Risk Factors for Heart Disease Among Women: Communicating Probabilities of Disease

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Approximately half of all deaths in women are attributable to coronary artery disease (CAD), which claims more lives than the next 14 causes of death combined [1]; however, awareness of CAD risk remains sub-optimal. CAD is preventable through the management of modifiable risk factors, such as obesity, diabetes, dyslipidemia, and smoking [2,3]. Although men and women have the same risk factors for CAD, the relative weight of a given risk may differ according to sex [4]. Targeting women for cardiac risk factor assessment, educating them about their risk, and motivating them to change behaviors are paramount to bridging the gender-disparity gap in cardiac outcomes and are at the crux of primary prevention.

Calculators and guides that predict risk for several cardiovascular endpoints have been developed. The following review summarizes the available evidence on CAD risk factors among women and includes examples of the use of risk calculators in communicating to women their probabilities of disease as a way of stressing disease prevention and risk factor modification.

Calculating Risk

Ten-year absolute risk of CAD events, such as myocardial infarction (MI) and death attributable to heart disease can be calculated using a woman’s individual risk factors and projections based on data from the Framingham Heart Study [5] and the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) [6]. Examples of risk calculators that are suitable for assessing women are listed in Table 1 [5–10]. The American College of Cardiology/American Heart Association (ACC/AHA) calculator [7] involves 6 important risk factors and their interaction and is especially helpful for evaluating the elderly and patients with multiple risk factors. The MedCal calculator is uniquely based on European studies [8,9] in addition to the Framingham study [5] and includes estimates for secondary as well as primary prevention. In addition to being helpful tools for risk stratification, these programs can facilitate new approaches towards educating women about their CAD risk factors. In this vein, some of the web sites (eg, MedCal) offer educational handouts tailored to the patient’s individual risk factor profile. These educational materials can be obtained by registering at the web site.

CAD Risk Factors Among Women

Cardiac risk factors among women include family history of premature CAD, age, timing of menopause, use of hormone replacement therapy (HRT), hypertension, diabetes mellitus, dyslipidemia, cigarette smoking, obesity, and sedentary lifestyle [2,3]. The strongest risk factors for CAD in women are diabetes (relative risk, 2.2 [95% confidence interval {CI}, 1.8–2.6]), smoking (relative risk, 1.7 [CI, 1.4–2.0]), and hypertension (relative risk, 1.4 [CI, 1.2–1.6]), all of which are modifiable or changeable factors [4,11].

When discussing CAD risk with women, providers must dispel the myth that heart disease is a “man’s disease.” One method of conveying this point is to use a female reference patient and compare the effects of different risk factors on her 10-year risk of CAD events. Figure 1 shows the relative risk of CAD for a 55-year-old woman with no other known risk factors versus the same women with each cardiac risk factor. Such a graph can help visually relay the importance of a single risk factor on a patient’s individual 10-year risk of MI or death attributable to heart disease. Relative risk is useful in providing the patient with a perspective of her overall risk status relative to a low-risk state, and higher relative risk estimates in young adults highlight the need for long-term risk reduction plans.

Approximately 70% of all U.S. women have at least 1 major cardiac risk factor, and the proportion of women with risk factors increases with age [1,11,12]. Figure 2 plots the “effective age” of women with different risk factors and increasing age compared with women without known risk factors, allowing the patient to see how she can decrease her effective age, and her risk, by reducing other risk factors.

Minimizing modifiable risk factors is the key to primary
prevention. This is especially true for women, in whom the first manifestation of disease may be death. In 63% of women who died suddenly of CAD, there were no previous symptoms of the disease [1].

Communicating Probabilities of CAD

Nonmodifiable Risk Factors

Age. The aging process includes the development of atherosclerosis over time, resulting in an increased burden of CAD in the elderly compared with younger patients. For women, an age of 55 years or older is considered a major risk factor for CAD [6]. There is a relationship between aging and CAD, independent of the risk of CAD related to menopause and the many comorbidities that accompany aging [2,13]. Secondary analysis of data from large clinical trials, such as the Thrombolysis in Myocardial Infarction III (TIMI III) Registry, have shown more extensive multivessel disease in the elderly (defined as ≥ 65 years old) as compared with younger patients [14,15]. In relaying how the relative risk of MI or heart death increases with age, using a risk calculator the provider can explain, for example, that a 75-year-old woman has a 67% increased risk of CHD in 10 years compared with a 55-year-old woman with a similar profile [10]. Prior studies have found that older women in particular have minimal insight into their CAD risk factors [16,17]. Unfortunately, lack of knowledge and awareness about heart disease is greatest among the subset of older postmenopausal women, those most at risk. Although age is an unmodifiable risk factor, explaining to the older patient that her risk is high because of her age presents an opportunity to impress upon her the importance of improving her modifiable risk factors.

