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Age at menopause, extent of coronary artery disease and outcome among postmenopausal women with acute coronary syndromes

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ABSTRACT

Background: Early menopause has been associated with increased cardiovascular mortality, but prospective studies investigating outcomes of postmenopausal women with acute coronary syndromes (ACS) in relation to menopausal age are lacking.
Methods: We analyzed the 1-year outcome of 373 women with acute myocardial infarction enrolled in the Ladies ACS study. All patients underwent coronary angiography, with corelab analysis. Menopause questionnaires were administered during admission. Menopausal age below the median of the study population (50 years) was defined as "early menopause". The composite 1-year outcome included all-cause mortality, recurrent myocardial infarction and stroke.
Results: The mean age at index ACS was 73 years (IQR 65–83) for women with early menopause, and 74 (IQR 65–80) for those with late menopause. Patients with early menopause had more prevalent chronic kidney disease (12.8% vs 5.9%, $p = 0.03$), whereas there were no differences in all other clinical characteristics, extent of coronary disease at angiography (as assessed by Gensini and SYNTAX scores), as well as interventional treatments. Within 1 year, women with late menopause had significantly better outcome as compared with those with early menopause (6.5% vs 15.3%, $p = 0.007$). At logistic regression analysis, late menopause was independently associated with better outcome (OR 0.28; 95% CI 0.12–0.67; $p = 0.004$). With each year's delay in the menopause the adjusted risk decreased by 12% (OR 0.88, 0.77–0.99, $p = 0.040$).
Conclusion: Despite comparable clinical and angiographic characteristics, women with late menopausal age experience better outcomes after an ACS as compared with those with early menopause.

1. Introduction

Age at onset of menopause has been shown to be an independent predictor of subsequent cardiovascular events and mortality, with later menopause associated with lower risk [1–6]. Among the potential mechanism of this association are genetic factors that would be responsible of both early reproductive and cardiovascular aging [7], early withdrawal of the vascular protective effect of estrogen [8,9], and a role of the classical cardiovascular risk factors which might be the cause or the consequence of early reproductive failure [10,11]. However, clinical studies investigating the outcomes of postmenopausal women with acute coronary syndrome (ACS) in relation to their age at menopause onset are lacking. In the report of the Ladies ACS study, we showed that age at menopause was not related to the extent of coronary artery disease among postmenopausal women with an ACS [12]. In the present paper, we report the one-year follow-up of that cross-

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sectional study, to address the issue of whether menopausal age is associated with clinical outcome after an ACS.

2. Methods

The Ladies ACS study (NCT01997307) is a prospective, multicenter investigation including postmenopausal women and age-matched men with an ACS, stratified in 4 ten-year age groups (55–64, 65–74, 75–85 and >85 years) with a sampling ratio of 2:1 of women vs men. The details of the study design have been described previously [12]. The focus of the study was angiographic, with a corelab analysis of the angiograms collected at the study sites. However, the investigators of 6 out of 10 participating centers (contributing with 94% of the study population) volunteered to perform a one-year follow-up to investigate the relation between their clinical and angiographic findings and outcome.

2.1. Inclusion criteria

For a patient to be eligible, the following characteristics were required: a) symptoms suggestive of acute myocardial ischemia; b) a typical rise and fall in serum troponin levels [13], and c) electrocardiographic signs of myocardial ischemia. Such characteristics are consistent with the diagnosis of acute myocardial infarction (MI), either with or without ST-segment elevation. All study participants had a clinical indication to coronary angiography as per routine in the participating centers. There were no exclusion criteria, besides a patient's inability to recall reproductive and menopause history, and inability or unwillingness to provide informed consent to the study. Fertile life and menopause history was collected using a specific questionnaire.

2.2. Data collection

A web-based case report form (Mediolanum Cardio Research, Milan, Italy) was used to collect data on the personal characteristics (age, body weight, body mass index), the relevant risk factors for coronary disease (hypertension, diabetes mellitus, smoking, dyslipidemia, physical activity), prior clinical history (MI, coronary angioplasty, bypass surgery, and stroke), prognostically relevant variables (such as serum creatinine, chronic kidney disease, blood haemoglobin, left ventricular ejection fraction [LVEF]); characteristics of the acute coronary syndrome (electrocardiographic changes, troponin elevation, Killip class, heart rhythm); angiographic data, coronary revascularization procedures and medications during admission, as well as drugs prescribed at discharge.

Coronary angiograms collected at the participating centers were assessed by an independent core laboratory blinded to patients' age, sex, ST-segment status, and clinical data (European Imaging Laboratory, Rome, Italy). The extent of coronary atherosclerosis at angiography was quantified for each patient using the Gensini score, which includes both angiographically nonsignificant and significant stenoses [14,15]. Diagnostic angiograms were also scored according to the SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery (SYNTAX) score algorithm, a comprehensive anatomic assessment of the coronary disease derived from various preexisting anatomic classifications [16].

