

## CARDIOVASCULAR DISEASE IN WOMEN

Cardiovascular disease is the first cause of death in the world, both in men and in women.(1)

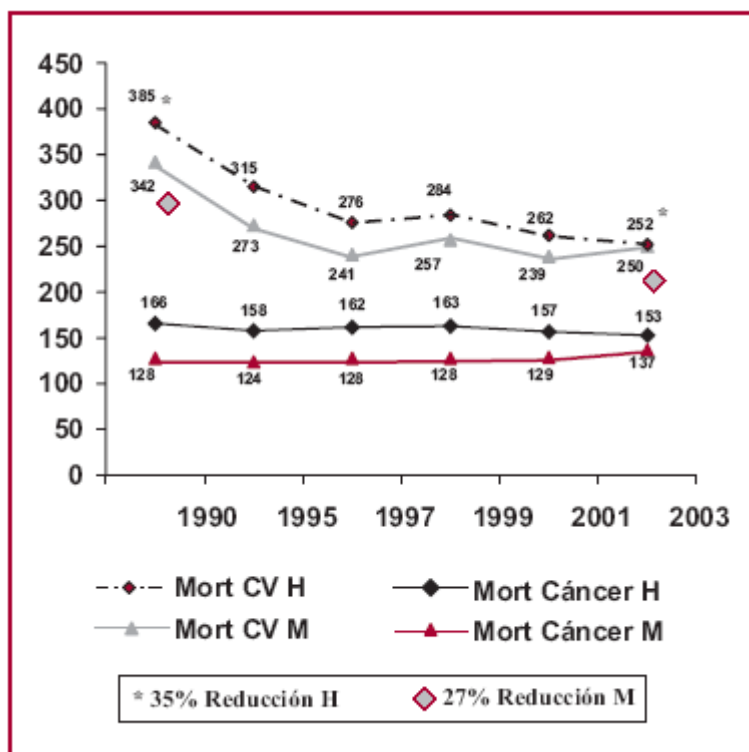
This includes coronary artery disease, stroke, and heart failure.

In Europe, cardiovascular death observed in women exceeds that of men (57% vs 49%).(2)

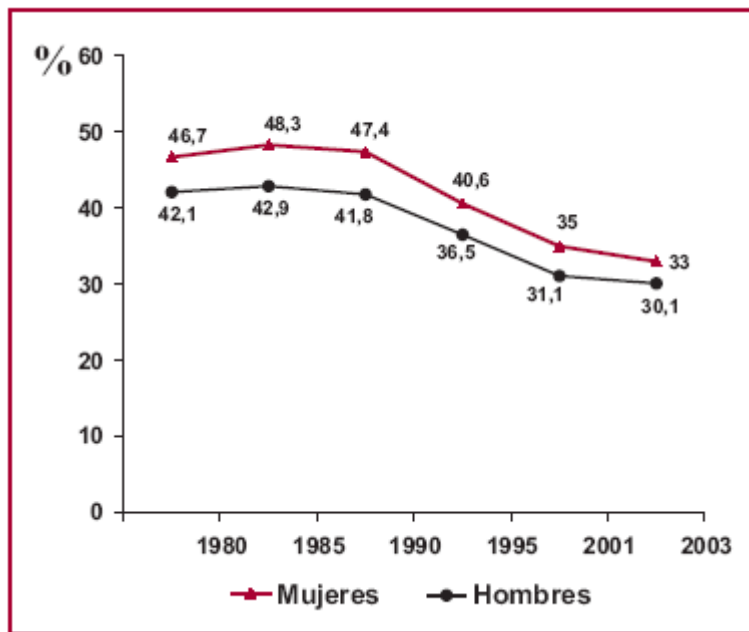
In USA, coronary mortality also leads the causes of death. Through the years, a decrease observed in cardiovascular mortality, though affecting both sexes, is more manifest in males.

(3)

In Argentina something similar occurs, since cardiovascular mortality is the first cause of death in women (33%), although the tendency to decrease was more noticeable in men. Since age 65, mortality by cardiovascular disease presents an ascending behavior in women and it exceeds that of men since 75 years of age.(4) Figures 1 and 2.



**Figure 1:** Tendencias en mortalidad rate by 100,000 inhabitants by cardiovascular disease and cancer in men and women during the 1980- period. (Mort CV H: cardiovascular mortality in men. Mort CV M: cardiovascular mortality in women. H: men. M: women. Mort Cáncer: mortality by cancer.) Taken from the Revista Argentina de Cardiología.



**Figure 2:** Relative frequency of cardiovascular mortality and trends between men and women during the 1980-2003 period (excluding mortality by congenital heart diseases). Source: Direction of Vital Statistics of the Direction of Statistics and Information of the Ministry of Health and Environment.

