

Inflammation, Metabolic Syndrome, and CV Risk Reduction

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Traditional CV risk factors: Necessary, but are they sufficient?

Richard Dunbar, MD, and Philippe O. Szapary, MD

University of Pennsylvania School of Medicine, Philadelphia

Upon completion of this CME activity, the reader should be able to:

- Review the risk-stratification model used by the National Cholesterol Education Program Adult Treatment Panel III report.
- Explain the shortcomings of risk assessment based on traditional cardiovascular risk factors.
- Identify emerging risk factors and discuss their potential use in clinical practice.

This article is the first of a series designed to review the role of emerging risk factors in practice. The articles will cover the relationship between the major and emerging risk factors, reasons to pursue additional risk factors, limitations of global risk scoring, and 3 broad areas of investigation: (1) metabolic syndrome, (2) biochemical markers of risk, and (3) noninvasive measures of atherosclerosis.

Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of death in the United States, despite the advent of multiple treatments that reduce mortality and morbidity. Given the dramatic impact of ASCVD on a population, practice, and individual level, physicians must remain vigilant about screening for and treating risk factors.

The recent National Cholesterol Education Program Adult Treatment Panel III (ATP III) report gives one of

the most thorough yet practical models for ASCVD prevention available.¹ One of the greatest strengths of the ATP III approach is an ASCVD risk prediction model that estimates the risk status of individual patients. ATP III classifies risks as underlying, major (or traditional), and emerging risk factors, as shown in Table 1 (page 4). The major risk factors consist of high low-density lipoprotein (LDL) cholesterol, low high-density lipoprotein (HDL) cholesterol, diabetes, smoking, hypertension, family history of premature coronary artery disease (CAD), age, and male sex.

The ATP III risk-stratification scheme is based on the Framingham Risk Score (FRS), an easily used model that quantifies risk from major traditional risk factors. The FRS estimates a person's absolute risk of a "hard" CAD event (myocardial infarction [MI] or CAD death) over the next 10 years. The FRS is a much more powerful tool than counting risk factors, since it uses con-



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tinuous data for most variables and is based on outcomes from an American population. Since medical treatment is not without hazard or cost, this helps clinicians and patients evaluate risks and benefits with much greater clarity and target drug therapy to those most likely to benefit from it.

Limitations of the FRS

Although the FRS is an indispensable tool for estimating risk, it does have limitations. Most important, the model does not consider family history of ASCVD. Having a first-degree relative with ASCVD raises risk from 2 to 12 times, and the odds are worse when family members presented at a younger age or when multiple relatives are affected.² Furthermore, the model may underestimate the risk for women, which may reflect underrepresentation of older women in the Framingham study. In addition, the FRS is heavily influenced by age for those older than 50 years of age, reflecting the strong association between age and plaque burden, and thus may not be representative of the lifetime risk for younger patients at high risk. For this reason, Grundy proposed that scanning for coronary artery calcification (CAC) may be helpful as a replacement for age in the FRS.³ Another limitation is that the FRS does not take into account several of the risk factors seen in the metabolic syndrome, such as hypertriglyceridemia, abdominal obesity, and impaired fasting glucose, which together are known to increase risk. Moreover, because the Framingham study had few patients with very high cholesterol levels, the FRS is unreliable for those with total cholesterol > 280 mg/dL.³ Finally, the FRS likely underestimates the risk of a patient who has

a solitary major risk factor that is markedly abnormal.³

Physicians should be aware of these limitations and should not let a low FRS supersede clinical judgment. Neither should they discount the FRS entirely. The FRS provides a valuable estimate of the minimum level of risk for a patient, with the understanding that certain emerging risk factors, such as metabolic syndrome and markers of inflammation, can add prognostic information in selected patients. Emerging risk factors should complement, rather than supplant the traditional risk factors.

Why should we consider clinical use of emerging risk factors?

