Coronary artery disease in women: a review on prevention, pathophysiology, diagnosis, and treatment

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Abstract: Despite numerous studies on women's cardiac health throughout the past decade, the number of female deaths caused by cardiovascular disease still rises and remains the leading cause of death in women in most areas of the world. Novel studies have demonstrated that cardiovascular disease, and more specifically coronary artery disease presentations in women, are different than those in men. In addition, pathology and pathophysiology of the disease present significant gender differences, which leads to difficulties concerning diagnosis, treatment and outcome of the female population. The reason for this disparity is all steps for female cardiovascular disease evaluation, treatment and prevention are not well elucidated; and an area for future research. This review brings together the most recent studies published in the field of coronary artery disease in women and points out new directions for future investigation on some of the important issues.
Keywords: coronary artery disease, women, risk factors, prevention, diagnosis, treatment.

Introduction

The first female-specific recommendations for preventive cardiology were published in 1999 (Mosca et al 1999). Even though research in the treatment of cardiovascular disease (CVD) had advanced in many areas, it remains the leading cause of death in women in most parts of the world. Studies have shown that 500 thousand women die of CVD every year in the United States, somewhat near one death every minute (American Heart Association 2003). Such index exceeds not only the number of deaths in men, but also the next seven causes of death in women combined, and more importantly, coronary artery disease (CAD) is believed to be the major cause responsible for these deaths (American Heart Association 2003). Over a quarter of a million deaths per year are attributed to CAD alone in the United States (Merz et al 2004). Although already high, these figures are expected to rise even more during the next decades, due to an increase of diabetes and obesity, as well as the aging of the world population (Merz et al 2004).

Even though women have a higher frequency of chest pain/angina than men, the incidence of obstructive CAD in the female population is lower when compared with men with similar symptoms (Kenedy et al 1982; Diamond et al 1983; Merz et al 1999). In addition, it would appear that young women with obstructive CAD have a worse prognosis after acute myocardial infarction (AMI), whereas older women in similar circumstances often present with larger number of comorbidities that adversely influence the outcome, when compared to men (Coronado et al 1997). Women with acute coronary syndromes (ACS) are also less likely to receive rapid effective diagnosis and treatment than are men (Ayanian and Epstein 1991; Maynard et al 1996; Pope et al 2000).

Regarding the North American population, the Women's Ischemic Syndrome Evaluation (WISE) study workshop (Hayes et al 2004; Maseri 2004; Nabel et al 2004; Pepine et al 2004; Shaw et al 2004; Waters et al 2004) from the National Heart, Lung and

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Blood Institute (NHLBI) released in 2004 an executive summary in which a strategy for cardiovascular research and education for women must be developed. A number of targets were set in a few different areas, such as improving understanding of pathology and pathophysiology of gender differences in ischemic heart disease (IHD), improving understanding of symptom description and diagnostic tools, conducting gender-specific clinical investigation, investigating mechanisms for adverse cardiovascular events in an early phase of hormone replacement therapy (HRT) and promotion of translation research—approaches into actual practice (Merz et al 2004).

It is recognized that a better understanding of the these topics is necessary for a meaningful communication between public, patients, and healthcare professionals. The aim of this paper will be to review the literature on the subject of CVD in women. The review will be in four sections, the first section will focus on contributions on mechanisms of pathophysiology, diagnosis, and treatment. The second section will concentrate on well known risk factors and novel risk markers. This will be followed by a section emphasizing new recommendations for clinical practice. Subsequently, attention will turn to preventive strategies recently established and recommendations for future research. The literature here reviewed leads to a request for future research regarding all steps of CVD evaluation, treatment and prevention focused on the female population.

Pathophysiology, diagnosis, and treatment of cvd in women

Diagnosis-related outcomes

Even though more women die of CVD than from all forms of cancer combined (American Heart Association 2003), this condition is seen as only a remote health risk by the public. Moreover, the functional expression and the disability caused in women by obstructive CAD are much greater when compared to men (Merz et al 2004). Yet, due to the incomplete understanding of gender-specific pathophysiology of ischemia and underdeveloped diagnosis and treatment strategies, a large number of women without obstructive CAD at coronary angiography present symptom-related disability and thus consume a considerable amount of healthcare resources (Merz et al 2004).

Diagnosis of the illness in women remains underdeveloped. One of the reasons is that chest pain in women is less likely to be related to flow-limiting coronary stenosis than chest pain in men (Kennedy et al 1982; Diamond et al 1983; Merz et al 1999), and the main instrument used to search for the cause of chest pain is still coronary angiography. In addition, it is the diagnosis of ischemia that will determine the patient's prognosis (Merz et al 2004).

