

## Original Investigation

# Sex Differences in Acute Coronary Syndrome Symptom Presentation in Young Patients

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**IMPORTANCE** Little is known about whether sex differences in acute coronary syndrome (ACS) presentation exist in young patients and what factors determine absence of chest pain in ACS presentation.

**OBJECTIVES** To evaluate sex differences in ACS presentation and to estimate associations between sex, sociodemographic, gender identity, psychosocial and clinical factors, markers of coronary disease severity, and absence of chest pain in young patients with ACS.

**DESIGN, SETTING, PARTICIPANTS** We conducted a prospective cohort study of 1015 patients (30% women) 55 years or younger, hospitalized for ACS and enrolled in the GENESIS PRAXY (Gender and Sex Determinants of Cardiovascular Disease: From Bench to Beyond Premature Acute Coronary Syndrome) study (January 2009–September 2012).

**MAIN OUTCOMES AND MEASURES** The McSweeney Acute and Prodromal Myocardial Infarction Symptom Survey was administered during hospitalization.

**RESULTS** The median age for both sexes was 49 years. Women were more likely to have non-ST-segment elevation myocardial infarction (37.5 vs 30.7;  $P = .03$ ) and present without chest pain compared with men (19.0% vs 13.7%;  $P = .03$ ). Patients without chest pain reported fewer symptoms overall and no discernable pattern of non-chest pain symptoms was found. In the multivariate model, being a woman (odds ratio [OR], 1.95 [95% CI, 1.23-3.11];  $P = .005$ ) and tachycardia (OR, 2.07 [95% CI, 1.20-3.56];  $P = .009$ ) were independently associated with ACS presentation without chest pain. Patients without chest pain did not differ significantly from those with chest pain in terms of ACS type, troponin level elevation, or coronary stenosis.

**CONCLUSIONS AND RELEVANCE** Chest pain was the most common ACS symptom in both sexes. Although women were more likely to present without chest pain than men, absence of chest pain was not associated with markers of coronary disease severity. Strategies that explicitly incorporate assessment of common non-chest pain symptoms need to be evaluated.

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Chest pain is the hallmark and critical distinguishing symptom used to initiate diagnostic testing for acute coronary syndrome (ACS) and urgent lifesaving therapy. However, up to 35% of patients with ACS do not report chest pain.<sup>1</sup> These patients are more likely to have a misdiagnosis in the emergency department and a higher risk of death compared with those with chest pain.<sup>2</sup> Numerous studies of elderly patient cohorts have shown that non-chest pain presentations are relatively common in women and men. However, women are more likely to present without chest pain than men or have only mild chest pain symptoms, and a higher prevalence of comorbid conditions like diabetes in elderly women may account for some of the sex-based differences in ACS presentation.<sup>3</sup>

Whether these sex differences in ACS presentation and predictors of non-chest pain presentation exist in young ACS populations remains unknown because this group has not been sufficiently studied. Approximately 18% of patients with ACS are younger patients (age  $\leq 55$  years).<sup>1</sup> Women younger than 55 years are more likely to have their ACS misdiagnosed in the emergency department compared with men,<sup>4,5</sup> and young women admitted to hospital with ACS have a higher risk of death compared with their male counterparts.<sup>1,6</sup> Presentations of ACS without chest pain, therefore, may occur more often in younger women compared with younger men.

To clarify this issue and inform the need for sex-specific ACS evaluation recommendations in young adults, we evaluated sex differences in symptom presentation in patients 55 years or younger using standardized data collection in patients hospitalized for ACS. We determined whether absence of chest pain presentation was associated with sex, sociodemographic characteristics, gender identity, psychosocial factors, comorbid conditions, differing severity of ACS, and extent of coronary disease compared with those with chest pain.

## Methods

### Study Participants

Subjects were participants of the GENESIS PRAXY (Gender and Sex Determinants of Cardiovascular Disease: From Bench to Beyond Premature Acute Coronary Syndrome), an ongoing prospective observational cohort study.<sup>7</sup> Patients included in this analysis were enrolled between January 2009 and September 2012. GENESIS PRAXY aims to identify the gender (ie, socially constructed roles, relationships, behaviors that societies ascribe to women and men) and sex (biological characteristics that distinguish women from men) determinants of presentation in patients 55 years or younger with ACS. Patients with ACS admitted to urban tertiary care and community hospital coronary care units, intensive care units, or cardiology wards were enrolled in 24 sites in Canada, 1 site in the United States, and 1 site in Switzerland. In Québec, Canada, a multicenter ethics review allowed the McGill University Health Centre to act as the central review board and coordinate ethics approval for all centers. All other centers received ethics approval from their respective hospital ethics review board.

