However, she had a family history of premature cardiovascular disease, as her father experienced an MI at age 50.

LM’s vital signs at the office visit were as follows:

- blood pressure (BP) of 138/82 mmHg
- pulse of 84 beats per minute (BPM)
- height of 63 inches
- weight of 180 pounds
- body mass index (BMI) of 32 kg/m²
- waist circumference of 39 inches.

When LM was reevaluated one week later, her vital signs were similar. Interim laboratory evaluation revealed the following:

- an FBG of 112 mg/dl
- total cholesterol level of 210 mg/dl
- HDL-C of 37 mg/dl
- TG level of 224 mg/dl
- calculated LDL-C of 128 mg/dl
- a normal thyroid stimulating hormone (TSH) level

Because LM had two or more traditional risk factors, a Framingham Risk Score was calculated. The 10-year Framingham risk for coronary heart disease (CHD) was 4%, which placed LM in the moderate risk category with a recommended LDL-C goal of less than 130 mg/dl.

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Because LM’s BP was less than 140/90 mmHg, her FBG was less than 126 mg/dl and her LDL-C was at goal at 128 mg/dl, she was told she did not need any therapy other than being placed on a low-fat, therapeutic lifestyle diet, as recommended by the ATP III.

LM was also scheduled for an exercise treadmill test prior to initiating a new exercise program. However, she suffered an MI before the test could be performed. LM later inquired if anything in her initial evaluation could have predicted her cardiac event.

Although LM denied having any chest pain, her history did include some shortness of breath that seemed to be getting worse while climbing one flight of stairs at home. In addition, she had been becoming more fatigued over the past month, and on occasion, she would have some difficulty sleeping.

These symptoms correspond with data collected by the National Institute of Nursing Research. The Institute evaluated women with documented acute MIs and determined that the three most common symptoms prior to the events were progressive fatigue, sleep disturbances and shortness of breath—all of which were more common than chest pain.4

Another significant hint from LM’s history was the fact that her father had an MI at age 50. Individuals with family histories of premature CHD, such as LM, constitute only 14% of the US population, yet they represent 72% of those who have premature coronary events.3

Beyond the historical clues, LM also met all five criteria for metabolic syndrome. A recent meta-analysis of clinical trials concluded that metabolic syndrome increases the risk of cardiovascular events by a factor of 1.78 independent of the baseline risk as determined by Framingham.6 In addition, there is a continuum in CHD risk as the number of metabolic risk factors increase, garnering a 1.5-fold increase risk when three risk factors are present, to between threefold and fivefold when all five are present.7 Because LM manifested all five metabolic risk factors, her CHD risk may have increased between threefold and fivefold.

Reynolds Risk Score for LM

From a cardiometabolic perspective, one additional risk factor to consider is an increase in subclinical inflammatory state as measured by hs-CRP. CRP has been shown to add predictive value beyond that noted with the Framingham Risk Score or associated with metabolic syndrome.9

The additional risks associated with inflammation as manifested by CRP and with a family history of premature CHD were added to the standard Framingham risk profile to create the Reynolds Risk Score.

The Reynolds Risk Score was measured in women from the Women’s Health Study and in men from the Physician’s Health Study.10,11 When the Reynolds Risk Score is applied to LM, her 10-year risk for a cardiovascular event increases from 4% to 8%. If LM had been a man, the risk would have changed from 13% to 19%.

When the additional risk from having all five metabolic risk factors is added to LM’s Reynolds Risk Score, her 8% 10-year risk increases threefold to
fivefold to 24% to 40%. Thus, by applying the positive family history, the inflammatory marker of hs-CRP and the presence of all five metabolic syndrome risk factors, LM’s risk for a CHD event increases from low risk (4%) to high risk (24% to 40%).

When LM’s symptoms of progressive fatigue, sleep disturbances and mild shortness of breath are factored in, this analysis strongly suggests that she was at high risk at the time of her initial evaluation—three weeks before her acute MI.

**Final notes**
The analyses of the Reynolds Risk Score in both women and men revealed improved accuracy in predicting global cardiovascular risk by enhancing the cardiometabolic risk assessment.

As was noted in LM’s case, 40% to 50% of women and 20% to 25% of men classified as moderate to moderate high risk by the Framingham Risk Score were reclassified to a different risk strata by the Reynolds Risk Score.10,11

The potential to augment cardiometabolic assessments by adding in components of metabolic syndrome—Reynolds Risk Score, progressive fatigue, sleep disturbances and mild shortness of breath—may improve our ability to identify individuals at risk for cardiovascular events. It is conceivable that if this type of analysis had been conducted at LM’s initial visit and had resulted in a more aggressive therapeutic regimen, she may have avoided an acute MI.

**References**


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