### Cardiovascular risk factors in women

1. **Age:** Atherosclerotic disease in women is rare before menopause, since during the fertile period, female sex hormones act as protective modulators. There are infrequent situations, in which coronary artery disease may appear in women in fertile age, and this is due to the presence of one or more risk factors, such as: smoking, diabetes, hypercholesterolemia, use of oral contraception methods associated to smoking.
2. **Smoking:** In the Western world, there are increasingly more smoking women, with the worsening factor of an earlier age to start with it. In the National Survey of Risk Factors, it was observed that 24.9% of the female population smokes, while 35.1% of males do it.(5) This survey showed that consumption in teenagers is greater in women than in men. Passive smokers are also exposed and have an increased risk of cardiovascular disease by 25%.(6)
3. **Hypertension:** Both epidemiological and interventional studies show the association between systolic and diastolic hypertension and the risk of cardiovascular disease.(7) The NHANES III showed that only 50% of women that were hypertensive took

medication, and from these only 21% was properly controlled.(8) It is advised to start with the pharmacological treatment when this exceeds 140/90 mmHg; in patients with diabetes or chronic renal failure the treatment should start with values of 130/80 mmHg. The national survey of risk factors showed a greater prevalence of high blood pressure in women.(5)

- 4. Diabetes mellitus:** There is an increase in the prevalence of this pathology associated to increase in obesity. In the National Survey, it was observed in 11.9% of the population, with a greater prevalence in women, at a greater age, in the Southern and Middle regions of the country.(5) The risk of presenting coronary artery disease is parallel to the increase of hemoglobin A1c with predominance in women vs men. The probability of developing cardiovascular disease at one year in diabetic women is 3 to 5 times greater in comparison to men, in whom it is 2 to 4 times.(9) The relative risk of presenting a new myocardial infarction is 1.5 to 4.5 between diabetic women in comparison to non-diabetic ones.(10) Considering the frequency and severity of cardiovascular disease in diabetes, it was assigned the condition of equivalent to coronary artery disease in the Adult Treatment Panel III.(11)
- 5. Dyslipemia:** The high levels of total cholesterol and LDL, as well as low HDL levels are cardiovascular risk factors both in men and women.(12) Women between 20 and 50 years old tend to present better cholesterol levels; after menopause these increase in a similar way to men. This increase could be due to the absence of estrogens, sedentarism, hypothyroidism (highly prevalent in women), smoking, obesity that not only increases total cholesterol, but that also decreases HDL. In women younger than 65 years old, there is a strong relationship of high LDL levels with cardiovascular disease, while in those older than 65 years old, this relationship is observed with low levels of HDL.(13) It was proven that low HDL levels are the most significant predictor of death by coronary disease in women.(14) The 1% increase in HDL levels is associated to a decrease in risk in women of 3-5%, while in men is just 2%.(15) The management with statins showed in the CARE study, that with pravastatin women show a greater reduction in endpoints.(16) In the Heart Protection Study, where

simvastatin was used, the benefit of treatment was similar in both sexes.(17)  
Hypertriglyceridemia appears as a significant risk factor in elderly women.(18)

- 6. Sedentarism:** The National Survey of Risk Factors showed that 46.2% of the population does not perform a minimal level of physical activity. Men develop more intense physical activity and women more moderate activity, with a similar prevalence in both groups.(5) The beneficial effects of exercise on CAD are less marked in women, with a lower increase of HDL and less weight loss.(19)
- 7. Overweight and obesity:** The estimations on obesity that are used more often are: body mass index ( $BMI = \text{weight in kg} / \text{height in cm}^2$ ) and measurement of abdominal waist. The BMI values obtained are translated in this way: between 18.5-24.9 normal weight; 25-29.9 overweight; 30 to 34.9 obesity degree I; 35-39.9 obesity degree II, more than 40 obesity degree III (morbid). Normal abdominal waist values are up to 88 cm in women and up to 102 cm in males according to ATP III, but the International Federation of Diabetes considers as normal values 80 cm for women and 94 cm for men.(11-20) In Argentina, 49.1% of people have overweight and/or obesity, being higher in men, in people between 50 and 64 years old, and those with lower income and less education.(5)
- 8. Female sexual hormones:** Powerful modulators of coronary risk factors; for this reason the presence of cardiovascular disease is rare before menopause.(21) Hormone replacement therapy (HRT) suggests having a cardioprotective effect, although randomized studies did not support its use because not only they do not reduce cardiac events, but in women with more than ten years of menopause it shows a mild increase of them.(22-23) We still have to clarify the risk of HRT in most of women that start the treatment close to the onset of menopause to control symptoms.
- 9. Special situations proper of women:** There are unique conditions in women that may lead to the appearance of cardiovascular disease, especially at an early age, such as polycystic ovary (that is associated to metabolic syndrome), early menopause (with central hypoestrogenemia), use of oral contraceptives (that when associated to another risk factor may generate severe situations) and hormonal replacement therapy.

