Transforming Cardiovascular Disease Prevention in Women: Time for the Pygmalion Construct to End

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Key Words

Cardiovascular disease · Gender-specific factors · Risk reduction

Abstract

The transformation of cardiovascular disease prevention for women must address that a number of nontraditional atherosclerotic cardiovascular disease risk factors are unique to or predominant in women. As well, many traditional atherosclerotic cardiovascular disease risk factors impart differential risks for women and for men. Gender-specific risk assessment and management have the potential to improve atherosclerotic cardiovascular disease outcomes in women.

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In George Bernard Shaw's 1912 play 'Pygmalion' [1], subsequently adapted for the stage and screen as 'My Fair Lady', the protagonist repeatedly asks, 'Why can't a woman be more like a man?' This paper details the rationale for transforming cardiovascular disease (CVD) prevention specifically for women. Three aspects are paramount:

- A number of nontraditional atherosclerotic CVD (ASCVD) risk factors are unique to or predominant in women.
- Traditional ASCVD risk factors impart differential risks for women and for men.
- Gender-specific risk assessment and management have the potential to improve ASCVD outcomes in women.

Magnitude of the ASCVD Problem in Women

CVD is the leading cause of both mortality and morbidity for women in the USA, with 1 in 4 eventually succumbing to this disease [2–4]. The annual CVD mortality for women is double that of all forms of cancer combined. Relevant for prevention, 2 in 3 women in the USA have at least 1 coronary risk factor, and this percentage increases with older age.

Examination of CVD mortality trends by gender in the USA between 1979 and 2010 [5] affirms that prior to the year 2000, the decline in cardiovascular mortality encompassed solely men. Subsequent to 2000, there has been a stunning decline in CVD mortality for both women and men, with this improvement being more prominent among women. Nonetheless, more women than men die annually from ASCVD in the USA, although the gender difference is diminishing. This favorable survival trend does not apply to younger women, aged 35–54 years, whose recent cardiovascular mortality has increased by 1% annually, thereby reversing the pattern of the past 4 decades. Concomitantly, during the past 2 decades, the Framingham Risk Scores of younger women have increased comparably, reflecting, to a great extent, the obesity epidemic and the high prevalence of a sedentary life-

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style. These variables highlight the importance of providing preventive cardiovascular screening for women, with ASCVD risk reduction interventions when appropriate.

Disparities among Women

Women, however, are not a homogeneous population [2, 5, 6]. Amongst African-American women in the USA, almost half have some form of CVD. They have a 34% prevalence of hypertension with an earlier onset than white women. African-American women are more likely to have metabolic syndrome, and higher rates both of CVD and CVD mortality than white women. Upon hospitalization for acute myocardial infarction, comparison of the risk factor burden according to gender and ethnicity reveals that the greatest risk factor burden is present in black women. In multiple cardiovascular studies, black women are less likely to receive evidence-based therapies.

Hispanic women have a doubled occurrence of diabetes compared to non-Hispanic white women (12.6 vs. 6.5%). The health paradox is that, despite the excess of diabetes, Hispanic women have a lower mortality rate and a greater life expectancy than non-Hispanic white women.

Nontraditional Risk Factors Unique to or Predominant among Women

Pregnancy Complications

A detailed pregnancy history is an integral component of the assessment of ASCVD risk for women of all ages. Complications of pregnancy including preeclampsia, gestational diabetes, pregnancy-induced hypertension, preterm delivery and low-for-estimated-gestational-age birth weight are all indicators of a subsequent increase in cardiovascular risk [7–11]. It has been suggested that pregnancy is the first stress test a woman undergoes, in that the responses to the cardiovascular and metabolic stresses of pregnancy have the potential for early prediction of a future cardiovascular risk. It remains uncertain whether the complications per se impart the subsequent risk or whether there are shared risk factors, e.g. in the case of preeclampsia and CVD; available data favor the latter concept.

