



Women and Coronary Artery Disease. Part I: Basic Considerations

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Abstract

Women die of cardiovascular disorders even more than a combination of breast cancer, stroke, chronic obstructive pulmonary disease, and lung cancer. Recent data show that while 1 out of 2.6 women die of coronary artery disease (CAD), only 1 out of 4.6 die from cancer. Whereas some studies show an increase in the age-adjusted mortality of CAD in both women and men, some other studies report an increase in mortality amongst young women. There is a significant decrease in sudden cardiac death in men without significant change in women, and more women die of CAD before their arrival at the emergency room of hospitals than do men. It is, therefore, regrettable that many women and their physicians are not sufficiently aware of the problem and this unawareness is believed to be a major culprit for the existing gender disparities and inaction on the part of women as regards risk modification. What is more, the bulk of our knowledge, preventive measures, diagnostic strategies, and treatment plans are on the basis of studies conducted chiefly in men, when powerful evidence-based gender-specific recommendations call for efforts to enroll more women in order to reach a desirable level of sex representation.

Given the significance of CAD assessment in women, it is essential that an acceptable risk score system be devised to estimate the risk of coronary events. The Framingham Risk Score, which has been used for this purpose for a long time, is no longer suitable for women and the Reynolds Risk Score seems to be a more appropriate tool.

Finally, from a pathophysiological point of view, endothelial and microvascular dysfunctions are the most salient contributors to the development of CAD in women by comparison with men and they give rise to non-obstructive CAD. Lamentably, most of the relevant studies conducted hitherto have focused predominantly on men; any attempt to redress the balance would be of great value in the endeavors to decrease the risk in women.

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Introduction

More women die of cardiovascular disorders (CVD) than of breast cancer, stroke, chronic obstructive pulmonary

disease, and lung cancer put together. Meanwhile, coronary artery disease (CAD) is responsible for half of those CVD deaths in women.¹ The most recent data from the Centers for Disease Control and Prevention indicate that whilst 1 out of

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2.6 women die of CAD, only 1 out of 4.6 die from cancer.²

For all the studies reporting a drop in the age-adjusted mortality of CAD in both women (49%) and men (52%) between 1980 and 2002,¹ there are others citing a 1.3% per-year rise in mortality among young women (between 35 and 44 years of age) between 1997 and 2002.³ Furthermore, recent data show that not only is there a significant decrease in sudden cardiac death in men without significant change in women,⁴ but also more women die of CAD before their arrival at the emergency room of hospitals than do men (52% vs. 42%).⁵

There are many challenging issues in the different aspects of CAD in female patients with respect to pathophysiology, risk factors, clinical presentations, diagnosis, and treatment. In this review, we seek to address some of those dissimilarities with a special emphasis on items that seem to have been hitherto neglected, be it in research or in daily medical practice. It is essential for everyone working in the domain of women's health, not least those involved in the field of cardiovascular disorders, to pay heed to them.

In part I of this review article, some major differences between men and women, ranging from general to pathophysiological issues are discussed. Part II elaborates upon different clinical presentations, diagnostic tools, and therapeutic measures in women with CAD.

Participation in Trials

There are considerable gender differences in CAD patients in as wide a range as pathology to treatment modalities. Unfortunately, most of our knowledge, preventive measures, diagnostic strategies, and treatment plans are based on studies conducted predominantly in men. A large number of analyses have underscored the underrepresentation of women in cardiovascular clinical trials.⁶⁻⁸ Indeed, the proportion of women enrolled in many a clinical trial fails to accurately reflect their actual representation in the disease populations receiving treatment. Melloni et al., in a recent analysis of 156 randomized clinical trials (RCTs) cited by the 2007 Women's Prevention Guidelines, showed that female enrollment in RCTs, albeit enjoying an increase, remained low relative to the women's overall representation in the disease populations.⁹ The authors in question found that both genders were represented in 135 of 156 (86.5%) trials; 20 trials enrolled only men and women were the only participants in one trial. Furthermore, in all the trials, the proportion of women increased significantly from 9% in 1970 to 41% in 2006. The investigators' analysis showed that female representation was significantly higher in international studies than in those conducted in the United States (32.7% vs. 26.7%). Melloni and his coworkers also found that in the RCTs used to support the 2007 American Heart Association (AHA) guidelines for cardiovascular

