CORONARY ARTERY DISEASE AFTER MENOPAUSE AND THE ROLE OF ESTROGEN REPLACEMENT THERAPY

S. Savonitto, D. Colombo°, F. Prati•*

*** Manzoni Hospital, Lecco.**
°Clinical Pharmacology, Milano.
• San Giovanni Hospital and Centro per la Lotta Contro l'Infarto CLI Foundation, Roma.

Abstract

Coronary artery disease risk in women increases after menopause, and this fact led to hypothesize a vascular protective effect of estrogen, either directly on blood vessels or mediated through metabolic factors (cholesterol and blood sugar). However, evidence of a vascular protective effect are inexistent, since angiographic studies have failed to show any relation between fertile lifespan and extent of coronary disease, as well as any effect of Hormone Replacement Therapy (HRT) on the age-related progression of coronary artery disease. Most studies on HRT and cardiovascular events were intrinsically limited by the fact that enrolled women were old (on average 65 years or more) and too late after menopause onset (on average 10 years). In addition, most studies enrolled women after myocardial infarction or coronary revascularization procedures. A more appropriate study testing the "timing hypothesis" of HRT should include early post-menopausal women: however, particularly if state-of-the-art control of established risk factors would be pursued, cardiovascular event rates in such a population would be so low as to require several thousands of patients and long-term follow-up. Current recommendations are reassuring with regard to the safety of HRT which, however, should not be prescribed in order to prevent cardiovascular events.

Cardiovascular disease represents the first cause of mortality among women, and in Europe more women than men are now dying of Coronary Artery Disease (CAD) [1]. However, premature coronary deaths, that is before the age of 65 and even 75 years, are more common among men [1]. This observation implies that, at younger age, women are protected against CAD, and this specific protection is the most likely cause of the overall survival advan-

tage of women over men. No such advantage is being observed for cancer, the second more frequent cause of death for both sexes [2].

The most plausible cause of this fact has been considered to be the protective effect of estrogen in premenopausal women [3]. Estrogen exerts direct effects on blood vessels as well as systemic effects that may delay the development and progression of atherosclerosis. Its rapid vasodilatory effects are mediated by direct actions on vascular endothelial cells. In addition, estrogen also alters serum lipid concentrations (reduced LDL and increased HDL cholesterol), coagulation and fibrinolytic systems, antioxidant systems, and the production of other vaso-active molecules, such as nitric oxide and prostaglandins, all of which can influence the development of vascular disease [3]. In terms of atherosclerosis, pathology data suggests that estrogen has an anti-inflammatory effect on atherosclerotic plaques, resulting in plaque stabilization, whereas plaque erosion, a peculiar substrate for thrombosis in premenopausal women, does not appear to be inhibited by estrogen [4]. Studies using IntraVascular UltraSound (IVUS) have shown less coronary atherosclerosis in women, with respect to men, despite a heavier burden of risk factors [5]. Prospective age and sex-matched data from the LADIES Acute Coronary Syndrome (ACS) study confirms that the 10-year advantage of women with regard to the amount of angiographically measurable coronary atherosclerosis persists beyond the eighth decade of age [6].

Fertile lifespan, mortality and cardiovascular events

This is a complex issue, difficult to address from the methodological point of view, but it represents the basis for the development of goal-directed treatment. This question was addressed by transversal [7] as well as longitudinal [8,9] studies investigating the relation between age at menopause and all cause as well as cardiovascular mortality. Some of these studies were specifically investigating cardiovascular health [9], whereas others were longitudinal studies on cancer [7]. An important longitudinal study on more than 12.000 women followed up for up to 20 years within a screening project of breast cancer in Utrecht found that any year of delay in menopause was associated with a 2% reduction in the risk of cardiovascular mortality, a benefit that extended for at least two decades after menopause. In this study, the benefit was consistent also among women having undergone oophorectomy, whereas in others the association was consistent only for naturally occurring menopause, and not for surgical menopause by bilateral oophorectomy [7,10]. Also, some studies have found a significant association between early menopause and mortality only in smokers, which may well be a confounder for cardiovascular mortality [9]. In the most recent and complete meta-analysis of 32 studies that included 310.329 women, those who experienced menopause below the age of 45 appeared to have a greater risk of CHD, CVD mortality, and all-cause mortality, whereas no association was found with stroke risk. By contrast, an age of 45 to 49 years at onset of menopause, compared with 50 years or older at onset, had no apparent association with adverse outcomes [11]. In the LADIES ACS study [6], the frequency of prior myocardial infarction was identical (15%) among women with menopausal age below or above median (50 years). In pa-

tients with no history of myocardial infarction, the mean age at acute coronary syndrome was 73+10 years both among women below median menopausal age, and among those above the median.

