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Primary Prevention of Atherosclerotic Cardiovascular Disease in Women

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Abstract Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of morbidity and mortality among women. Despite improvements in cardiovascular disease prevention efforts, there remain gaps in cardiovascular disease awareness among women, as well as age and racial disparities in ASCVD outcomes for women. Disparity also exists in the impact the traditional risk factors confer on ASCVD risk between women and men, with smoking and diabetes both resulting in stronger relative risks in women compared to men. Additionally there are risk factors that are unique to women (such as pregnancy-related factors) or that disproportionately affect women (such as auto-immune disease) where preventive efforts should be targeted. Risk assessment and management must also be sex-specific to effectively reduce cardiovascular disease and improve outcomes among women. Evidence supports the use of statin therapy for primary prevention in women at higher ASCVD risk. However, some pause should be given before prescribing aspirin therapy in women without known ASCVD, with most evidence supporting the use of aspirin for women ≥65 years not at increased risk for bleeding. This review article will summarize (1) traditional and non-traditional assessments of ASCVD risk and (2) lifestyle and pharmacologic therapies for the primary prevention of ASCVD in women.

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Introduction

Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of morbidity and mortality in women in the United States [1–3]. ASCVD accounted for 400, 332 deaths among women in 2010, more than deaths due to accidents, cancer, lower respiratory disease, and Alzheimer's disease combined [4]. While ASCVD-related mortality declined in the US population prior to 2000, this decline was largely observed in men, with rates of ASCVD death remaining relatively stable in women. The American Heart Association (AHA) published the first women-specific guidelines for ASCVD prevention in 1999, which were last updated in 2011 [5•], and subsequently there has been progress in the prevention, detection, and treatment of ASCVD in women with associated declines in ASCVD mortality in both women and men. However, coronary heart disease (CHD) still remains the leading cause of death in women of every major developed country and the majority of developing countries [6], with major health and economic implications.

Despite a clear decline in ASCVD-related mortality among women since 2000, age and racial disparities exist. Among younger women aged <55 years, there has been stagnation in the decline in CHD mortality with minimal improvement between 1999 and 2011 [7]. Furthermore, in the United States, the rate of ASCVD in black females is 286/100,000 compared to 206/100,000 among white females, with lower documented rates of awareness of CHD and stroke among black compared to white women [4, 8–10]. Despite the racial disparity, awareness has improved among both black and white women: a 2006 survey showed that 57 % of women were aware that heart disease was the leading cause of death in women compared to only 30 % in

1997 [8]. However, this survey also found that only 53 % of women surveyed would call 9-1-1 if they thought they were having a heart attack and 23 % would take aspirin, demonstrating a need for improved ASCVD awareness and prevention among women.

Among women, stroke accounts for a higher proportion of ASCVD events than CHD, while among men, CHD dominates [5•]. Each year in the USA, 55,000 more women than men have a stroke before age 75. Atrial fibrillation is responsible for 15–20 % of all ischemic strokes, and physicians underutilize anticoagulation therapy to treat known atrial fibrillation, increasing the risk of recurrent stroke [4, 11, 12]. These statistics emphasize the need to focus on global ASCVD prevention for women, rather than just the prevention of CHD, which was reflected in the goals of both the 2011 Effectiveness-Based Guidelines for the Prevention of Cardiovascular Disease in Women [5•] and the 2013 AHA/American College of Cardiology (ACC) Risk Assessment Guidelines [13].

The lifetime risk of ASCVD is high among women, with approximately 40 % of women at risk of developing ASCVD after the age of 50 compared to a 13% lifetime risk of developing breast cancer [14]. However, the management of modifiable ASCVD risk factors can substantially reduce the lifetime risk of ASCVD and improve survival. One study showed that women with an optimal risk profile (total cholesterol <180 mg/dL, systolic and diastolic blood pressures <120 and <80 mmHg, non-smoking, non-diabetic) had a 6 % lifetime risk of ASCVD death compared to a 21 % risk among women with ≥2 major risk factors and lower lifetime risks of CHD and stroke [14]. While efforts to improve the awareness and prevention of ASCVD in women have been successful, there is ample opportunity for further improvements to lower morbidity and mortality associated with ASCVD.

