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REVIEW

# A call for a gender specific approach to address the worldwide cardiovascular burden

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**Summary** Cardiovascular diseases (CVD) among non-communicable diseases are already a major public health challenge worldwide. A further increase in CVD is projected to occur over the next 25 years as a result of both adverse lifestyle changes and demographic shifts in the population age profile. The adverse impact of these health problems will affect women in particular, given the steady rise in the proportion of the aging population that will be women.

The critical issue presently in the management of CVD is that we are not even adequately using the data that are available. Women still remain unaware that they are at risk, and information about women is not easily accessible to their physicians. This is a global issue and the need remains for worldwide initiatives with greater vigilance to identify these factors and make efforts to control them effectively.

Currently, in scientific research, it is expected that the results of clinical research be analyzed for sex differences, sex- and gender-appropriateness, and sex- and gender-specific approaches for prevention, diagnosis, treatment, and counseling. To address the care discrepancy, the global community needs to develop a conducive environment within a comprehensive policy and operational framework to achieve favorable lifestyles, and CVD risk factor reduction for both men and women.

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## Introduction

Cardiovascular diseases (CVD) among non-communicable diseases are already a major public health challenge worldwide. A further increase in CVD is projected to occur over the next 25 years as a result of both adverse lifestyle changes and demographic shifts in the population age profile. The adverse impact of these health problems will affect women in particular, given the steady rise in the proportion of the aging population that will be women. Reviews of the literature at this point convincingly attribute CVD to the conventional risk factors. Among the nine risk factors recently reviewed in 52 countries, total cholesterol, cigarette smoking, diabetes and high blood pressure are of particular importance [1]. Collectively, the nine risk factors account for 90% of the population attributable risks in men and 94% in women.

The critical issue presently in the management of CVD is that we are not even adequately using the data that are available. Women still remain unaware that they are at risk, and information about women is not easily accessible to their physicians. In addition, women receive differential treatment particularly in developing countries and in patriarchal cultures, as women's health is seen to be synonymous with reproductive health only. Investing in other diseases such as CVD is not a priority given the less dramatic onset of risk factors or the absence of visible distress. This is a global issue and the need remains for worldwide initiatives with greater vigilance to identify these factors and make efforts to control them effectively.

## Background

CVD are a leading cause of mortality, and nearly 80% of this global mortality and disease burden occurs in developing countries [2]. According to the Global Burden of Disease Study, the probability of a man or a woman dying from a non-communicable disease is higher in sub-Saharan Africa and other developing regions than in established market economies [3]. Worldwide in 1990, non-communicable diseases accounted for more than

28 million deaths; and on the top of the list of the leading causes were ischemic heart and cerebrovascular diseases. Communicable, maternal, perinatal, and nutritional disorders accounted for 17.2 million deaths. Further growth in the epidemic of CVD is projected to occur over the next 20 years as a result of both adverse lifestyle changes and demographic shifts in the population age profile [4]. The adverse impact of these health problems will affect women in particular, given the steady rise in the proportion of the aging population that tends to be comprised of more women than men. Even though there is evidence for a decline in cardiovascular deaths in a majority of Western countries, the overall decline in the rate of cardiovascular deaths in women in the world remains unchanged or is increasing [5]. This gender gap in mortality continues to widen worldwide.

In a scientific statement in 2004, the World Heart and Stroke Forum emphasized the impact of increasing longevity and longer periods of exposure to CVD risk factors [6]. This impact will be felt preferentially by women who tend to live longer than men. It has been concluded that removal of major risk factors would not only increase healthy life expectancy in every region, but also reduce some of the differences among regions [7].

Heart disease is the leading cause of death for women both in the United States and in most of the world. The onset of clinical manifestations of coronary heart disease (CHD) in women lags behind men by about 10 years and by as much as 20 years for more ominous events such as myocardial infarction and sudden cardiac death. Moreover, clinical manifestation of CHD in women is different from that in men [8,9]. CHD in women has a later age of onset and consequently there is a greater prevalence of co-morbid diseases when CHD emerges. In addition, women have a higher rate of silent ischemia and subtle cerebral white matter changes associated with hypertension and diabetes [10]. As a result, the care of CVD in women faces more complex diagnostic and management challenges. The diagnosis of CHD in women is even more difficult because of the increase in co-morbid disease burden as well as the resulting lower specificity of symptoms and lower diagnostic accuracy of non-invasive testing.

Research has shown that over 80% of patients who developed clinically significant CHD and more than 95% of patients who experienced a fatal CHD event had at least 1 major cardiac risk factor [11,12]. However, while risk factors are sensitive, they are not specific, as many people with risk factors do not develop CHD, i.e., low positive predictive value. In addition, in women with low levels of major vascular risk factors, CHD and CVD are rare [13]. Furthermore, the prevalence of risk factors and their impact vary by gender, a fact that may alter risk stratification measures. For example, the relationship between diabetes mellitus (DM) duration and CHD mortality varies by gender. Women with a recent diagnosis of DM have a risk for CHD death equivalent to women with a history of MI, while those with longstanding DM have an even greater risk [14]. Therefore, current cardiovascular prevention recommendations in women may need to be further refined to match the intensity of treatment to CHD mortality risk.