prevention in women, only 30% of the enrolled patients were women. In addition, only in one third of those RCTs were the results reported for women and men by subgroups. Whether this constitutes sufficient support for guidelines in women is open to debate. Powerful evidence-based gender-specific recommendations require efforts to enroll more women to reach a level of sex representation that is proper and adequate. Melloni et al. also reported that women were more likely to be included in primary rather than secondary prevention trials, and this carries a bias.⁹ Some other studies have demonstrated that female patients who are at greater risk or are less aware of their risk factors are less willing to participate in clinical trials.¹⁰⁻¹² Despite this unwillingness on the part of some women to participate in clinical trials, sometimes the reason for the lower proportion of women in RCTs can be the presence of such exclusion criteria as older age or childbearing potential. Since CAD tends to affect females later in life, women are more likely to be excluded from RCTs with age cut-offs that exclude the elderly.

Awareness and Misconceptions

Women develop CAD later in their life than do men. Salim Yusuf et al., in an international study entitled INTERHEART, enrolled more than 52,000 patients with myocardial infarction (MI) around the world and showed that across various socioeconomic status, cultures, and climatic environments, the first onset of CAD is about 8 to 10 years later amongst women.¹³ They also found that much as this age gap at the time of onset was universal, CAD was presented earlier in less developed countries. In fact, Africa and Middle East had the earliest manifestation of CAD and Western Europe had the latest.

The late onset of CAD in women gives rise to the misconception that females are not as vulnerable as men to CAD. The integral part of any preventive measure and treatment plan for female patients with CAD should be awareness of the problem. Awareness of risk correlates with preventive actions taken by women to lower the risk. It seems that many women and their physicians are not fully aware of this problem, which may play a major role in gender disparities. In a survey conducted by Mosca et al. in 2006, only 55% of women knew that cardiac disorder is the leading cause of death in women. Surprisingly, 38% of them stated that they had not spoken about their cardiac problems with their physicians because of a lack of physician-initiated discussion.¹⁴ These findings have also been supported by some other studies indicating that only half of the women recruited identified heart disease spontaneously as the leading cause of mortality in women.¹⁵ Moreover, women are believed to be less likely to modify their own life style in a cardioprotective way.¹⁶ This lack of awareness and its concomitant misconceptions can cause female patients



to delay seeking medical advice for their cardiac-related symptoms.¹⁷ Interestingly, another survey by Mosca et al., conducted in 2005, showed that less than 20% of physicians knew that CVD is the leading cause of death in women.¹⁸ Some other studies have also demonstrated that physicians' awareness of women's cardiovascular risk is suboptimal.¹⁹ In a survey directed by Legato et al., only 41% of women reported that their physicians had ever talked to them about heart disease.²⁰ Any risk reduction in female patients requires considerable efforts to alter this unawareness or carelessness.

Risk Assessment

Between 1956 and 1966, investigators in the Framingham Study defined age, hypertension, smoking, diabetes, and hyperlipidemia as the major determinants of coronary heart disease and they introduced the term "coronary risk factors".²¹⁻²⁵ The researchers thereafter codified these markers into global risk scores for the assessment of cardiovascular risk, known as the Framingham Risk Score (FRS).^{26, 27} The FRS is drawn upon to estimate patients' ten-year risk of CAD-related death or MI. People classified as high risk by the FRS should receive intensive therapeutic and lifestyle recommendations. Unfortunately, the FRS may underestimate risk, especially in younger women.²⁸⁻³¹ In other words, the FRS, classifies more than 90% of female patients as low risk and only a few of them would be classified as a high-risk group before the age of 70.³² In addition, in women, up to 20% of all coronary events happen in the absence of the major risk factors,³³ whilst a large number of them with traditional risk factors do not experience any coronary events.³⁴ It is deserving of note that despite the recent rethinking of the pathophysiology and the introduction of new risk factors, risk algorithms for women have remained largely unchanged compared to those recommended four decades ago. The new risk markers that have been suggested include apolipoprotein A-I, apolipoprotein B-100, non-high-density lipoprotein cholesterol, lipoprotein(a), high-sensitivity C-reactive protein (hsCRP), soluble intercellular adhesion molecule 1 (sICAM-1), fibrinogen, glycated hemoglobin A1c, plasma creatinine, and plasma homocysteine. Therefore, some new alternative algorithms such as the Reynolds Risk Score (RRS) have been proposed.^{29, 35} To develop a new cardiovascular risk algorithm for women, based on a large panel of both traditional and novel risk factors, Ridker et al. conducted a cohort study on 24,558 initially healthy women and followed them for the development of MI, stroke, coronary revascularization, or cardiovascular death for a median of 10.2 years.³⁵ They subsequently developed and validated two novel algorithms for global risk prediction: a best-fitting model (model A) and a clinically simplified model (model B, the Reynolds Risk Score). Their best-fitting model