The detection of unstable angina carries a much more severe prognosis than chronic stable angina. On the other hand, the detection of angina does not carry an increased risk of infarction or sudden cardiac death, and the relevance of such detection lies on the knowledge of its causes and of what can be done to treat them (Maseri 2004).

Syndrome X is a typical condition that illustrates the challenge of the diagnosis of myocardial ischemia. It has a 10%–15% incidence in patients submitted to coronary angiography and is characterized as angina pectoris and normal coronary angiography (Maseri 2004). Such criteria include heterogeneous patients with and without cardiac origin of pain, which turns diagnosis of myocardial ischemia even more difficult.

A new program which has been initiated by the WISE study researchers is designed to examine the outcome from all patients that present themselve at emergency department with their very first manifestation of IHD (Maseri 2004). The ongoing study relies on a standardized questionnaire focused on possible differences in symptoms and presentation for each of the various ischemic syndromes. A blood sample is obtained for traditional risk factors and a sample is stored in biological banks. All patients undergo clinically required tests and interventions, special pathogenic studies, and join a regular follow-up program that will identify patients with different outcomes. These efforts are aimed at obtaining new information on pathogenic mechanisms and on predisposing and protective factors, which will be used for developing novel, rational treatment strategies for patients with IHD. It is expected that this study will reveal important information since a lack of appropriate diagnosis can have a devastating effect on the long-term health of patients.

Stable angina

The traditional view of the chronic stable ischemia syndrome was related to typical effort-induced angina pectoris (Pepine 2004). This view consisted of reversible myocardial ischemia, caused by obstructive CAD that limits blood flow during periods of increased myocardial oxygen demand. It was believed that dynamic changes in coronary blood vessel size were infrequent and contributed little to the etiology, as well as microcirculation was thought to be relatively spared from this disease. This syndrome did not appear to afflict women

until they became elderly with the exception of diabetic women (Friedberg 1966).

A more contemporary view includes variable thresholds for ischemia and symptoms that may vary. This view involves ischemia due to dynamic changes in coronary size that also compromise the microcirculation (Panting et al 2002). Endothelial dysfunction, and higher risk of atherosclerosis is prevalent in women with hypertension, diabetes, and dyslipidemia (Quyyumi 1998).

Once again regarding the WISE workshop, symptom recognition should evolve. Coronary angiography has limited symptom assessment, since it depends on the prevalence of obstructive CAD (Pepine et al 2004). Prior literature illustrates that women referred for angiography have lower likelihood of obstructive CAD than men (Diamond 1984). In the WISE study, only 39% of the women had CAD, defined as over 50% stenosis, in more than one coronary artery. In addition, evidence from the Coronary Artery Surgery Study (CASS) demonstrated that although typical angina was predictive of CAD in both men and women, the higher prevalence of non-obstructive CAD in women compared with men suggested that symptoms were less diagnostic in the female group (Kennedy et al 1982). Furthermore WISE investigators found that the typical angina classification missed 65% of women who actually had CAD. Symptoms experienced by women without CAD may be related to microvascular ischemia or constriction of coronary arteries (Johnson et al 2003).

The American Heart Association (AHA) approved, in 2003, the publication of a summary that points out new methods in evaluating women with chest pain (Pepine 2004). According to this article, several studies demonstrate the limited value in women undergoing evaluation for CAD of standard stress testing and evaluation of electrocardiographic changes, myocardial perfusion defects, and regional wall motion abnormalities. The document determines perfusion imaging with magnetic resonance imaging (MRI) and magnetic resonance spectroscopy (MRS) as feasible methods for chest pain evaluation. The first method has shown evidence of subendocardial hypoperfusion in the absence of large-vessel obstruction, whereas the MRS also has the potential to detect myocardial ischemia by demonstrating transient reduction in myocardial high energy phosphates and increases in organic phosphate during stress testing. Nevertheless, the Association proposes additional studies to determine their diagnostic accuracy.

Carotid ultrasound, MRI, and test on the functionalty of endothelium have advantages over other invasive techniques in detecting atherosclerosis in its earliest stages. On the other hand, such screening requires sophisticated equipment and skillful expertise (Pepine 2004). Regarding the invasive techniques, intravascular ultrasound (IVUS) not only visualizes coronary lumen, as does coronary angiography, but also arterial wall characteristics. The WISE IVUS substudy has released preliminary data suggesting that the majority of women without flow limiting lesions had abnormalities of endothelial function and/or microvascular flow reserve, with the potential to limit coronary perfusion (Tuzcu et al 1996).

