

# Stable angina and female gender

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## Abstract

Cardiovascular disease has been considered a disease of men, while women have been attributed a very low risk of heart disease. However, it is now recognized that heart disease is the first killing disease also in women, and they present often for the evaluation of chest pain symptoms, with stable angina constituting the most common initial presentation of cardiovascular origin. Nonetheless, for the same degree of symptoms as men, women present with less obstructive coronary artery disease. Although clinical evidence for myocardial ischemia in the absence of epicardial obstruction is not a new concept, few studies have assessed its impact on clinical outcomes. In this regard, women represent a very prototypic population subset where presence of ischemia in the absence of coronary artery disease has been associated with worse clinical outcomes.

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Over the past decades cardiovascular disease has been considered a disease of men, while women have been attributed a very low risk of heart disease. However, it is now recognized that heart disease is the first killer of women, with an increase at middle age [1]. Following an acute event, women are also reported to have worse outcomes, with about two-thirds of women never fully recovering.

Despite a general decline in the incidence of myocardial infarction [2], the prevalence of angina continues to be high [3]. Compared to men, women present more often for the evaluation of chest pain symptoms [4,5], with stable angina constituting the most common initial presentation of cardiovascular origin [6].

Interestingly, available data suggest that, for the same degree of symptoms as men, women present with less obstructive coronary artery disease (CAD) [7,8], with about half of all women with chest pain undergoing coronary angiography not presenting with obstructive CAD, compared with 17% of men [9]. In an era in which the search for the “holy grail of cardiology” is directed towards obstructive CAD, these and other previous observations have led to the development of the “high rate of false positives” myth in women. Practical consequences of such an assumption are a less-detailed risk factor assessment, less referral for cardiac evaluations such as stress

testing, coronary angiography and less aggressive preventive treatment (i.e., antiplatelet agents and statins) in women compared with men [10,11].

However, recent data have suggested that symptoms may be equally predictive of adverse prognosis in women and men [12]. In a large-scale population study [13], women presenting with stable angina had an increased coronary mortality relative to women in the general population and, similarly, high absolute rates of prognostic outcomes when compared to men.

The Wise (Women’s Ischemia Syndrome Evaluation) study is the largest clinical trial that has evaluated ischemic syndrome and its potential mechanism with respect to clinical outcomes in the female gender. In a sub-study analysis, women who presented with angina, non obstructive coronary arteries and evidence of ischemia at nuclear magnetic resonance spectroscopy (MRS) had increased coronary event rates as compared with women with no evidence of ischemia, irrespective of CAD extent [14]. In this cohort of WISE women with chest pain, when compared with reference WISE women with CAD, members without CAD were significantly younger (56 versus 64 years,  $P < 0.0001$ ) and had lower rates of diabetes (16% versus 38%,  $P = 0.0002$ ), hypertension (55% versus 68%,  $P = 0.02$ ), and dyslipidemia (45% versus 69%,  $P = 0.0002$ ). In another, more

recent, WISE sub-study [15], authors tried to correlate reduced coronary flow reserve (CFR) in response to intracoronary adenosine administration to mid-term clinical outcomes. They reported that an impaired response to adenosine was associated with increased risk for major adverse coronary events, even in the absence of significant obstructive CAD. The link between CFR and major adverse outcomes remained significant, regardless of the presence or absence of obstructive CAD or multiple risk conditions. There was only a borderline association of this component of coronary reactivity with CAD severity. However, among 152 women without any obstructive coronary lesion, the link between impaired coronary microvascular function and adverse outcomes remained statistically significant.

These findings suggest an obvious paradox: while angina prevalence and cardiovascular outcomes in women are similar to those in men [16], the extent of coronary artery disease is relatively low in this patient population [17,18] when compared with men of similar age.

CAD is a widely accepted predictor of adverse clinical outcomes in the general population and its association with myocardial ischemia has been the basis for development of treatment strategies primarily focused on removal of focal coronary obstructions. Unfortunately, studies aimed at assessing the impact of removal of coronary stenosis have yielded disappointing results, both on prognosis and symptoms relief.

CAD extension and severity is also considered an important prognostic factor in women with ischemic syndrome. In a study evaluating gender differences in CAD prevalence and in-hospital mortality of stable angina patients, the risk adjusted overall response (OR) for significant stenosis was 0.34 for women compared with men ( $P < 0.0001$ ) [9]. Besides being older, when compared to men, women with coronary artery disease, present more often with co-morbidities, and therefore constitute a distinct high-risk subset [19].

The WISE investigators investigated coronary vascular endothelium-dependent and -independent function using intracoronary acetylcholine and nitroglycerin, respectively, in 163 women undergoing angiography. Almost 75% of the women had mild or no angiographic CAD, and during a four-year follow-up period cardiovascular events were predicted by coronary vascular endothelial function, independently from risk factors and extent of CAD [2,15].

Findings such as augmented CAD severity in postmenopausal women have led to the common belief that estrogen may serve as a "protective agent" against atherosclerosis and, consequently, ischemic events. As a matter of fact, estrogen seems to play a relevant role in women's cardiovascular efficiency,

improving the arterial wall response to injury and inhibiting the development of atherosclerosis by promoting re-endothelialization, and limiting both smooth muscle cell proliferation and matrix deposition following vascular injury [20]. Estrogen also decreases systemic vascular resistance, improves coronary and peripheral endothelial function, and prevents coronary artery spasm in women with and without coronary atherosclerosis. Interestingly enough, intracoronary infusion of estradiol improves endothelial function and coronary blood flow in female patients, but not in male patients with coronary artery disease [21]. Moreover, estrogen modulates myogenic vascular responses by reducing the basal tone of microvessels [22].

Unfortunately, randomized studies have concluded that hormone therapy not only did not reduce cardiovascular risk in secondary prevention [23], but may even result in increased coronary events, stroke and breast cancer [24–26]. However, it has recently become clear that hormone therapy has complex biological effects, e.g., it has both anti-inflammatory and proinflammatory effects and it both activates coagulation and improves fibrinolysis [20].

These observations do not deny the prognostic relevance of CAD in cardiovascular disease which, as we know, is a systemic disease, associated with increased age and comorbidities. In this regard, women with CAD and stable angina represent a particularly ill subset of patients. However, in the premenopausal phase, women with stable angina tend to have less CAD, yet similar outcomes. Although clinical evidence for myocardial ischemia in the absence of epicardial obstruction, including metabolic, electrocardiographic, scintigraphic, and histologic findings [27–29] is not a new concept, few studies have assessed its impact on clinical outcomes.

Studies in women would therefore be of particular importance for a better understanding of ischemic heart disease, with or without CAD. ■

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