Risk Assessment

All prevention guidelines recommend that adults undergo a global risk assessment. The 2013 ACC/AHA Pooled Cohort Equation (PCE) predicts the 10-year risk for development of a first ASCVD event in adults aged 40–79 years old. There are now separate models by race (non-Hispanic whites and blacks) and by gender for more refined risk prediction. The PCE is intended for primary prevention of total ASCVD, defined as myocardial infarction (MI), CHD death, and stroke. The PCE does not apply to those with established ASCVD or other subgroups such as unusually high-risk patients or those with symptoms strongly suggestive of ASCVD. The variables that are included in the PCE are identical to those in the Framingham Risk Score (FRS) and include age, total and high-density lipoprotein cholesterol (HDL-C), systolic blood pressure (including treated or untreated status), diabetes, and current smoking.

The intensity of preventive efforts is intended to match the individual's absolute risk (low [0–5 %], intermediate [5–7.4 %], or high [≥7.5 %]), rather than the previous paradigm of treating to specific low-density lipoprotein cholesterol (LDL-C) targets. This approach balances the potential treatment benefits against the potential absolute harms from therapy such that treatment can be targeted to those most likely to benefit. Formal risk assessment should begin at age 40 and should be repeated every 4 to 6 years in individuals who are at low 10-year risk. Lifetime risk estimation is recommended for patients between 20–39 years of age and for those aged 40–59 years who are at a low 10-year-risk [15•].

The ACC/AHA PCE has several advantages but it is not without limitations. Similar to the FRS, the PCE has also been shown to overestimate cardiovascular events in certain populations [16, 17] and thus increases the number of patients who are potentially eligible for statin therapy [18, 19].

Traditional ASCVD Risk Factors

The traditional risk factors associated with ASCVD apply to both men and women; however, there are certain differences by sex in the burden and impact of these risk factors [20].

Cigarette Smoking

Differences in smoking habits have decreased over the years between men and women [21], but smoking is more common among men in younger age groups [22]. Cigarette smoking is a more potent risk factor for MI in women compared to men with relative risk estimates ranging from 2- to 5-fold [23, 24]. First MI also occurs more prematurely in women smokers suggesting that twice as many years are lost compared to male smokers [25].

Diabetes Mellitus

The prevalence of diagnosed diabetes is similar for men and women [26] across all ages [22], although highest in general among black females. Diabetes mellitus is a stronger risk factor for CHD mortality in women, which may be explained by a more adverse risk profile in diabetic women compared to men [23, 27, 28].

Hypertension

Ambulatory blood pressure monitoring has shown that systolic blood pressure is higher in men than women until the age of menopause when levels become higher in women [29]. Blood pressure levels are associated with comparable risk of MI in men and women [30–33].

Lipids

Men have higher levels of triglycerides, apolipoprotein B, and total cholesterol to HDL-C ratio, but lower levels of HDL-C compared to women [34]. Increased serum total cholesterol and LDL-C are risk factors for CHD in both men and women, while low HDL-C and higher triglyceride levels are stronger risk factors for CHD in women compared to men [33–37].

Family History of CHD

A family history of premature CHD is associated with an increased risk of incident ASCVD events in both men and women, independent of traditional risk factors [38]. The ACC/AHA Guidelines suggest that when one's risk estimation is uncertain, the presence of a family history of premature ASCVD could support revising one's risk estimation upward [15•].

Obesity and Lifestyle

The prevalence of obesity is greater in women than men [39]. The greatest weight gain in women is at younger ages, whereas men tend to be obese later in life [40]. Obesity is associated with hypertension and an adverse lipid profile, including higher levels of triglycerides and lower HDL-C [34]. However, obesity has been shown to be an independent risk factor for ASCVD [41].

More than half of women report having no regular physical activity [33]. Females are more sedentary compared to males before the age of 30; however, this pattern is reversed after age 60 years [42]. In a large meta-analysis of men and women, sedentary behavior was found to be associated with ASCVD incidence and mortality independent of physical activity levels [43].

Risk Factors Unique to Women

There are ASCVD risk factors that are unique to women (such as the pregnancy-related outcomes of gestational diabetes and pre-eclampsia) or that disproportionately affect women (i.e., auto-immune disorders), which are summarized below. The 2011 AHA Women's Guidelines consider these disorders to be significant risk factors for ASCVD–on par with traditional risk factors such as smoking and hypertension [5•].