The challenges lie not only in diagnosis but also in treatment. Unfortunately, evidence for therapy in women is not as robust as in men because gender specific issues have not been well studied. In heart disease trials, the male population outnumbers the female at a ratio of 3.66–1 [15], and the assumption that treatments of these risk factors have the same clinical outcome in both sexes could be misleading. For instance, the Women's Health Initiative observational study showed a higher risk of CVD mortality in postmenopausal women with hypertension treated with a 2-drug-class regimen of calcium channel blockers plus diuretics in comparison to B-blockers plus diuretics [16]. The anti-hypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT) with 49% women in the study sample provided clinical data on monotherapy and indicated that diuretics were equal or superior to other antihypertensive agents as first-line therapy [17]. Recently, the Women's Health Study showed that low-dose-aspirin (100 mg every other day) is ineffective in preventing myocardial infarction in women but can decrease the risk of stroke by 25% [18]. It appears that the minimum dose of aspirin needed for a cardioprotective effect is higher in women than in men and is greater than 75 mg per day [19]. However, the issue of the lowest effective dose in both women and men requires further research.

The diagnostic and therapeutic challenges in addressing CVD in women are compounded by attitudinal differences between the two genders. Compared to men, women are less likely to attribute their symptoms to cardiac-related causes and are also more surprised to hear that their symptoms

are due to a heart attack [20]. In North America, despite many initiatives over the past decade aimed at educating women about their risk of heart disease [21], most women still do not internalize their risk from cardiovascular disease and thus do not act to reduce it. They remain more concerned about prevention and treatment strategies for breast cancer.

The other major factor that contributes to health disparity is poverty. More than 20% of women in the world – more than twice the population of Western Europe – live in poverty and per-capita health expenditure ranges only between 11 and 20 US dollars [22]. The WHO is intensifying its focus on non-communicable diseases such as CVD and the major common risk factors that predict them. The Global Health Forum, convened in 1997 to address this widening health and poverty gap, as investment in health research and development remains focused largely on the health problems of the 10% of the population that is the world's richest. Only 10% of funds available are directed at improving the health of 90% of the world's population [23].

There is substantial evidence in the health economic literature that medication treatments for many cardiovascular conditions are highly cost effective [24]. Cardiovascular medications, the largest drug expenditure category, account for more than one fourth of all pharmaceutical expenditures [25]. Practically, 1.5 billion people live on less than a dollar/day, and if it is expected that CVD prevention includes primary care, then poverty reduction strategies are essential. Women in many cultures are economically dependent on their husbands. Long-term and sustained improvements in women's health require rectification of the inequalities and disadvantages that women and girls face in education and economic opportunity. The Millennium Development project in general aims to eradicate poverty and hunger, and take action to improve women's health through gender equality and empowerment of women [26]. However, this project may not address directly the disparity in cardiovascular disease and risk factor reduction in older women either in developed or in developing countries. Nevertheless, the key to ending the poverty trap is for the high-income countries to help developing countries make the necessary investments in health, education, and basic infrastructure. Political commitment at the highest international and national levels is needed to institute these policies and to allocate the resources necessary to improve women's health.

Many other barriers in the care of CVD in women have contributed to well documented discrepancies

between the two sexes in screening for and treatment of risk factors for CVD. Even in developed countries, sub-optimal screening and treatment of vascular risk factors in women was demonstrated as recently as in 2003, by the American Heart Association, as only 60% of high-risk women with CHD had their cholesterol checked over the previous year [27]. Men were significantly more likely to be on lipid lowering therapy than were women (55% vs. 35%) [28]. The use of statin therapy for secondary prevention in the older person was inversely correlated with their baseline cardiovascular risk, and statins were less likely to be prescribed for older women than men [29]. Women also received significantly less aspirin and beta-blocker treatment following an acute MI [20]. In stroke care, a large European study of hospital admissions for acute stroke showed that women had higher rates of both hypertension and atrial fibrillation [30]. Women had a longer hospital stay and remained more disabled than men and had a higher rate of institutionalization. Women underwent less investigation and less carotid surgery. Older men, on the other hand, were more likely than older women to receive antiplatelet therapy [31].

These data indicate that information collected on men with CHD, stroke and other diagnoses in the spectrum of CVDs cannot be assumed to apply similarly or with the same magnitude to women. This further emphasizes the importance of accounting for these differences in designing future clinical trials, highlighting the need for both stratifying entry by gender, and enrolling more women into clinical trials. Moreover, due to exclusion of patients over the age of 75 from most clinical trials, the effectiveness of multifactorial CVD prevention remains uncertain in older patients. Inclusion of older patients with multiple comorbidities, reflecting real world clinical practice, is necessary for the gathering of relevant data for this older population, as a larger proportion of them are women.

In order to address these issues, the AHA has developed the first set of evidence-based guidelines for the prevention of CVD in adult women with a broad range of cardiovascular risk factors [32]. The recommendations include lifestyle interventions (such as cessation of cigarette use), treatment of major risk factors (such as blood pressure), and the utilization of preventive drug interventions. The guidelines recommend against the use of hormone therapy, and antioxidant vitamins as methods of preventing heart disease or reducing its recurrence. These recommendations are meant to assist clinicians on the basis of the current state of evidence and they supersede previous AHA prevention guidelines pertaining to women.

## Conclusion

Awareness of CVD has increased, although a significant gap between perceived and actual risk of CVD in women remains. It is recommended not only that physicians make diagnostic and treatment decisions based on the sex of the patient, but that they also respond to gender differences in the approach to health concerns. While sex is defined as a biological difference, gender refers to economic, social, and cultural attributes. Currently, in scientific research, it is expected that the results of clinical research be analyzed for sex differences, sex- and gender-appropriateness, and sex- and gender-specific approaches for prevention, diagnosis, treatment, and counseling. To address the care discrepancy, the global community needs to develop a conducive environment within a comprehensive policy and operational framework to achieve favorable lifestyles, and CVD risk factor reduction for both men and women.

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