

## Menopause, atherosclerosis and cardiovascular risk: a puzzle with too few pieces

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**Summary.** Ischemic heart disease represents the first cause of death among women, and the total number of coronary deaths among women in Europe is higher than among men. However, the rates of “premature” deaths (below the age of 75) are higher by far in men. It has been hypothesized that this biological advantage for women, as compared to men, with regard to ischemic heart disease, may depend, at least in part, on the protective effect of estrogen on the cardiovascular system, and that women with an earlier menopause may be at higher risk of subsequent cardiovascular events. Longitudinal studies on breast cancer and osteoporosis have observed a lower risk of cardiovascular events among women with “later” menopause, as well as among those taking hormone replacement therapy (HRT) from the early post-menopausal years. However, the majority of prospective randomized trials investigating the effects of HRT on cardiovascular events have failed to show any protective effect. Recent angiographic data seem to contradict the protective effect of a prolonged fertile lifespan on the extent of coronary atherosclerosis. The present review is aimed at discussing the available data on the relation between age at menopause and ischemic heart disease.

**Key words:** menopause, coronary artery disease, coronary angiography, atherosclerosis.

### **Menopausa, aterosclerosi e rischio cardiovascolare: un mosaico con troppo poche tessere**

**Riassunto.** La cardiopatia ischemica rappresenta la principale causa di morte tra le donne, con un numero assoluto di morti in Europa superiore che nel sesso maschile. Tuttavia, il tasso di mortalità cardiovascolare “prematura” (prima dei 75 anni di età) è di gran lunga superiore negli uomini. È stato ipotizzato che questo vantaggio biologico per quanto riguarda la cardiopatia ischemica nelle donne rispetto agli uomini sia almeno in parte dovuto a un effetto protettivo degli estrogeni sul sistema cardiocircolatorio in età pre-menopausale e che, pertanto, una menopausa precoce possa individuare una categoria di donne a maggior rischio di eventi cardiovascolari. Studi longitudinali su cancro della mammella e osteoporosi hanno osservato un minor rischio di eventi cardiovascolari nelle donne con menopausa “tardiva”, come pure in quelle che assumevano terapia sostitutiva ormonale, a patto che fosse iniziata precocemente dopo la menopausa. La maggior parte degli studi prospettici fin qui condotti sulla terapia ormonale sostitutiva non ha osservato invece un effetto protettivo. Recenti dati angiografici paiono contraddire l’ipotesi di

un effetto protettivo di una prolungata vita fertile sull’estensione della malattia coronarica. Questa revisione ha lo scopo di descrivere in maniera critica la relazione esistente tra età alla menopausa e cardiopatia ischemica.

**Parole chiave:** menopausa, coronaropatia, angiografia coronarica, aterosclerosi.

 Interview to **Stefano Savonitto**  
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### Introduction

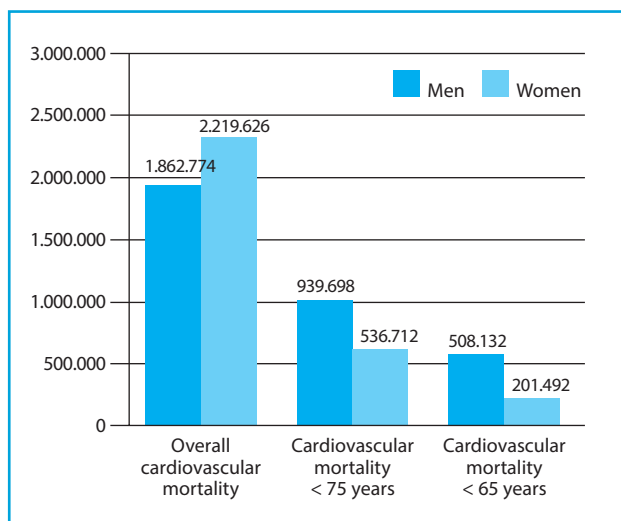
During fertile age, women are exposed to the risk of cardiovascular events to a lesser extent than men, so that “premature” deaths (below 65, as well as 75 years of age) due to cardiovascular events are significantly greater in males. This gap is gradually filled after menopause, so that the absolute number of women who die due to cardiovascular events is higher than that of men (Figure 1). This is the result both of the general population statistics drawn up by the WHO<sup>1</sup> or by the American Heart Association<sup>2</sup> and of the observation of specific pathology registries, such as those of the Italian Coronary Units conducted by the Italian Association of Hospital Cardiologists (ANMCO). As shown in Figure 2, as age advances, the number of women increases as well, doing worse than men only beyond the eighth decade.

