Primary Prevention of Cardiovascular Disease in Women: New Guidelines and Emerging Strategies

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ABSTRACT

PURPOSE: Cardiovascular disease (CVD) is the leading cause of death in women, and primary prevention of the disease is critical for preventing morbidity and mortality. This article reviews available strategies for preventing CVD in women and discusses how clinicians may choose among these strategies.

EPIDEMIOLOGY: Nearly half a million women die every year from CVD in the United States. Preventive strategies should be tailored to a woman's future risk of suffering a CVD event assessed using standard risk factors. Lifestyle interventions that aim for a healthy diet, moderate physical activity, smoking cessation, and weight maintenance/reduction are safe, inexpensive, and probably effective strategies for preventing CVD in most women. In women with high blood pressure (≥140/90 mm Hg), there is good evidence that pharmacologic intervention prevents future CVD. Aspirin or lipid-lowering medications generally should be limited to women whose 10-year risk of CVD is ≥10%. Refining risk estimation using serum C-reactive protein levels, coronary artery calcium scanning, or other novel risk factors may be useful in women at intermediate risk for CVD when a difficult clinical decision is at hand, though validation of these evolving strategies is lacking. Hormone replacement therapy should not be used to prevent CVD.

TYPE OF AVAILABLE EVIDENCE: Randomized-controlled trials, cohort studies, systematic reviews and meta-analyses, and nationally recognized treatment guidelines.

GRADE OF AVAILABLE EVIDENCE: Good.

CONCLUSION: Where evidence is adequate to assess, strategies for preventing CVD appear to be similarly effective in women and men, and should be tailored to patients' estimated cardiovascular risk.


Cardiovascular disease (CVD) is the leading cause of death in women in the United States. Although men tend to develop CVD earlier than women, more women than men eventually die from the disease, and the proportion of adults over age 55 years who are living with a CVD is actually higher in women than men. Furthermore, whereas CVD mortality has decreased in men over the last 20 years or so, mortality has remained high in women (Figure). This disparity argues for reviewing prevention strategies that have been shown to be specifically effective in women.
plecations associated with CVD events. As such, this article reviews effective strategies for primary prevention of CVD in women.

**Pitfalls of Primary Prevention—Importance of Estimating Risk**

Before embarking on this review, it is important to recognize the risks of primary prevention. Preventing disease before it occurs necessarily implies intervention with persons who have not yet developed the disease. Such individuals may think of themselves as completely healthy, may have no current manifestations of the disease (and therefore no motivation for improving the way they feel), and may not suffer consequences from CVD in the near future or ever. Persons who never develop the disease cannot benefit from prevention strategies. All persons exposed to preventive interventions, however, are at risk for developing side effects and unintended consequences from those interventions. Even measuring serum cholesterol may lead to decreased perception of health and could lower quality of life. Interventions also may be costly, especially when applied to large segments of the population as is typically necessary to prevent disease in an otherwise healthy population.

It is important, therefore, to make sure the expected benefits from an intervention outweigh the expected harms, and that they justify the expected financial costs. Expected benefit from an intervention can be quantified in terms of the absolute risk reduction, which is the difference between an individual’s native risk of a disease without the intervention, and the individual’s risk with the intervention. Expected benefit, therefore, is a function not only of how good the intervention is (in terms of the relative risk reduction), but also of the individual’s chance of developing the disease. We expect more benefit from any given intervention in individuals who are at high risk than from those at low risk.

For preventive interventions that are essentially risk free and cost neutral (eg, smoking cessation), a careful assessment of an individual’s future risk is not necessary; the intervention can be recommended for everyone. For preventive interventions associated with either significant risk (eg, aspirin) or significant cost (eg, cholesterol-lowering medications), care must be taken to target those individuals whose risk of future CVD (and therefore their expected benefit) justifies the expected morbidity and cost associated with treatment.