To quantify the adverse impact of preeclampsia and gestational hypertension on subsequent cardiovascular risk, these impart a 3- to 6-fold excess of subsequent hypertension and a doubled risk for ischemic heart disease and stroke. Although preeclampsia subsides with delivery of the placenta, residual endothelial dysfunction persists,

and there are reports documenting the association of this endothelial dysfunction with the increased presence of coronary artery calcium.

Oral Contraceptive Therapy

Oral contraceptive (OCP) therapy does not impart an increase in cardiovascular risk for healthy women who have no traditional cardiovascular risk factors. However, OCP use by women who are cigarette smokers is associated with a 7-fold increase in risk, and hypertensive women are likely to have an elevation in blood pressure in association with OCP therapy. OCP therapy increases the risk of stroke by 1.4- to 2.0-fold, with this risk more prominent among older women [12–16].

Different OCPs impart differential risks. For example, second-generation OCPs, such as levonorgestrel, increase the risk for myocardial infarction whereas fourth-generation OCPs, those with drospirenone, indeed lower blood pressure, although the excess risk of venous thromboembolism remains.

The recommendation is for risk factor assessment and control among women who use OCP therapy.

Hormonal Fertility Therapy

Just recently, the question has been raised about the impact of hormonal fertility therapy on cardiovascular risk, with the best information available from a Canadian population cohort for the period 1993–2010 [17]. Among these women, successful fertility therapy was associated with a decreased risk of all-cause mortality, nonfatal coronary ischemia, stroke, transient ischemic attack, thromboembolism and heart failure evident in all age and income groups. An unexplored study variable relates to those women who did not have successful fertility therapy; their cardiovascular risk outcomes were unknown, and this raises questions as to whether these data reflect a healthy cohort selection bias.

Menopausal Hormone Therapy

Clinical trial data have dramatically altered both clinical recommendations and practice regarding the use of menopausal hormone therapy [18–22]. Based on data from the secondary prevention cohort in the Heart and Estrogen Replacement Study (HERS) and the primary prevention study, the Women's Health Initiative, menopausal hormone therapy is not recommended for the primary or secondary prevention of CVD. The 2012 recommendations of the US Preventive Services Task Force identified that menopausal hormone therapy was not recommended for the primary prevention of chronic conditions.

Systemic Autoimmune Disorders

Systemic autoimmune disorders are highly prevalent among women, who have an increased risk of coronary heart disease (CHD) and cerebrovascular accident in the presence of systemic autoimmune collagen vascular disorders [7, 23, 24]. CHD is the leading cause of morbidity and mortality among women with systemic lupus erythematosus. There is a 2- to 3-fold increase in myocardial infarction and CVD mortality in women with rheumatoid arthritis. These adverse outcomes warrant screening and intervention for ASCVD risk factors in these populations.

Traditional ASCVD Risk Factors

Hypertension

Hypertension is the leading cause of CVD worldwide, but the population-adjusted risk of cardiovascular mortality is greater for women than for men, i.e. 29.0 versus 14.9% [5, 25–28]. Until the age of 45 years, men are more likely than women to have hypertension, with the trend reversing and women more likely to be hypertensive than men after the age of 65 years. Noteworthy is the impressive correlation of increased body mass index and elevated systolic blood pressure in women; 80% of women in the USA aged 75 and older have hypertension. Of interest is that this increase in blood pressure with aging is not present in nonindustrialized societies, which likely reflects the relevance of environmental factors on the development of hypertension. Of concern is that only 29% of elderly women have adequate blood pressure control, in contrast to 41% of men.

Cigarette Smoking

Among women in the USA, 16.7% are cigarette smokers, and smoking is more prevalent among younger women than among younger men [5]. The CVD risk for women who smoke is 25% greater than that for men smokers [29]. In addition, cigarette smoking triples the risk for the occurrence of myocardial infarction among women. Smoking cessation has been identified as the most cost-effective cardiovascular risk modification in the USA for both genders.