The diagnosis of ACS was determined by the treating physician based on symptoms and signs at presentation and at least one of the following:

1. Electrocardiographic changes in 2 or more contiguous leads (transient ST-segment elevations of  $\geq 1$  mm, ST-segment depressions of  $\geq 1$  mm, new T-wave inversions of  $\geq 1$  mm, pseudonormalization of previously inverted T waves, new Q waves [one-third the height of the R wave or  $\geq 0.04$  seconds], new R wave  $>$  S wave in lead V<sub>1</sub> [posterior myocardial infarction {MI}], or new left bundle branch block).
2. Increase in cardiac enzyme levels (positive troponin I or T [which all hospitals used] or creatine kinase-MB [CK-MB] value  $> 2 \times$  upper limit of the hospital's normal range or, if no CK-MB value available, total creatinine phosphokinase [CPK] value  $> 2 \times$  upper limit of the hospital's normal range).<sup>8</sup>

The presence of chest pain was not explicitly required for diagnosis.

### Data Collection

#### Symptom Presentation

Symptom presentation for the acute phase of ACS was determined in all participants during hospitalization for ACS using the McSweeney Acute and Prodromal Myocardial Infarction Symptom Survey (MAPMISS).<sup>9</sup> The MAPMISS assesses the presence and intensity of 37 acute MI symptoms present from onset to time of diagnosis. Validation studies for the MAPMISS have been conducted in women and have demonstrated good test-retest validity ( $r = 0.84$ ).<sup>9</sup> Shortness of breath was collected from medical records. Presentation without chest pain was defined as absence or low intensity of any chest pain symptom (general chest pain, pain high in the chest, or left breast pain).

#### Demographic, Psychosocial, Gender Role, and Clinical Characteristics

Patient age, socioeconomic status (SES) as indicated by annual household income (high if  $> \$50$  000), education level (higher if any postsecondary education), marital status, primary earner status, and ethnicity (white vs other) were determined by self-report. Body weight and height to calculate body mass index (BMI, with obesity defined as  $\geq 30$  [calculated as weight in kilograms divided by height in meters squared]), admission blood pressure, and heart rate were obtained from the medical record. Menopausal status in women (premenopausal or perimenopausal vs postmenopausal) was based on self-report (date of last menstrual period and menopausal status). The presence of diabetes mellitus and hypertension were based on self-report and medical records of diabetes, hypertension, or use of diabetes or antihypertensive medications. Feminine and masculine personality traits were determined using the validated short form of the Bem Sex Roles Inventory (BSRI) questionnaire.<sup>10,11</sup> Scores for the BSRI are rated 1 to 7 on a Likert scale for each masculine and feminine self-identified personality trait, with mean scores of 4.9 considered normatively masculine and feminine respectively.<sup>11</sup> Men and women with high scores for both masculinity and femininity are considered to be better able to engage in situationally appropriate behavior, without being impeded by stereo-

typical conceptions of being a man or woman. Depression and anxiety symptoms in the 2 weeks preceding the index hospitalization for ACS were assessed using the Hospital Anxiety and Depression Scale (HADS), with a score higher than 8 on each subscale indicating probable depression or anxiety.<sup>12</sup>

#### ACS Severity and Coronary Anatomy

Severity of ACS was assessed by ACS type (ST-segment elevation myocardial infarction [STEMI] vs non-STEMI [NSTEMI] or unstable angina), as determined by medical record, by peak troponin levels (tertiles above normal value) obtained from day of admission from the medical record, and by the presence and extent of coronary stenosis and Global Registry of Acute Coronary Events (GRACE) score, a validated score used to predict in-hospital and long-term mortality or reinfarction in STEMI and NSTEMI patients.<sup>13</sup> Details on coronary anatomy were provided by cardiac catheterization data included in the medical chart review. These data contained information on presence of coronary stenosis (defined as obstruction of >50% in at least 1 vessel). We also computed a variable for extent of coronary obstruction by adding the number of coronary vessels with stenosis greater than 50%. We obtained data on disease location (left main coronary disease, left anterior descending artery, right coronary artery, and circumflex artery).

#### Statistical Analysis

Baseline characteristics and symptom presentation were compared between men and women using  $\chi^2$  and *t* tests for categorical and continuous variables, respectively. Sex differences in symptom presentation were further stratified by ACS type (ie, STEMI, NSTEMI, unstable angina), but because the findings were similar to the entire study population, we presented data on symptom presentation for all patients with ACS.