comprised age, systolic blood pressure, hemoglobin A1c, hsCRP, lipoprotein(a), apolipoprotein A-I, apolipoprotein B-100, current smoking, and family history of premature MI, whereas model B (the Reynolds Risk Score) consisted of age, systolic blood pressure, hemoglobin A1c, hsCRP, high-density lipoprotein cholesterol, current smoking, and family history of premature MI. According to the Reynolds Risk Score for the reclassification of women marked as being at intermediate risk by the FRS, 40% to 50% of them can be categorized into higher or lower risk groups.³⁵ Unfortunately, none of the risk score systems already proposed has examined the potential of atherosclerotic imaging tests for serving as an alternative method for risk evaluation. Further cohort studies should be conducted to incorporate these imaging tests as well.

Pathophysiology

Women have a smaller coronary artery diameter and less collateral circulation than do men;³⁶ they, therefore, exhibit a larger tendency toward ischemia, especially during exertion or stress. Knowledge of the pathophysiology of atherosclerosis helps determine the differences present between men and women in terms of CAD.

Plaque Erosion and Plaque Rupture

Coronary atherosclerosis occurs in the wake of the chronic inflammation of coronary arteries, which leads to vascular narrowing or obstruction. This process is accompanied by vascular dysfunction. Endothelial injury and/or excess circulating lipids can be considered as the inciting events for the development of atherosclerosis.³⁷ These result in the formation of an early atherosclerotic lesion and a fatty streak, representing the subendothelial accumulation and deposit of lipids and low-density lipoprotein in the vessel wall.³⁸ The subsequent vascular response is characterized by inflammation involving a number of different cells, including monocytes.³⁹ Smooth muscle proliferation and migration from the media to the intima, through the internal elastic lamina, aids the growth of the atherosclerotic plaque, which is driven in part by endothelial-derived cytokines and chemoattractants. After a period of time, an abnormal matrix capable of further promoting abnormal cellular proliferation and entrapment of modified lipids in the vessel wall is developed by the media. This lesion may continue to grow in the vessel wall, with more advancement and encroachment on the lumen. After that, intramural calcification and vascular dilatation occur as adaptive vascular responses to the atherosclerotic plaque formation. Plaque formation can also beget the development of a fibrous cap, which may be prone to fissure, rupture, or erosion.⁴⁰

Sudden luminal thrombosis is responsible for most coronary events. Three different pathologies contribute to luminal thrombosis: plaque rupture, plaque erosion, and calcified nodules.⁴¹ Calcified nodules are the least common type. It has been reported that thrombi are responsible for 60% of sudden deaths, with 55% to 60% of them being due to plaque rupture, 30% to 35% due to plaque erosion, and only 2% to 7% due to calcified nodules. Ruptured plaque is a lesion with a necrotic core and an overlying thin ruptured fibrous cap and it leads to thrombosis due to the contact between platelets and a highly thrombogenic necrotic core. Plaque erosion is an acute thrombus which has direct contact with the intima in an area of damaged endothelium, exposing the blood and platelets to the subendothelial basement membrane containing collagen. This triggers platelet aggregation and activation and eventually results in thrombosis. More often than not, an erosive plaque has no necrotic core, but when present, due to a thick fibrous cap, the core does not communicate with the lumen. It seems that coronary vasospasm may play a role in the pathophysiology of the erosion. Plaque erosion has association with smoking (especially in women) and compared to plaque rupture, the narrowing at the site of thrombosis is less severe in plaque erosion and patients are younger.⁴¹⁻⁴³ Plaque erosion is responsible for more than 80% of thrombi occurring in women less than 50 years of age; and generally, plaque erosion occurs twice as much in women (37% vs. 18%), whilst the underlying provoking event in men is more frequently plaque rupture (82% vs. 63%).⁴¹