Diabetes Mellitus

Diabetes confers a greater cardiovascular risk for women than for men, 19.1 versus 10.1% [26, 30–34]. Compared to diabetic men, diabetic women have a 40% increase in the risk of incident CHD and a 25% greater risk of stroke. At the time of initial myocardial infarction, women are more likely than men to have concomitant diabetes mellitus, i.e. 25.5 versus 16.2%.

Diabetes correlates more strongly with CVD mortality in women than in men. It is uncertain whether this is related to increased adiposity, increased abdominal adiposity, insulin resistance or other features in diabetic women. Nonetheless, diabetic women have a far more adverse cardiovascular risk profile than diabetic men, with the diabetic women tending to have clustering of multiple conventional ASCVD risk factors.

Comparing the improvement in survival between the periods 1971–1975 and 1982–1984, diabetic women were the sole subgroup without mortality improvement. There was a decline in mortality among men with and without diabetes and among women without diabetes of 13, 36 and 27.1%, respectively, but the mortality in diabetic women increased by 23%. Related to the emphasis on prevention for women, diabetic women are less likely than diabetic men to be treated for ASCVD risk factors and to have control of these risk factors.

Cholesterol Management

Hypercholesterolemia imparts the highest population-adjusted CVD risk for women of 47% and, notably, the benefits obtained from statin therapy are similar for women and men [26, 38].

The 2013 ACC/AHA (American College of Cardiology/American Heart Association) guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults [36] has occasioned significant changes in the management of dyslipidemia for both genders. These include the use of the new pooled-cohort risk equations, which are gender-specific [35], and lifestyle guidelines (particularly dietary and physical activity) [37] for the lowering of low-density lipoprotein cholesterol, which apply to both genders. The fixed-dose statin therapy for women is based on their risk categorization, and the use of target low-density lipoprotein cholesterol levels is no longer recommended. Importantly, moderate-dose statin therapy is recommended after the age of 75 years for both genders, even with established ASCVD, owing to the paucity of data to support statin recommendations in the elderly population. Nonstatin pharmacotherapies are not recommended for either gender.

The likely results of this guideline on cholesterol management for women will be an increase in indicated statin use, a decrease in inappropriate statin use, a decrease in the use of nonstatin therapies and a decrease in laboratory testing to measure low-density lipoprotein cholesterol.

Obesity

In 2010, 2 in 3 women in the USA were either obese or overweight. Obesity has as its adverse associations hypertension, dyslipidemia, physical inactivity and insulin resistance [26, 39, 40]. It increases coronary risk more for women than for men, i.e. 64 versus 46%.

To examine this problem with a global perspective, in low- and middle-income nations, there is double the amount of obesity in women than in men. However, in high-income nations, obesity is equivalent among women and men. This highlights the need for addressing control of obesity as a risk factor for women in the developing world.

Physical Inactivity

Despite the fact that the INTERHEART study showed greater protective effects of exercise for women than for men, 32% of US adults are physically inactive, more women than men (33.2 vs. 29.9%) [26]. Indeed, physical inactivity is the most prevalent risk factor for women, in that a quarter of US women report no regular physical activity and three quarters report less than the recommended amount [37].

Data from the Nurses' Health Study identify a decrease in the development of diabetes in the women who exercised regularly and, among the diabetic women, physical activity decreased the risk of cardiovascular events [41, 42].

Finally, although exercise-based rehabilitation is a class I (level A) recommendation in all ACC/AHA coronary secondary prevention guidelines, women are 55% less likely to participate than men, with women experiencing lower rates of referral, enrollment and completion of cardiac rehabilitation than their male counterparts.

Depression

Psychosocial problems, particularly depression, preferentially disadvantage women [43–46]. In the INTERHEART study, psychosocial factors were associated with CVD mortality for women more than for men, i.e. 45.2 versus 28.8%. Such factors included stress at work and at home, financial stress and major life events [26].