Therefore, a better comprehension of the patho-physiologic mechanisms of stable angina in the female population can improve symptom recognition, which leads to more appropriate treatment strategies. It is such an effort that will help minimize deaths or disabilities caused by the disease.

Acute cardiac ischemia

Substantial scientific information on acute cardiac ischemia (ACI) has been available in scientific literature for many years. However, the diagnosis and treatment are far from the finest, as women tend to present to the emergency department at older ages, with more comorbidity and with differences in symptoms when compared with men (Jayes et al 1992; Coronado et al 1997; Maynard et al 1997; Zucker et al 1997; Pope et al 1998; Milner et al 1999; Goldberg et al 2000). Missed diagnosis and treatment lead to unnecessary deaths.

A recent study on diagnosis and treatment on ACI from the NHLBI (Nabel et al 2004) recommends improvement in four different domains with the intention of improving healthcare in this area. These recommendations begin with effectiveness of the diagnosis, which consists of "a need to develop and test ways to improve use of existing diagnostic methods and new ways of diagnosing ACI in women, not only by Emergency Department by physicians, but also by prehospital, nonhospital, and nonphysician clinicians". The next recommendation is the effectiveness of treatment that like above, depends on development and testing of methods to improve treatment and decision making in management of women with ACI. The document also acknowledges the importance of dissemination and communication of the best use of effective diagnostic technologies and improved treatment strategies in order to translate them into actual practice. Finally, the understanding of the disease is necessary to communicate the right message to all public, patients and healthcare professionals. Moreover, the same document recommends that the better understanding should come together with research, for example, on prodromal syndromes

for ACI, in which all patients would be questioned about presenting symptoms and signs in the early stages of the disease.

All these recommendations represent a growing trend in the recognition and treatment of ACS, leading to a significant lowering of the rate of mortality in patients with CAD.

Innovations on traditional risk factors and novel risk markers in CVD in women

The effects of aging, dyslipidemia, hypertension, cigarette smoking, and diabetes, among other risk factors, promote the sequelae of endothelial dysfunction, inflammation, and atheromatous plaque deposition in women, as well as men. The five risk factors mentioned above are all well known traditional risk factors and their correlation to pathophysiology of CAD has been well documented (Sharret et al 2001).

Moreover, several novel risk markers have been identified over the past 10 years, which include new forms of lipid particles, metabolites, hemostatic factors, and inflammatory markers. Acknowledged risk markers such as C-reactive protein (Bayes-Genis et al 2001) and Pregnancy Associated Plasma Protein (Coronado et al 1997) help identify patients with ischemic syndromes and provide better insight into the arterial dysfunction as well as on the underlying risk. A document on CAD risks from the WISE workshop (Shaw et al 2004) asserts that these are best classified as risk markers rather than risk factors because causal status has not yet been established unequivocally, even though it appears that they contribute to underlying pathophysiological processes. In that manner, novel studies include not only new scientific information on the traditional risk factors but also the latest acknowledgments and future research suggestions on the recently proposed risk markers.

Traditional risk factors

The Atherosclerosis Risk In Communities (ARIC) study assembled over 15 thousand middle-aged men and women and analyzed their traditional risks for CAD (ie, age, cholesterol levels, blood pressure levels, smoking habit, and diabetes) with the intention of building a global risk score to predict a 10-year risk of CAD events (Hubbard et al 1999; Wong et al 2002). This study has determined that the equations relating the risk factors have higher predictive values in women than in men and also non-traditional risk factors and subclinical atherosclerosis measures improve prediction only in the male population.

Diet and lifestyle

Many of the scientific gains on the subject of CVD include improvement in pharmacological therapies and surgical interventions, which have most certainly helped to decrease related mortality. Nevertheless these treatments are expensive, present various side effects, and require medical intervention. Against this background, a cohort study was developed in the US, the Nurses' Health Study, proving that the adherence to lifestyle guidelines involving diet, exercise, and abstinence from smoking is associated with a very small risk of CAD while appropriate adjustments were made for age, family history, hypertension, dyslipidemia, and menopausal status (Stampfer et al 2000).

