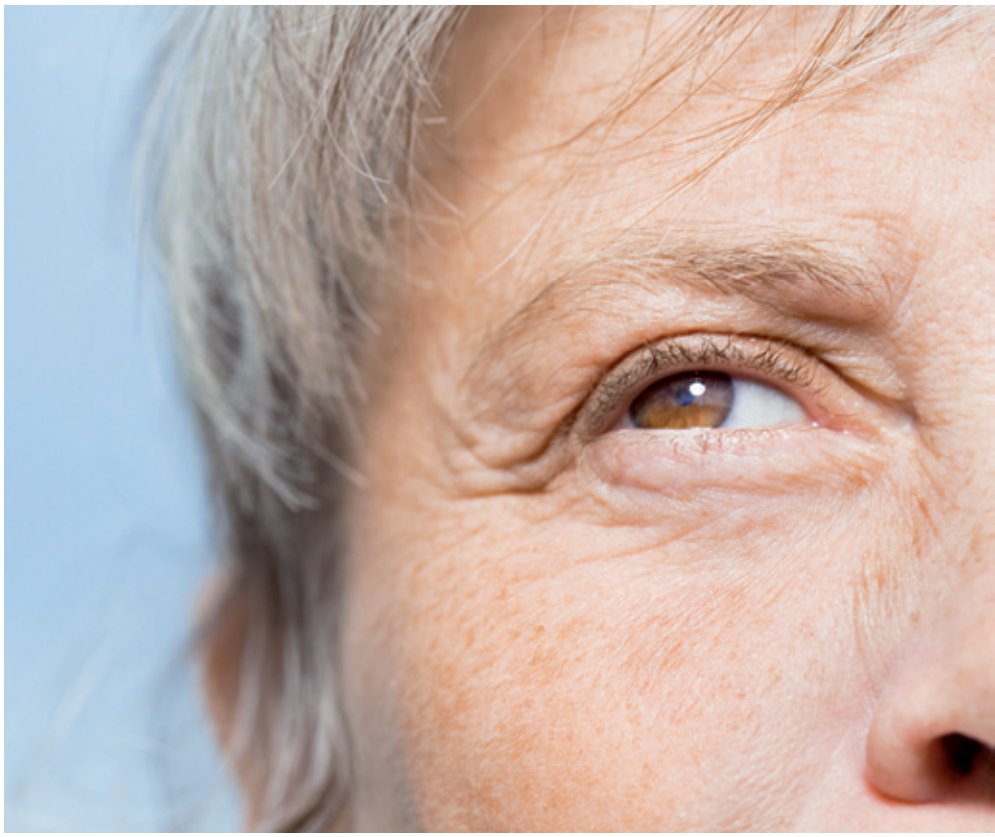
Age at menopause and infarction. Results of an Italian study

Interview with ***Stefano Savonitto***
Cardiovascular Department,
Manzoni Hospital, Lecco, Italy



Your team carried out a study on coronary heart disease in women with myocardial infarction after menopause. Could you illustrate the results of this study and their significance?

The "LADIES ACS" study[1] ("study in women with myocardial infarction"), published in the *American Journal of Medicine*, is a collaborative effort of nine Italian hospitals and the Rome Centre for the Fight against Infarction. The study, made possible also by financial support from Novartis, aimed to assess whether the age at which a woman reaches menopause affects the extent of coronary disease in post-menopause years. In fact, contrary to what many women believe, the leading cause of death in post-menopausal women is not cancer, but cardiovascular diseases. Epidemiological data suggest that early menopause (before the age of 50) may be associated with a higher and earlier risk of heart attack compared to women with late menopause (after 55). However, no one had ever verified whether this risk could be associated with a more severe coronary disease. To clarify this, we reviewed the coronary angiograms of 675 consecutive patients hospitalized for myocardial infarction, dividing them prospectively into four age groups, from 55 onwards. For each age group, we evaluated 133 women and 67 men (ratio of 2:1), considering men as control group for the age factor. In women, we used a specific questionnaire to collect data on their fertile history (menarche, number of children, any miscarriages, hormone therapies and gynaecologic procedures) and menopause (age at menopause, hot flashes, hormone replacement therapy).

Coronary angiograms performed in the participating Hospitals were sent for centralized analysis to the European Imaging Laboratory in Rome, which measured the extent and severity of coronary disease according to the Gensini score: essentially, the higher the score, the greater the extent of the disease. Our data clearly demonstrated that, for each of the age groups considered (up to over 85 years), coronary disease is less severe in women than in men. The extent of coronary disease increases progressively with age in both sexes, while the age of menopause does not show any relationship with the extent of coronary artery disease. In itself, a relatively late menopause has no protective effects against coronary disease. These data are consistent with those of recent studies conducted in the United States with less reliable methods, such as measurement by computerized tomography of the amount of calcium in the coronary arteries.