### Gender differences in coronary disease

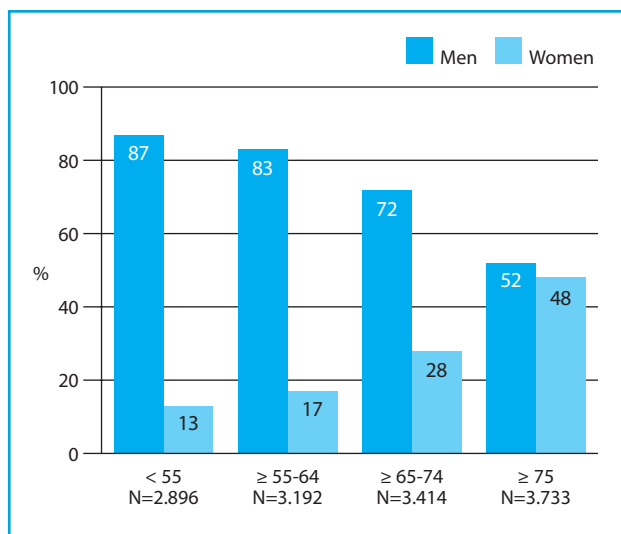
Although coronary atherosclerosis and myocardial infarction risk are intuitively and epidemiologically related, their bond is truly elusive<sup>3</sup>. There are patients with coronaries affected by atherosclerosis that is barely visible with imaging techniques in whom infarction is caused by the rupture of an almost isolated plaque, while there are others with widespread disease that do not experience infarction or do so at a very advanced age. The pathogenesis of infarction differs between women and men at younger ages, but tends to equalize at more advanced ages.

In younger women, in whom myocardial infarction is truly rare, the most typical mechanisms are those of spontaneous coronary artery dissection<sup>4</sup> (typically in

women who have recently given birth, but not only), or of coronary thrombosis in the absence of plaques (e.g., in the course of therapy with estrogen and progestin associated with other thrombotic risk factors, such as smoking). Serious inflammatory pathologies, such as systemic lupus erythematosus and certain forms of arteritis, may also be a rare cause of infarction. The juvenile diabetes may cause accelerated atherosclerosis, as well as myocardial infarction in both men and women. In young males, the association of familiarity of early infarction and cigarette smoking constitutes a deadly pro-infarction combination<sup>5</sup>.



**Figure 1.** Overall and “early” cardiovascular mortality in Europe broken down by gender. (WHO data referred to in Nichols M et al, 2014<sup>1</sup>).



**Figure 2.** Percentages of men and women with ST Segment Elevation Myocardial Infarction (STEMI) hospitalized in Italian Coronary Units. Data of the registries of the Italian Association of Hospital Cardiologists (ANMCO).