To assess the independent association of sex with ACS presentation without chest pain, we estimated risk-adjusted multivariate logistic regression models that included sex, age, gender characteristics, household income, diabetes, hypertension, obesity, depression, anxiety, ACS type, troponin level, and admission heart rate and blood pressure on all patients with ACS in our study. We also repeated the logistic regression model but only including those patients who underwent coronary angiography regardless of revascularization. Ten percent of men and 11% of women did not undergo angiography. In this model, we additionally included presence or absence of stenosis and left main disease.

Furthermore, we used principal components analysis, a pattern-finding and data reduction technique, for the non-chest pain symptoms among those without chest pain to identify key patterns of symptoms. Non-chest pain symptoms were also evaluated for their association with markers of ACS severity (ACS type and troponin tertile using logistic regression and extent of coronary stenosis using linear regression). Patients with missing data (smoking, 1.4% men and 2% women; obesity, 1.4% men and 0% women; troponin level, 0.9% men and 3.6% women; and STEMI status, 1.4% men and 3% women) were excluded in the multiple regression analyses. Analyses were performed using SAS version 9.2 (SAS Institute Inc).

## Results

Of the 1174 eligible patients who were approached for study enrollment (27% women and 73% men), 10% of women and 18% of men declined participation in the study resulting in a final participation rate of 86% (*n* = 1015).

#### Patient Characteristics

The median age of women and men was 49 years, 40% were obese, and more than half of women enrolled in the study were premenopausal or perimenopausal (Table 1). Women were more likely than men to have hypertension, diabetes, and depression. Men had higher mean feminine ratings than average, whereas women did not have higher mean masculine ratings (with mean scores of 4.9 considered normatively masculine and feminine). Women had lower troponin levels and fewer STEMI events but had similar GRACE scores components compared with men. Among those who underwent coronary angiography, men were more likely to have greater than 50% coronary stenosis in at least 1 vessel than women. However, there was no significant sex difference in prevalence of triple-vessel disease or presence of left main disease.

#### Symptoms at Presentation

Of all patients in the ACS cohort, 96.6% of men and 97.0% of women reported at least 1 symptom: either chest pain, shortness of breath, or one of the non-chest pain MAPMISS symptoms. Chest pain was the most common symptom for men and women regardless of ACS type (Figure and Table 2). Women reported a greater number of symptoms than men. The most common non-chest pain symptoms in both sexes regardless of ACS type were weakness, feeling hot, shortness of breath, cold sweats, and pain in the left arm or shoulder.

Women were more likely to present without chest pain than men (19.0% vs 13.7%; *P* = .03). Young women without chest pain had fewer symptoms in general compared with women with chest pain (mean number of symptoms, 3.5 vs 5.8; *P* < .001), with similar findings in men (2.2 vs 4.7; *P* < .001) (Figure). Women without chest pain, however, had more symptoms than men without chest pain. Of those who did not report chest pain, 84.5% of women and 78.4% of men reported at least 1 non-chest pain symptom. The principal component analysis failed to identify a clinically predictive pattern of presenting symptoms in those with and without chest pain and this was found in both women and men.

#### Determinants of ACS Presentation Without Chest Pain

In the univariate analysis, patients with and without chest pain were similar except that patients without chest pain were less likely to have STEMI, had lower troponin levels, and were less likely to have greater than 50% coronary stenosis but were more likely to have left main disease (Table 3). However, in the multivariate model, after adjusting for baseline characteristics including ACS severity, only being a woman (odds ratio, 1.95 [95% CI, 1.23-3.11]) and tachycardia (OR, 2.07 [95% CI, 1.20-3.56]) were

Table 1. Demographic, Clinical, and Anatomic Characteristics According to Sex<sup>a</sup>