Remodeling

In females, atherosclerosis can occur with seemingly normal coronary arteries due to the remodeling that occurs in the vessel wall in response to plaque formation. Two different types of remodeling have been introduced. Positive remodeling (expansion), which occurs predominantly in women, maintains the luminal size of the coronary artery in spite of plaque accumulation, whereas negative remodeling (shrinkage), which occurs more frequently in men, contributes to the stenosis of the coronary lumen, independent of plaque accumulation.⁴⁴ In the positive remodeling state, due to the outward direction of plaque growth, coronary angiography may detect no significant stenosis before an acute event, but other imaging techniques such as intravascular ultrasonography (IVUS), computed tomography (CT), and magnetic resonance imaging (MRI) may allow the detection of the plaque and the related coronary arterial remodeling in such a clinical setting.⁴⁴ From a histological point of view, the pathophysiology of arterial remodeling is more complex than a mere compensatory process. Some histological studies have shown that positive remodeling has association with the histological characteristics of inflammation, including

increased macrophage content and matrix metalloproteinase expression, whereas negative remodeling is characterized by increased fibrosis and decreased cellularity.^{45, 46} In addition, some other histological studies have demonstrated similarities in the pathophysiology of plaque vulnerability and remodeling; in both of them an inflammatory response at the lesion site results in the degradation of the extracellular matrix.⁴⁷ Furthermore, the Schoenhagen et al. study found that positive remodeling was significantly more prevalent in unstable than in stable lesions (51.8% vs. 19.6%) and negative remodeling was more prevalent in stable lesions (56.5% vs. 31.8%, p value = 0.001).⁴⁸ Histological and IVUS studies in young symptomatic and asymptomatic patients have shown diffuse atherosclerotic disease involvement, extending beyond the focal area of angiographic stenosis, which is mainly related to remodeling and allows plaque accumulation without significant stenosis in the lumen of the coronary vessel.^{49, 50} In other words, in positive remodeling, the disease is more diffuse with less segmental stenosis; therefore, plaque and narrowing result in no focal obstruction. In this state, the internal elastic lamina thickens as the vessel dilates to accommodate the plaque. When plaque burden is greater as the vessel has already compensated, the patient will be symptomatic. However, in negative remodeling, there is more segmental stenosis of the vessel wall, with no diffuse narrowing. Consequently, in women, ischemia can be presented because of diffuse CAD and in the absence of segmental obstruction.

Microvascular and Endothelial Dysfunction

Additional contributors to the development of non-obstructive CAD in females may include microvascular and endothelial dysfunctions.⁵¹ Impaired coronary vascular function is suggested as a precursor to atherosclerosis and a predictor of coronary events.⁵²⁻⁵⁴ Until recently, most of the relevant studies focused on men, and there was no clear clue about women. Nonetheless, the Women's Ischemia Syndrome Evaluation (WISE) study⁵⁵ sought to address the issue by enrolling 163 women, who underwent quantitative angiography and intracoronary Doppler study before and after an intracoronary administration of acetylcholine, adenosine, and nitroglycerine. The result of this study showed that even though all the studied women had chest pain, 75% of them had only mild CAD. During the follow-up with a median duration of up to 48 months, 35.6% (58 out of 163) of the women developed cardiovascular events. Based on bivariate analysis, the study reported that women with an event had less change in the cross-sectional diameter of the coronary arteries in response to acetylcholine and to nitroglycerin (p value < 0.01, and p value = 0.04, respectively) than did women without events. Those women who showed abnormal response to acetylcholine had significantly less time free



from coronary events (p value = 0.04). Finally, multivariate analysis revealed that the change in the cross-sectional diameter of the coronary arteries with acetylcholine was the only independent factor for the prediction of coronary events (p value = 0.01). Some other studies have also demonstrated that brachial artery flow-mediated dilation, which is a peripheral measure of the endothelial function, is impaired in women⁵⁶ with exacerbation after menopause.⁵⁷ In a large cohort study of 2,264 postmenopausal women in 2008, Rossi et al. also showed that abnormal flow-mediated dilation was associated with a 1.3-4.4 fold increase in the risk of CAD (p value < 0.0001).⁵⁸ Because the improvement in the endothelial function is associated with improved outcome, any study seeking to contribute to a better understanding of the endothelial dysfunction mechanism or finding a way to restore it will be of great importance. Modena et al., in a study of 400 hypertensive postmenopausal women, showed that women who had an improvement in their endothelial function had a 7.3-fold lower risk for developing coronary events, compared to those with no improvement.⁵⁹