The Nurses' Study included over 84000 US female nurses who were free of CVD, cancer, and diabetes and were followed for 14 years. Low-risk subjects were defined as "those who were currently not smoking, had a body mass index under 25 kg/m^2, consumed an average of at least half a drink of an alcoholic beverage per day, engaged in moderate-to-vigorous physical activity (which could include brisk walking) for at least half an hour per day on average, and scored in the highest 40% of the cohort for consumption of a diet high in cereal fiber, marine n-3 fatty acids, and folate, with a high ratio of polyunsaturated to saturated fat, and low in trans fat and glycemic load, which reflects the extent to which diet raises blood glucose levels (Stampfer et al 2000).

Only 3% of the population were in the low-risk category, and when compared with all other women this percentage had a relative risk of coronary events of 0.17. This index suggests that if all women had been in the low-risk group, 82% of the coronary events would have been prevented. The most important risk factor was cigarette smoking: women who smoked 15 or more cigarettes per day and had a relative risk of 5.48 compared with non-smokers. It was emphasized that even women who smoke 1 to 14 cigarettes per day have a tripled risk of coronary event. It is also evident that the rising incidence of obesity in various occidental countries points a high body-mass index (BMI) as another important female-specific risk factor. The risk was found to increase when the BMI exceeded 23 kg/m^2, reaching a relative risk of 1.57 for BMI above 30 kg/m^2. In addition, each individual component of the low-risk profile (ie, dietary score, exercise, body-mass index, smoking, and alcohol consumption) showed a significant and substantial association with risk, and the

elevation of the risk gradient was related to the presence of a crescent number of components (Stampfer et al 2000).

The Nurse's Health Study is an important etiologic study. It illustrates the benefits of simple interventions in the prevention of a substantial number of CAD events in women.

Anemia

For both men and women, limited coronary flow caused by coronary artery obstruction, and endothelial and/or microvascular dysfunction can be worsened by low hemoglobin (Hgb) levels (Arant et al 2004). Recent studies suggest that decreased Hgb is an independent predictor of increased morbidity and mortality in patients presenting with acute myocardial infarction (AMI) (Wu et al 2001; Al Falluji et al 2002; Sarnak et al 2002).

Iron deficiency is an important public health issue. Approximately 2%–5% of American teenage girls are sufficiently iron-deficient to have anemia and more than half a billion people worldwide are at the risk of adverse effects as a result of iron deficiency (Andrews 1999). Anemia has been documented in approximately 15% of patients presenting with AMI and in 43% of elderly patients that present with the latter medical condition (Chesebro et al 1987; Wu et al 2001).

Two mechanisms are believed to worsen the ischemic insult in the myocardium in AMI and other ACS: decreased oxygen content of the blood supplied to the myocardium (Most et al 1986) and increased myocardial oxygen demand, due to a higher cardiac output, necessary to maintain adequate systemic oxygen delivery (Levy et al 1996).

Anemia has been shown to be an independent risk factor for adverse cardiovascular outcomes in community cohorts (Sarnak et al 2002), in patients with heart failure (Al-Ahmad et al 2001; Ezekowitz et al 2003), and in patients undergoing percutaneous coronary intervention (McKechnie et al 2004). More recent studies have been designed to relate anemia to clinical outcomes in patients with ACS.

Sabatine et al (2005) examined the association between baseline Hgb and major adverse cardiovascular events through 30 days in almost 40000 patients with ACS. In patients with ST-elevation AMI, Hgb between 14 and 15 g/dL were used as reference, and cardiovascular mortality increased as Hgb fell below 14 g/dL, with an adjusted odds ratio (OR) of 1.21 ($p < 0.001$) for each 1 g/dL decrement in Hgb. Patients with non-ST-elevation ACS (reference Hgb 15–16 g/dL) also had an increased rate of death or ischemic events, as Hgb fell below 11 g/dL, with an adjusted OR of 1.45 ($p < 0.001$) for each 1 g/dL. Hemoglobin higher than 16 g/dL was also seen to increase adverse cardiovascular events. The association of lower Hgb with short-term mortality in patients with AMI was confirmed by Lipsic et al (2005) in which a hazard ratio (HR) of 1.76 ($p = 0.02$) was demonstrated for patients with Hgb < 10 g/dL.

The association between anemia and adverse cardiovascular outcomes was also verified in larger-term follow-up studies. Langston et al (2003) demonstrated a mortality rate at one year after AMI of 30.7% (OR 1.35: $p = 0.0067$) for hematocrit between 30% and 35%. Vaglio et al (2005) assessed a two-year survival rate among patients who had ACS that were classified by discharge hematocrit values. Worsening anemia was associated with a decreased 2-year survival rate, with a HR of 2.46 ($p = 0.025$) in patients with moderate/severe anemia (hematocrit < 33%).