Characteristic	Men (n = 710)	Women (n = 305)	P Value
<b>Demographic</b>			
Age, median (IQR), y	49.0 (45-53)	49.0 (46-52)	.59
Postsecondary education	64.8	52.1	<.001
Household income ≥\$50 000	75.4	60.7	<.001
White race	87.3	89.8	.26
Married	51.4	48.2	.35
<b>Gender related</b>			
Primary earner	76.3	42.6	<.001
Masculinity, BSRI mean score (SD)	5.0 (0.9)	4.8 (0.9)	<.001
Femininity, BSRI mean score (SD)	5.5 (0.9)	6.0 (0.8)	<.001
<b>Clinical</b>			
BMI ≥30	39.6	41.8	.51
Smoking	39.7	44.3	.18
Cocaine use, ever	16.2	12.8	.17
Hypertension	45.5	54.1	.01
Diabetes	13.8	24.6	<.001
Family history of premature CAD	20.0	27.5	.01
Previous AMI	14.5	18.0	.16
Previous PCI	12.4	17.7	.03
Previous CABG	3.1	2.0	.31
Previous stroke	1.8	4.6	.01
Previous heart failure	1.1	2.9	.04
Postmenopausal	-	45.6	
Depression	21.0	28.5	.01
Anxiety	37.2	54.8	<.001
STEMI	63.2	50.3	<.001
NSTEMI	30.7	37.5	.03
Unstable angina	5.8	11.8	<.001
Nonelevated troponin level	6.1	9.5	.06
<b>Troponin tertiles</b>			
Lowest	8.3	45.1	<.001
Intermediate	35.0	27.1	.02
Highest	36.6	27.8	.01
GRACE score mean (SD)	70.2 (18.0)	70.8 (19.0)	.66
<b>Patients with angiography<sup>b</sup></b>			
Stenosis, at least 1 vessel >50%	94.8	88.9	<.001
Single vessel disease	33.1	32.8	.95
Double vessel disease	31.7	26.9	.16
Triple vessel disease	30.3	28.8	.66
Left main disease	9.7	11.1	.52
Left anterior descending artery disease	71.2	72.2	.75
Left circumflex artery disease	51.8	47.4	.23
Right coronary artery disease	64.3	54.1	.004

Abbreviations: AMI, acute myocardial infarction; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); BSRI, Bem Sex Roles Inventory (scores for the BSRI are rated 1-7 on a Likert scale for each masculine and feminine self-identified personality trait with mean scores of 4.9 considered normatively masculine and feminine respectively<sup>11</sup>); CABG, coronary artery bypass grafting; CAD, coronary artery disease; CVD, cardiovascular disease; GRACE, Global Registry of Acute Coronary Events score; IQR, interquartile range; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

<sup>a</sup> Data are given as percentage of patients unless otherwise specified.

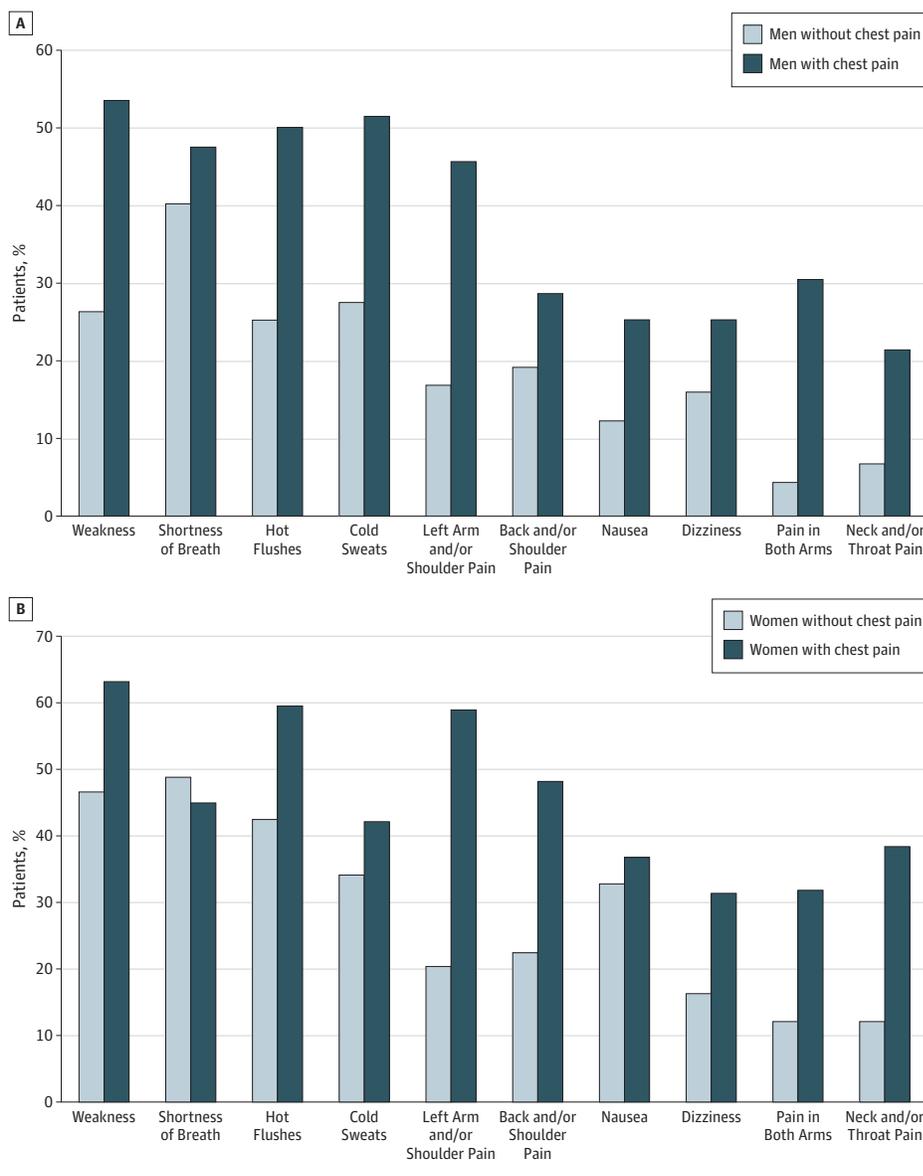
<sup>b</sup> Among 638 men and 271 women with available angiographic data.