Recently, a gender specific role for coronary microvascular dysfunction has been reported for CAD pathophysiology. An autopsy series showed that, independent of the type of the thrombus or the presence of necrosis, women had a greater prevalence of distal microvascular embolization in the setting of a fatal epicardial thrombosis than did men.⁶⁰ In addition, other autopsy data from the victims of sudden cardiac death showed that women more frequently had coronary plaque erosion and distal embolization than did men.⁶¹⁻⁶⁵ Interestingly, the Wong et al. study showed that retinal arterial narrowing, which is a measure of microvascular disease, was related to CAD in women but not in men.⁶⁶ Furthermore, a combination of smaller arterial size and more prominent positive remodeling in women may result in a greater role of microvascular dysfunction in CAD in women.⁶⁷ The microvascular dysfunction of coronary arteries, as a prominent disorder in women, may also justify the higher rates of angina, ischemia, and acute coronary syndrome in the absence of obstructive CAD.^{67, 68} Recently, Shaw et al. posited that coronary microvascular dysfunction, in consequence of risk factor clustering, vascular remodeling, and hormonal alteration, is responsible for the atypical symptoms, ischemia, and adverse outcomes in women.⁵¹ The term "microvascular angina" was also proposed by them to describe the symptoms of myocardial ischemia due to coronary microvascular dysfunction.

Some recent data have shown that both endothelial-dependent (epicardial endothelial dysfunction) and endothelial-independent (microvascular dysfunction) impairments can predict adverse coronary events in patients who undergo diagnostic coronary angiography, in patients with single-vessel coronary angioplasty, in patients with post acute coronary syndrome, and in victims of MI.^{53, 69-71}

Spontaneous Coronary Artery Dissection

Spontaneous coronary artery dissection happens in the absence of coronary atherosclerosis. This event is much more common in women, and only about 20% of the cases occur in men.^{72, 73} Spontaneous coronary artery dissection can result in acute MI and sudden death. This type of dissection can involve every coronary artery, but the left anterior coronary artery is more frequently involved in women, whereas the right coronary artery is more prevalently involved in men.⁷³

Sex Hormones

Sex hormones play a major role in the pathophysiology of cardiovascular disorders. Evidence such as lesser incidence of CAD in younger women compared to men with similar ages, higher incidence of CAD after menopause, and higher risk of CAD in female patients with hyperandrogenism have suggested a key role for sex hormones in cardiovascular pathophysiology.^{74, 75} Estrogens and androgens, albeit present in either sex, are respectively the main sex hormones in women and men. Estrogens are believed to be protective, and androgens are thought to increase the risk of cardiovascular problems.⁷⁶ Some animal studies have demonstrated that vascular contraction is similar in castrated and intact male rats, whereas the vascular tone is enhanced in ovariectomized female rats. These studies have also suggested that sex differences in vascular tones are mainly related to estrogens in both genders.^{77, 78} Be that as it may, it seems that there is a gender-related response in this regard because the intracoronary infusion of estradiol in CAD patients can improve the coronary blood flow in women but not in men.⁷⁹ Sexual hormones can also affect the vasomotor tone by adjusting the response to different vasoactive substances, including noradrenalin, angiotensin II, and aldosterone.⁸⁰ In fact, noradrenalin is known to induce less vasoconstriction in women than in men.⁷⁶ Furthermore, estrogen may enhance the endothelial function by increasing the production or the release of relaxing factors from the endothelium.⁸¹ Estrogen has also positive effects on lipid profiles and thus confers a reduction in low-density lipoprotein cholesterol and increase in high-density cholesterol.⁸² Some studies have reported that estrogen deficiency is associated with a rise in insulin resistance.⁸³ Finally, it seems that estrogen may modulate pain perception in women⁸⁴ and it may have a direct anti-anginal effect by attenuating the pain-producing effects of adenosine to induce ischemic-like chest pain.⁸⁵

Conclusion

Provision of optimal care to women with CAD requires not only a multidisciplinary approach but also a thorough understating of the pathophysiology. Designing and

conducting international, multi-central, double-blind randomized clinical trials, recruiting sufficient numbers of women, codifying different markers into acceptable global risk scores for the assessment of coronary events risk, and last but not least, increasing the awareness of both women and their physicians about the entity of CAD in women to battle the existing misconceptions are recommended.

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