Given the added expense and non-pecuniary factors, such as anxiety over abnormal findings, why should we bother with the emerging risk factors when the traditional risk factors are so well established? The answer lies in the staggering prevalence and cost of the disease in question; such effort would not be reasonable for a less common or less morbid disease. Close to 1 million Americans die of ASCVD each year, and 64 million live with it.⁴ Thus, large numbers of those with low risk as assessed by the FRS will die of ASCVD every year.

To illustrate this, consider the population between 45 and 54 years of age, which includes around 20 million women and 19 million men. If the average 10-year hard event rate is 4.5% (low risk by ATP III criteria), we would expect that over 10 years, more than 800 000 low-risk women will have an MI, many of them fatal; perhaps 80 000 of them will occur this year. Similarly, if the rate is 8% for men this age, we can expect 1.5 million of these low-risk men to have an event within 10 years, or 150 000 this year. For any other disease this would be considered

an epidemic. Thus, the clinician should not be overly surprised when a supposedly low-risk patient unexpectedly dies of an MI.

Furthermore, screening schemes based on the major risk factors do not have perfect sensitivity or specificity. Although 85% to 90% of patients with ASCVD have at least 1 major risk factor,⁵ there is also a large group of people who have major risk factors but do not have high event rates. And many who have only 1 major risk factor are not eligible for medical therapy by current guidelines. Refining risk assessment could therefore help target preventive therapies to those who are most likely to benefit and thereby potentially confer substantial public health benefits.

A case study

Case history. JR is a 54-year-old Mexican American woman who presented for a routine examination without complaints and with an unremarkable medical history. She is not a smoker, eats a typical Western diet, and has been doing aerobic exercise for several months. Her family history is notable for the sudden death of her father, who had diabetes, from an MI at the age of 57 years. Her mother survived an MI at age 68, but died of a cerebrovascular accident in her mid-70s. Her brother has type 2 diabetes.

On presentation, JR's blood pressure (BP) was 132/88 mm Hg, and her pulse was 98 bpm. She stands 5 feet 4 inches and weighs 154 pounds (body mass index, 26.4 kg/m²), with a waist circumference of 36 inches. Her examination was unremarkable except for abdominal obesity. Fasting laboratory values were as follows: total cholesterol, 236 mg/dL; LDL cholesterol, 152 mg/dL; HDL cholesterol, 38 mg/dL; and triglycerides, 232 mg/dL. Her glucose level was 102 mg/dL, and her microalbumin/creatinine ratio was 40 mg/g. Since she was reaching the age at which her father died, she wanted to be aggressive with prevention.

Her physician counseled her on weight loss and referred her to a nutritionist and a personal trainer but did not initiate any drug therapy at this visit.

Challenges for clinicians. The FRS for this patient is only 2%. This means that among a group of mostly white, nonsmoking women living in Framingham,

Massachusetts, about her age with similar cholesterol and BP, 2% of them had a coronary event within 10 years. In JR's case, the physician does not know whether she is like the vast majority who escaped an event, or the minority who had an event. If it were more certain that she was closer to the group that had an event, one might offer her more aggressive treatment. A positive emerging risk factor might tip the scale.

Although the FRS is helpful most of the time, it is not uncommon to see patients whose FRS does not match the warning signs from the rest of their history. JR is certainly a candidate for therapeutic lifestyle changes, but she does not qualify for drug therapy by the ATP III guidelines. A case such as this one poses challenges for the practitioner:

1. Are you confident that the FRS accurately estimates this woman's risk? If not, what aspects of her history suggest greater risk?
2. Would you do any other tests to learn more about her risk?
3. If you learned from emerging risk factors that her risk was in the moderate range, would you treat her differently? What if they suggested high risk?
4. Does the fact that she is highly motivated to take an aggressive preventive approach influence your decision making?

This dilemma turns up frequently in clinical practice: a patient has a constellation of mild risk factors, but the FRS yields an estimate that is lower than clinical suspicion. Although JR has a low FRS, she has multiple clinical characteristics that may confer elevated CV risk. These include at least 4 of the components of the metabolic syndrome (central obesity, elevated BP, low HDL, and high triglycerides; and perhaps impaired fasting glucose according to the new American Diabetes Association [ADA] definition).⁶ In addition, she has an ominous family history, albeit, just outside of the traditional age ranges established by ATP III. The ATP III does not advocate pharmacologic therapy for patients with this FRS-based level of risk, yet if she were found to be at substantially higher risk, she would potentially be a candidate for drug therapy.

