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Cases in Precision Medicine: A Personalized Approach to Stroke and Cardiovascular Risk Assessment in Women

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Abstract

Cardiovascular disease is the leading cause of death for women in the United States and stroke, separate from cardiovascular disease, is third. This article uses a case scenario to examine female-specific cardiovascular risk factors across the lifespan, and describes a precision medicine based approach to risk factor modification and primary prevention. It also presents recent updates in the role of genetic testing and polygenic risk scores for the prediction of stroke and cardiovascular disease.

The following case is a composite history of several women, designed to illustrate the approach to cardiovascular and stroke risk assessment, including discussion of genetic factors.

Your next patient, a 46-year-old African-American woman, is here today to establish primary care. A brief review of her electronic medical record reveals that she is seen annually by one of your obstetrics colleagues and has had negative cervical and breast cancer screenings that are up to date. She is not taking any medications. Before meeting her, you quickly scan the data the medical assistant has obtained today: blood pressure 136/91 mmHg, heart rate 67 bpm, height 5 feet 4 inches, weight 174 pounds, BMI 29.9 kg/m² (*overweight*), and waist circumference 82 cm (*increased*). Upon entering the room, she tells you her older sister recently had a stroke at the age of 50 and she is very worried about her own risk for stroke. Similar to the majority of U.S. women, she utilizes her obstetrician/gynecologist as a primary care provider. She has not visited an internist or had her lipid profile checked since college. She wants your advice on how to minimize her risk for cardiovascular disease, especially stroke. She is worried that she is also at risk for stroke because of her sister's recent experience, and she has been told that strokes run in her family. She asks if there are tests you can order to see if stroke is "in her genes."

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What is the risk of cardio- and cerebrovascular morbidity and mortality among women in the general population?

Heart disease is the leading cause of death in U.S. females, stroke is the third, and more than 70% of women aged 40–60 have at least one cardiovascular risk factor (1, 2). Together heart disease and stroke account for more deaths than all cancers combined, at a direct cost of \$213 billion to the U.S. economy in 2015 (3). Despite these sobering statistics, only 21% of women report discussing their personal risk with a physician, though women who know another woman with cardiovascular disease, like the patient described here, are substantially more likely to discuss cardiovascular health with a physician than those who do not (2).

Women are consistently less likely than men to receive guideline-indicated diagnostic testing and therapies for the primary and secondary prevention of cardiovascular disease (4). Sex-specific gaps in health care quality and equity have been delineated in an attempt to identify strategic pathways to improve the cardiovascular health of women and reverse alarming increases in morbidity and mortality that have emerged, especially among racial and ethnic minority women (3, 5). Physician education is a critical component of this strategy; only a minority of primary care physicians and cardiologists feel extremely well prepared to assess cardiovascular risk in women (2). Through this case, we will discuss the traditional and unique cardiovascular risk factors that affect women, and demonstrate a personalized approach to the identification and treatment of cardiovascular risk in a woman.

What are the standard risk factors for cardiovascular disease that may help estimate this patient's risk for a stroke?

Traditional, modifiable risk factors for cardiovascular disease, including smoking, hypertension, dyslipidemia, obesity, and diabetes mellitus, account for more than 90% of the population attributable risk of heart disease in both men and women (6). There are sex-specific interactions with these risk factors that are important to account for when determining a woman's personal risk of cardiovascular disease. For example, women with diabetes mellitus have an 8-fold higher risk of cardiovascular disease compared to men with an otherwise similar risk profile (7). There are also multiplicative interactions between risk factors and sex-specific exposures. Women who smoke in combination with oral contraceptive use have a 25% increased risk for coronary heart disease, compared to men who smoke (8). A thorough ascertainment of modifiable and fixed risk factors is essential to the accurate estimation of cardiovascular risk.

The recently updated American College of Cardiology/American Heart Association Guidelines on the Primary Prevention of Cardiovascular Disease recommend that the first step in screening any asymptomatic patient aged 40 to 75 years is to apply the race- and sex-specific pooled cohort equation (PCE) to estimate 10 year risk (<http://tools.acc.org/ASCVD-Risk-Estimator-Plus/#!/calculate/estimate/>) (9). This equation includes age, sex, race, systolic and diastolic blood pressure, total, high-density, and low-density lipoprotein cholesterol, history of diabetes and smoking, as well as current therapy for hypertension, and use of aspirin and statin to calculate a 10-year and lifetime risk of atherosclerotic