Depression is associated with a 1.64% increase in cardiovascular mortality in women, independent of the severity of the depression. To what extent high-risk behaviors, nonadherence to therapies or depression per se contribute to excess mortality remains uncertain. Nonetheless, mortality is excessive in depressed young women, i.e. younger than 55 years of age, who have established coronary disease.

Depression is also a risk factor for adverse outcomes with acute coronary syndromes [44]. Depression and other psychosocial issues will likely increase with the excessive stress associated with increased global violence and the current global financial instability. The problem is complicated by many cultural taboos, both in the USA and internationally, regarding the access to care for depression and other psychosocial issues.

Aspirin for CVD Prevention

Aspirin is used as an example of gender-specific issues in pharmacotherapy. Although there are comparable gender recommendations for the use of aspirin for the secondary prevention of ASCVD, aspirin is routinely recommended for the primary prevention of CVD for men but not for women [47].

In the Women's Health Study [48] which involved 38,876 healthy, low-risk women older than 45 years of age, aspirin (a dose of 100 mg every other day) prevented stroke in women younger than 65 years of age, but had no effect on myocardial infarction or cardiovascular death and the potential for gastrointestinal bleeding was significant. For women older than 65 years, there was prevention of stroke, myocardial infarction and cardiovascular death with aspirin administration, but the excess risk of gastrointestinal bleeding was virtually comparable to the protective effect. The recommendation, therefore, is for the individualization of aspirin use for women beyond the age of 65 years.

In contrast, in the Physicians' Health Study, which involved only men, again with aspirin therapy of 100 mg every other day, a benefit was seen for myocardial infarction but not for stroke.

Women's Awareness of CVD

Currently only 54% of US women recognize that heart disease is their leading cause of death. Even 15 years after the education and awareness endeavors of the National Heart, Lung, and Blood Institute, the 'Heart Truth' campaign and the American Heart Association's 'Go Red for Women' campaign, there has only been an increase in awareness from 30 to 56%, with a recent plateau in the appreciation of women's CVD risk [49, 50]. The lack of awareness was greatest in the highest-risk populations, i.e. women from racial and ethnic minorities. There was also a lack of awareness of the burden of CVD for wom-

en among healthcare providers. This lack of awareness translated into suboptimal application of preventive interventions, less appropriate diagnostic testing, less adherence to evidence-based cardiovascular guidelines and consequent poorer outcomes for women.

The underrepresentation of women in clinical trials and longitudinal studies on CVD and the lack of gender-specific analysis when women were included has limited the scientific database for women and led to uncertainties in clinical practice among healthcare providers. The first step to personalized medicine is incorporating information about sex and gender differences, as highlighted here.

Adherence

Questions have been raised about the adherence to recommended therapies by gender, with most studies showing a comparable adherence among women and men [51]. The nonadherence characteristics are also comparable by gender and include lower socioeconomic status, lower educational levels and depression. However, a number of barriers to preventive interventions appear specific to women, such as family and caretaking responsibilities, fatigue, stress and lack of personal time.

An International Perspective

In September 2011, the United Nations (UN) held a summit on noncommunicable diseases (NCDs), only the second time in history that a UN summit on health issues has been convened [52]. The highlights relating to women identified gender disparity with regard to risk and the access to diagnosis and treatment, showing the link of this gender disparity with the empowerment of women and the education of girls. In 2008, 9,127,416 cardiovascular deaths occurred in women worldwide, representing 33.3% of all deaths in women. The conclusions of the UN summit were that NCDs, in particular CVD, adversely impact women's contributions to society in both their productive and reproductive roles and as consumers and providers of health care. The emphasis was on the vulnerability of women, who represent 60% of the world's poor and two thirds of illiterate adults.