This “risk-based” philosophy is woven throughout the rest of this discussion. The following section reviews available interventions that may be effective for preventing CVD in women; those interventions that appear to be “risk sensitive” are highlighted. For each emerging prevention strategy reviewed, a discussion will follow as to how risk guides clinical decisions. Finally, in the discussion of novel risk factors, specifics of estimating risk for an individual patient using traditional methods are addressed along with the role novel risk factors might play in refining risk estimates and guiding the aggressiveness with which we pursue risk-sensitive preventive interventions.

**Overview of Prevention Strategies—New American Heart Association Guidelines**

The American Heart Association (AHA) recently published evidence-based guidelines for the prevention of CVD in women. The authors of these guidelines undertook a systematic search of the literature, reviewing nearly 7000 abstracts and 1300 full-text articles (including 92 meta-analyses). Nearly 400 articles were selected for data abstraction and inclusion in summary evidence tables. The strength of evidence supporting each specific preventive intervention was then reviewed and rated, including a “generalizability index” that indicates how likely the results are to generalize to women (Table 1).

The expert panel members gave class I recommendations to standard lifestyle interventions, including smoking cessation, physical activity, heart-healthy diet, and weight maintenance/reduction. This general endorsement comes despite a lack of randomized-controlled trial evidence proving that persons randomized to lifestyle interventions actually have fewer cardiovascular events than others (thus the level B recommendation). However, given the minimal side effects and low costs of these interventions, they are considered “top priority” interventions for all women (Table 2).

Pharmacologic treatment of hypertension received a class I recommendation with A level evidence that very likely generalizes to women. Pharmacologic treatment of hyperglycemia in patients with diabetes, with a goal...
Table 1. Classification and Levels of Evidence Used in American Heart Association Guidelines for Prevention of Cardiovascular Disease in Women

<table>
<thead>
<tr>
<th>Classification</th>
<th>Strength of Recommendation</th>
<th>Level of Evidence</th>
<th>Generalizability Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>Intervention is useful and effective</td>
<td>A</td>
<td>A1</td>
</tr>
<tr>
<td>Class IIa</td>
<td>Weight of evidence/opinion is in favor of usefulness/efficacy</td>
<td>A</td>
<td>A–C‡</td>
</tr>
<tr>
<td>Class IIb</td>
<td>Usefulness/efficacy is less well established by evidence/opinion</td>
<td>B</td>
<td>A–B†</td>
</tr>
<tr>
<td>Class III</td>
<td>Intervention is not useful/effective and may be harmful</td>
<td>B</td>
<td>B1</td>
</tr>
</tbody>
</table>

Level of Evidence:
- A: Sufficient evidence from multiple randomized trials
- B: Limited evidence from single randomized trial or other nonrandomized studies
- C: Based on expert opinion, case studies, or standard of care

Generalizability Index:
- 1: Very likely that results generalize to women
- 2: Somewhat likely that results generalize to women
- 3: Unlikely that results generalize to women
- 0: Unable to project whether results generalize to women


Table 2. Summary of Recommendations Regarding Primary Prevention Strategies From the American Heart Association Guidelines for Prevention of Cardiovascular Disease in Women

<table>
<thead>
<tr>
<th>Lifestyle interventions</th>
<th>Classification</th>
<th>Strength of Recommendation</th>
<th>Level of evidence</th>
<th>Generalizability index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cigarette smoking cessation</td>
<td>I</td>
<td>A</td>
<td>B</td>
<td>1</td>
</tr>
<tr>
<td>Physical activity</td>
<td>I</td>
<td>A</td>
<td>B</td>
<td>1</td>
</tr>
<tr>
<td>Heart-healthy diet</td>
<td>I</td>
<td>A</td>
<td>B</td>
<td>1</td>
</tr>
<tr>
<td>Weight maintenance/reduction</td>
<td>I</td>
<td>A</td>
<td>B</td>
<td>1</td>
</tr>
<tr>
<td>Pharmacologic treatment of major risk factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High blood pressure</td>
<td>I</td>
<td>A</td>
<td>B</td>
<td>1</td>
</tr>
<tr>
<td>Hyperlipidemia*</td>
<td>I–IIa</td>
<td>A–B‡</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Glycemic control in diabetics</td>
<td>I</td>
<td>A</td>
<td>B</td>
<td>1</td>
</tr>
<tr>
<td>Other pharmacologic prevention interventions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin*</td>
<td>I–III</td>
<td>A–B‡</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Omega-3 fatty acid supplementation</td>
<td>IIb</td>
<td>B</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Folic acid supplementation</td>
<td>IIb</td>
<td>B</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Antioxidant supplementation</td>
<td>III</td>
<td>A</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Hormone replacement therapy</td>
<td>III</td>
<td>A–C§</td>
<td>N/A</td>
<td></td>
</tr>
</tbody>
</table>