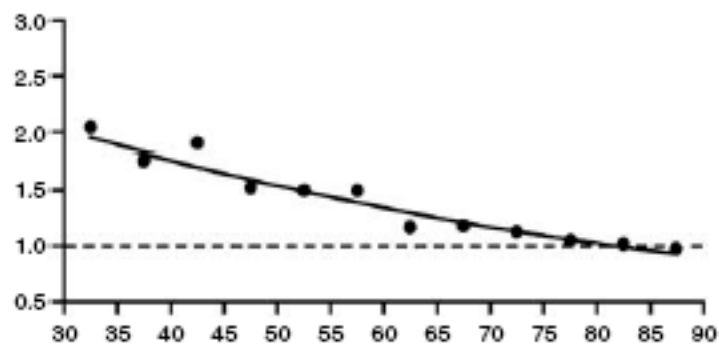
Also, history of pregnancy of high risk by hypertension, diabetes, or history of children with low weight (these children usually develop HTN when adults) are conditions that increase cardiovascular risk.

Other pathologies such as thrombophilia and vasculitis (systemic lupus erythematosus, arteritis, Takayasu disease) may predispose to appearance of non-atherosclerotic CAD.

### **Differences of gender in CAD**

In women, there are differences that are important to be able to make an early diagnosis and a proper treatment of CAD. Between them, we highlight that women present a greater age at the beginning of symptoms, a greater prevalence of co-morbidities (hypertension, diabetes, and heart failure) and differences in the initial manifestation of cardiovascular disease:

1. The most frequent presentation is chest angina in contrast to men who present myocardial infarction and sudden cardiac death.
2. Presentation symptoms of acute myocardial infarction are atypical, such as nausea or jaw pain.
3. Myocardial infarction not acknowledged in women is 50% vs 33% in men.(24)
4. The prognosis of acute coronary syndromes (ACS) in women has a worse prognosis than men in ACS with ST elevation, equal evolution in ACD, without ST elevation and better prognosis in unstable angina.(25) Recently, it was found that the differences in the evolution of women that presented acute myocardial infarction during hospitalization only applies to the group younger than 65 years old, since in elderly women mortality is similar to that of men. See Figure 3.



**Figure 3:** Odd ratios of in-hospital death due to myocardial infarction in women compared to men adjusted by age.

**Diagnosis of suspicion of cardiovascular disease in women**

Historically, diagnostic accuracy of non-invasive tests in women was associated with low sensitivity and specificity to detect CAD. It was thought that this occurred due to the low prevalence of cardiovascular disease in women.(26) In fact, evidence based on diagnostic tests was low and besides, underestimated results and those women with abnormal tests received less treatment.(27)

In some registries, it is observed that women with stable angina had less stress tests and less coronary angiographies in spite of having a greater functional class.

The American Heart Association proposes an algorithm to evaluate women with suspicion of CAD based on risk.

Table 1.

<b>Age</b>	<b>Typical/defined angina</b>	<b>Atypical/probable angina</b>	<b>N o n - a n g i n a precordial pain</b>
50-59	Intermediary	Intermediary	
60-69	High	Intermediary	Intermediary
> 70	High	Intermediary	Intermediary

**Table 1:** Candidates for diagnostic tests by pre-test risk. (Modified from Exercise testing guidelines of the American College of Cardiology.)

If they present low risk, it can be evaluated effectively with ergometer test or stress echo. If the risk is intermediary or high, it benefits from strain myocardial perfusion (using SPECT or PET techniques) and using the technetium-99 radiotracer, which is the proper one in obese women or men. In recent years, evidence is growing about using calcium score to evaluate asymptomatic women, given its high negative predictive value.(28)

As to treatment, there is clinical evidence of benefits with aspirin, beta blockers, ACEI, and statins in women after myocardial infarction. In spite of this, it was observed that in the female sex, there is less statins and anti-platelet therapy indicated.(29)

There are other differences in the results of the treatment of CAD.

- With the use of **fibrinolytic** treatment, mortality reduction is lower in women. More bleeding complications occur, especially in elderly women and more risk of re-infarction is observed.
- **CABG** presents more complications in the post-operative period and greater mortality in the female sex. Women benefit with arterial bypass and pump-less surgery. During the post-operative period, they present less relief of symptoms and less recovery of functional class.
- When performing **coronary angioplasty**, greater complications and mortality, and cardiac events are observed, as well as the need for CABG. Using glycoprotein IIb/IIIa inhibitors is associated to a greater risk of bleeding, probably related to doses administered.