TABLE 1

Risk factors for ASCVD (modified from ATP III)

Underlying risk factors

- Obesity
- Disinclination to exercise
- Atherogenic diet

Major (or traditional) risk factors

- High LDL cholesterol
- Low HDL cholesterol (< 40 mg/dL)
- Diabetes
- Smoking
- Hypertension (\geq 140/90 mm Hg or on BP medication)
- Family history of premature CAD in first-degree relative (male < 55 years old, female < 65 years old)
- Age \geq 45 years old for men, \geq 55 years old for women
- Male sex

Emerging risk factors

- Metabolic syndrome
- Triglycerides
- Lp(a)
- Lp-PLA₂
- Remnant lipoproteins
- Small, dense LDL
- Fibrinogen
- Homocysteine
- Urine microalbumin/creatinine ratio
- High-sensitivity CRP
- Impaired fasting glucose (110-125 mg/dL, per ATP III, or 100-125 mg/dL per American Diabetes Association)
- Measures of subclinical ASCVD
 - Ankle brachial index
 - Exercise testing (with or without nuclear imaging)
 - Electron-beam tomography
 - MRI
 - Carotid intimal medial thickness
 - Carotid ultrasound

ASCVD = atherosclerotic cardiovascular disease; ATP III = Adult Treatment Panel III; LDL = low-density lipoprotein; HDL = high-density lipoprotein; BP = blood pressure; CAD = coronary artery disease; Lp(a) = lipoprotein(a); Lp-PLA₂ = lipoprotein-associated phospholipase A₂; CRP = C-reactive protein; MRI = magnetic resonance imaging.

Principles for the use of emerging risk factors

Because research into novel risk factors proceeds rapidly, it is important to maintain a clear perspective of the role of the new risk factors, especially as they relate to the major ones. We offer the following principles regarding emerging ASCVD risk factors:

1. The traditional risk factors predominate: We not only have unimpeachable evidence that the traditional risk

factors contribute to ASCVD, but also that correcting the modifiable risk factors reduces events. It probably does little good to treat emerging risks when the major risks are uncontrolled.

2. The emerging risk factors are subordinate: The absence of an emerging risk factor should never be used as a pretext for downgrading the risk suggested by the major risk factors. For example, a patient should not receive less aggressive treatment than indicated by major risk factors because the high-sensitivity C-reactive protein (hs-CRP) level or the CAC score is normal.

3. The emerging risk factors may enhance risk assessment: The value of a given emerging risk factor depends on its ability to add to the baseline risk estimated from the major risk factors. Thus, the presence of a persistent elevation of hs-CRP might suggest that the FRS is understating a patient's risk. The physician could compensate by choosing a more aggressive goal or therapy. Based on this principle, checking emerging risk factors is often fruitless in a patient who already has high risk by the major risk factors. The new risk factors are best used when there is uncertainty about the level of therapy a patient should receive. For example, in a patient with moderate risk, the presence of an emerging risk factor might justify treatment normally reserved for those at high risk.

4. The emerging risk factors should not be used routinely for risk assessment: According to the ATP III, the use of emerging risk factors is an option "only in selected persons, and then only on the basis of considered clinical judgment."¹ The report continues, "Several of these tests are not readily available, not well standardized, and are relatively expensive ...above all, they should not be given undue weight relative to the major risk factors." Naturally, as evidence for certain risk factors improves, some emerging factors may enter into the routine risk calculation. For instance, metabolic syndrome is not yet considered a major risk factor, but nonetheless receives special mention in the ATP III report.

5. At this time, emerging risk factors are generally not helpful in tracking response to therapy: Because the clinical significance of treating the emerging risk factors is largely unknown, at this time there is little evidence to support serial testing of these factors. For that matter, recalculating the FRS with posttreatment

values for the major risk factors is not scientifically valid either.