The implications of this study are partially speculative, because the relationship between the extent of coronary atherosclerosis and the risk of infarction is not as strict as many believe: in other words, some people (especially women) may have a heart attack although their arteries are in fairly good condition, while others with heavily atherosclerotic coronary arteries never had a heart attack. On the other hand, these data provide a partial explanation of why, so far, maintaining estrogen levels through drugs in menopause has not proved to be an effective preventive measure against heart attacks. This, without entering into a discussion about the limits of the studies conducted so far on hormonal replacement therapy. Conversely, it has been clearly demonstrated that reducing classic coronary risk factors, such as hypertension, diabetes, hypercholesterolemia, smoking and sedentary lifestyle, has strong protective effects.

The WHO has emphasized the need to develop gender medicine in order to optimize therapies and prevention for the female target, in which drugs and diseases behave differently than in the male target. As a cardiologist, what directions do you think should be taken to develop gender research?

For precautionary reasons, partly related to the sensitive nature of clin-

ical research, women of childbearing age are less likely to be enrolled in clinical trials. In later ages, the incidence of cardiovascular diseases is in any case higher in men up to the eighth decade. On the other hand, when women become prevalent (i.e. after the age of 80), clinical trials become more difficult to conduct due to the presence of comorbidity and increased follow-up problems. For these reasons, on the whole women are less studied.

WHO data on causes of death in Europe show that currently more women than men die from cardiovascular causes (2,220,000 women die every year from cardiovascular disease in Europe, versus 1,863,000 men), but early mortality (before age 65 and even before age 75) is far higher in men. The study of cardiovascular diseases in women is therefore partly connected to the study in old age.

On the other hand, many of the treatments that women need at any age are badly designed in terms of gender-specific use. Drug doses for adults are not adjusted for weight (lower in women) and for distribution volume (smaller in women). This has an impact on many of the side effects of drugs, such as hypotension and the risk of bleeding. Women's coronary arteries are smaller than those of men and less suitable to receive, for example, the stents we use to keep the vessels open after angioplasty.

Over the past year, both the European Society of Cardiology and the American Heart Association have published papers denouncing the lack of specific data in women; however, ad hoc studies, like our own, are still very rare. This can be partly explained by the difficulty of obtaining funding for this type of studies. Our collaborative group for the study of infarction in elderly patients (Elderly ACS Collaboration) is one of the very few active examples, if not the only one at the moment. Even in our case, however, the 'gender-related' focus came as a consequence, due to the fact that, as our population is over 75 years of age, exactly half of our patients are women. In a study published in 2015 in the *Journal of the American College of Cardiology* we demonstrated that an aggressive approach (aimed at early revascularization) in women with infarction aged over 75 years was just as effective as in men.

"Younger" women, while not entirely immune from atherosclerotic disease (especially in the case of smokers, diabetics and dyslipidemic patients), often have a worse prognosis than men of the same age, perhaps precisely because they are treated less aggressively and with less suitable tools. Therefore, on the one hand we should concentrate on elderly women because of their epidemiological prevalence. On the other hand, we need to develop diagnostic and therapeutic tools that are more targeted for relatively younger women. Italian data collected through the Periodic logs of the Hospital Cardiologists Association (ANMCO) show that over the past 15 years we have significantly increased the aggressiveness of treatment for heart attack in both men and women of all ages, with significant reduction in mortality.

However, at all ages, the mortality of women with infarction remains higher than that of men. Therefore, there is ample room for improvement through greater attention to the female gender.

In this regard, it would be desirable to achieve a greater synergy between researchers, industry, clinicians, scientific societies and regulatory bodies, with the aim to promote ad hoc studies. Scientific journals often require contributors to present their data broken down by sex and age groups, but this is merely a retrospective evaluation of data which is not intended for a specific evaluation of the disease and treatment in women. Prospective studies like the LADIES ACS are extremely rare.

Interview by
Mariapaola Salmi

Sources:

1. Savonitto S, Colombo D, Franco N, et al. Age at menopause and extent of coronary artery disease among post-menopausal women with acute coronary syndromes: a prospective age and sex-matched study. The LADIES ACS study. Am J Med. 2016; 129(11):1205-12.

See also: Romano IJ, Lenatti L, Franco N, Misuraca L, Morici N, Leuzzi C, Corrada E, Colombo D, Savonitto S. Menopause, atherosclerosis and cardiovascular risk: a puzzle with too few pieces. Ital J Gender-Specific Med 2016; 2(3): 110-116.