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 end-point 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

Table 1
Baseline characteristics stratified according to menopausal age.

Variable	All patients n = 373	Menopausal age ≤ 50 n = 203	Menopausal age > 50 n = 170	p Value
Age (y)[a]	73 (65–82)	73 (65–83)	74 (65–80)	0.79
Age at menopause (years)[a]	50 (47–53)	47 (45–50)	53 (52–55)	<0.001
Fertility life span (years)[a]	38 (34–40)	34 (31–37)	41 (39–42)	<0.001
Age from menopause to ACS (years)[a]	23 (15–32)	27 (19–37)	19 (12–27)	<0.001
Body mass index (Kg/m^2)[a]	25.8 (23.0–29.3)	25.9 (22.9–29.4)	25.7 (23.1–29.3)	0.76
Hemoglobin (gr/dL)[a]	12.8 (11.6–14.0)	12.7 (11.6–14.0)	12.8 (11.6–13.8)	0.62
Creatinine (mg/dL)[a]	0.81 (0.7–1.06)	0.84 (0.7–1.08)	0.80 (0.7–1.05)	0.36
Creatinine clearance (mL/min)[a]	72.6 (53.6–88.4)	70.7 (52.5–88.4)	74.5 (54.5–88.2)	0.39
Left ventricle ejection fraction[a]	50 (40–55)	50 (40–55)	50 (40–55)	0.58
Hypertension	295 (79.1)	164 (80.8)	131 (77.1)	0.24
Hypercholesterolemia	215 (57.6)	115 (56.6)	100 (58.8)	0.41
Smoking habit	118 (31.6)	64 (31.5)	54 (31.8)	0.43
Family history of CAD	73 (19.6)	43 (21.2)	30 (17.6)	0.28
Diabetes mellitus	104 (27.9)	61 (30.0)	43 (25.3)	0.24
Chronic kidney disease	36 (9.6)	26 (12.8)	10 (5.9)	0.03
COPD	22 (5.9)	12 (5.9)	10 (5.9)	0.43
Prior stroke or TIA	31 (8.3)	19 (9.4)	12 (7.1)	0.30
Peripheral artery disease	46 (12.3)	26 (12.8)	20 (11.8)	0.41
Malignancies	32 (8.6)	16 (7.9)	16 (9.4)	0.38
Prior MI	52 (13.9)	30 (14.8)	22 (12.9)	0.37
Prior angina	59 (15.8)	38 (18.7)	21 (12.3)	0.10
Prior revascularization				
Prior PCI	52 (13.9)	29 (14.3)	23 (13.5)	0.42
Prior CABG	27 (7.2)	13 (6.4)	14 (8.2)	0.35
Diagnosis				
STEMI	189 (50.7)	104 (51.2)	85 (50.0)	0.81
NSTEMI	184 (49.3)	99 (48.8)	85 (50.0)	
Killip class presentation				
I	304 (81.5)	164 (80.8)	140 (82.3)	0.89
II	36 (9.6)	19 (9.4)	17 (10.0)	0.96
III	24 (6.4)	14 (6.9)	10 (5.9)	0.91
IV	5 (1.3)	4 (2.0)	1 (0.6)	0.51
Cardiovascular medications taken during the last 30 days prior to hospital admission				
Beta-blockers	143 (38.3)	76 (37.4)	67 (39.4)	0.19
Acetil salicylic acid	131 (51.1)	71 (34.9)	60 (35.3)	0.27
P2Y$_{12}$ inhibitors	40 (10.7)	24 (11.8)	16 (9.4)	0.29
ACE-inhibitors	113 (30.1)	75 (36.9)	38 (22.3)	0.01
Angiotensin receptor antagonists	40 (10.7)	21 (10.3)	19 (11.2)	0.49
Statins	130 (34.8)	68 (33.5)	62 (36.5)	0.16
Diuretics	126 (33.8)	76 (37.4)	50 (29.4)	0.16
Calcium channel blockers	64 (17.1)	33 (16.3)	31 (18.2)	0.23
Oral anticoagulants	26 (7.0)	14 (6.9)	12 (7.1)	0.32
Nitrates	33 (8.8)	20 (9.8)	13 (7.6)	0.29
Anti-arrhythmics	15 (4.0)	9 (4.4)	6 (3.5)	0.32

CABG = coronary artery bypass grafting; CAD = coronary artery disease; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; MI = myocardial infarction; NSTEMI = non-ST-elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-elevation myocardial infarction. TIA = transient ischemic attack.

[a] Expressed as median and interquartile range. Categorical data are expressed as numbers and percentage.

with a 3% reduction in the risk of events, particularly stroke and angina [19].

The pathophysiological mechanism of this association remains disputed so far. Since modifiable risk factors have been shown to account for 90% of MIs in both sexes [20], the relation of menopausal age with the subsequent evolution of these risk factors has been investigated. In an analysis derived from the EPIC-INTERACT study, women with an early age at menopause onset (defined as <42 years) were at higher risk of developing type-2 diabetes [10]. However, a study in a large population-based cohort in the Netherlands showed only a modest impact of menopause on risk factors [21]. An opposite view that a worse heart disease profile determines an earlier menopause was suggested by data coming from Framingham Heart study [11]. In that analysis, 695 women who were premenopausal at the study entry had their cardiovascular risk factors measured and were followed until the time of their natural menopause, showing that every 1% increase in premenopausal Framingham risk score was associated with a decrease in menopausal age of 1.8 years.