Staging emerging risk factors

The inadequacy of the major risk factors for predicting ASCVD risk has understandably motivated researchers, clinicians, and patients to search for ways to refine risk assessment. We think about the emerging risks in 3 broad categories based on information gleaned from: (1) the routine clinical evaluation, (2) advanced laboratory tests, and (3) noninvasive measures of atherosclerosis. For each category, Table 2 lists risk factors that have already made their way into clinical practice to some degree. The order intentionally suggests a rudimentary staging process.

For example, consider a patient whose clinical evaluation revealed multiple additional risk factors, such as metabolic syndrome or an extraordinary family history. One might intensify that patient's goals on that basis alone and not need to order additional tests. After all, if the extra laboratory values were normal, they would not negate the risk conferred by clinical factors. Likewise, screening with an atherosclerosis imaging study may not be necessary for a patient with an abnormal result on 1 or more of the advanced laboratory tests since a normal study would not negate the risk implied by the laboratory test.

Metabolic syndrome

Of the additional risk factors gleaned from the clinical evaluation, perhaps the best established is metabol-

ic syndrome, a collection of major and emerging CV risk factors that stem from underlying insulin resistance. Although not a major risk factor, it is a secondary target of therapy in ATP III and thus should be assessed routinely. Metabolic syndrome is a common precursor to both ASCVD and type 2 diabetes, and affects up to one fourth of Americans older than 20 years of age. The prevalence of metabolic syndrome is expected to increase over the next several years as Americans grow older and heavier.

Metabolic syndrome likely develops from obesity, physical inactivity, and an atherogenic diet, although a genetic predisposition may contribute. These factors lead to insulin resistance, which, in turn, contributes to a typical set of major and emerging risk factors¹: abdominal obesity; elevated BP; atherogenic dyslipidemia (high triglycerides, low HDL, and small, dense LDL); impaired fasting glucose or glucose intolerance; proinflammatory state; and prothrombotic state.

According to the ATP III, patients with 3 or more of the clinical criteria shown in Table 3 have metabolic syndrome.¹ Recently, the ADA recommended that the glucose cutpoint that defines impaired fasting glucose should be lowered from ≥ 110 mg/dL to ≥ 100 mg/dL.⁶ A subsequent consensus conference on the definition of metabolic syndrome suggested that this new cutoff should be used for metabolic syndrome as well.⁷

Although there is no doubt that metabolic syndrome is a risk for ASCVD, the degree of additional risk is not yet firmly established. The ATP III cited abundant evi-

TABLE 2

Emerging risk factors commonly encountered in practice

Source of risk factor	Common examples
Routine clinical evaluation	Family history beyond age range, MetSyn, triglycerides, IFG
Advanced laboratory tests	hs-CRP, Lp(a), Lp-PLA ₂ , HCYS, GTT, fibrinogen
Noninvasive measures of atherosclerosis	ABI, EBT, MRI

MetSyn = metabolic syndrome; IFG = impaired fasting glucose; hs-CRP = high-sensitivity C-reactive protein; Lp(a) = lipoprotein (a); Lp-PLA₂ = lipoprotein-associated phospholipase A₂; HCYS = homocysteine; GTT = glucose tolerance test; ABI = ankle brachial index; EBT = electron-beam tomography; MRI = magnetic resonance imaging.

TABLE 3

ATP III criteria for metabolic syndrome. By definition, ≥ 3 of the below risk factors constitutes the metabolic syndrome¹

Risk factor	Defining level
Abdominal obesity	Waist circumference > 40 inches (men) > 35 inches (women)
Triglycerides	≥ 150 mg/dL
HDL cholesterol	< 40 mg/dL (men) < 50 mg/dL (women)
Blood pressure	$\geq 130/\geq 85$ mm Hg
Fasting glucose	≥ 110 mg/dL*