*“Risk-sensitive” interventions in which recommendations differ depending on the individual’s level of cardiovascular risk recommended (class I) for high-risk individuals, but recommended less strongly or contraindicated in lower-risk individuals.

†The level of evidence differs depending on the level of risk, the type of cholesterol-lowering medication used, and the patient’s initial low-density lipoprotein cholesterol level (there is less evidence for lipid lowering when a high-risk individual already has low cholesterol levels).

‡The level of evidence differs depending on the level of risk of the patient.

§The level of evidence differs depending on the type of hormone used (more evidence of harm with estrogen-progestin combinations and the clinical scenario (more evidence of harm for initiating, rather than just continuing hormone replacement therapy).
During the last decade or so, dietary intervention trials and large epidemiologic studies such as the Nurse’s Health Study have suggested a different approach to preventing heart disease that deemphasizes the role of total serum cholesterol (and therefore dietary fat) as the only/primary mediator of CVD. Systemic inflammation, insulin sensitivity, oxidative stress, and endothelial function, for example, also appear to be involved in cardiovascular pathophysiology and are affected by diet. In particular, the types of fats and carbohydrates people choose to consume may be more important in determining cardiovascular risk than the overall macronutrient content (ie, percentage of calories from fat). Trans-fatty acids (eg, those found in stick margarine, vegetable shortenings, and commercially baked and deep-fried foods) appear to be the most harmful type of fat to consume, whereas mono- and polyunsaturated fats, particularly those that contain high levels of omega-3 fatty acids and alpha-linoleic acid (such as olive, fish, flaxseed, canola, and soybean oils) appear to be protective against coronary heart disease. Nuts and legumes, which tend to contain these more beneficial types of fat, also are associated with better cardiovascular outcomes, and may deserve more dietary emphasis. Carbohydrates also require differentiation: simple and processed starchy foods such as baked potatoes and white bread appear to raise blood glucose levels quickly (high glycemic index), induce higher insulin levels, increase serum triglyceride levels, and are associated with CVD. By contrast, complex whole-grain foods, especially those with high fiber content, are associated with decreased rates of disease. Recent experimental evidence explicitly testing some of these principles demonstrated more effective lowering of cholesterol among persons following a low-fat plant-based diet that emphasized vegetables, legumes, and whole grains than among persons following a more typical US low-fat diet. The new Dietary Guidelines for Americans 2005 also recognizes these principles and recommends, for example, very low intake of trans-fatty acids, high fruit and vegetable consumption (including nonstarchy vegetables), and higher intake of whole grains and fiber.