An interesting new prospective study developed as part of the WISE study linking lower Hgb with higher risk for adverse cardiovascular outcomes, to women with ischemic-type symptoms, regardless of the presence or severity of CAD (Arant et al 2004). According to this study, such association appears with only a modest reduction in Hgb during intermediate term follow-up. Hemoglobin levels were compared with cardiovascular risk factors, core laboratory interpreted angiograms, inflammatory markers, and adverse cardiovascular outcomes. The researchers affirmed lower Hgb in women presenting with ischemic-type symptoms which was significantly and independently associated with adverse cardiovascular outcome (Arant et al 2004).

Regarding yet unknown prognostic importance and prevalence of low Hgb in the female population, researchers recommend further study on pathophysiology and benefits of intervention in these women with suspected ischemia. Although previous research suggests that patients with low hematocrit who receive transfusions had improved outcomes (Wu et al 2001; Al Falluji et al 2002; Sarnak et al 2002), while Rao et al (2004) associated blood transfusion in the setting of ACS with higher mortality. Specific therapeutic strategies should be considered in anemic ACS patients.

Oral contraceptives

The use of oral contraceptives (OC) has been associated with an increased risk of atherosclerosis as well as venous thrombosis since their introduction in clinical practice (Tanis et al 2003). Many efforts have been made in order to lower such risks by reducing estrogen dosage and modifying the progestagen compound. Over 100 million women use OC worldwide (Tanis et al 2003), which makes safety a matter of great importance. Of note is an interesting case-control study

that was developed in the Netherlands to investigate the association between the risk of myocardial infarction and the use of OC, according to the type of progestagen, the dose of estrogen, and the presence or absence of prothrombotic mutations. The data revealed a 2-fold increased risk of AMI among users of any type of OC, whereas the relative risk of OC users with no conventional risk factors was 3.1 when compared with non-users (Tanis et al 2001). When different generations of these medications were compared, the risk for AMI for those who used second-generation contraceptives was increased by a factor of 2.5 while third-generation OC did not increase the risk significantly (OR1.3), suggesting a lower risk, but the overall findings remain inconclusive. The generation is defined by type of progestagen: second generation includes levonorgestrel and third generation includes desogestrel and gestodene. The prothrombotic mutation did not alter the risks. It was concluded that the recommendation to clinicians should be to screen for traditional cardiovascular risk factors and events before prescribing OC (Tanis et al 2001). The recommendation was based on the alarming figures found: the odds ratio among OC users who smoked was 13.6, among diabetic women 17.4, and those with dyslipidemia 24 (Tanis et al 2001).

A later publication (Tanis et al 2003) suggests that the inconclusive benefits of third generation OC concerning AMI do not counterbalance the adverse effect of this generation on venous thrombosis.

Pregnancy

Another risk factor related to CAD in women is parity. Pregnancy exaggerates atherogenic responses, including insulin resistance and dyslipidemia, manifesting as preeclampsia and gestational diabetes. These complications increase the post-partum risk of CVD, with a 2-fold increased risk of CAD and cerebrovascular disease (Kaaja and Greer 2005). It has been shown that women with gestational diabetes can progress to type 2 diabetes mellitus (Kaaja and Greer 2005). In many studies the conversion from gestational diabetes to type 2 diabetes has been variable, but the long-term (>10 year) risk is approximately 70% (Buchanan and Xiang 2005). Pre-eclampsia is associated with insulin resistance, as well as hypertension, lower high density lipoprotein (HDL) concentrations, higher plasma levels of triglycerides, uric acid, and insulin. It is also recognized as a state of sympathetic overactivity and proinflammatory changes (Kaaja and Greer 2005). Thus, pre-eclampsia may be the first manifestation of the metabolic syndrome. A large Scottish study (Smith et al 2001) found a significant association between preeclampsia and maternal hospital admission for ischemic heart disease or death (hazard ratio 2.0; 95% CI 1.5–2.5).

Pregnancy also increases the risk of venous thrombosis by 7- to 10-fold (Martinelli et al 2002). This risk is approximately 3-fold higher than that associated with OC use (Wu et al 2005). There is also a 50% increase in plasma volume, which can unmask glomerulopathies, peripartum cardiomyopathy, arterial aneurisms, or ateriovenous malformations (Kaaja and Greer 2005).