Family history. Family history of premature CAD (defined as MI or sudden death before age 55 years in a first-degree male relative or before age 65 years in a first-degree female relative) is strongly predictive of risk for future development of CAD [18]. Women presenting with acute coronary syndromes are more likely than men to have a family history of CAD [19,20]. Although a family history of inherited conditions is not modifiable, many environmental influences common to a family, including behaviors, physical activity, tobacco exposure, education, and diets are modifiable. Thus, women with a family history of CAD represent an important group to target for increasing awareness and changing behavior to minimize any added risk for heart disease.

Menopause. Until menopause, women have a protective advantage over men with regard to CAD development. Multiple studies have found it difficult to separate out the effects of menopause from the effects of aging [21]. CAD rates in women after menopause are 2 to 3 times those of women of the same age before menopause [1]. Surgical menopause entails a twofold increase in the risk of CAD [12]. The mechanism for this increase in risk is unclear, but decreasing levels of endogenous estrogen at menopause are associated with several adverse effects on cardiac risk factors, including increased total and low-density lipoprotein (LDL) cholesterol levels, lipoprotein (a), circulating procoagulants, homocysteine, and decreased high-density lipoprotein (HDL) cholesterol levels [22,23]. Women approaching menopause need to be more focused on modifiable CAD risk factors in light of their worsening cardiac risk factor profile. For clinicians caring for perimenopausal

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<th>Table 1. Examples of Risk Calculators*</th>
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ACC/AHA = American College of Cardiology/American Heart Association; NCEP-ATP III = National Cholesterol Education Program Adult Treatment Panel III.

*For calculating 10-year risk of myocardial infarction or coronary death.
women, this time represents an important “teachable moment.”

Modifiable Risk Factors

Dyslipidemia. The risks of dyslipidemia in women have been well studied. Serum total cholesterol in women increases steadily from the mid-30s to age 55 to 60 years. Low HDL is a stronger risk factor for women than elevated LDL [24]. Increased triglycerides also may be an independent risk factor for CAD in women [25].

The Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) [26], a primary prevention trial, demonstrated that postmenopausal women with no known vascular disease, low HDL (< 47 mg/dL), and an average to mildly elevated total cholesterol (180–264 mg/dL) had a 46% reduction in CAD events when treated with lovastatin versus placebo. In the more recent Heart Protection Study, the largest statin trial to date with 20,536 patients, treatment with a statin decreased CAD risk by a third and total mortality by 12% in men, women, and the elderly (absolute risk reduction, 1.5%) [27]. Despite multiple trials showing the efficacy of lipid lowering in women for primary and secondary prevention of major coronary events, including the Scandinavian Simvastatin Survival Study (4S) [26,28], Murdock showed that among 250 randomly selected patients, only 59% knew their cholesterol status and only 19% could accurately recall their cholesterol values [29].

Using a Framingham-based 10-year risk calculator [10], patients can be shown how individual risk factors contribute to their 10-year absolute risk of CAD. The impact of dyslipidemia on heart disease risk can be conveyed to patients by stating, for example, that a 55-year-old woman with a total cholesterol of 260 mg/dL or an HDL of 25 mg/dL has the same risk for MI or heart death as a 64- or 66-year-old woman, respectively, with normal cholesterol [10]. Put in different terms, this same woman has a relative risk for CAD of 1.55, so she has a 55% greater risk compared with a 55-year-old woman with normal cholesterol [10]. Patients informed of their cholesterol status have been shown to take subsequent steps to decrease their CAD risks [29]. Thus, education has been shown to be a valuable step in prevention. For clinicians, a few minutes dedicated to discussing CAD risk factors can yield important benefits.

Hypertension. Among the U.S. population aged 45 years or older, 60% of white women and 79% of black women are classified as having hypertension, a prevalent and significant cardiac risk factor in women [12]. Older women in particular have a higher incidence of isolated systolic hypertension [12]. In addition, left ventricular hypertrophy, associated with long-term hypertension, removes the survival advantage of female sex [2].

Having hypertension puts younger women at the same risk for CAD as older women without hypertension. Using a risk calculator, hypertension risk can be effectively communicated to the 55-year-old patient in understandable terms by explaining, for example, that if her systolic blood pressure is 200 mm Hg, then she has the same risk as a 70-year-old without hypertension [10]. Specifically, she is at 260% greater risk of developing CAD than the 55-year-old woman without hypertension [10].