Several other recent studies have lent support to more comprehensive and specific diets such as the “Mediterranean” and “portfolio” diets. A Mediterranean diet is characterized by high consumption of monounsaturated fat (olive oil rather than other types of fats), legumes, nuts, seeds, fruits and vegetables, whole grains, and fish. New observational evidence indicates that older adults who self-reported following such a diet show a markedly lower risk of death (hazard ratio: 0.77; 95% confidence interval: 0.68-0.88) even after adjusting for multiple demographic, lifestyle, and other potentially confounding factors. Though residual confounding may be present in this study, an accompanying article in the same journal issue described a randomized-controlled trial of a similar Mediterranean-style diet that is less prone to confounding. In this study, the diet intervention consisted of recommending specific targets for fruits, vegetables, whole grains (including legumes) and walnuts, and increased olive oil consumption, compared with a control diet with the same macronutrient content but more vague advice about healthy food choices. All patients in the study had the metabolic syndrome (defined by abdominal adiposity, dyslipidemia, hypertension, and/or impaired glucose homeostasis). At a 2-year follow-up, the patients adhering to the Mediterranean diet had lost more weight, showed marked improvement on a wide range of physiologic indicators predictive of CVD, including serum lipids, and were much less likely to continue to meet criteria for the metabolic syndrome (40/90 vs 78/90 controls, $P < .001$). A similar experimental study focusing only on young obese women showed similar results, indicating likely generalizability of these findings to women.

In patients with high cholesterol levels, simply eating a low-fat and low-cholesterol diet may not be sufficient to meet cholesterol target levels. Recent evidence indicates that combining a low-fat diet with a dietary “portfolio” of other foods that are known to reduce cholesterol, such as soy protein, plant sterols, viscous fibers, and almonds (the portfolio diet), may reduce serum cholesterol to a much greater extent than a standard low-fat diet, and possibly as much as statin therapy. These results, however, should be considered preliminary based on small sample size and short follow-up; furthermore, adherence to this somewhat unusual diet may be difficult. Table 3 compares the dietary components of old and new USDA Food Guide Pyramids with 3 specific diets shown to improve markers of health in randomized-controlled trials.

Altogether, these new lines of evidence strengthen the case for refining our dietary recommendations. All women, no matter what their cardiovascular risk, should be advised to eat a healthy diet. Healthy diet recommendations should focus less on a particular macronutrient content goal (ie, <30% of calories from fat), and more on eating “quality” foods including fruits and vegetables, whole grains, and the right kinds of fat. These simple guidelines should be feasible for most women and, along with regular physical activity (emphasized in the 2005 Dietary Guidelines for Americans), should be recommended to all women. For patients at higher risk of CVD, it may be reasonable to recommend a more specific whole-diet solution such as a plant-based, Mediterranean, or portfolio diet as described above and in Table 3. These specific diets are harder for patients to comply with, and take more physician/dietician time to explain and monitor; but for higher-risk patients with more expected benefit, these costs may be worth bearing.

**New Lipid-Lowering Guidelines From the National Cholesterol Education Program**

The NCEP has recommended a risk-based
approach to cholesterol lowering since 1988, when the Adult Treatment Panel guidelines first were released. The NCEP guidelines recommended counting a patient’s cardiovascular risk factors and matching the aggressiveness of cholesterol-lowering therapy to the level of risk. These dichotomized risk factors (present or absent) included age (men ≥ 45 years; women ≥ 55 years), cigarette smoking, hypertension (blood pressure ≥ 140/90 or on antihypertensive medication), low high-density lipoprotein (HDL) cholesterol (<40 mg/dL), and family history of premature coronary heart disease (CHD) (in a first-degree relative; male <55 years or female <65 years of age). In the 2001 Adult Treatment Panel III (ATP III) guidelines, the NCEP acknowledged that counting risk factors produces only a crude estimate of risk, and recommended estimating 10-year CHD risk using the Framingham equation (implemented directly by computer or via a point scheme based on the equation) for patients with 2 or more risk factors but without known CVD. The risk score is then used to decide which of these patients actually is at “high” risk (equivalent to those patients with established CHD, or >20%), and which is at “moderately high” (10% to 20%) or “moderate” risk (≤10%); patients with 0 to 1 risk factor are considered to be at “lower” risk. Recommendations for low-density lipoprotein (LDL) goals and treatment thresholds are based on results of this 2-step approach (first count risk factors, then estimate risk if 2 or more risk factors are present) (Table 4).