At older ages and especially in post-menopausal women, the pathological mechanisms that lead to infarction tend to equalize between men and women. In the nineties, the WISE (Women’s Ischemia Syndrome Evaluation)<sup>6</sup> study revealed that the incidence of obstructive coronary artery disease in women with angina increases dramatically after the age of 50, with a prevalence of 48% in the 55-64 age group and 79% for women >75 years of age. Autopsy studies have shown that 76% of fatal acute myocardial infarctions in men is determined by the rupture of an atherosclerotic plaque, whereas, in women, plaque rupture occurs only in 55% of cases, with an increased prevalence of plaque erosion in women, and particularly in women under 50 years of age<sup>7</sup>. The more recent PROSPECT study has confirmed that although women with acute coronary syndrome have more comorbidities and risk factors than men, coronary angiography shows that coronary artery disease was less extensive by both angiographic and IVUS (Intravascular Ultrasound) measures<sup>8</sup>. The more recent advent of OCT (Optical Coherence Tomography) has made it possible to study *in vivo* the characteristics of the atherosclerotic plaque in patients with myocardial infarction. The data of the recent Italian OCTAVIA<sup>9</sup> study, which investigated by OCT 140 patients presenting with myocardial infarction (STEMI) undergoing primary angioplasty, showed that plaque rupture is the most frequent cause of coronary thrombosis and that there are no differences in the morphology of the coronary lesion responsible for infarction between age-matched men and women. In accordance with the epidemiology of myocardial infarction, in this study the mean age of men was 65 years and that of women 68 years.

As a whole, these data show:

- Partially different mechanisms and risk factors for myocardial infarction in the two sexes in young age (pre-menopausal women);
- Lower overall extension of atherosclerosis in women with myocardial infarction;
- Final mechanism similar between women and men in advanced age.

The LADIES ACS study<sup>10</sup> demonstrated a lower extent of atherosclerosis in women after menopause compared to age-matched men beyond the age of 85 years; the study evaluated prospectively the coronary angiograms of male and female patients with acute coronary syndrome compared by age classes.

### Menopause and cardiovascular risk

A direct consequence of menopause is a reduced production of estrogens that could expose women to an increased risk of cardiovascular events. Risk appears to be double in women with menopause induced by bilateral

ovariectomy, as it is associated with a sudden, earlier drop in hormone levels<sup>11</sup>. However, it is yet to be determined whether the loss of cardiac protection in menopausal women is attributable to reduced estrogen production alone. The protective effect of estrogen on the cardiovascular system has been attributed to several mechanisms<sup>12</sup>

- Increased expression of genes involved in prostacyclin synthetase and nitric oxide synthetase that ultimately has a vasodilatory effect;
- Inhibition of the development of atherosclerosis with an anti-inflammatory and anti-oxidant mechanism which could prevent plaque rupture, while there seems to be no protection against plaque erosion (which is rarer);
- Rapid re-endothelialization following vascular injury;
- Improved levels of blood lipids with reduced levels of total and LDL cholesterol and increased values of HDL cholesterol;
- Recent data also seem to demonstrate a lower incidence of diabetes in women with later menopause and longer reproductive life span (total number of years from menarche to menopause)<sup>13</sup>.

This biological rationale has led to attempts to assess whether menopausal age may somehow affect cardiovascular risk in women and, in particular, if premature menopause can expose women to a greater extent of atherosclerosis. Menopause at young age may result in a shorter period of estrogen exposure with a relative anticipation of the physiological process of aging. In the past, two major prospective studies (The Framingham Heart Study<sup>14</sup> and The Nurses' Health Study<sup>15</sup>) had confirmed an increased risk of cardiovascular disease in women in menopause, with inconclusive results regarding the relationship between age at menopause and cardiovascular risk. In particular, The Nurses' Health Study observed a significant association between early menopause and increased cardiovascular risk; this risk was however observed only in women smokers with the possibility, therefore, that exposure to smoke could represent a confounding factor. Once the data were adjusted by age and cigarette smoking, women with natural menopause (even if early) did not show a higher risk of coronary artery disease than premenopausal women<sup>16</sup>. However, the main problem of both studies was the post-menopause follow-up, which was too short to have a significant number of cardiovascular events. In subsequent years, various studies have been carried out always with mixed results. An analysis carried out on a large cohort of American women with natural menopause showed that a younger age at menopause is associated with a small increase in mortality for all causes, including cardiovascular diseases<sup>17</sup>. In a study carried out on Dutch women enrolled in a breast cancer screening project, it was ob-