independently associated with ACS presentation without chest pain. Among patients who underwent angiography, being a woman (OR, 1.83 [95% CI, 1.11-3.02]), higher household income (OR, 1.80 [95% CI, 1.06-3.05]), tachycardia (OR, 1.93 [95% CI, 1.08-3.44]), and left main disease (OR, 1.94 [95% CI, 1.04-3.63]) were associated with ACS presentation without chest pain, but markers of ACS severity were not.

### Non-Chest Pain Symptoms and Their Association With ACS Severity

The most common non-chest pain symptoms reported in those without chest pain (weakness, feeling hot, shortness of breath, cold sweats, and pain in the left arm or shoulder) were not associated with markers of ACS severity (ACS type, troponin elevation, or extent of coronary stenosis) except for cold sweats

**Figure. Symptoms at Presentation for Acute Coronary Syndrome by Sex and Presence and Absence of Chest Pain**



A, Men with acute coronary syndrome; B, women with acute coronary syndrome.

and weakness. Cold sweats and weakness were associated with increased odds of STEMI compared with NSTEMI or unstable angina (OR, 2.05 [95% CI, 1.50-2.79] vs OR, 1.55 [95% CI, 1.12-2.13], respectively). Total number of ACS symptoms was not significantly associated with ACS type, troponin level elevation, or extent of coronary stenosis.

### Discussion

The most significant findings in this study were that chest pain was the most predominant symptom of ACS in both men and women 55 years or younger, regardless of ACS type. Women had a higher likelihood of presenting without chest pain than men. Most women and men who presented without chest pain,

however, reported at least 1 other non-chest pain symptom, such as shortness of breath or weakness. Presentation without chest pain in the young was not independently associated with differences in ACS type, troponin level, or extent of coronary stenosis.

The majority of evidence supporting that women are more likely to present without chest pain at ACS presentation were derived from elderly patient studies, and only a few studies examined younger populations. Younger patient studies yielded conflicting results and had a limited adjustment for potentially confounding factors.<sup>1,14</sup> To our knowledge, this analysis is the first to extensively adjust for potentially confounding baseline factors such as anxiety, depression, gender identity, comorbid conditions, and extent of coronary disease in a young ACS cohort.

Table 2. Frequency of Symptoms in Men and Women<sup>a</sup>

Symptoms	Men (n = 710)	Women (n = 305)	P Value
Chest pain	86.3	81.0	.03
Weakness	46.9	58.0	.001
Feeling hot or flushed	45.1	55.4	.003
Shortness of breath	44.9	44.6	.92
Cold sweats	46.8	40.3	.06
Pain in left arm and/or shoulder	41.3	49.5	.02
Back pain between and/or under shoulders	26.8	42.6	<.001
Pain in both arms	25.8	28.5	.36
Nausea	22.8	35.4	<.001
Dizziness	23.5	26.6	.30
Pain in right arm and/or shoulder	19.2	25.6	.02
Neck and/or throat pain	18.9	33.1	<.001
Vomiting	12.7	17.7	.04
Headache	16.3	23.0	.01
Jaw and/or tooth pain	13.0	23.9	<.001
Choking	10.9	10.2	.75
Change in taste of cigarettes	9.2	9.2	.99
Pain in legs	5.6	7.2	.34
Arms swollen	2.4	3.6	.28
Non-chest pain symptoms, mean (SD), No.	4.3 (3.0)	5.3 (3.4)	<.001
0 symptoms	6.9	5.9	.56
1-2 symptoms	25.6	16.4	.001
3-7 symptoms	51.8	51.8	.99
>7 symptoms	15.6	25.9	<.001

<sup>a</sup> Data are given as percentage of patients unless otherwise specified.