cardiovascular disease (ASCVD), which encompasses coronary death, nonfatal myocardial infarction and fatal or nonfatal stroke. 10-year risk is categorized into four groups: low-risk (<5%), borderline risk (5% to 7.4%), intermediate risk (7.5% to 19.9%) and high risk ($\geq 20\%$). For individuals at borderline and intermediate risk, the consideration of additional risk-enhancing factors is recommended to revise the 10-year ASCVD risk estimate. These risk-enhancing factors include: family history of premature ASCVD (<65 years or male age <55 years); high risk race/ethnicity (e.g. South Asian ancestry); metabolic syndrome; chronic kidney disease; chronic inflammatory conditions; history of premature menopause (before age 40 years); history of pregnancy-associated-conditions that increase later ASCVD risk (preeclampsia, gestational diabetes, pre-term birth, small for gestational age baby); lipids/biomarkers associated with increased ASCVD risk (primary hypercholesterolemia, elevated high-sensitivity C-reactive protein, elevated Lipoprotein(a), elevated apolipoprotein B, ankle brachial index <0.9) (9). Additional markers of elevated ASCVD risk not mentioned in the updated guidelines that are particular to or more common in women and should be asked about as part of a thorough history include an oncologic history (i.e. cardiotoxic chemotherapeutic agents and radiation exposure to the heart), polycystic ovarian syndrome, hypothalamic amenorrhea, and the use of hormone replacement therapy or oral contraceptives (10).

Is there a role for genetic testing in the estimation of cardiovascular disease risk?

Your patient posed an astute question regarding whether there is a role for genetic testing in the assessment of her cardiovascular risk, in particular her risk for stroke. Each person's genetic makeup, in tandem with exposures, can lead to disease. The goal of genetic testing is to identify individuals at risk and provide preventive strategies to delay or thwart the appearance of disease. Harnessing an understanding of traditional Mendelian inheritance patterns has been essential to the discovery of key cardiovascular risk factors and the design of targeted interventions to reduce cardiovascular risk. A prime example of this is our understanding of lipid metabolism and the development of statins and cholesterol ester transfer protein inhibitors. Despite the elucidation of key mechanisms of cardiovascular disease development that have sprung from the study of affected families exhibiting Mendelian inheritance patterns, these monogenic disease states account for a small minority of the burden of cardiovascular disease and screening for these variants through genetic testing is unlikely to be beneficial or cost-effective.

The vast majority of cardiovascular diseases, including stroke, are polygenic. This has led to a shift in focus from monogenic causality to the incorporation of hundreds of genetic alterations into genetic risk scores and genome-wide polygenic scores (11, 12). Genetic risk scores comprise allelic variations that achieved statistically significant associations with a given disease in genome-wide associations studies (GWAS). In contrast, polygenic risk scores remove redundancy, but also include variants that do not meet genome-wide significance to potentially correct for underpowered studies. This comes at the expense of including false positives. There have been promising results of polygenic risk scores adding incremental risk estimation to traditional markers, and showing that the results of genetic

testing can improve shared decision-making regarding statin adherence (13). A major limitation of current genetic risk scores and polygenic risk scores is their derivation from predominantly European populations. We must accumulate genetic information from diverse populations to improve risk prediction beyond that of clinical factors alone. The role and utility of genetic testing will continue to evolve with the accumulation of large datasets of genetic and phenotypic information, as well as advancements in statistical methodologies. It is crucial that these studies include adequate numbers of women and obtain a detailed reproductive history as part of the phenotypic information. We believe the inclusion of a comprehensive reproductive history in ongoing, large-scale biobank projects is critical to accelerating this area of research.

Next Steps for Your Patient

You elicit a comprehensive history, including a pregnancy history, which reveals that she experienced preeclampsia during two of her three pregnancies, and she delivered one of her children pre-term at 32 weeks because of severe preterm preeclampsia. She did not have gestational diabetes. She reports occasional tobacco and rare alcohol use. Past medical history is notable for migraine with aura, especially around her menses. She has had no prior surgeries, and has a copper intrauterine device. In addition to an early stroke, her sister also had preeclampsia, her father has hypertension that was previously poorly controlled and is now complicated by stage III chronic kidney disease, and her mother has hypertension and diabetes mellitus. Several aunts and uncles have had strokes, but she does not know further details.

You order a complete blood count, lipid panel, metabolic panel including fasting glucose, urinalysis, and electrocardiogram. You ask her to measure her blood pressure at home for 1 week and come back in 2 weeks to discuss her risk for cardiovascular disease. You also counsel her on smoking cessation and lifestyle modification including increased physical activity and healthy dietary choices. She is amenable to this plan.

Two weeks have gone by and your patient is back to discuss her risk for stroke and the steps she should take to modify her ASCVD risk. Her blood pressure in the office today is 156/92 mmHg, and again falls into the Stage 2 hypertension range ($\geq 140/90$ mmHg). It was also elevated on her home readings, (average 144/88 mmHg) confirming a new diagnosis of sustained hypertension. Her complete blood count, metabolic panel and urinalysis are within normal limits, but her lipid panel was suboptimal: total cholesterol 5.69 mmol/L (220 mg/dL), high-density lipoprotein cholesterol 1.14 mmol/L (44 mg/dL), and low-density lipoprotein cholesterol 4.55 mmol/L (176 mg/dL).