We studied the coronary angiograms of postmenopausal women with acute MI, of which 85% were at their first episode [12], and correlated this data with menopausal age, and prospectively with one-year 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. 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 significantly 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

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

Variable	All patients n = 373	Menopausal age ≤ 50 n = 203	Menopausal age > 50 n = 170	p Value
Radial access site	298 (79.9)	160 (78.8)	138 (81.2)	0.77
Gensini score[a]	46 (24–68)	47 (27–67)	44 (22–68)	0.50
Gensini score[b]	49.7 ± 31.5	50.2 ± 29.9	49.2 (33.3)	0.78
SYNTAX score[a]	12 (6–21)	12 (7–22)	12 (5–21)	0.89
SYNTAX score[b]	14.9 ± 12.4	14.9 ± 11.9	15.0 ± 12.8	0.94
Coronary revascularization				
PCI	267 (71.6)	153 (75.4)	114 (67.1)	0.24
CABG	13 (3.5)	5 (2.5)	8 (4.7)	
Total number of lesions treated[a]	1 (1–1)	1 (1–1)	1 (1–1)	0.75
Total number of stents implanted[a]	1 (0–1)	1 (0–1)	1 (0–1)	0.27
Drugs at discharge				
Beta-blockers	304 (81.5)	163 (80.3)	141 (82.9)	0.47
Acetil salicilic acid	348 (93.3)	189 (93.1)	159 (93.5)	0.42
P2Y$_{12}$ inhibitors	309 (82.8)	171 (84.2)	138 (81.2)	0.43
Clopidogrel	162 (43.4)	83 (40.9)	79 (46.5)	
Prasugrel	70 (18.8)	44 (21.7)	26 (15.3)	
Ticagrelor	77 (20.6)	44 (21.7)	33 (19.4)	
ACE-inhibitors	248 (66.5)	141 (69.5)	107 (62.9)	0.14
Angiotensin receptor antagonists	85 (22.8)	43 (21.2)	42 (24.7)	0.15
Statins	336 (90.1)	183 (90.1)	153 (90)	0.40
Diuretics	169 (45.3)	89 (43.8)	80 (47.1)	0.44
Calcium channel blockers	74 (19.8)	34 (16.7)	40 (23.5)	0.15
Oral anticoagulants	39 (10.5)	19 (9.4)	20 (11.8)	0.39
Oral anti-diabetics	53 (14.2)	33 (16.3)	20 (11.8)	0.21
Insulin	41 (11.0)	21 (10.2)	20 (11.8)	0.46
Nitrates	48 (12.9)	25 (12.3)	23 (13.5)	0.48
Anti-arrhythmics	23 (6.2)	13 (6.4)	10 (5.9)	0.48
Proton pump inhibitors	288 (77.2)	165 (81.3)	123 (72.3)	0.02

CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention.
Categorical data are expressed as numbers and percentage.
  [a] Expressed as median and interquartile range.
  [b] Expressed as mean and standard deviation.

outcome, most likely of multifactorial origin and needing more focused investigation.

According to the Ladies ACS study [12], a greater coronary atherosclerotic burden may not play a major causative role with respect to the risk of developing an ACS among women with early menopause. However, coronary angiography is not a sensitive method for investigating coronary atherosclerosis; it stands midway between the calcium score, suitable for screening studies, and more sophisticated imaging techniques, such as those based on intravascular ultrasounds and optical computerized tomography (OCT). The more sophisticated study so far [26], using OCT to characterize plaque morphology and composition among (mostly post-menopausal) women and age-matched men with ST-elevation MI, did not find any quantitative or qualitative difference between sexes, though women had significantly smaller coronary arteries, a feature that might expose them to a higher impact of vasomotor stimuli and more frequent anginal symptoms. However, even these 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.

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

Table 3
In-hospital and follow-up events according to age at menopause (median age 51 years).

Variable	All patients n = 373	Menopausal age ≤ 50 n = 203	Menopausal age > 50 n = 170	p Value	Adjusted odds ratio (95% C.I.)	p Value[a]
Composite 1-year outcome (death, myocardial infarction, and stroke)	42 (11.3)	31 (15.3)	11 (6.5)	0.007	0.28 (0.12–0.67)[b]	0.004
In-hospital death	8 (2.1)	6 (3.0)	2 (1.2)	0.24	0.36 (0.06–1.96)	0.24
Follow-up death	13 (3.5)	9 (4.4)	4 (2.3)	0.27	0.71 (0.19–2.71)	0.63
In-hospital & follow-up death	21 (5.6)	15 (7.4)	6 (3.5)	0.11	0.50 (0.17–1.50)	0.22
In-hospital & follow-up cardiovascular death	6 (1.6)	5 (2.4)	1 (0.6)	0.25	0.32 (0.08–1.29)	0.11
Recurrent myocardial infarction	18 (4.8)	13 (6.4)	5 (2.9)	0.07	0.24 (0.06–0.95)	0.04
Stroke	3 (0.8)	3 (1.5)	0	0.07	–	–
Rehospitalization for cardiovascular causes	42 (11.3)	23 (11.3)	19 (11.2)	0.27	0.97 (0.39–2.37)	0.95
Overall outcome events	77 (20.6)	50 (24.6)	27 (15.9)	0.04	0.54 (0.31–0.94)[b]	0.03

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.

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