Menarche

The age at menarche is receiving increasing attention as an ASCVD risk factor. The onset of menarche during puberty results from a complex interplay of multiple genes, hormonal regulation, and external modifying factors, such as nutrition status, childhood adiposity, and the resulting hormonal and metabolic changes [44]. Several longitudinal studies and meta-analyses have shown that age of onset of menarche is related to cardiovascular risk factors and ASCVD-related death later in life. Early menarche has been associated with increased risk of all-cause and cardiovascular mortality, as well as hypertension and diabetes even when adjusted for body mass index (BMI). In addition, there is a U-shaped relationship with late menarche over the age of 17, also associated with increased cardiovascular death [45–50].

Menopause

ASCVD is rare in young women, although rates are increasing [51], but is the leading cause of death in post-menopausal women [52]. Estrogen alters the lipid profile favorably by increasing HDL-C and improving vascular function and reducing atherosclerosis. Menopause and the period of transition have a negative impact on body fat redistribution, glucose tolerance, lipids, blood pressure, sympathetic tone, endothelial function, and vascular inflammation [52]. Initially during the menopausal transition, there is both weight gain and redistribution of fat from a gynoid to android pattern [53]. Weight gain increases the risk of dyslipidemia, diabetes, and hypertension [54].

The Study of Women's Health across the Nation (SWAN) showed that during the menopausal transition period, there was an acute change in lipids with an increase in both LDL-C and HDL-C, but then HDL-C plateaus or declines [55]. On the other hand, other risk factors showed a more linear trend over time consistent with chronological aging. Studies suggest that the anti-inflammatory and anti-atherogenic properties of HDL-C are lower in post-menopausal women [55]. There are also detrimental effects in vascular endothelial function associated with lower estrogen levels: estrogen increases levels of nitric oxide, decreases endothelin, and affects vasodilation/vasoconstriction due to influence of the sympathetic nervous system.

The understanding of post-menopausal hormone therapy has evolved over the past decade. Animal and observational studies had suggested beneficial effects of hormone therapy in reducing the risk of ASCVD when it is initiated early in the peri-menopausal period or before the development of significant atherosclerosis. However, randomized, placebo-controlled trials in older women have not shown any benefit in either primary or secondary prevention of ASCVD, with a concerning trend toward harm [56]. Hormone therapy initiated within 10 years of menopause was associated with less coronary artery calcium (CAC), a marker of subclinical atherosclerosis [57]. However, timing is important and women who initiate hormone therapy closer to menopause tend to have reduced ASCVD risk compared to those women more distant from menopause [58]. Currently, hormone therapy is not recommended for the sole purpose of ASCVD prevention.

Parity

Physiologic changes occur during pregnancy in multiple ASCVD-related pathways including inflammation, endothelial function, and hemostasis. Studies relating parity to later-life ASCVD have yielded conflicting results. However, two recent studies showed that parity was associated with maternal ASCVD in a J-shaped fashion, with the lowest risk occurring among women with two births and the highest risk among women with ≥5 births, even when adjusted for socioeconomic status and pregnancy-related complications [59, 60].

Gestational Diabetes

Gestational diabetes has immediate adverse effects to both the mother and neonate, including pre-eclampsia, increased birth weight, shoulder dystocia, and increased risk of cesarean section [61, 62]. Gestational diabetes is associated with long-term adverse maternal ASCVD risks, such as type 2 diabetes mellitus, hypertension, and metabolic syndrome [63–65]. However, gestational diabetes is also a risk factor for the development of ASCVD independent of conventional risk factors, especially among women with elevated BMI [66].

Pre-eclampsia

Pre-eclampsia is a multi-system disease that occurs after 20 weeks of gestation, mediated by abnormalities in the placental vasculature leading to both short-term and long-term endothelial dysfunction and inappropriate vasoconstriction in multiple vascular beds [67]. It presents with hypertension and proteinuria and complicates about 2–8 % of pregnancies [68]. Women with prior pre-eclampsia have a higher prevalence of metabolic syndrome and hypertension [69, 70] and an increased risk of developing ASCVD later in life [71, 72, 73•].