The proportion of men and women with non-chest pain presentations in our study (19.0% in young women and 13.7% in young men) was substantially lower than what is reported in elderly patients.<sup>1,3,14</sup> A US registry analysis (1994-2006) reported that 47% of women and 41% of men 65 years or older presented without chest pain, whereas 20.6% of women and 14.8% of men younger than 55 years presented without chest pain in that study.<sup>1</sup> The underlying reasons for a lower prevalence in younger patients is unclear given the lack of studies in younger patients. Advanced age has been shown to be a powerful predictor of non-chest pain presentations, and the prevalence of factors such as hypertension and diabetes that might contribute to non-chest pain presentations in our study was lower than that reported in elderly patient studies.<sup>1,14</sup> However, it is also possible that there is greater selection bias in younger patients because previous studies found younger patients, especially women, to have a missed ACS diagnosis.<sup>4</sup>

This study identified that women and men generally reported similar non-chest pain symptoms, but women reported a greater number of these symptoms than men. This observation is consistent with findings from elderly patients but similar evaluations in young patients are lacking.<sup>1,15</sup> Although systematic reviews identified that elderly women are more likely than men to report shortness of breath, nausea, vomiting, back pain, and jaw and neck pain, these findings are inconsistent across studies.<sup>15,16</sup> As in our study, no discernible pattern of non-chest pain symptoms has been found to better identify these men and women with ACS. These find-

ings highlight the need for standardized symptom assessment in all patients with suspected ACS.

Although women and men without chest pain at ACS presentation reported fewer symptoms than those with chest pain, the majority of these patients still reported at least 1 non-chest pain symptom or shortness of breath. Thus, relying on the presence of chest pain alone may further the underdiagnosis of ACS, particularly in young women. Underdiagnosis of ACS in the emergency department has been reported to occur in up to 11% of patients, predominantly among women 55 years or younger and those without chest pain at ACS presentations.<sup>4</sup> In the Rotterdam Study, the estimated incidence of unrecognized MI was 3.8 per 1000 patient-years, with a higher proportion of unrecognized MI in women (54% vs 33%) compared with men.<sup>17</sup> The implications of a missed ACS diagnosis at the emergency department are significant because these patients have high rates of readmission to hospital and increased risk of death compared with those hospitalized for ACS.<sup>4</sup>

Although absence of chest pain is commonly thought to occur with less severe ACS events, our study found that absence of chest pain was not associated with markers of lower ACS severity. This finding is generally consistent with an analysis of the GRACE data registry that found a similar likelihood of ischemic changes on electrocardiography and high-risk features including higher Killip classification,<sup>2</sup> but it contrasts with the findings in 2 other studies.<sup>1,18</sup> Moreover, earlier studies used retrospective medical record review to identify patients with-

Table 3. Baseline Characteristics According to Absence or Presence of Chest Pain

Characteristic	Without Chest Pain (n = 155)	With Chest Pain (n = 860)	P Value
Women, %	37.4	28.7	.03
Age, median (IQR), y	49.0 (46-52)	49.0 (45-53)	.78
Household income ≥\$50 000, %	75.5	70.1	.18
Masculinity, BSRI mean score (SD)	4.9 (0.9)	5.0 (0.9)	.35
Feminity, BSRI mean score (SD)	5.6 (1.0)	5.7 (0.9)	.58
BMI ≥30	42.1	39.9	.61
Diabetes mellitus type 2, %	21.3	16.3	.13
Postmenopausal, %	41.4	46.6	.48
Depression, %	17.2	24.4	.045
Anxiety, %	32.5	44.4	.005
STEMI, %	45.8	61.8	<.001
NSTEMI, %	41.3	31.2	.01
Unstable angina, %	11.0	7.0	.09
Systolic BP, mean (SD), mm Hg	136.7 (28.8)	139.3 (25.5)	.27
Diastolic BP, mean (SD), mm Hg	85.4 (19.01)	85.6 (16.8)	.90
Heart rate, mean (SD), bpm	83.6 (24.6)	78.6 (18.7)	.004
Troponin tertiles, %			
Intermediate	36.4	32.2	.32
Highest	25.0	35.7	.01
Stenosis, at least 1 >50%, % <sup>a</sup>	88.5	94.0	.02
Left main disease, % <sup>a</sup>	14.4	9.4	.07

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); BP, blood pressure; BSRI, Bem Sex Roles Inventory; IQR, interquartile range; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction.