Treated and controlled hypertension still may confer some risk, highlighting the need for diligence in reducing all other risk factors. For example, a 55-year-old woman being treated for hypertension with a blood pressure of less than 120/80 mm Hg has the same risk as a 60-year-old woman without hypertension [10]. Nonetheless, hypertension treatment is well proven to decrease relative risk for CAD and the morbidity and mortality associated with heart disease in both sexes [30]. The Joint National Committee on the Treatment of Hypertension VI guidelines [30] are not gender-specific; women with hypertension benefit from therapy and should be treated aggressively.

Diabetes. Diabetes is a powerful risk factor in women,
increasing CAD risk three- to sevenfold [1,11,13]. Diabetes and related dyslipidemia, with their associated risks, have been shown to be more prevalent in women and may account for the increased frequency of silent MI [1]. Diabetes adversely contributes to CAD risk through various proposed mechanisms, including lipoprotein changes, abnormal endothelial and coagulation function, and increased oxidative stress, while contributing to obesity, increasing the risk for hypertension, and acting synergistically with tobacco exposure to markedly increase cardiac risk [31,32]. Diabetes is now recognized as carrying a risk of major coronary events equal to established CAD [6].

The risk of diabetes can be made clear to a patient by explaining that she is at the same risk for MI or heart death as a woman who has already had a heart attack. Additionally, a 55-year-old woman with diabetes has the same total cardiovascular risk (MI, stroke, angina, and other vascular diseases) as a nondiabetic woman over 70 years [10]. In fact, she is at 123% greater risk of developing CAD than the nondiabetic 55-year-old woman [10]. This information generated by a risk calculator can be used to encourage diet, exercise, and medication adherence. Studies by the United Kingdom Prospective Diabetes Study Group (UKPDS) show that long-term aggressive metabolic control is associated with improvements in microvascular complications of diabetes [33]. Determining whether optimal control of diabetes decreases macrovascular dysfunction and cardiac complications remains an active area of research [34], which is being evaluated prospectively in the ongoing Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) randomized trial sponsored by the National Heart Lung and Blood Institute.

**Figure 2.** Effect of risk factor in terms of age. BP = blood pressure; HDL = high-density lipoprotein; LDL = low-density lipoprotein.
(Risk estimates derived from CHD Risk calculator [10].)
Obesity and physical inactivity. Up to one third of the nation is obese [39], and about three fourths report no leisure-time or irregular physical activity [40]. In the Nurses Health Study, the risk of CAD was 3 times greater in women with a body mass index (BMI) greater or equal to 29 [41]. Weight loss is effective, with even a 5-kg loss being associated with a 50% decreased risk of developing diabetes mellitus independent of family history [42] and a decrease in blood pressure and LDL, both independent risk factors for CAD.

Although BMI or obesity is not part of the Framingham risk calculation, the metabolic syndrome is mentioned by NCEP-ATP III as a secondary target of therapy. Clinical identification of the metabolic syndrome include abdominal obesity (waist circumference > 88 cm [> 35 inches] in women), triglycerides of 150 mg/dL or higher, HDL lower than 50 mg/dL in women, systolic blood pressure of 130 mm Hg or higher, diastolic blood pressure of 85 mm Hg or higher, and fasting glucose of 110 mg/dL or greater. In aggregate, 3 or more metabolic risk factors enhance risk of CAD independent of LDL level. The goal in management of the metabolic syndrome is to reduce the underlying causes (eg, obesity and physical inactivity) and treat associated risk factors [6].

Psychosocial issues. Social support positively affects general health perceptions, physical, emotional, and social functioning and may result in increased knowledge of risk factors. Social support has been associated with enhanced survival and reduced risk of recurrent MI [43]. Recent research suggests that the maintenance of emotional well being is critical to cardiovascular health. Compared with those who have adequate social support, people who feel lonely, depressed, and isolated have been found to be significantly more likely to suffer illnesses and to die prematurely of cardiovascular diseases. Thus, it is important for the provider to include psychosocial issues in their risk factor minimization planning. Interventions to improve the emotional health of women with certain psychosocial risk factors may increase the life expectancy of people at risk and may save millions of dollars in medical care costs [44].

Estrogen-related CAD Risk Factors

HRT and selective estrogen-receptor modulators. There is an ongoing controversy surrounding estrogen, with much of the confusion being related to the fact that retrospective registry data have suggested that HRT is useful in preventing CAD while randomized controlled trials have cast serious doubt on the usefulness of HRT in reducing cardiovascular risks. The Postmenopausal Estrogen/Progestin Interventions (PEPI) randomized controlled trial of healthy postmenopausal women showed that estrogen decreased serum total cholesterol and LDL, increased HDL cholesterol and triglycerides, and decreased serum lipoprotein (a) concentrations [45]. Despite the beneficial effect of estrogen therapy on lipoprotein concentrations, there has been a disappointing failure of these favorable effects on intermediate biomarkers to translate into expected clinical benefits in terms of angiographic [46] and survival outcomes [47]. Already observing the same types of early hazard observed in the Heart and Estrogen/Progestin Replacement (HERS) study in preliminary analyses [48], the ongoing Woman’s Health Initiative (WHI) randomized trial will shed additional light on the benefits versus risks of HRT in CAD primary prevention with both opposed and unopposed estrogen [49].