The hypothetical link between a longer fertility lifespan and a lower risk of cardiovascular events after menopause might be found in a more favorable risk factor profile as calculated using the Framingham risk score [12], or through a lower risk of subsequent diabetes mellitus [13]. An alternative hypothesis considers age at menopause as a biological marker of health and aging: that is, women that are biologically destined to a longer life tend to have also a longer fertile life [7], whereas women with any kind of evident or latent disease tend to experience menopause at a younger age [7,10]. Finally, among 695 premenopausal women followed up in the Framingham Heart Study, a significant association was found between an earlier age at menopause and higher premenopausal serum cholesterol and blood pressure [14], leading the Investigators to conclude that "heart disease risk determines menopausal age rather than the reverse".

Extent of coronary artery disease in women with more prolonged exposure to estrogen, either physiological or pharmacological

As previously mentioned, pathology [4], IVUS5 and angiography [6] data have shown less CAD in women as compared to men, an advantage that persists for decades after menopause. This advantage has been plausibly attributed to the effect of estrogen through a number of vascular protective mechanisms [3]. Direct consequences of this vision would be that: a) women with "early" menopause should have more extensive CAD and an earlier occurrence of clinically manifest CAD; and b) the therapeutic administration of estrogen might reduce, or delay, atherosclerosis. This evidence does not exist, and prospective studies to investigate this issue have been scarce so far. The LADIES ACS study was the first to specifically investigate the relation between age at menopause and the extent of coronary artery disease [6]. The Investigators enrolled 426 women and 249 men (with sampling ratio 2:1 of women vs age-matched men) undergoing coronary angiography due to an ACS. Enrolment was stratified in 4 age classes from 55 years to >85 years, with mean age 74 years (IQR 65-82 years). The extent of coronary atherosclerosis was assessed in a corelab and classified by using the Gensini score, which considers both critical and subcritical stenoses in a hierarchical order. A specific menopause questionnaire was administered to women during index hospital stay. The mean Gensini score was 60+36 in men vs. 50+32 in women (P <.001), being higher in men at any age. The Gensini score in women showed a weak association with age (R2 0.127; P=0.0129), but not with menopausal age (R20.063; P=0.228). As shown in figure 1 also no significant association was found between fertility lifespan (i.e. the time in years between menarche and menopause) and Gensini score [6]. A recent metanalysis [11] assessed the relation between age at menopause and carotid atherosclerosis (only two studies with these measurements): pooled RR (95% CI) for the risk of carotid atherosclerosis for 3388 participants was 0.74 (0.63-0.87) when comparing women 50 years or older with women younger than 50 years at onset of menopause.

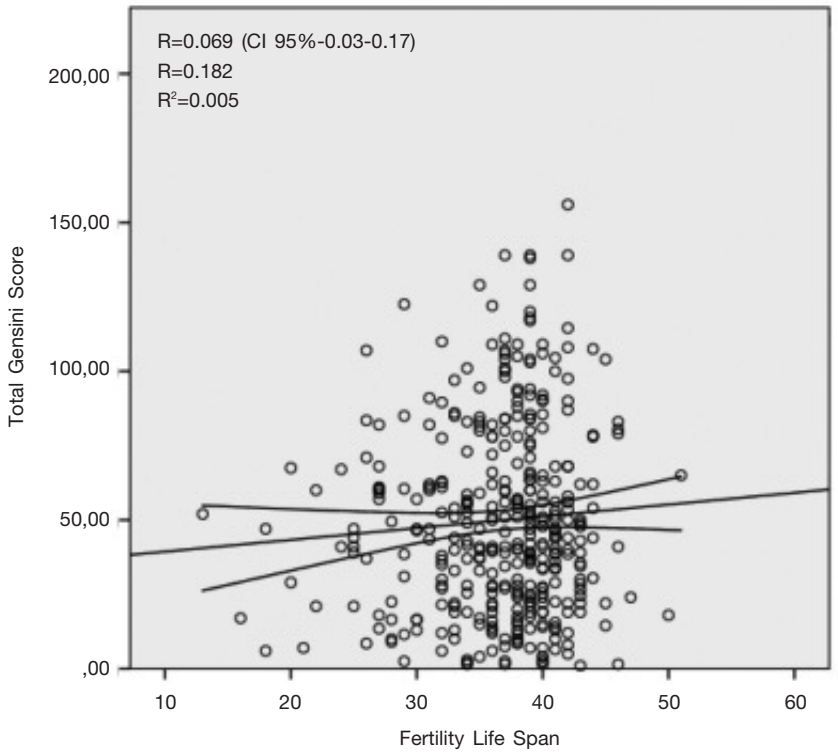

Fig. 1. Correlation between Gensini score and fertile lifespan (years), calculated as age at menopause minus age at menarche.