<sup>a</sup> Among those who underwent angiography (90.8% of patients without chest pain; 89.3% of patients with chest pain).

out chest pain, which are likely less precise than interview using standardized symptom questionnaires. Our study also found on multivariate analysis that absence of chest pain was associated with left main disease. This finding needs to be confirmed in other studies.

The reasons for sex differences in ACS symptom presentation are not clearly established. Younger women had a higher prevalence of diabetes compared with men,<sup>19</sup> a finding similar to elderly patient cohorts, as diabetes is associated with sensory denervation from cardiac autonomic neuropathy.<sup>20</sup> However, even on adjusting for diabetes, women were still at greater risk for ACS presentation without chest pain. Other possible determinants for sex-based differences in presentation include gender differences in assertiveness to report symptoms, a higher prevalence of mood disorders that mimic ACS symptoms in women,<sup>21-23</sup> menopausal status,<sup>24</sup> lower burden of coronary stenosis,<sup>22</sup> or increased resting blood pressure<sup>19,22</sup> in women. However, we found no associations with these factors in women or men with absence of chest pain. Tachycardia was more prevalent in women than men at presentation. Although tachycardia reflects sympathetic overactivity commonly associated with pain, we found an association between higher heart rates and absence of chest pain, a finding consistent with other studies.<sup>1,18</sup> Men were more likely to have a higher annual household income compared with women. However, in those who underwent angiography, higher household income was associated with presentation without chest pain.

The strengths of this study include the use of a standardized validated symptom questionnaire administered during hospitalization for ACS and the detailed psychosocial, clinical,

and anatomic data collected. However, there are several limitations to note. We only included patients who were ultimately diagnosed as having ACS. Therefore, we missed patients with ACS who were misdiagnosed, who did not seek medical care, or who died prior to coming to hospital. This process would likely underestimate the true prevalence of ACS presentation without chest pain in women and men. We were also not able to interview patients who died in the emergency department or shortly after admission. However, rates of death in the emergency department are reported to be low (3.8% of women and 3.4% of men).<sup>5</sup> We used the MAPMISS, which was only validated in women with acute MI. Nevertheless, in our cohort, 96.6% of men reported shortness of breath or at least 1 MAPMISS symptom. The study was underpowered to detect sex differences within each ACS type (STEMI and NSTEMI or unstable angina) group. However, this does not alter our overall findings of sex differences in ACS presentation even on adjustment for patient and clinical factors. Finally, our patient sample included a large proportion of patients with STEMI and fewer patients with unstable angina because patients were enrolled from coronary care units and cardiology wards. Therefore, these results may not be generalizable to patients with unstable angina or lower risk NSTEMI admitted to non-critical care or noncardiology settings.

## Conclusions

Our findings indicate that chest pain is the predominant symptom that should direct diagnostic evaluation for ACS and be used for public health messages for young women and men,

similar to older patients. However, health care providers should still maintain a high degree of suspicion for ACS in young patients, particularly women, given that 1 in 5 women with diagnosed ACS do not report chest pain. Importantly, ACS severity was similar in patients with and without chest pain. Given that the majority of patients without chest pain ex-

press at least one other non-chest pain symptom, standardized collection of all ACS related symptoms is needed. Strategies that explicitly incorporate standardized assessment of common non-chest pain symptoms or signs, such as weakness, shortness of breath, or tachycardia in emergency departments also need to be evaluated.

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#### REFERENCES

- Canto JG, Rogers WJ, Goldberg RJ, et al; NRMII Investigators. Association of age and sex with myocardial infarction symptom presentation and in-hospital mortality. *JAMA*. 2012;307(8):813-822.
- Brieger D, Eagle KA, Goodman SG, et al; GRACE Investigators. Acute coronary syndromes without chest pain, an underdiagnosed and undertreated high-risk group: insights from the Global Registry of Acute Coronary Events. *Chest*. 2004;126(2):461-469.
- Canto JG, Goldberg RJ, Hand MM, et al. Symptom presentation of women with acute coronary syndromes: myth vs reality. *Arch Intern Med*. 2007;167(22):2405-2413.
- Pope JH, Aufderheide TP, Ruthazer R, et al. Missed diagnoses of acute cardiac ischemia in the emergency department. *N Engl J Med*. 2000;342(16):1163-1170.
- Kaul P, Chang WC, Westerhout CM, Graham MM, Armstrong PW. Differences in admission rates and outcomes between men and women presenting to