In July 2004, the NCEP published an update to the ATP III guidelines based on the results of recent clinical trials. The update does not change the basic categorization of persons based on numbers of risk factors and 10-year risk, but does change the LDL goal and treatment thresholds recommended. The 3 major changes recommended (which are considered “optional”) are: (1) high-risk patients may benefit from HMG-CoA reductase inhibitors (“statins”) even if their initial cholesterol level is already low (<130 mg/dL, or even <100 mg/dL); (2) high-risk patients may benefit from more intensive cholesterol lowering (ie, to a goal of <70 mg/dL rather than <100 mg/dL); and (3) in any patient requiring drug ther-

<table>
<thead>
<tr>
<th>Table 3. A Comparison of Different Low-Fat 2000-kcal Diets: Daily Servings* and Special Emphases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grains</td>
</tr>
<tr>
<td>Vegetables</td>
</tr>
<tr>
<td>Fruits</td>
</tr>
<tr>
<td>Milk and dairy</td>
</tr>
<tr>
<td>Meat and eggs</td>
</tr>
<tr>
<td>Legumes</td>
</tr>
<tr>
<td>Nuts, seeds</td>
</tr>
<tr>
<td>Oils</td>
</tr>
<tr>
<td>Sweets</td>
</tr>
<tr>
<td>Other/special emphasis</td>
</tr>
</tbody>
</table>

*We calculated serving-equivalents using the following rough conversion: 1 serving = 1 ounce = 28.3 g.
†Data from The Food Guide Pyramid using sample diets on pg 9.
‡Data from US Department of Agriculture. MyPyramid.gov inputs: 50-year-old woman with 30-60 min exercise/day.
§Data from Gardner et al.18 This diet lowers cholesterol more than a “standard” low-fat diet with the same macronutrient composition.
‖Data from Esposito et al.21 This diet lowers markers of inflammation, endothelial dysfunction, and the metabolic syndrome in comparison with a usual diet with the same macronutrient composition. Note that this diet specifically called for 400 g (about 14 oz) of either whole grains or legumes, and also 25-50 mg of walnuts/day.
¶From Jenkins et al.23 This diet lowers cholesterol nearly as much as lovastatin therapy. Note that this diet specifically called for approximately 2 g of plant sterol in the form of sterol-enriched margarine, 20 g of viscous fiber in the form of oats, barley, and psyllium, 43 g of soy protein, 28 g of almonds, and either eggplant (200 g) or okra (100 g) every day.
Whole = whole grains; sub = substitute.
apy, the goal should be a reduction in LDL of at least 30% to 40%. The basic premise of these changes is that cholesterol lowering reduces risk of major CHD events by about 1% for every 1% LDL cholesterol is lowered, regardless of the initial cholesterol level—a finding further supported by another recently published trial.

However, it should be noted that these updates mainly affect high-risk individuals; in low-risk women, especially, a less aggressive approach still is indicated, as these women have less to gain from statins and the data supporting primary prevention with statins is weaker for women than it is for men.

In addition to these updates, we recommend a more purely risk-based approach than is currently advocated by NCEP. Rather than counting risk factors, which only very crudely estimates risk, we advocate estimating the 10-year risk score for any woman for whom cholesterol-lowering therapy is being considered. This approach more accurately identifies high- and low-risk women by taking full account of age, very high or low HDL cholesterol levels, and other information embedded in risk factors that are measured on a continuous scale. It also allows for better communication with patients about actual risks of disease and the expected benefits of statins. For example, a 57-year-old woman with systolic blood pressure of 140 mm Hg on treatment, total cholesterol of 230, LDL of 164, and HDL of 47 has about a 4% 10-year risk of MI or CHD death. Per NCEP guidelines this patient, with 2 risk factors (age and hypertension), would be considered at “moderate risk” for CHD and would qualify for drug therapy. However, her low predicted risk of disease and the low expected benefit from statins (decreasing 10-year risk from 4% to 3%), argues for a less aggressive approach. For women interested in taking an active role in decision making, we often have found discussion of the actual expected benefits of treatment in terms of real numbers, such as in this example, to be very helpful.