*Note that the recommended cutoff for impaired fasting glucose has been changed to fasting glucose ≥ 100 mg/dL.⁶ ATP III = Adult Treatment Panel III; HDL = high-density lipoprotein.

dence showing that metabolic syndrome rivals smoking as a contributor to premature ASCVD. In the absence of quantitative risk models for metabolic syndrome, the panel recommended using the FRS to determine the minimum treatment goals for those with metabolic syndrome. The FRS is at a distinct disadvantage, however, since it derives from major risk factors, whereas metabolic syndrome mostly depends on emerging risk factors. As anticipated, mounting evidence confirms that both the major risk factors^{8,9} and the FRS¹⁰ underestimate the risk of the metabolic syndrome population. Accordingly, the ATP III advises that “the presence of the metabolic syndrome provides the option to intensify LDL-lowering therapy after LDL cholesterol goals are set with the major risk factors.”¹¹

Based on this, metabolic syndrome has gained a prominent role in clinical practice. Although the FRS underestimates the dangers of metabolic syndrome, we emphasize that FRS remains an indispensable tool, as it is still helpful to know the minimum level of risk. While we faithfully calculate the FRS, we also regularly invoke ATP III’s option to intensify lipid therapy for our patients with metabolic syndrome. Unfortunately, because some of the criteria for metabolic syndrome are subtle, the condition is easily missed in practice. Therefore, we urge clinicians to maintain a heightened suspicion for metabolic syndrome in patients with any of the components. Any patient who has 1 of the components should be screened for the other 4.

Advanced laboratory testing

The advanced laboratory tests most commonly ordered in clinical practice are: hs-CRP, homocysteine, lipoprotein(a) (Lp[a]), lipoprotein-associated phospholipase A₂ (Lp-PLA₂), advanced lipoprotein testing, and fibrinogen (Table 2). High levels of any of these values might justify intensifying treatment goals (eg, upgrading a patient with moderate risk by FRS to the high-risk category). The effect of treatment on these laboratory values is unknown; hence, we typically use them to aid prognosis and not as a target of therapy. There is substantial uncertainty regarding the role of Lp(a), homocysteine, and fibrinogen in clinical practice.¹¹ An elevated level might warrant more aggressive treatment in patients who have high-risk family histories but few other risk factors.

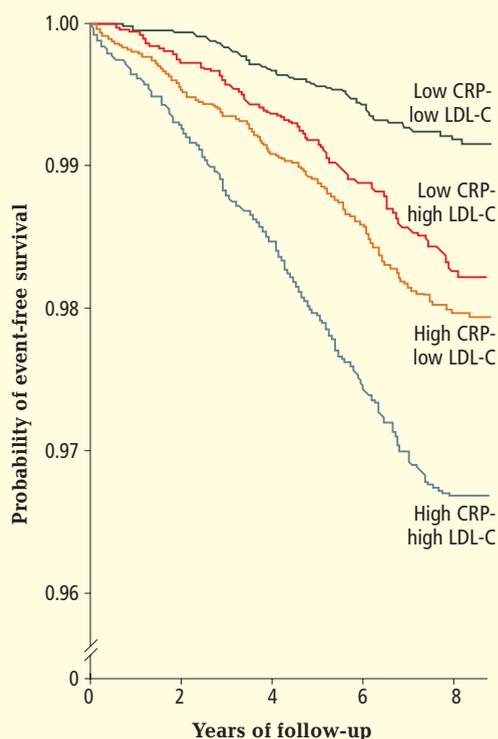
The test most widely used in practice is hs-CRP, a

marker of inflammation. Studies have shown that patients with high levels of hs-CRP but low LDL cholesterol may be at higher risk for vascular disease than those with high LDL cholesterol but low hs-CRP (Figure).¹²

The American Heart Association (AHA) and the Centers for Disease Control and Prevention recently issued a statement on the use of hs-CRP and other inflammatory markers to guide clinicians.¹³ Although affirming that hs-CRP is an independent risk marker, they recommend against using the other inflammatory markers. They believe that the weight of evidence favors the optional measurement of hs-CRP in patients at moderate risk for ASCVD (eg, FRS 10%-20%) to guide evaluation and treatment in the primary prevention setting. The benefit of doing so is unknown, however. In