served that every year of delay of menopause is associated with a reduced risk of cardiovascular death, supporting the hypothesis that a reduced exposure to endogenous estrogen increases the risk of mortality due to cardiac causes<sup>18</sup>. A meta-analysis of 18 studies on the relationship between menopause and cardiovascular events did not find instead any significant relationship between the post-menopausal status and cardiac events; a slight excess of cardiovascular risk was associated only with early menopause, especially in women with artificially induced menopause<sup>11</sup>. A more recent population study, the Multi-Ethnic Study of Atherosclerosis, has demonstrated instead a positive association between early menopause and coronary artery disease and stroke<sup>19</sup>, thus joining that body of evidence according to which early menopause can identify a category of women "at risk" who could benefit from aggressive primary cardiovascular prevention. According to this approach, early menopause is a causal factor of atherosclerosis, mediated by the earlier disappearance of the protective effect of estrogen.

A complementary, or opposite, vision considers early menopause as a "marker" of a state of physical and/or social frailty that is scarcely modifiable by strictly hormonal interventions, such as hormone replacement therapies. Or even, as suggested by an *ad hoc* analysis of the Framingham Heart Study, it could be the same set of cardiovascular risk factors (smoking, hypertension, diabetes, dyslipidemia, obesity and physical inactivity) to cause both "reproductive aging" and early menopause<sup>20-22</sup> (Figure 3). Also pathologies associated with early atherosclerosis (chronic inflammatory diseases, kidney diseases) can be associated with early menopause. In this case, there seems to be no need to indicate hormone replacement therapy, but rather an aggressive treatment of these risk factors and comorbidities. This is a very complex puzzle in which there are very few pieces, and even less perspectives.

### Age of menopause and extent of atherosclerosis

The recent LADIES ACS Study<sup>10</sup> specifically investigated whether the age at menopause is linked to the extent of coronary artery disease. This study enrolled women in post-menopausal age stratified over 4 decades, undergoing coronary angiography for acute coronary syndrome. For each decade of age from 55 years to over 85 years, the study enrolled 200 patients with a ratio of 2:1 between women and men (age and sex matching), with the men serving as controls with regard to age and risk factors. The severity of the coronary disease was assessed by coronary angiography (through coronary angiographic scoring), with centralized analysis of the exams. The main result of this study was that after 55 years, the

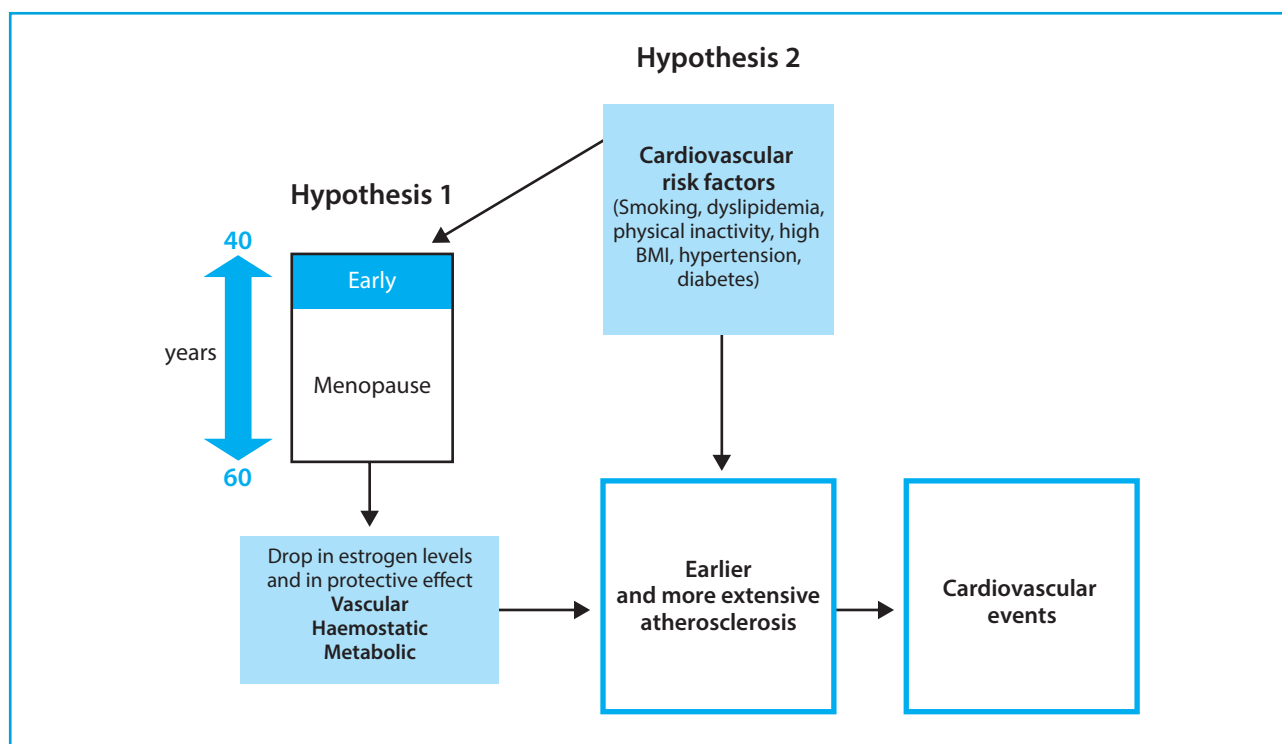
extent of the coronary disease shows a modest correlation with absolute age, but no correlation with the age of menopause. The study concluded that, on the one hand, women in post-menopausal age have less coronary damage than age-matched men and, on the other hand, that age is in itself a determinant of coronary atherosclerosis, probably because it represents the “area under the curve” of exposure to atherogenic risk factors.