**Novel Risk Factors and Improvements in Risk Estimation**

To use a risk-based approach to CVD prevention, the clinician must be able to estimate 10-year risk for individual patients. The simplest way of making these estimates is to use a Framingham equation risk calculator, such as the one available online on the NCEP Web site. This calculator asks for the patient’s age, gender, total cholesterol, HDL cholesterol, smoking status, and systolic blood pressure (on or off treatment), and then calculates the 10-year risk of having an MI or dying from CHD. A very similar estimate can be obtained without a calculator using the point-based implementation of the same equation available in the ATP III written report, though this approach is more cumbersome and more difficult to implement in real time during an office visit.

Unfortunately, all risk estimation calculators do not use the same algorithm. One may notice, for example, that the official NCEP calculator does not include diabetes or family history of premature CVD—both traditional risk factors. Diabetes is not included because the NCEP considers any diabetic automatically “high risk.” Other risk calculators available online use different algorithms, and include different subsets of predictors. Large differences in these estimates (3% to 12% for the case presented above) are partially due to the inclusion of “soft” events such as angina and revascularization events in some algorithms, which markedly drives up the 10-year risk for women. Calculators also clearly use different risk equations, some of which are derived from published Framingham data, and others that are not clearly referenced or proprietary. For most purposes, we recommend using a risk calculator that includes only “hard” events (MI or CHD death), and that is clearly based on Framingham data, such as the calculator on the NCEP Web site.

**Table 4. Summary of Guidelines for Lipid-Lowering Therapy From the National Cholesterol Education Program Adult Treatment Panel III**

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>LDL Cholesterol Goal, mg/dL*</th>
<th>LDL Cholesterol Treatment Threshold, mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>High risk (“CHD or CHD risk equivalent”)</td>
<td>LDL &lt;100 (&lt;70 optional†)</td>
<td>≥100 (&lt;100 optional†)</td>
</tr>
<tr>
<td>Moderately high risk</td>
<td>2 or more risk factors§ with 10-year risk 10%–20%</td>
<td>&lt;130</td>
</tr>
<tr>
<td>Moderate risk</td>
<td>2 or more risk factors§ with 10-year risk &lt;10%</td>
<td>&lt;130</td>
</tr>
<tr>
<td>Lower risk</td>
<td>0–1 risk factors§</td>
<td>&lt;160</td>
</tr>
</tbody>
</table>

*Updated National Cholesterol Education Program (NCEP) treatment guidelines recommend aiming for at least a 30%–40% reduction in cholesterol when starting a cholesterol-lowering medication, as is generally obtained using a standard dose of a “statin” medication (~40 mg of an older statin or ~10 mg of a newer, high-potency statin such as atorvastatin).
†Other atherosclerotic disease counting as a “CHD risk equivalent” include peripheral arterial disease, abdominal aortic aneurysm, and symptomatic carotid artery disease.
‡Established CHD risk factors counted here include age (men ≥45 years; women ≥55 years), cigarette smoking, hypertension (blood pressure ≥140/90 or on antihypertensive medication), low HDL cholesterol (<40 mg/dL), and family history of premature CHD (male first-degree relative <55 years or female <65 years).
§Established CHD risk factors counted here include age (men ≥45 years; women ≥55 years), cigarette smoking, hypertension (blood pressure ≥140/90 or on antihypertensive medication), low HDL cholesterol (<40 mg/dL), and family history of premature CHD (male first-degree relative <55 years or female <65 years).
Other characteristics apart from those included in traditional risk calculations (age, gender, blood pressure, cholesterol, smoking, diabetes, and family history of CHD) may help refine risk estimates. Body mass index, for example, is not included in traditional risk calculations though it clearly is associated with future CVD.35 Some proprietary calculators do include anthropomorphic measurements,32,34 and one also includes physical activity and stress levels, exposure to secondhand smoke, and postmenopausal status,35 though it is unclear what data these are based on.