Follow-up data were collected by hospital visits or telephone calls. The study was conducted in conformity with the Declaration of Helsinki.

2.3. Menopause questionnaire

Women's questionnaire included age at first and last menstrual period, the number of full-term pregnancies, use of oral contraceptives, ongoing and past hormone replacement therapy and whether a hysterectomy and/or oophorectomy had been performed. Age at menarche was defined as the age at the first menstrual period. Age at menopause was defined as age at last menstrual period. Duration of reproductive life span was generated by subtracting age at menarche from age at menopause [17].

2.4. Endpoints

The composite study outcome was the 1-year occurrence of all-cause death, recurrent MI (same definition used for the index ACS event) and stroke. As secondary outcome, we considered also re-hospitalization for cardiovascular causes (including severe recurrent ischemia, heart failure, cardiac arrhythmia and systemic embolism).

2.5. Statistical analysis

We compared demographics, clinical and angiographic characteristics according to age at menopause, dichotomized by the median of 50 years, which corresponds to the median age at menopause in Europe [18]. Continuous variables were compared using the Student *t*-test for symmetric variables and the Mann-Whitney test by ranks for skewed variables; the results are presented as means and standard deviations (SD) or medians and 25th and 75th percentile, respectively. Discrete variables were compared using the chi squared test and presented as absolute and relative frequencies per category. The exact date of post-discharge events within one-year follow up was not available. Therefore, we fitted a multivariable logistic regression model in order to derive the odds ratio (ORs) and the 95% confidence interval (CI) of the composite event, adjusted for the following variables: age, LVEF, chronic kidney disease, age at menopause (tested as dichotomous and continuous variable) and SYNTAX score. All analyses were performed using the package STATA/SE 14 (StataCorp LP, College Station, TX).

3. Results

3.1. Baseline characteristics

The study population consists of 373 patients, and the median age at menopause was 50 years: 203 women had had menopausal age of ≤50 years, and 170 ≥ 50 years. The mean menopausal age was 47 years in women with early menopause, as compared with 53 years in those with late menopause ($p < 0.001$). Menopause was physiological in 79% of women with early menopause, as compared with 97% of those with late menopause ($p < 0.001$). Hormone replacement therapy was assumed by 18% of women with early menopause as compared with 9.4% of those with late menopause ($p = 0.021$).

As shown in Table 1, the baseline clinical characteristics, including cardiovascular risk factors, prior medical history and clinical presentation at index ACS events were similar in the two menopausal age groups, except for chronic kidney dysfunction, which was more frequent among women with early menopause. Women with early menopause were taking significantly more ACE-inhibitors. The coronary angiographic findings and revascularization procedures were also similar between menopausal age groups, as were the treatments administered at discharge (Table 2).

3.2. One-year outcomes

As reported in Table 3, the rate of the aggregate outcome events was significantly lower in women with late menopause. All individual endpoint components (all-cause mortality, recurrent MI and stroke) were numerically lower in women with late menopause. The adjusted odds ratios for the composite endpoint of death, MI and stroke (OR 0.28; 95% CI 0.12–0.67; $p = 0.004$), as well as for the composite endpoint including rehospitalization for cardiovascular causes (OR 0.54; 95% CI 0.31–0.94, $p = 0.026$) were significantly reduced for women with late menopause. The association of late menopause with better outcome was confirmed at a sensitivity analysis including only women with natural menopause: OR 0.25; 95% C.I. 0.10–0.65, $p = 0.004$ for the primary outcome, and OR 0.41; 95% CI 0.20–0.84, $p = 0.015$ including cardiovascular rehospitalizations. A further sensitivity analysis excluding patients with chronic kidney dysfunction yielded similar results. When age at menopause vas modeled as a continuous variable, each year's delay in the menopause was associated with a 12% reduction in risk of the composite outcome event (OR 0.88, 0.77–0.99, $p = 0.04$).

4. Discussion

The LADIES ACS study was aimed at investigating whether age at menopause is associated with the extent of angiographically quantified coronary atherosclerosis in the post-menopausal decades [12]. The answer was clearly that it is not: the extent of coronary disease increased with aging, but didn't show any correlation with menopausal age, both in terms of the overall burden of coronary lesions (Gensini score), and in terms of critical lesions (SYNTAX score). However, despite the similarity in coronary atherosclerosis, the present follow-up data show that women with earlier menopause had significantly worse 1-year outcome as compared with those with age at menopause above median.

The higher cardiovascular risk associated with early menopause, particularly in terms of cardiovascular mortality, has been shown in a longitudinal study of 12,115 postmenopausal women living in Utrecht, Netherlands, aged 50–65 years at enrolment in a breast cancer screening project [1]. In that study, with each year's delay in the menopause the cardiovascular mortality risk decreased by 2%. That finding was confirmed by subsequent metanalyses of longitudinal studies of women without overt heart disease at baseline [2–5]. A recent report of the U.S. National Health and Nutrition Examination Survey also showed that a 1-year increase in the reproductive duration was associated

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