Effect of Hormone Replacement Therapy (HRT) on atherosclerosis and CV outcomes

Post-hoc analyses of prospective cohort studies in the 1980s indicated that postmenopausal HRT was associated with a significantly lower risk of coronary heart disease [15], which prompted speculation that such therapy could be used to prevent coronary events. However, subsequent randomized trials failed to show any benefit of HRT with regard to coronary events (tab. I). One explanation is that in observational studies, women were younger (approximately 50 years of age) and closer to menopause (typically within 2 years) when they initiated HRT than were the women included in randomized trials (mean age about 65 years, typically >10 years past menopause). This so-called "timing hypothesis" suggests that the effects of HRT on atherosclerosis and coronary heart disease depend on the timing of the initiation of hormone therapy relative to menopause.

Studies on the progression of atherosclerosis (carotid and coronary) seem to be, at least in part, in agreement with this hypothesis (tab. I). In fact, the Estrogen in the Prevention of Atherosclerosis Trial (EPAT) of early HRT intervention in healthy postmenopausal women did show some benefit in terms of reduced progression of carotid intima media thickness [16], whereas the Wom-

Table II - Issues and possible actions to increase the impact of the new agent sacubitril/valsartan in clinical practice.

Study ref (n)	*endpoint*	*intervention*	*Follow-up (Y)*	*Men Age (Y)*	*Years from MP*	*Prior CVE*	*Result*
EPAT [16] (222)	Progression of carotid IMT	E vs placebo in healthy women with LDLc>130 mg/dL	2	60	Not reported	excluded	Reduced progression of ATS only in w not taking statins
WELL-HEART [17] (226)	Angiographic CDS	E vs E+P vs placebo	3.3	63.5	18	At least 1 coronary stenosis	No effect in both groups
ERA [18] (309)	Angiographic CDS	E vs E+P vs placebo	3.2	66	Not reported	MI 45% PCI 51%	No effect in both groups
WAVE [19]	Angiographic CDS	E vs E+P vs placebo	2.8	65	Not reported	MI 45%	No effect in both groups
ELITE [20] (643)	Carotid IMT, Angiographic CDS	E or E+P vs placebo	5	55 EG, 64 LG	3.5 ET 14 LT	excluded	Reduced CIMT progression only in ET. Coronary ATS no change
HERS [21] (2763)	CHD death or MI	E + P vs placebo	4.1	67	18	QWMI 17% PCI 45% CABG 42%	No effect Increased thrombosis
WHI [22] (16,608)	CHD death or MI	E + P vs placebo	5.2	63	Not reported	10%	No effect Increased MI
DANISH [24] (1006)	Death, HF, MI	E or E+P vs control in healthy women	11-16	50	0.5	excluded	Reduced CV events

ATS= Aterosclerosis; CDS= Change in Diameter Stenosis; CABG= Coronary Artery Bypass Grafting; CV= Cardiovascular; E= Estrogen; ET= Early Treatment; IMT= Intima-Media Thickness; LT= Late Treatment; MI= Myocardial Infarction; P= Progestin; PCI= Percutaneous Coronary Intervention;

en's Estrogen–progestin Lipid-Lowering Hormone Atherosclerosis Regression Trial (WELL-HART), failed to show any benefit of HRT in secondary prevention with regard to coronary lesions [17].

Similarly, the Estrogen Replacement and Atherosclerosis trial [18] and the Women's Angiographic Vitamin and Estrogen (WAVE) trial [19], compared HRT and placebo in postmenopausal women with regard to the angiographic progression of CAD: no effect was observed with treatment in both trials which, however, enrolled women with a mean age of 65 years, and about half had had a prior MI. In the ELITE study [20], 643 healthy women were randomly assigned, in a 1:1 ratio, to receive oral [17] β-estradiol (plus progesterone vaginal gel in the case of intact uteri) or matching placebo within strata of early postmenopause (<6 years since menopause) and latepost-menopause (≥10 years since menopause). The median age at enrollment was 55 years in the early-post-menopause stratum, and 64 years in the late-post-menopause stratum, and the median time since menopause was 3.5 years in the early-post-menopause stratum and 14 years in the late-post-menopause stratum. HRT significantly reduced the rate of progression of CIMT (primary endpoint) in the early treatment group, whereas no such effect was observed in the late treatment group (p=0.03 for interaction between strata). However, no effect at all was observed in both groups with regard to coronary CT data (secondary endpoint).