The situation in Argentina can be known through the data from the Survey on Acute Myocardial Infarction that was carried out in 2005.(30) The analysis showed that women were older (71.3 vs 60.5 years old), there was a higher percentage of hypertensive patients and women took longer to consult. All these differences observed, had statistically significant value.

As to the management, there were also differences observed that coincide with international literature, as a lower percentage of successful reperfusion, and less female patients who underwent primary angioplasty.

### **Significance of prevention:**

#### **Guidelines of prevention of cardiovascular disease in women from the American Heart Association, 2007**

The American Heart Association, in the prevention guidelines, proposes a new risk classification for women and divides it in: **high risk, with risk, and optimal risk.**(28)

The objective of this new classification is providing a proper prevention to all women, in whom with the life expectation increase also increase the risk of cardiovascular disease. Moreover, taking into account the limitations of the Framingham Score, since it does not add family history of CV disease, underestimates the risk of women, young men, and non-white population.

This is how it proposes the following risk classification:

- **High risk:** Established CAD, cerebrovascular disease, peripheral arterial disease, abdominal aortic aneurysm, final stage of chronic renal disease, and diabetes mellitus. The risk at 10 years of the Framingham Score >20%.
- **With risk:** One or more **risk factors** (smoking, poor diet, sedentarism, obesity, family history, hypertension, dyslipemias.) Subclinical evidence of vascular disease, metabolic syndrome, low capacity for exercise in graduated ergometer test.
- **Optimal risk:** Risk at 10 years of the Framingham Score lower than 10% and healthy life style, without risk factors.

Once the risk is established, recommendations should be established, to perform both primary and secondary prevention.

### **Recommendations to prevent CV disease in women. Class I**

Quitting smoking: women should not smoke and should avoid environments with cigarette smoke. It should be advised, nicotine replacement therapy should be indicated, or another pharmacotherapy to quit smoking along with the program to quit it.

Physical activity: 30 minutes of moderate-intense physical activity is advised every day of the week. The recommended time is 60-90 minutes.

Rehabilitation: cardiovascular or neurological rehabilitation programs are suggested (for patients with ACS, chronic angina, or that has recently started, stroke, peripheral vascular disease.)

Diet: Diets rich in fruits and vegetables should be consumed, with a high content in fibers; fish at least twice a week. Limit the ingest of saturated fatty acids <10%, if possible <7%, and cholesterol <300 mg/day; alcohol: one cup/day; sodium ingest <2.3 g/day. Consumption of “trans” fatty acids consumption should be the least possible.



Maintain the weight: A proper balance between ingest and physical activity should be made to maintain or shed weight.

Consumption of Omega 3: In women with CAD, capsules of Omega 3 fatty acids could be added to the diet (850-1000 mg) and for hypertriglyceridemias, high doses (2-4 g).

Depression: Bare in mind the association of CAD and depression. Refer to the specialist for diagnosis and treatment.

#### Interventions for risk factors:

Hypertension: Diet with restriction of sodium, alcohol, consumption of fruits, vegetables, and skimmed dairy products, doing physical activity, and controlling weight. The pharmacological treatment should start when BP exceeds 140/90 or in diabetic patients with renal failure, 130/80.

Lipids: the objective should be: LDL <100 mg/dl, HDL >50 mg/dl, and triglycerides <150 mg/dl and noHDL (total cholesterol - HDL) <130 mg/dl. To reach these values, a proper diet should be followed, along with physical activity, and pharmacological treatment with statins, fibrates, and niacin.

Diabetes mellitus: The objective is reaching HbA1c <7% with changes in life style and pharmacotherapy.

#### Preventive intervention with drugs:

Aspirin: In women of high risk, unless there is contraindication. If there is intolerance, indicate clopidogrel.

Beta blockers: Always in women with ACS, left ventricular dysfunction, with or without symptoms, unless there is contraindication.

ACEI-sartanes: In women after infarction with clinical evidence of heart failure or left ventricular dysfunction <40% or diabetes. If they present intolerance to ACEI, sartanes should be indicated.

Aldosterone blockers: In women with myocardial infarction that receive ACEI and beta blockers with left ventricular dysfunction <40% symptomatic.

### **Class III (not useful or effective, possibly dangerous)**

Hormone replacement therapy: It should not be used based on the Hers II and WHI studies. (31-32)

Antioxidant supplements, such as Vitamin E, Vitamin C, beta-carotene should not be used in primary or secondary prevention.

Aspirin to prevent myocardial infarction in women younger than 65 years old is not advised.

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