Polycystic Ovarian Syndrome

Polycystic ovarian syndrome (PCOS) affects up to 10 % of young women of reproductive age, making it the most common endocrine disease among this population [74]. PCOS increases the risk of many traditional cardiovascular risk factors. The central pathogenic factor in PCOS is insulin resistance and is associated with a 3- to 7-fold increase in the risk of diabetes mellitus [75]. PCOS is associated with dyslipidemia—decreased HDL-C and increase in non-HDL-C [74]. PCOS is also associated with vascular dysfunction and early atherosclerosis [76, 77].

Autoimmune Disease

Autoimmune diseases, such as systemic lupus erythematous, scleroderma, and rheumatoid arthritis, affect approximately 8 % of the population, 78 % of whom are women [78]. Inflammation underlies the development of atherosclerosis, and autoimmune rheumatic diseases are associated with higher rates of cardiovascular morbidity and mortality due to accelerated atherosclerosis. Multiple studies have demonstrated the association between rheumatoid arthritis and systemic lupus erythematous and increased cardiovascular risk [79, 80].

"Novel" Risk Factors

When initial 10-year risk estimation treatment decisions remain uncertain, the 2013 ACC/AHA Guidelines allow for revising one's risk status upward if one of the following is present: high-sensitivity C-reactive protein (hsCRP) ≥2.0 mg/L, abnormal CAC score, or ankle-brachial index <0.9. These novel factors may help guide risk assessment [15].

Inflammation and hsCRP

Higher levels of hsCRP, an inflammatory risk marker, are associated with cardiovascular events in healthy women. Indeed, there is a 7-fold increased risk of MI or stroke in women with the highest baseline hsCRP levels [81, 82]. However, there are significant racial and sex differences in hsCRP levels with black individuals and women tending to have higher hsCRP levels compared to white individuals and men, respectively [83]. This could portend higher ASCVD risk or alternatively could mean that reliance on absolute hsCRP levels alone for ASCVD risk assessment in black individuals and women may overestimate their risk.

Coronary Artery Calcium

Traditional risk estimators such as the ACC/AHA PCE can under- or overestimate risk for future ASCVD events, especially in women [15•]. CAC measured by non-contrast CT is a useful surrogate measure of total coronary atherosclerotic burden and can be used to refine risk prediction. Compared to men, CAC is less prevalent in women at a given age. However, detectable CAC is highly predictive of subsequent events in women, independent of traditional risk factors. Among women the relative risk ratios for MI or fatal CHD increased from 4.9-fold, 5.5-fold, and 8.7-fold for mild-, moderate-, and high-risk CAC scores, respectively, compared to the absence of CAC [84]. Furthermore, the ability of CAC to risk stratify was similar between men and women. In a multi-ethnic population, 30 % of women previously characterized as low risk by FRS had CAC >0, and nearly 5 % had CAC >300 [85]. Women with elevated CAC scores had a greater risk of ASCVD events [85].

In addition to its role in upgrading risk in younger women when significant CAC is present, perhaps a more important

potential role of CAC testing in the modern era may be for downgrading risk in an older adult with CAC = 0 who might otherwise be recommended for pharmacologic therapy based on chronologic age-based models. Individuals with CAC = 0 have very low event rates [86, 87]; thus, the number needed to treat to prevent one event with statin therapy may be prohibitively high in this group.

Exercise Capacity and Fitness

Cardiorespiratory fitness is a function of the heart's maximal ability to pump blood and the ability of the skeletal muscle to extract and use oxygen. Women with higher fitness, as assessed by METS on treadmill testing, have lower risks for mortality independent of traditional risk factors [88–90]. Women with low cardiorespiratory fitness have a less favorable ASCVD risk profile [91]. However, only moderate fitness levels are required to improve the coronary risk factor profile [91].

Stress, Depression, and Cardiovascular Risk

Women tend to report higher baseline stress than men, which is associated with worse prognosis after an MI [92]. Stressors such as multiple divorces impact women greater than men [93]; indeed, women suffer more often from depression than men and have worse cardiovascular outcomes from these stressors [94]. Many individuals respond to stress and depression with unhealthy coping habits. It is important to recognize psychosocial stressors and help patients cope with life in healthier ways.

Treatment: Lifestyle Modification

A healthy lifestyle is critical to preventing ASCVD, and in 2011, the AHA published lifestyle modification guidelines for women [5•]. Additionally, in 2013, the AHA and ACC formulated lifestyle guidelines on recommended dietary patterns and physical activity goals [13].