Although selective estrogen-receptor modulators (SERMs) have shown beneficial effects on some surrogate markers of CAD, whether this will translate into a decrease in CAD events is nebulous [50] but may be further clarified by the Raloxifene Use for The Heart (RUTH) trial, which is currently testing the effect of raloxifene on cardiovascular end points in more than 10,000 postmenopausal women with documented CAD [51]. Until randomized trials with adequate clinical outcomes are completed, SERMs should not be used solely for prevention of CAD. As with HRT, the potential benefits of SERMs also must be weighed against the possible risks, including increased incidence of thromboembolic events [52].

The most recent ACC/AHA guidelines for acute coronary syndromes recommend that postmenopausal women taking HRT may continue to do so but that HRT should not
be initiated for the secondary prevention of coronary events, taking into consideration that there may be other indications for HRT in postmenopausal women (eg, prevention of hot flashes and night sweats) [53,54]. Similarly, an AHA position statement on HRT recommends that the decision to continue or stop long-term HRT in women with CAD should be based on established noncoronary benefits and risks and patient preferences [50,52].

Although HRT use is not included in the existing CAD risk calculators, there are HRT decision aids and web sites available that discuss the risks and benefits with patients [55]. Although online risk calculators for HRT use also exist, these generally should not be used as a replacement for physician judgment. The decision to use HRT remains an individualized process to be evaluated on a case-by-case basis [52].

Oral contraceptive use. There was a clear synergy between older, first-generation oral contraceptive pills and smoking that led to a marked increase in the risk for CAD in smokers [56]. The newer, lower-dose oral contraceptive formulations are not associated with increased risk of MI in nonsmokers [57,58], but there is an exponential risk of MI and stroke in women over 35 years who smoke and take oral contraceptives [59]. Smokers, especially those older than 35 years, should quit smoking, and if unable to do so, should use an alternative birth control method.

Multiple Risk Factors
The presence of multiple risk factors is common, especially with advancing age. The provider should stress to the patient with multiple risk factors that her risk may be more than the sum of the contribution of each of her risk factors, as 1 or more risk factors will frequently potentiate the harmful effects of others [11,12]. In fact, having multiple cardiac risk factors negates the protective advantage of female sex, rendering women equally vulnerable to CAD as aged-matched men [13]. The ACC/AHA global risk assessment score [7] can be used to determine relative and absolute risk estimates for CAD endpoints. For example, a 70-year-old woman with hyperlipidemia and hypertension has a tally of 16 points; the ACC/AHA score shows that she is 3 times more likely to have a heart attack or heart-related death than a 70-year-old woman without these risk factors and has an absolute risk of 24% (compared with 8% in the low-risk group) for developing CAD in 10 years. Absolute risk increases with age; using the global risk assessment scoring clarifies the importance of increasing age along with multiple risk factors by conveying more information at a glance, and thus is an effective tool for relaying risk in the elderly.

Conclusion
Screening, education, prevention, and vigorous treatment of CAD risk factors with lifestyle interventions and pharmacotherapy is vitally important in women, since death is the first manifestation of CAD in a high proportion of this population [1,39]. Screening and education must be a priority for the busy provider. Despite evidence supporting the efficacy of physician counseling in modifying CAD risk behaviors (including diet, exercise, and smoking), the prevalence of counseling remains less than optimal in primary care settings. Provider reasons for this include inadequate time, inadequate counseling training, and doubt regarding the effectiveness of counseling [60]. We hope our review helps to address these barriers, and that physicians will use the information presented to help them in stratifying women according to risk and individualizing counseling.

Being well informed about medical conditions [61] is associated with improved preventive health behaviors, yet women are not well informed about cardiac risk factors. Recent surveys indicate that most women (62%) still believe cancer is their greatest health threat, and less than 10% of women perceive heart disease as their greatest health threat [62]. Women need to be educated to modify risks, to take steps to prevent CAD, and to learn the early warning signs of CAD so that they can avoid delay in seeking and receiving help. Self-motivated, prolonged risk factor modification will not be possible until the provider adequately conveys, and the woman understands, her risk for heart disease and its consequences.

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