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.

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Keywords:
Acute coronary syndromes
Sex
Menopause
Coronary angiography
Outcome

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 medical history for coronary disease (hypertension, diabetes mellitus, smoking, dyslipidemia, physical activity), prior clinical history (MI, coronary angioplasty, bypass surgery, and stroke), and past vascular conditions (hysterectomy and/or oophorectomy had been performed). Age at menarche 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].

2.3. 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 menopause was defined as age at the 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 (OR) 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).
The pathophysiological mechanism of this association remains disputed so far. Modifiable risk factors have been shown to account for 90% of MIs in both sexes [20], the relation of menopausal age with the risk of events, particularly stroke and angina showed an association with adverse cardiovascular outcome independent of other powerful predictors, such as age, LVEF and SYNTAX score. These findings are consistent with the results of longitudinal studies in women without known cardiovascular disease at baseline, and showing an increased risk of subsequent cardiovascular mortality among women with early onset menopause [1–6]. Early menopause has also been found associated with an increased risk of developing type-2 diabetes [22], which was more frequent among women with early menopause. Whereas age at menopause was not associated with the extent of coronary disease at angiography [12], women with earlier menopause showed significantly worse outcome. All the ischemic components of the composite outcome were more frequent among women with earlier menopause, except rehospitalizations. Importantly, menopausal age showed an association with adverse cardiovascular outcome independent of other powerful predictors, such as age, LVEF and SYNTAX score. These findings are consistent with the results of longitudinal studies in women without known cardiovascular disease at baseline, and showing an increased risk of subsequent cardiovascular mortality among women with early onset menopause [1–6]. Early menopause has also been found associated with an increased risk of developing heart failure later in life [23–25]. In the present study, women with early menopause were taking more ACE-inhibitors prior to admission, which may be an indirect index of prior heart failure symptoms, although baseline LVEF was the same in both groups. Altogether, these data consolidate the concept that early menopause is associated with worse cardiovascular outcome. We found no material differences in baseline characteristics, except for the presence of chronic kidney dysfunction, a powerful prognostic indicator and marker of macro- and microvascular damage [22], which was more frequent among women with early menopause.
Categorical data are expressed as numbers and percentage.

In-hospital and follow-up events according to age at menopause (median age 51 years).

Whether the dynamic component of coronary circulation may differ according to menopausal age, particularly in women with a higher atherosclerotic burden may be matter for further investigation.

4.1. Limitations

The Ladies ACS study enrolled only patients aged ≥55 years. Therefore, patients with very young menopausal age and with an ACS before 55 years were not included. The study was an investigation on angiographically assessed coronary atherosclerosis, including only women undergoing coronary angiography because of an ACS with ischemic ECG changes and elevated troponin levels. Therefore, our conclusion is limited to this study population which, however, represents the large sophisticated imaging methods are not suitable for investigating the vasomotor and microvascular components of coronary circulation, which may play a key role in the causation and outcome of ACS [27,28]. Whether the dynamic component of coronary circulation may differ according to menopausal age, particularly in women with a higher atherosclerotic burden may be matter for further investigation.

Table 2
Angiographic and interventional data stratified according to classes at menopause.

<table>
<thead>
<tr>
<th>Variable</th>
<th>All patients n = 373</th>
<th>Menopausal age ≤ 50 n = 203</th>
<th>Menopausal age ≥ 50 n = 170</th>
<th>p Value</th>
<th>Adjusted odds ratio (95% C.I.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CABG</td>
<td>13 (3.5)</td>
<td>6 (3.0)</td>
<td>7 (4.1)</td>
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<td>0.36 (0.06–1.96) b 0.24</td>
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<td>0.67 b 0.004</td>
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Table 3
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</thead>
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<tr>
<td>Radial access site</td>
<td>298 (79.9)</td>
<td>160 (78.8)</td>
<td>138 (81.2)</td>
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Categorical data are expressed as numbers and percentage.

a Adjusted for age, ejection fraction and SYNTAX score.

b The reference category is age at menopause <51 years.
majority of ACS patients in Europe. The most severe cases (such as those with out of hospital cardiac arrest), and also patients with unstable angina and no troponin elevations (such as many of those with variant angina or pure microvascular angina) have not been included in the Ladies ACS population. However, our results are in the same direction of longitudinal studies with no overt cardiac disease at baseline [1–6], and reinforce their conclusion of an increase cardiovascular risk associated with younger menopausal age.

We had no information on the date of the follow-up events. Considering the short follow-up, the implications of this are however limited.

The limits of menopause reporting using questionnaires several years after actual menopause have been quantified within one year of variation in recall studies [29–31], and appear acceptable for the purposes of the present analysis.

5. Conclusions

Women reporting menopausal age below median have significantly worse outcomes within one year after an ACS, as compared with women with later menopause. This worse outcome is not explained by differences in cardiovascular risk factors, prior cardiovascular events, age at index ACS, severity of coronary angiographic findings and ejection fraction. The pathophysiological reasons behind these findings should be further investigated using functional testing of the endothelium and microvasculature beyond the limits of current imaging methods [28].

Disclosures

None of the authors report any conflict of interest with the specific subject of the study.

References