What evidence-based primary prevention interventions should you recommend to reduce this patient's risk of stroke?

Based on these data, her 10-year ASCVD risk is 5.1% (borderline), and her lifetime ASCVD risk is 39%. Of note, she also has the following ASCVD risk-enhancing factors: family history of premature ASCVD, metabolic syndrome, and a history of early preterm preeclampsia. Her migraine history, too, likely imparts additional risk. Importantly, you

share with her the knowledge that if all of her modifiable risk factors are optimized, her 10-year risk can be reduced by 78%, from 5.1% to 1.1%.

A personalized approach to the management of hypertension and dyslipidemia that incorporates ASCVD risk is now recommended to determine thresholds for the initiation of therapies and goals of treatment (9, 14, 15). A process of shared decision making, to discuss the potential risks and benefits of lifestyle and drug therapies for primary prevention in the setting of personal risk, should be undertaken with every patient. With the confirmation of Stage 2 hypertension, both nonpharmacological therapy and the initiation of blood pressure lowering medication are indicated at this time. A blood pressure target of less than 130/80 mmHg is reasonable, and blood pressure should be reassessed in 1 month. First line therapies include thiazide diuretics, calcium channel blockers and angiotensin-converting-enzyme inhibitors or angiotensin II receptor blockers, and it is reasonable to consider the use of 2 first-line agents given the presence of stage 2 hypertension with an average blood pressure more than 10 mmHg above the diastolic target. Meta-analyses have not demonstrated any sex-specific differences in blood pressure lowering or cardiovascular risk prevention; however, there is a recommendation to initiate two or more antihypertensive medications, including a thiazide-type diuretic or calcium channel blocker in black adults without heart failure or renal dysfunction (15). Black patients have been previously shown to have a smaller reduction in blood pressure in response to angiotensin-converting-enzyme inhibitors or angiotensin II receptor blockers, and since your patient does not have diabetes mellitus, you discuss with her that there is no strong indication to start one of these agents. Together you discuss her options for lifestyle and medications to lower her blood pressure to target. In addition to lifestyle modifications, including the DASH diet and initiation of an exercise regimen, she opts to start a once-daily combination pill of chlorthalidone/amlodipine.

With regards to her dyslipidemia, based on her borderline 10-year ASCVD risk alone, lifestyle changes would be recommended. However, the presence of risk enhancers that are not encapsulated within the risk calculator necessitate a discussion with the patient regarding the initiation of moderate intensity statin therapy to reduce ASCVD risk (Class IIb recommendation). The addition of a thiazide diuretic also comes into play in this scenario. During your discussion about antihypertensive medications, you reviewed with the patient that despite its proven ability to reduce blood pressure, one of the potential negative effects of chlorthalidone, is its tendency to cause elevations in total as well as low-density lipoprotein cholesterol (14). In light of the presence of her risk enhancing factors and the planned initiation of a thiazide diuretic, together you decide to start a low dose of atorvastatin.

Although not necessary in this case, the most recent primary prevention guidelines also suggest that coronary artery calcium testing (CAC), to evaluate for the presence of subclinical atherosclerosis, can be considered in patients at intermediate risk (7.5%–<20%) (Class II A recommendation) in whom the risk/benefit ratio of statin initiation is not certain. CAC provides improved prognostication and discrimination over traditional risk scores (16), and in patients with a CAC score of 0 there is little benefit to the use of intensive statin therapy.

Should you factor in the patient's history of preeclampsia and migraine headache when assessing her risk for a future stroke?

As illustrated in this case, there are several cardiovascular risk-enhancing factors that are specific to or more common in women, and are not always elicited during a routine history. These factors vary across the lifespan, and should be asked about during the initial evaluation and intermittently as life milestones occur (Figure).

Preeclampsia, a hypertensive disorder of pregnancy that both the patient and her sister experienced, is one such risk factor. There is a growing body of evidence that preeclampsia, which was traditionally thought to be “cured” at the time of delivery, is associated with a statistically significantly increased risk of future cardiovascular disease (17, 18). A history of preeclampsia can be used to identify women at elevated risk for premature and in certain phenotypic cases, such as early onset preeclampsia, more severe manifestations of cardiovascular disease, including stroke. The pathophysiologic mechanisms that underlie this increased risk remain to be fully elucidated, but work in animal models and humans suggests that angiogenic imbalance, inflammation, and vascular/endothelial dysfunction play a role. Preeclampsia, like cardiovascular disease, is presumed to be polygenic in nature but the identification of candidate genes related to preeclampsia has been limited. The identification of the mechanisms through which preeclampsia and other adverse pregnancy outcomes exert their effects on the cardio- and cerebrovascular systems has the potential to provide individualized targets for prevention and interventions that are distinct from and may enhance traditional approaches to ASCVD prevention (19).