An association between number of children and CAD risk factors and prevalent CAD in women and men aged 60–79 has also been established (Lawlor et al 2003). The comparison of gender indexes determines whether the association is due to biological processes or lifestyle factors. The results include association of increasing number of children and increasing obesity in both sexes. In women only, some association was found between number of children and CAD after adjustment for obesity and metabolic factors. Before the adjustment, both sexes showed an increasing risk of cardiac events: after the second pregnancy, each additional child increased the age-adjusted odds for CAD in by 30% (OR 1.3; 95% confidence interval [CI] 1.17–1.44) for women and 12% (OR 1.12; 95% CI 1.02–1.22) for men. The biological mechanisms for the association are still unclear. Some possibilities include a reduced lifetime exposure to estrogen due to pregnancy "resets" of ovarian function as well as a permanent effect on lipid and glucose metabolism resulting from repeated pregnancy-induced insulin resistance (Rossouw et al 2002).

Pregnancy can reveal preexisting risk factors for metabolic syndrome and CVD, which makes these women appropriate candidates for careful screening of CVD risk factors and for possible interventions. Primary prevention should be considered after pregnancy for these high risk individuals.

Menopause and hormone replacement therapy (HRT)

A Review on the International Position Paper on Women's Health and Menopause (Paoletti and Wenger 2003) defines the original document, published in 2002, as a valuable resource not only for healthcare professionals but also for policy makers, scientists as well as individual women seeking information on menopausal health. It defines menopause as "the permanent cessation of menstruation resulting from the loss of ovarian follicular activity", emphasizing that it is a normal event in a woman's life, not a disease. However, aging increases significantly the incidence of CVD and previous observational studies suggested that postmenopausal

hormone replacement therapy (HRT) might prevent or reduce heart disease as well as alleviate menopause symptoms (Paoletti and Wenger 2003).

In that setting, many studies of IHD were analyzed by the WISE workshop, which identified certain important issues (Waters et al 2004). The researchers identified potential benefits of ovarian hormones on the cardiovascular system, such as antiatherogenic and vasodilator actions. They acknowledge that estrogen increases coronary blood flow in response to acetylcholine in post-menopausal women, prolongs exercise time until the beginning of myocardial ischemia in these women who have coronary disease, and increases fibrinolytic activity. On the other hand, estrogen activates coagulation pathways, presenting a final procoagulant effect, and increases C-reactive protein levels, an independent predictor of future coronary events (Waters et al 2004). The adverse vascular effects of HRT might be associated with the last mentioned mechanism.

The WISE workshop mentioned several studies relating CVD risks to HRT. The Heart Estrogen/progestin Replacement Study (HERS) showed no difference for the primary end point of coronary death or non-fatal AMI between post-menopausal women using conjugated equine estrogen (CEE) and medroxyprogesterone acetate (MPA) or placebo, in a 4.1-year follow-up (Hulley et al 2002). The Estrogen Replacement and Atherosclerosis (ERA) trial included women with CAD using estrogen, estrogen plus MPA, or placebo in order to assess minimum lumen diameter changes through coronary angiography (Herrington et al 2000). Again no differences were found. Women's Angiographic Vitamin and Estrogen (WAVE) trial randomized women to estrogen alone, estrogen plus MPA or corresponding placebo (Waters et al 2002). Women were also randomized to vitamin C and E supplements or placebos. The change in minimum lumen diameter was assessed and it was found that the risk of stenosis was increased in women going through HRT.

Finally, the Women's Health Initiative designed two parallel clinical trials of HRT to determine whether CEE alone or combined with MPA would reduce cardiovascular events in mostly healthy postmenopausal women (The Women's Health Initiative Committee 2004). The estrogen + progestin trial randomized over 16,000 intact uteri postmenopausal women without known CAD to CEE with MPA or placebo and was brought to an early closure, after a mean 5.2 years of follow-up, due to an excess of occurrence of breast cancer among women assigned to HRT, as well as an increase of risk of CHD, stroke, venous thromboembolic disease (Rossouw et al 2002). The Women's Health Initiative estrogen-alone trial continued until it reached an average of 6.8 years of follow-up (The Women's Health Initiative Committee 2004). It determined that CEE increases the risk of stroke (HR 1.39; $p = 0.007$), decreases the risk of hip fracture (HR 0.61; $p = 0.01$), and did not affect the incidence of CHD (HR 0.91; CI 0.75–1.12) in postmenopausal women. A possible reduction in breast cancer risk, despite the estrogen + progestin results, met an HR of 0.77 ($p = 0.06$) and requires further investigation. As the burden of incident disease events was equivalent in the CEE and placebo groups, indicating no overall benefit, CEE should not be recommended for chronic disease prevention in postmenopausal women.