- emergency departments with coronary syndromes. *CMAJ*. 2007;177(10):1193-1199.
6. Vaccarino V, Parsons L, Peterson ED, Rogers WJ, Kiefe CI, Canto J. Sex differences in mortality after acute myocardial infarction: changes from 1994 to 2006. *Arch Intern Med*. 2009;169(19):1767-1774.
  7. Pilote L, Karp I. GENESIS-PRAXY (GENdEr and Sex determinantS of cardiovascular disease: From bench to beyond-Premature Acute Coronary SYndrome). *Am Heart J*. 2012;163(5):741-746; e2.
  8. GRACE Variable Definitions—Version of March 2006. [www.outcomes-umassmed.org/grace/Files/Standard\\_Definitions.pdf](http://www.outcomes-umassmed.org/grace/Files/Standard_Definitions.pdf). Accessed November 18, 2012.
  9. McSweeney JC, O'Sullivan P, Cody M, Crane PB. Development of the McSweeney Acute and Prodromal Myocardial Infarction Symptom Survey. *J Cardiovasc Nurs*. 2004;19(1):58-67.
  10. Oswald PA. An examination of the current usefulness of the Bem Sex-Role Inventory. *Psychol Rep*. 2004;94(3 Pt 2):1331-1336.
  11. Bem SL. The measurement of psychological androgyny. *J Consult Clin Psychol*. 1974;42(2):155-162.
  12. Doyle F, McGee HM, De La Harpe D, Shelley E, Conroy R. The Hospital Anxiety and Depression Scale depression subscale, but not the Beck Depression Inventory-Fast Scale, identifies patients with acute coronary syndrome at elevated risk of 1-year mortality. *J Psychosom Res*. 2006;60(5):461-467.
  13. Eagle KA, Lim MJ, Dabbous OH, et al; GRACE Investigators. A validated prediction model for all forms of acute coronary syndrome: estimating the risk of 6-month postdischarge death in an international registry. *JAMA*. 2004;291(22):2727-2733.
  14. Arslanian-Engoren C, Patel A, Fang J, et al. Symptoms of men and women presenting with acute coronary syndromes. *Am J Cardiol*. 2006;98(9):1177-1181.
  15. DeVon HA, Zerwic JJ. Symptoms of acute coronary syndromes: are there gender differences? a review of the literature. *Heart Lung*. 2002;31(4):235-245.
  16. Chen W, Woods SL, Puntillo KA. Gender differences in symptoms associated with acute myocardial infarction: a review of the research. *Heart Lung*. 2005;34(4):240-247.
  17. de Torbal A, Boersma E, Kors JA, et al. Incidence of recognized and unrecognized myocardial infarction in men and women aged 55 and older: the Rotterdam Study. *Eur Heart J*. 2006;27(6):729-736.
  18. El-Menyar A, Zubaid M, Sulaiman K, et al; Gulf Registry of Acute Coronary Events (Gulf RACE) Investigators. Atypical presentation of acute coronary syndrome: a significant independent predictor of in-hospital mortality. *J Cardiol*. 2011;57(2):165-171.
  19. Egiziano G, Akhtari S, Pilote L, Daskalopoulou SS; GENESIS (GENdEr and Sex Determinants of Cardiovascular Disease) Investigators. Sex differences in young patients with acute myocardial infarction. *Diabet Med*. 2013;30(3):e108-e114.
  20. Langer A, Freeman MR, Josse RG, Armstrong PW. Metaiodobenzylguanidine imaging in diabetes mellitus: assessment of cardiac sympathetic denervation and its relation to autonomic dysfunction and silent myocardial ischemia. *J Am Coll Cardiol*. 1995;25(3):610-618.
  21. Myers CD, Robinson ME, Riley JL III, Sheffield D. Sex, gender, and blood pressure: contributions to experimental pain report. *Psychosom Med*. 2001;63(4):545-550.
  22. DeVon HA, Ryan CJ, Ochs AL, Shapiro M. Symptoms across the continuum of acute coronary syndromes: differences between women and men. *Am J Crit Care*. 2008;17(1):14-24.
  23. Steptoe A, Brydon L. Emotional triggering of cardiac events. *Neurosci Biobehav Rev*. 2009;33(2):63-70.
  24. Méthot J, Hamelin BA, Bogaty P, Arsenault M, Plante S, Poirier P. Does hormonal status influence the clinical presentation of acute coronary syndromes in women? *J Womens Health (Larchmt)*. 2004;13(6):695-702.