Dietary Patterns and Weight Management

The 2013 AHA/ACC guidelines recommend that diets should emphasize vegetables, fruits, and whole grains, as well as low-fat dairy products, poultry, fish, legumes, vegetable oils, and nuts. Individuals should limit sweets, sugar-sweetened beverages, and red meat [13]. The DASH (Dietary Approaches to Stop Hypertension) diet generally follows these patterns and is recommended by the guidelines. Among adults who would benefit from LDL-C lowering, the dietary guidelines recommend a dietary pattern that reduces the percent of calories from trans- and saturated fat, with a recommended limitation of 5 to 6 % of calories from saturated fat. Among adults who would benefit from blood pressure lowering, the AHA/ACC guidelines also recommend reduced sodium intake, with no more than 2400 mg of sodium daily.

The 2011 AHA guidelines for women recommend that BMI and waist circumference be evaluated and monitored. These guidelines define a desirable BMI as between 18.5 and 24.0 kg/m^2 and a waist circumference <88 cm (<35 in.) and recommend initiation of caloric restriction and measures to increase caloric expenditure if BMI and/or waist circumference are above goal [5•].

Physical Activity

The 2013 AHA/ACC guidelines recommend that adults engage in aerobic physical activity 3 to 4 times per week, with sessions lasting an average of 40 min and involving moderate- to vigorous-intensity activity, in order to reduce non-HDL-C and blood pressure [13]. The 2011 AHA women's guidelines are similar, with recommendations for 150 min/week of moderate exercise, 75 min/week of vigorous exercise, or an equivalent combination of moderate- and vigorous-intensity activity [5•]. These guidelines also recommend muscle-strengthening exercises at least twice a week.

Smoking Cessation

Clinicians should (1) ask women about current and past smoking as well as secondary tobacco smoke exposures; (2) assess readiness to quit; (3) strongly encourage patient and/or family members to stop smoking at each visit; (4) provide counseling, offer nicotine replacement or other pharmacotherapy combined with a behavioral modification program; and (5) be prepared to give advice on weight control strategies as weight gain may be a concern for some women regarding quitting.

Treatment: Pharmacotherapy

Antihypertensive Therapy

Pharmacotherapy is indicated when blood pressure is ≥140/90 mmHg (although recent guidelines suggest treating at a threshold ≥150/90 mmHg for adults older than 60 years without chronic kidney disease or diabetes) [95]. Antihypertensive treatment recommendations do not vary by gender, although there are a few special considerations for women [96]. Angiotensin-converting enzyme inhibitors (ACE-I) are contraindicated in pregnancy and should be used with caution in women who may become pregnant. For women who develop hypertension while taking oral contraceptives, the first

treatment is to stop the oral contraceptives and switch to another form of birth control. ACE-I induced cough and peripheral edema associated with calcium channel blockers are more common in women than in men.

Statins

In secondary prevention to prevent recurrent ASCVD events, the benefit of statin therapy in women is well established [97]. Previously, the role of statins for primary prevention of ASCVD in women had been controversial given the low numbers of women in prior trials. However, after completion of the largest primary prevention trial to date, JUPITER, which enrolled 6801 women, an updated meta-analysis including JUPITER and other exclusively primary prevention trials concluded that statins are effective for primary prevention in selected women [98]. Statins were shown to significantly reduce ASCVD events in women (RR 0.63 [0.49–0.82]) with no difference when compared with men and a trend toward reduced mortality (RR 0.78 [0.53–1.15]) [98].

A larger meta-analysis of primary and secondary prevention trials ($N = 141,235$ including 40,275 women) also examined sex-specific outcomes [99•]. A statistically significant decrease in total ASCVD events was observed in women (OR 0.81 [0.75–0.89]) as well as men, with similar lowering in both sexes. The number-needed-to-treat a woman over a 4-year period to prevent one ASCVD event was 148 for primary prevention and 36 for secondary prevention [the corresponding numbers in men are 43 and 29, respectively]. The authors also found a benefit for all-cause mortality with statins in women when predominantly primary prevention trials were analyzed separately (OR 0.87 [0.78–0.97]).