### Data from studies on hormone replacement therapy

Hormone replacement therapy (HRT) is used in menopause in order to reduce vasomotor symptoms, osteoporosis, and dyspareunia and to improve mood. The data on the cardiovascular protective effect of HRT in post-menopausal women are conflicting. While broad observational studies had observed an association between HRT and lower cardiovascular risk<sup>23-26</sup>, the two main randomized studies showed a detrimental effect, particularly in terms of risk of thromboembolism<sup>27,28</sup>. These studies had a number of methodological shortcomings, such as having enrolled women in menopause for years and with previous coronary artery disease

events, and having used estrogen-progestin mixtures that were not ideal in terms of cardiovascular disease. The more recent KEEPS Trial compared the effects of HRT versus placebo on carotid intima-media thickness (CIMT) and on cardiovascular risk markers, in a population of post-menopausal women without prior cardiovascular events. The results of this study showed no advantage of HRT over placebo in reducing the progression of carotid artery sclerosis or endothelial function, despite the improvement of some cardiovascular risk markers<sup>29,30</sup>. Similarly, the ELITE Trial<sup>31</sup> demonstrated that HRT with estradiol in post-menopausal women is not associated with less coronary atherosclerosis as assessed by coronary artery CT.

According to the “hormone timing hypothesis”, the majority of studies on HRT were biased by a very late start of therapy after menopause<sup>32</sup>. The ELITE Trial<sup>31</sup> too compared the effects of estrogen therapy started less than 6 years or ten years after menopause on atherosclerosis. The data of a randomized Danish study on osteoporosis bucked the trend. In this study, HRT (17-β-estradiol and norethisterone acetate [a progestin of the androgen line!]) was administered to women with an average age of 50 years, within one year from menopause<sup>33</sup>. In this study, with a 10-year follow-up plus an additional 6 af-



**Figure 3.** Two hypotheses on the relations between menopause (and “early” menopause), atherosclerosis and risk of cardiovascular events. “Hypothesis 1” indicates that estrogen has a protective effect on the progression of atherosclerosis, and that the earlier drop in estrogen levels reduces estrogen exposure time, accelerating atherosclerosis and increasing the risk of cardiovascular events in women with “early” menopause<sup>12</sup>. “Hypothesis 2” argues that the same risk factors of cardiovascular disease, in addition to causing *per se* accelerated atherosclerosis, are themselves involved in causing early menopause, with the adverse consequences mentioned above<sup>21</sup>. The two hypotheses do not exclude one another. BMI, body mass index.

ter discontinuation of therapy, the group treated with HRT had a significantly lower incidence of the combined endpoint of death and hospitalization for myocardial infarction or heart failure, without any increase in thrombotic or neoplastic events. This endpoint was not however pre-specified and the study was not sized to exclude problems of cardiovascular safety.