The major lessons from the WISE workshop document were that HRT "is not useful for cardiovascular protection and should not be used except for short term control of menopausal symptoms" and that there are other means of reducing vascular disease, for instance by use of statins and angiotensin-converting enzyme inhibitors and even diet and exercise. It also recommends further research into apparent beneficial effects of endogenous estrogen.

Surgical interventions for obesity

Excess weight has been associated with higher mortality and cardiovascular events (Melanson et al 2001; Ezzati et al 2002). The United States had an important increase in the median percent of adult obesity from 1991 to 2000, according to the World Health Organization (Pan American Health Organization 2006). In 1990 the median percentage of the country's adult population that was obese (BMI ≥ 30) by state was 12%. With steady increases; in 2000, the median percentage reached 20%.

The mechanisms that explain the impact of obesity in CVD include indirect effect on the vascular system through factors such as dyslipidemia, hypertension, obstructive sleep apnea, and insulin resistance, as well as increased leptin level, enhanced systemic inflammation, and higher turnover of free fatty acids with lipotoxic effects on myocardial cells (Eckel et al 2002). Obesity is considered an independent risk factor for CVD (Eckel 1997) and recommendations for weight loss begin when BMI exceeds 25 kg/m^2 (Smith et al 2001). It has been shown that women have a lower prevalence of being overweight (BMI 25–29.9) than men, 25% vs 40%, but a higher prevalence of obesity (BMI > 30), 25% vs 20%, respectively. There are studies that have assessed the effect of weight loss in CAD patients, but women-specific trials are few.

Liposuction is a very prevalent surgical procedure. The American Society of Plastic Surgeons reported 324891 procedures during 2004 in the country, 90% of these in women (American Society of Plastic Surgeons 2005). A study on the

effects of liposuction on CHD risk factors was developed after the proposition that this procedure is a potential treatment for the metabolic complications associated with obesity (Klein et al 2004). The study evaluated insulin sensitivity of various organs along with levels of inflammatory mediators and other risk factors for CHD in 15 obese women before and 10 to 12 weeks after abdominal liposuction of a mean of 10 kg of adipose tissue. It was concluded that decreasing adipose tissue mass alone does not achieve the metabolic benefits of weight loss, as abdominal liposuction did not improve any of the markers in study. However, the researchers responsible for the study acknowledge positive outcomes from the surgical intervention, not measured in their work (Klein et al 2004). The removal of abdominal fat facilitates deambulation and improves appearance, "which has important psychological benefits" (Wood 2004).

Another common procedure is bariatric surgery, accounting for over 52000 surgeries in 2003 in the United States (American Society of Plastic Surgeons 2004). Studies assessed bariatric surgery in obese patients with CAD. Lopez-Gimenez et al (2005) determined the safety and efficacy of vertical, disconnected Roux-en-Y gastric bypass. Patients with documented CAD were compared with patients without CAD for a mean 2.5 years follow-up. Weight, BMI, fasting serum glucose, glycosylated hemoglobin, and blood pressure all decreased signifcantly ($p < 0.001$) post-operatively. Low-density lipoprotein and triglycerides also decreased significantly ($p < 0.01$). Thus it was suggested that bariatric surgery was a feasible method for treating patients with obesity and CAD (Lopez Gimenez et al 2005).

The evidence from Program on the Surgical Control of Hyperlipidemias (POSCH) trial seem to suggest that partial ileal bypass as a modality would decrease overall mortality in such patients (Buchwald et al 2002). A mean 18 years follow-up demonstrated that the lipid profile normalization, guaranteed by the surgical procedure, decreased overall mortality and maintained a persistent and constant increase in life expectancy. There was a 35% decrease in the mortality rate from CHD combined with confirmed nonfatal AMI ($p < 0.001$), as well as significant decreases in disease progression and in treatment procedures such as percutaneous coronary angioplasty and coronary artery bypass grafting. Further evidence from POSCH trial with a follow up of 10 years seems to support the view of the occurrence of a regression in coronary artery atherosclerosis (Campo and Buchwald 1993).

The Swedish Obese Subjects (SOS) group also studied obese patients with numerous CVD risk factors, assessing the effects of bariatric surgery over a 2- and a 10-year period (Sjöström et al 2004). It presented significant recovery rates from many risk factors, such as obesity, diabetes, hypertriglyceridemia, low levels of HDL cholesterol, hypertension, and hyperuricemia, when conventionally treated obese patients were compared to patients that had undergone surgery. These rates were seen in both the short- and the long-term follow-up. However, the incidence of hypercholesterolemia and the rates of recovery did not differ between the two groups over the 2- and the 10-year periods (Sjöström et al 2004). Nonetheless, the latter findings were not consistent with previous data presented in Nurses' Health Study (Stampfer et al 2000), but the SOS group believe that the long-term effects of maintained weight loss cannot always be estimated from short-term observations.