A follow-up to the UN summit addressed the programs, policies and national plans for CVD prevention, targeting women. The 65th World Health Assembly in May 2012 in Geneva adopted a broad target of a reduction of 25% in premature mortality from NCDs by 2025. The

Fig. 1. Estimated and calculated global temporal trends among women for significant cardiovascular risk factors over a period of 20–25 years. Published with permission from Gupta and Wenger [53].

World Heart Federation and the NCD Alliance used targeted advocacy to insure that NCDs were recognized as the major cause of poverty, a barrier to economic development and a global emergency. At the 66th World Health Assembly in 2013, 9 targets and 25 indicators were adopted. The 9 voluntary global NCD targets were: a 25% reduction in premature mortality from NCDs, 80% coverage of essential NCD medicines and technologies, 50% coverage of drug therapy and counseling, a 25% reduction in raised blood pressure, a 30% reduction in tobacco use, a 30% reduction in salt/sodium intake, a 10% reduction in physical inactivity and a 10% reduction in the harmful use of alcohol. A global monitoring framework was established with 25 indicators encompassing areas of mortality and morbidity, risk factors and national systems response. NCDs were identified as a priority for women's health and development in order to stimulate policy dialogue, in particular addressing issues that affect women, and to facilitate advances in informed action by all partners. This document identified entrenched poverty, gender inequality, the stigma associated with NCDs, women's family responsibilities and the cost of seeking care as significant barriers to accessing cost-effective prevention as well as the early detection, diagnosis, treatment and care of NCDs.

Globally, there are major differences between women and men with regard to the risk factors for CVD [53]. As seen in figure 1, women have an excess of hypertension, a lower smoking risk, a comparable risk due to dyslipidemia and obesity and a greater risk due to diabetes and psychosocial issues.

Global Challenges and Opportunities

As noted, CVD represents 38% of deaths from NCDs, 80% of which occur in low- and middle-income countries. It is estimated that between 2010 and 2020, the global prevalence of CVD will increase by 15–20%. Much of this problem relates to the changes in lifestyle in developing nations that are unfavorable for cardiovascular health: urbanization, a Western diet and consumption of processed foods with consequent increases in obesity, hypertension, dyslipidemia and diabetes [53–55].

Between 1990 and 2020, there will be an estimated 120% increase in CVD mortality for women in developing countries, in contrast to a 29% increase among women in industrialized nations. Of the women who will die from CHD, 80% of the deaths will occur in low- and middle-income countries.

Importantly, in the INTERHEART study [26], modifiable risk factors accounted for 94% of the population-adjusted cardiovascular mortality in women. The recommended interventions are not costly. Both in the USA and globally, there is a need to educate the population, but women in particular, about CVD risk factors with an emphasis on the modifiable behavioral risk factors. Women should be informed that basic lifestyle modifications have the potential to decrease hypertension, dyslipidemia, obesity, diabetes and cardiovascular risk. Tantamount is

smoking cessation, but also a diet low in sodium and saturated fats and more fruits and vegetables. An increase in exercise behavior is mandatory. Messages should be targeted at women, particularly in low- and middle-income nations. All organizations directed toward women's heart health should engage women on a community level as well as developing national risk reduction priorities. This is necessary to lessen the risk among women of CVD, myocardial infarction and sudden death.

At the 2013 World Health Assembly, CVD was identified as the largest killer of women worldwide, increasingly impacting women in developing countries. Very few women perceive CVD as the greatest threat to their health. Basic health interventions that educate people on healthy lifestyle choices can be effective in reducing mortality rates and risk factors associated with CVD. Poverty, however, limits women's ability to make healthy choices, making women in low- and middle-income countries living in poverty particularly vulnerable to CVD. As an example, the proportion of CVD deaths in women aged 35–44 years in South Africa is 150% higher than that for women in the USA. There is also a significant gender gap in the diagnosis and treatment of CVD in women. Warning signs for women differ from those for men, contributing to an underdiagnosis of CVD. More women-specific clinical research is needed to address this issue, as the majority of clinical CVD trials to date have been undertaken in men.

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