In conclusion, though the studies are currently inconclusive in terms of cardiovascular events, there are no signs of a protective effect in terms of coronary atherosclerosis.

### “Gender-related” aspects

Despite men and women share similar cardiovascular risk factors, some of them, such as cigarette smoking, type 2 diabetes mellitus and psychosocial factors (gender-related), seem to have a greater weight in women. In particular, the INTERHEART<sup>34</sup> trial identified 9 modifiable risk factors for myocardial infarction in women: smoking, arterial hypertension, diabetes mellitus, obesity, diet, physical activity, alcohol consumption, serum lipid and lipoprotein levels and psychosocial factors. According to this study, precisely the latter seem to influence particularly the onset and the clinical course of ischemic heart disease in women who seem to be more exposed to psychosocial risk factors, such as depression and stress at work and at home. Also the lesser propensity of women to do regular physical activity, mediated by various “gender-related”<sup>35</sup> reasons, can have a significant impact on the subsequent incidence of coronary events<sup>36,37</sup>.

### Conclusions

Several studies show that women appear to be protected against coronary heart disease compared with men. This “advantage” was attributed generally to the anti-atherogenic effect of estrogen. In the past, this hypothesis was supported by certain studies which showed an association between early menopause (physiologically or surgically induced) and increased risk of cardiovascular events in the years following the onset of menopause. The most recent data in the literature, however, have not supported this hypothesis, demonstrating unequivocally that there is no significant correlation between age at menopause and extent or severity of coronary artery disease. What, however, seems to be confirmed is that female patients in menopause have a significantly lower degree of coronary injury compared to male patients and that, regardless of age, in the post-menopausal period, women have a lower prevalence of coronary obstructive disease than men as regards the entire spectrum of acute coronary syndromes. Several

pathology studies have shown that the coronary artery diseases in women is delayed from 10 to 15 years compared to men. In the recent LADIES ACS Study this “advantage” of women persists until the ninth decade of age. The fact that the age at menopause does not correlate with the severity of coronary injury suggests that factors other than estrogen blood levels may play an important role in the “advantage” of women over men in terms of the incidence of coronary atherosclerosis. It is possible to assume that this advantage can be mediated by a more favorable cardiovascular risk profile in younger women<sup>38</sup> characterized, for example, by a better lipid profile and a later onset of type 2 diabetes mellitus<sup>13</sup>. Alternatively, it can be assumed that early menopause is merely a “marker” of poorer health in women and that it is therefore associated with early mortality. Moreover, it cannot be excluded that some typical features of vascular disease in women (positive remodeling, arteriosclerosis with widespread pattern, endothelial dysfunction, microvascular disease) play a significant role in ischemic heart disease in women and are decisive for the onset of angina, ischemia and disability. Overall, the number of studies specifically designed to study ischemic heart disease in women is very modest<sup>39</sup>, so the pathophysiological framework appears to be confused, almost like a puzzle with too few pieces. The recent “call for action” from European and American associations to focus on ischemic heart disease in women<sup>40,41</sup> is more than justified.

#### Key messages

- In premenopausal age, women are more protected than men against ischemic heart disease.
- Also in post-menopausal age, women have on average a lesser extent and severity of coronary artery disease.
- Age at menopause does not correlate with a different degree of coronary artery disease.
- Age is, *per se*, a determinant of the degree of coronary disease.
- At present, there is no evidence for the use of hormone replacement therapy in order to prevent cardiovascular events in women in menopause.

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*Conflict of interest statement:* the Authors declare no potential conflicts of interest or any financial or personal relationships with other people or organizations that could inappropriately bias conduct and findings of this study.

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