



Sex Differences in the Presentation and Perception of Symptoms Among Young Patients With Myocardial Infarction

Evidence from the VIRGO Study (Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients)

Editorial, see p 791

BACKGROUND: Some studies report that women are less likely to present with chest pain for acute myocardial infarction (AMI). Information on symptom presentation, perception of symptoms, and care-seeking behaviors is limited for young patients with AMI.

METHODS: We interviewed 2009 women and 976 men aged 18 to 55 years hospitalized for AMI at 103 US hospitals participating in the VIRGO study (Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients). Structured patient interviews during the index AMI hospitalization were used to collect information on symptom presentation, perception of symptoms, and care-seeking behaviors. We compared patient characteristics and presentation information by sex. Multivariable hierarchical logistic regression was used to evaluate the association between sex and symptom presentation.

RESULTS: The majority of women (87.0%) and men (89.5%) presented with chest pain (defined as pain, pressure, tightness, or discomfort). Women were more likely to present with ≥ 3 associated symptoms than men (eg, epigastric symptoms, palpitations, and pain or discomfort in the jaw, neck, arms, or between the shoulder blades; 61.9% for women versus 54.8% for men, $P < 0.001$). In adjusted analyses, women with an ST-segment–elevation AMI were more likely than men to present without chest pain (odds ratio, 1.51; 95% confidence interval, 1.03–2.22). In comparison with men, women were more likely to perceive symptoms as stress/anxiety (20.9% versus 11.8%, $P < 0.001$) but less likely to attribute symptoms to muscle pain (15.4% versus 21.2%, $P = 0.029$). Approximately 29.5% of women and 22.1% of men sought medical care for similar symptoms before their hospitalization ($P < 0.001$); however, 53% of women reported that their provider did not think these symptoms were heart-related in comparison with 37% of men ($P < 0.001$).

CONCLUSIONS: The presentation of AMI symptoms was similar for young women and men, with chest pain as the predominant symptom for both sexes. Women presented with a greater number of additional non–chest pain symptoms regardless of the presence of chest pain, and both women and their healthcare providers were less likely to attribute their prodromal symptoms to heart disease in comparison with men.

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Key Words: delay ■ diagnosis ■ help-seeking behavior ■ medical care ■ myocardial infarction ■ women

Sources of Funding, see page 789

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Clinical Perspective

What Is New?

- Sex differences in symptom presentation for acute myocardial infarction have been shown in older populations, but less is known about potential sex differences in self-reported symptoms, perception of symptoms, and self-reported care-seeking behavior in young patients with acute myocardial infarction.
- Based on direct patient interviews, almost 90% of young women and men presented with chest pain, pressure, tightness, or discomfort; women were more likely to present with ≥ 3 additional non-chest pain symptoms in comparison with men.
- Among patients who sought care for symptoms before their hospitalization, women were less likely to be told their symptoms were heart-related.

What Are the Clinical Implications?

- Chest pain, pressure, tightness, or discomfort is the hallmark symptom for young patients presenting with acute myocardial infarction.
- Presentation with multiple non-chest pain symptoms may influence the decision to initiate a workup for ischemic heart disease, particularly if chest pain or the various ways chest pressure is described is not the primary or most emphasized symptom.
- Most of the young patients in the VIRGO study (Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients) had ≥ 1 traditional cardiac risk factor; physicians should listen carefully and consider the diagnosis of heart disease in young patients, particularly those with multiple cardiac risk factors who mention chest pain, pressure, tightness, or discomfort in a history.

Young women with heart disease have a higher risk of dying of their acute myocardial infarction (AMI) in comparison with similarly aged men.¹⁻³ Despite the burden of heart disease in this population, the symptom presentation of young women with AMI remains poorly understood and has been hypothesized to lead to delays in treatment. The few studies that have included analyses of sex differences in symptom presentation among young patients with AMI report that chest pain is the most common symptom for both women and men.^{4,5} However, women are more common in the subgroup presenting without chest pain, are more likely to have a greater variety of other symptoms, and have higher inhospital mortality.^{4,5} Prior studies have been limited by a narrow description of symptom presentation based on chart review,⁴ a small sample of young patients with AMI,⁵ and a lack of information on the perception of symptoms and care-seeking be-

haviors of young women presenting with AMI.^{4,5} Given the increased mortality associated with premature AMI in women, it is critical to fully investigate the number and type of acute symptoms of heart disease in young patients, and explore how symptom recognition influences patients' care-seeking behaviors and early interactions with healthcare providers, as well.

To address the gaps in knowledge concerning potential sex differences in the recognition and presentation of AMI symptoms in younger patients, we conducted this study as part of the VIRGO study (Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients).⁶ We conducted prospective patient interviews during the index AMI hospitalization to collect detailed information on prodromal and acute symptoms, perception of symptoms, and self-reported care-seeking behavior for prior and acute symptoms for women and men 18 to 55 years of age.

METHODS

The VIRGO investigators have the intent to share study data and are investigating mechanisms and funding to make it possible. We are currently working on 2 pilot data-sharing efforts.

Patient Population

The VIRGO study recruited patients hospitalized with AMI between August 21, 2008, and January 5, 2012, from 103 geographically diverse academic and nonacademic hospitals across the United States using a 2:1 female:male enrollment design. The methods of VIRGO have been described previously.^{6,7} In brief, eligible patients were 18 to 55 years of age and had increased cardiac biomarker levels, with at least 1 of these biomarkers >99 th percentile of the upper reference limit at the recruiting center within 24 hours of admission. Additional evidence of acute myocardial ischemia was required, including either the symptoms of ischemia or ECG changes indicative of new ischemia (new ST-T changes or the development of pathological Q waves). Patients must have presented directly to the enrolling site or been transferred within the first 24 hours of presentation. We obtained institutional review board approval at each participating institution, and patients provided written informed consent for their study participation.