FIGURE

Event-free survival with CRP and LDL-C levels above or below study population median



Data are shown for the entire cohort (27 939 women), including those taking hormone replacement therapy at baseline (12 139 women). Median values were as follows: CRP, 1.52 mg/L; LDL-C, 123.7 mg/dL (3.20 mmol/L). CRP = C-reactive protein; LDL-C = low-density lipoprotein cholesterol. Reprinted with permission from Ridker PM, et al. *N Engl J Med*. 2002;347:1557-1565.

patients with either low or high risk, hs-CRP is generally less helpful, and population-wide screening is discouraged. One exception is a possible role in patients with stable CAD, in whom the marker may aid in evaluating the risk of recurrent ASCVD events. However, clinicians should not attempt to use serial hs-CRP to monitor efficacy of treatment. An hs-CRP level that is persistently > 10 mg/L should prompt a search for other causes of inflammation. Because the risk associated with hs-CRP is well established, we have few reservations about using this test in intermediate-risk patients when we suspect their risk might be greater. Repeatedly elevated hs-CRP levels would prompt us to manage the patient as high risk.

Noninvasive measures of atherosclerosis

Although biochemical markers are useful in assessing a patient's metabolic milieu, noninvasive measures of atherosclerosis are useful in detecting subclinical atherosclerosis and quantifying its extent. The concept is that patients with subclinical disease then move from the realm of primary prevention into secondary prevention and warrant the aggressive treatment reserved for those at high risk. This notion has broad conceptual appeal to both patients and clinicians as a preventive strategy.

These tests are generally classified as imaging and nonimaging modalities. The primary nonimaging modality is the ankle brachial index (ABI), which is used to detect subclinical peripheral artery disease (PAD), a well-established CAD-risk equivalent. ABI is simple and inexpensive, can be done in the office setting, and has excellent test characteristics (sensitivity 97%, specificity 100%), especially in asymptomatic patients older than 50 years of age.¹⁴ An ABI < 0.90 is diagnostic of PAD and has been shown to independently predict CV morbidity and mortality in a number of observational studies.¹⁴ Thus, in an asymptomatic patient like JR, the presence of subclinical PAD, as measured by an office ABI of 0.85 by a staff nurse, would justify starting her on a statin and targeting an LDL cholesterol level of < 100 mg/dL.

Noninvasive atherosclerosis imaging modalities include carotid artery intimal medial thickness (IMT) measures, CAC by electron-beam tomography (EBT), and magnetic resonance imaging. These modalities, however, are not yet widely used in clinical practice. For example, although carotid IMT is probably the best-val-

idated direct measure of subclinical atherosclerosis with supporting data from large observational trials, it is not often used in clinical practice because of the time and cost involved in data acquisition.

On the other hand, EBT of the coronary arteries takes little time, is not operator-dependent, and is widely available. However, EBT is not as widely accepted by the scientific community as a validated tool.¹⁵ Nonetheless, EBT scores of CAC > 100 have reasonable test characteristics for angiographically proven CAD (sensitivity 89%, specificity 77%) and have been shown to predict CAD mortality in several cohorts.¹⁶ Thus, while the most recent AHA position statement on EBT did not fully endorse its use, it did concede that elevated CAC scores in intermediate-risk patients might help guide medical therapy.¹⁵ This idea was born out most recently in a prospective study of CAC scoring combined with FRS: CAC scores > 100 added substantially to global risk prediction, but only in subjects with FRS > 10%.¹⁷

Conclusion

Individuals with major risk factors or high FRS scores should be aggressively treated with preventive therapies, including drug therapy. Most individuals who develop ASCVD, however, do not have multiple major ASCVD risk factors or high FRS scores. Therefore, CV risk assessment that goes beyond traditional risk factors and incorporates other clinical risks (eg, metabolic syndrome), advanced laboratory tests, or measures of subclinical atherosclerosis may be indicated.

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