In terms of CAD events, no benefit from HRT was observed in the Heart and Estrogen/progestin Replacement Study (HERS) (tab. I), again as secondary prevention in women with average age of 67 which had had prior Q wave MI, PCI or CABG [21]. The primary endpoint in the Women Health Initiative (WHI) was the rate of CHD (defined as CHD death plus total myocardial infarction rate). Combined estrogen and progestin therapy showed a trend toward an increased risk for CHD after 5 years of follow-up, which persisted through 8.6 years (HR, 1.22 [CI, 0.99 to 1.50]) [22]. For the overall enrolled population, there was no reduction in the risk for CHD with estrogen alone after nearly 8 years of follow-up (HR, 0.95 [CI: 0.78 to 1.15]), though subgroup analysis in the unopposed estrogen part of the study of women having undergone hysterectomy did reveal a potential reduction in CHD in women aged 50 to 59 years (HR, 0.59 [CI: 0.38 to 0.90]) but not in women aged 60 to 69 or 70 to 79 years, a finding that warrants confirmation in future studies.

A study more suitable to prove the timing hypothesis was the Danish Osteoporosis Prevention Study [23], which involved a cohort of women who were, on average, 50 years of age and 7 months past menopause when they were randomly assigned to receive estradiol alone or in combination with sequential norethisterone acetate. This study showed a significantly lower risk of coronary heart disease (a composite of death, admission to hospital for heart failure, and myocardial infarction) at 10 years of follow-up among women who received treatment than among women who received no treatment (hazard ratio 0.48, 95% CI 0.26 to 0.87; P=0.015). In this study, no excess risk of any cancer, breast cancer, stroke and venous thrombus embolism was observed in the HRT group. However, as expected from the young women's age at enrolment, the number of events was relatively small to draw any definite conclusion.

Current recommendations for HRT

As briefly discussed in the present review, experimental evidence of a protective effect of estrogen with regard to coronary atherosclerosis and cardiac events is scarce [24]. Angiographic studies neither show a relation between menopausal age and coronary atherosclerosis, nor an effect of HRT on CAD progression. Most studies on HRT have included women which were too old and after too many years of menopause, whereas the better designed study [23] was too small to be conclusive. Among the issues not discussed here are the type (type of estrogen and progestin) and duration of HRT. Some expert committees and scientific societies, such as the US Preventive Services Task Force [25], the Canadian Task Force on Preventive Health Care and the American Academy of Family Physicians, have taken a strong position against the postmenopausal use of HRT (either estrogen alone in women without uteri, or combined estrogen and progestin in women with uteri) for the prevention of chronic conditions. Other Societies have discouraged the use of HRT for the sole aim of preventing CAD events, though reassuring doctors and patients about the cardiovascular safety of HRT when administered to cure menopausal symptoms. Two important sets of recommendations have been issued recently.

The National Institute for Clinical Excellence (NICE) has the following recommendations [26] in order to assist patients and physicians in decision making:

- HRT does not increase cardiovascular disease risk when started in women aged under 60 years, but does not affect the risk of dying from cardiovascular disease;
- HRT with oestrogen alone is associated with no, or reduced, risk of coronary heart disease;
- HRT with oestrogen and progestogen is associated with little or no increase in the risk of coronary heart disease;
- taking oral (but not transdermal) oestrogen is associated with a small increase in the risk of stroke (which, however, is very low in women aged under 60 years).

The 2016 Revised Global Consensus Statement on menopausal hormone therapy (MHT) [27] has been endorsed by The International Menopause Society, The North American Menopause Society, The Endocrine Society, The European Menopause and Andropause Society, The Asia Pacific Menopause Federation, The International Osteoporosis Foundation and The Federation of Latin American Menopause Societies. With regard to the specific issue of HRT and cardiovascular events, this statement conclude that:

- RCTs and observational data as well as meta-analyses provide evidence that standard-dose estrogen-alone MHT may decrease the risk of myocardial infarction and all-cause mortality when initiated in women younger than 60 years of age and/or within 10 years of menopause.
- Data on estrogen plus progestogen MHT initiated in women younger than age 60 years or within 10 years of menopause show a less compelling trend for mortality benefit, and evidence on cardio-protection is less robust with inconsistent results compared to the estrogen-alone group.

With the inherent limits described in the present review, these recommendations may assist patients and physicians when deciding for type and duration of HRT in early postmenopausal women in order to improve quality of

life, sexual function and other menopause-related complaints, such as joint and muscle pains, mood changes and sleep disturbances.

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