Acute coronary syndromes

After reviewing the results of several new studies on IHD to understand the existing gender differences, the WISE workshop brought together a number of recommendations for practice. The document points to a similar or even better outcome in women compared with men presenting ACS when the pathophysiological differences can be overcome with early, aggressive therapies (Hayes et al 2004).

The recommendations are based on the Rapid Early Action for Coronary Treatment (REACT) study designed by the NHLBI, in which multistrategy campaigns were tested to reduce patient delay to seek care for ACS symptoms (Simons-Morton et al 1998). It was emphasized that reducing time to treatment can significantly reduce death and disability caused by AMI (Simons-Morton et al 1998). This includes education not only of healthcare providers, but also patients, individual women and the general public about recognition of and response to early symptoms.

The document has some direct recommendations. One of them is patient awareness of symptoms: there are many symptoms in addition to chest pain, pressure, or discomfort and the symptom presentation may not be dramatic or sudden. In addition, the recognition of symptoms by women and healthcare providers requires further research about prodromal syndromes and dissemination of not only public messages but also information aimed at healthcare providers. Lastly, the NHLBI document once more encourages better understanding of all pathophysiological basis of ACS in women in order to optimize treatment recommendations and develop earlier symptom recognition.

Preventive strategies and future recommendations

The AHA has developed a document containing specific guidelines for CVD prevention in adult women with a broad range of cardiovascular risk (Mosca et al 2004). It highlights the importance of preventing CVD, as two thirds of sudden deaths in women have no previously recognized symptoms. Additionally, prevention on CVD brings great benefits for the prevention of non-coronary atherosclerosis, such as cerebrovascular disease and peripheral atherosclerosis.

The concept of CVD relies on a growing appreciation for the existence of a continuum of CVD risk. AHA guidelines include an illustrative table showing the spectrum of CVD risk and risk groups (higher or lower risk) defined by their absolute probability of having a coronary event in 10 years according to the Framingham Risk Score for Women (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults 2001). The table aims to help healthcare providers determine the type of risk intervention necessary in each case. Clinical recommendations include interventions in lifestyle, major risk factors, and preventive drug use as well as a list of useless or even harmful interventions including HRT, antioxidant supplements, and aspirin use in low-risk individuals. The priorities for prevention in practice are carefully pointed out and separated according to each risk group.

The study recognizes several limitations such as individual differences that do not fit into the recommendations. The population used to generate these recommendations might not reflect general patients' characteristics. Moreover, there might be variability in efficacy and effectiveness of various interventions within the same risk intervention category. Finally, even though the Framingham risk score may not apply equally to all populations, it performs well within subgroups and AHA intends to disseminate these guidelines for its better implementation worldwide. However, it must be emphasized that guidelines are definitely not a good substitute for clinical judgment.

It is well recognized that implementation of these guidelines may differ across countries and regions for cultural, medical, and economic reasons and their application should also consider individual factors such as frailty and life expectancy.

Clearly women, and particularly post-menopausal women, remain at high risk for CHD. This may be justified at least in part because women have been under-represented in clinical outcome trials, tend to be under-treated in the clinical setting, and might be misdiagnosed when their presenting symptoms differ from those observed in men (Mosca et al 2004).

An observational study describing all symptoms of women experiencing ischemic-like events compared with male description could be helpful to relate these data to diagnostic tests, outcomes, strategies of treatment, and forms of investigating symptoms on future patients of both genders. Furthermore, all the current information on CAD prevention, diagnosis, and treatment available should be collected, brought together, analyzed, and targeted to specific populations regarding all social, cultural, and economic particularities in the different regions, economic classes, and genders. Information regarding all these aspects should not only be disseminated to scientists and healthcare providers but also among individual women, since patient information is known to promote prevention, decrease time to treatment, and improve patient prognosis.

Even though contemporary lifestyle and the increase of life expectancy throughout the world have contributed to an increase of CAD incidence, the progress in the scientific sphere is the major factor responsible for holding back these figures. As all pathophysiological mechanisms are not yet fully understood, improvements in CAD knowledge are a promise for future innovations on healthcare in order to positively affect mortality rates in both women and men globally.

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