Other measurements also may help estimate risk. Such “novel” risk factors include serum levels of C-reactive protein, homocysteine, lipoprotein A, fibrinogen, and LDL particle size and number. Evidence of subclinical CVD also may be a strong risk predictor for future events. In fact, left ventricular hypertrophy on electrocardiogram is already included in some Framingham calculators.31 Other subclinical markers include ankle-arm blood pressure ratio, carotid intima-media thickness (measured via ultrasound), and coronary artery calcification (CAC) (measured via computed tomography). Of these, the strongest predictor of cardiovascular risk appears to be CAC, though it also is the most difficult and most expensive to measure. Cohort studies (some of which include substantial numbers of women) show that persons with high CAC scores may have up to 10 × the CHD risk of persons with a CAC score of 0,36 and one large follow-up study demonstrates even stronger relative mortality for CAC in women than in men.37 A risk calculator that uses both traditional risk factors and the CAC score to produce an integrated risk estimate has been published along with the supporting documentation in an open-access format by BioMed Central,38 though the risk estimate produced includes both hard and soft events and should be adjusted downwards for use with NCEP guidelines. No similar documentation is available for risk calculators using other novel risk factors, but current evidence indicates that a high C-reactive protein level (-3 mg/dL or higher) appears to increase risk by about 20% to 30%,39 and that this excess risk is independent of cholesterol levels in women.40

In the future, risk calculators will take into account more detailed physical, psychologic, environmental, genetic, and physiologic measurements in estimation of risk, and should be more accurate in predicting which patients will actually go on to suffer consequences from CVD. At the present, however, use of novel risk factors for guiding preventive interventions has not been thoroughly validated as an effective strategy for prevention of CVD. We therefore recommend the following approach: (1) use a Framingham-based calculator including traditional risk factors only that calculates risk for “hard” events (such as the one on the NCEP Web site40); (2) add a small “fudge-factor” (increasing risk by about 20%; eg, from 5% to 6%) for obesity, low physical activity levels, strong family history, or other established factors not included in the equation; and (3) consider measuring C-reactive protein or CAC only in an intermediate-risk patient with a hard decision to make, such as someone who has never taken medications before and is considering starting statin or aspirin therapy.

CONCLUSION

Primary prevention of CVD in women is an important topic that should be high on the list of priorities for any outpatient physician who cares for adult women. In most cases, prevention strategies shown to be effective in men are probably also effective in women, including the basic lifestyle interventions that should be the cornerstone of prevention for all people, regardless of sex. Notable exceptions are use of aspirin for primary prevention and use of statins in low-risk women. These interventions are supported by less evidence for women than they are for men. It therefore is prudent to be somewhat less aggressive in treating low-risk women with these medications—particularly aspirin—than we might be with low-risk men. Future research should aim to clarify the role of aspirin in primary prevention for high-risk women and especially for women who smoke; confirm the benefits of primary prevention with cholesterol-lowering drugs in women; explore better ways of predicting which women are at highest risk for future events, including use of novel risk factors; and continue to pursue dietary interventions that are efficacious, affordable, and acceptable to patients.

We recommend that interventions should be tailored to patients’ estimated cardiovascular risk. This recommendation should be explicitly followed for lipid lowering (as recommended by the NCEP) and aspirin therapy (as recommended by the US Preventive Services Task Force41), but also should guide other prevention strategies including use of special whole-diet interventions (such as the Mediterranean or portfolio diet); intensive physical activity counseling; dietary supplements with less firm supporting evidence (such as omega-3 fatty acid supplementation); and even smoking cessation, which is important for any woman, but graverly so for women already at high risk. Estimating risk is easily accomplished via online risk calculators,42 may be refined by other extenuating circumstances (eg, a strong family history) or novel risk factor measurement when a difficult decision is under consideration, and aids not only in decision making but also in communicating the importance of prevention to our patients.

REFERENCES