Migraine, another non-traditional risk factor, also warrants consideration in this patient. While migraine occurs in both sexes, it is three times more common in women (20). The long-running Nurses' Health Study II cohort demonstrated a 50% increased risk of overall cardiovascular disease, 39% increased risk of myocardial infarction and 62% increased risk of stroke in women with a history of migraine, even after controlling for other cardiovascular risk factors; the effect was not modified by age, smoking, hypertension, or hormonal contraceptive use (21). The association between migraine, particularly migraine with aura, and cardiovascular disease has been consistent across multiple studies, with the most well-established association between migraine with aura and ischemic stroke (21). In the Northern Manhattan Study (NOMAS), a history of migraine doubled the odds of having subclinical or “silent” brain infarcts on MRI, adjusting for other risk factors (22). Proposed mechanisms of the association between migraine and cardiovascular risk share features with the proposed mechanisms of preeclampsia, including an underlying pathophysiology of endothelial dysfunction, inflammation, platelet activation, or vasoreactivity (20). Furthermore, migraine with visual aura is associated with patent foramen ovale and with incident atrial fibrillation, factors which may contribute to an increased risk of cardioembolic stroke (23).

In addition to this patient's migraine history informing your assessment of her cardiovascular and stroke risk, her cardiovascular risk may inform your approach to migraine treatment, should her migraines become problematic. A longitudinal, population based study of 5,227 American women with episodic migraine and no prior cardiovascular

events, found that 18.6% of them had 3 or more cardiovascular risk factors (24). The authors recommended caution with use of vasoconstrictive medications (triptans and ergot derivatives) for migraine treatment in patients with multiple cardiovascular risk factors, and consideration of alternative, non-vasoconstrictive migraine treatments.

You are about to leave the room when she says, “The doctors told my sister to start taking aspirin every day after her stroke. Shouldn’t I take one too?”

The Role of Aspirin in the Primary Prevention of Coronary Heart Disease and Stroke in Women

The American Heart Association/American Stroke Association Guidelines for Prevention of Stroke in Women note that low dose aspirin as primary prevention for ischemic stroke “may be reasonable” in some women between 45 and 65 years of age, depending on their other risk factors (Class IIb recommendation) (25). This recommendation is based on findings from the randomized Women’s Health Study showing a preventive effect specifically for ischemic stroke, with a statistically non-significant increase in risk of hemorrhagic stroke. A large meta-analysis showed that aspirin appears to have a benefit for primary ischemic stroke prevention in women, but not men (26). More recent data have not demonstrated a benefit of aspirin for primary prevention in healthy older adults (27), and another meta-analysis of randomized controlled trials of aspirin for primary prevention demonstrated the preventive effects of aspirin against ischemic events, including stroke, is coupled with an increased rate of nonfatal bleeding (28). It is hard to know whether these results are generalizable to your patient given her personal risk factors, though observational data showed a benefit for aspirin for stroke prevention in women with a history of preeclampsia (17). You discuss the possible benefits of low dose aspirin with your patient, including a discussion of the accompanying risks of intracranial and gastrointestinal hemorrhage. She appreciates your frank discussion of the uncertainties, and ultimately, opts not to take an aspirin and to focus instead on her lipids, weight management, smoking cessation and blood pressure at this time.

Summary

The identification of traditional and novel cardiovascular risk factors in women is an important first step towards accurate risk stratification and implementation of evidence-based, guideline directed care. Employing a precision medicine based approach to the primary prevention of cardiovascular disease that incorporates ASCVD risk as well as risk-enhancing factors in women is crucial to reducing sex-based health care disparities in cardiovascular morbidity and mortality. Future developments in genomics may soon allow us to further risk stratify and tailor therapy for women and men alike.

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Box:**Take Home Points**

- A comprehensive history, including a reproductive history, should be part of a thorough, personalized approach to cardiovascular risk assessment in women.
- In women aged 40–75 years, routine assessment of cardiovascular risk for the primary prevention of ASCVD should include assessment of 10 year ASCVD risk by using the pooled cohort equations which require the measurement of total and high density lipoprotein cholesterol levels, blood pressure, and incorporates personal history of diabetes and tobacco use.
- Clinicians should take into consideration the presence of risk-enhancing factors such as family history of premature ASCVD or pregnancy complications when determining eligibility for primary preventive therapies.
- For select patients in whom the decision to use statins remains uncertain, the use of coronary artery calcium (CAC) testing can be used to augment the shared decision-making process.
- There is currently no indication for the routine use of genetic testing to estimate cardiovascular risk in women.

Figure.
Female-specific cardiovascular risk factors across the lifespan