Decisions to initiate treatment with statin therapy and the intensity of that therapy should be matched to the absolute risk of the patient. The 2013 Cholesterol Guidelines [100] identified four groups of patients that would benefit from statin therapy: (1) those with clinical ASCVD, (2) those aged 40–75 years with diabetes mellitus, (3) those with LDL-C ≥190 mg/dL, and (4) those aged 40–75 years old with LDL-C of 70–189 mg/dL with an estimated 10-year risk ≥7.5 % (with moderate evidence also supporting consideration of a moderate intensity statin for those at 5–7.5 % 10-year risk). The guidelines caution, particularly in this fourth group, that a clinician-patient discussion be conducted before statin initiation. This discussion should address the potential for ASCVD risk reduction, the potential for adverse effects, patient preferences, and encourage heart-healthy lifestyle and management of other risk factors.

Aspirin Therapy in Women

Again, in secondary prevention, the role of aspirin is well established. Among patients with known ASCVD, aspirin reduces subsequent ASCVD events and mortality, with similar benefit among men and women [101]. In primary prevention, the use of aspirin is more controversial. A meta-analysis of nine randomized clinical trials including over 100,000 patients (54 % women) did not find any reductions in cardiovascular or cancer death despite a 20 % reduction in non-fatal MI, but there also was a 31 % increase in "non-trivial" bleeding [102]. There was no sex difference for the benefit for total ASCVD.

The largest primary prevention study of aspirin in women was the Women's Health Study (WHS) which randomized nearly 40,000 initially healthy women >45 years to 100 mg alternate-day dosing of aspirin or placebo. The WHS found that low-dose aspirin reduced the risk of stroke over a 10-year follow-up without reducing the risk of MI. Subgroup analyses showed that aspirin significantly reduced the risk of major cardiovascular events, ischemic stroke, and MI among women ≥65 years old [103]. Women assigned to aspirin therapy also had higher bleeding risk, which cautioned the use of aspirin for primary prevention, particularly in women aged <65 years. A long-term follow-up of the study found that aspirin modestly reduced colorectal cancer and ASCVD in women, but when considering the increased risk of bleeding, aspirin treatment only resulted in very small benefit or even harm. Age was the most important determinant for benefit; the 15-year number-needed-to-treat to prevent one event among women ≥65 years of age was 29 [104•].

Therefore, a clinician-patient discussion is also critical before prescribing aspirin therapy for women without known ASCVD. In addition to assessing one's 10-year ASCVD risk, this shared decision-making may also involve further risk stratification using modalities such as CAC [105] or hsCRP, considering whether a family history of colon cancer is present, and incorporating the patient's risk of bleeding, to guide recommendations for aspirin therapy. For women ≥65 years of age, low-dose aspirin may be reasonable for prevention of ischemic stroke and MI if blood pressure is controlled and if the benefits outweigh the bleeding risks (class IIa). Aspirin should not routinely be prescribed in women <65 years of age, but may be considered in select women at higher risk if the benefits outweigh the bleeding risks.

Concluding Thoughts

Women are at increased ASCVD risk at older ages, but the prognosis after MI in younger women is worse. Since two thirds of sudden cardiac deaths in women occur without prior symptoms [4], this statistic highlights the importance of risk factor screening and implementation of primary prevention therapy as appropriate. Women have unique risks related to hormonal changes and pregnancy. When there remains uncertainty about a patient's risk after traditional global risk

assessment, selective use of advanced risk assessment tools tests such as CAC may help refine risk assessment, allowing patients to move both up and down the risk spectrum after testing and help guide shared decision-making.

A healthy lifestyle serves as the foundation for ASCVD risk reduction. In addition, women at higher absolute ASCVD risk benefit equally as men do from statin therapy. However, the use of aspirin in women for primary prevention remains controversial. Continued efforts need to be made to include representative numbers of women in future clinical trials of cardiovascular interventions with sex-specific reporting of outcomes. Despite substantial progress over the past two decades, more work remains to be done to further improve cardiovascular health in women.

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Compliance with Ethical Standards

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Pooled Cohort Equation from racially and geographically diverse prospective cohorts. This new risk assessment tool estimates 10-year risk for global ASCVD (i.e. MI and stroke), and has separate equations by gender and by race (non-Hispanics whites and blacks).

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