Symptom Presentation, Perception of Symptoms, and Care-Seeking Behavior

Patient-reported information on symptoms experienced before hospital presentation, perceived cause of symptoms, and prior interactions with the healthcare system for similar symptoms was collected by standardized direct patient interviews administered by trained personnel during the index hospitalization for AMI (see [Methods in the online-only Data Supplement](#) for interview questions). The questions were developed based on prior qualitative research conducted in young patients hospitalized with AMI.⁸ Questions included prespecified response categories, and VIRGO participants were

also given the opportunity to provide open-ended responses to structured questions. The additional self-reported descriptions were recorded by the interviewer. Four authors reviewed the open-ended responses and determined, by consensus, whether to reassign the response to an existing response category, create a new category, or retain the response in an “other response” category (J.H.L., E.C.L., M.D., G.D.).

Participants were asked what symptoms they had before arriving at the hospital, including chest pain, pressure, tightness, or discomfort; dizziness; indigestion or stomach pain, pressure, burning, or discomfort; nausea; pain or discomfort in jaw, neck, arms, or between shoulder blades; palpitations; shortness of breath; sweating; weakness or fatigue; confusion; or other symptoms. Participants were asked if they thought something was wrong with their heart when they first experienced the reported symptoms. If they did not believe the symptoms were heart-related, participants were asked what they thought was causing their symptoms. Possible response categories included indigestion or acid reflux, stomach illness or flu, muscle pain, fatigue, stress or anxiety, asthma, diabetes mellitus, or other causes. We asked participants why they decided to get help for their symptoms. Responses included symptoms would not go away, pain was too bad to ignore, worried about heart problem, worried about other health problems (eg, diabetes mellitus), a family or friend told me to get help, or other reasons.

Respondents were asked if they had seen their doctor in the week before going to the hospital for any of their symptoms. If yes, they were asked whether their doctor told them that their symptoms might be related to a heart problem. If they reported their doctor did not think their symptoms were heart-related, we asked them what they had been told was the cause of the reported symptoms. Response categories included indigestion or acid reflux, stomach illness or flu, muscle pain, fatigue, stress or anxiety, asthma, diabetes mellitus, or another cause. Among participants who responded that their doctor suspected heart disease, we asked whether they were tested for a heart problem (eg, ECG, stress test).

Sociodemographic and Clinical Variables

Sociodemographic characteristics were also collected by standardized in-person interviews during the index AMI admission. These characteristics included age, sex, self-identified race (white, black, or other), Hispanic ethnicity, residential area (categorized according to the Rural-Urban Commuting Area codes:⁹ metropolitan [population $\geq 50\,000$], micropolitan [population 10 000–49 999], or small town/rural [population $< 10\,000$]), marital status (married or living as married versus not married), greater than a high school education, working full- or part-time, lack of health insurance or self-pay, and avoidance of health care in the past because of cost.

We abstracted medical history data for prior coronary artery disease (CAD; includes AMI, percutaneous coronary intervention, or coronary artery bypass graft surgery), prior angina, congestive heart failure, prior stroke or transient ischemic attack, chronic kidney disease, and chronic lung disease. We ascertained risk factor information from both the medical record and interview for hypertension (documented history or self-report), diabetes mellitus (documented history, use of glucose-control medication on arrival, or self-report),

hypercholesterolemia (documented history, use of lipid-lowering medication on arrival, or self-report), smoking within the past 30 days, obesity (body mass index ≥ 30 kg/m²), and family history of CAD.¹⁰ Clinical presentation characteristics included vessel stenosis $>50\%$, final AMI diagnosis (ST-segment-elevation AMI [STEMI] versus non-ST-segment-elevation AMI [NSTEMI]), Killip class (III/IV versus I/II), absence of chest pain, and timing of hospital presentation (≤ 2 hours, >2 –6 hours, or >6 hours; weekday, weeknight, or weekend). When a specific symptom-onset time was not reported, we reviewed physician narratives for details on symptom presentation and used a standardized approach to assign an approximate time interval for symptom onset.

Statistical Analysis

We compared sociodemographic factors, medical history, clinical characteristics, AMI symptoms, patient interpretation of and response to symptoms, and time to hospital presentation by sex using χ^2 tests for categorical variables and *t* tests or rank sum tests for continuous variables. We also compared AMI symptoms by sex for patients not reporting chest pain, pressure, tightness, or discomfort and by type of AMI (STEMI or NSTEMI). In post hoc comparisons, we stratified analyses by symptom duration >1 day, prior CAD/angina (prior AMI, percutaneous coronary intervention, coronary artery bypass graft surgery, or angina), education beyond high school, and diabetes mellitus.

We used multivariable hierarchical logistic regression models, which accounted for clustering effects of patients within sites (using a random effect) and adjusted for sociodemographic and clinical characteristics, to evaluate the relationship between sex and AMI presentation without chest pain, pressure, tightness, or discomfort for the overall cohort and among prespecified subgroups defined by type of AMI and age. All statistical analyses were conducted using SAS version 9.4 (SAS Institute), with 2-tailed tests for statistical significance and $\alpha=0.05$. We used the stepdown Bonferroni method to adjust the *P* values for multiple pairwise comparisons.

RESULTS

Patient Characteristics

Among the 2985 patients enrolled in the VIRGO study, 2009 were women and 976 were men. Patients were, on average, 47 years old and predominately white (76%). Table 1 presents the participant characteristics for the overall VIRGO sample and among subgroups defined by chest pain presentation (includes pain, pressure, tightness, and discomfort). Comorbidities were common for both sexes, but women were more likely than men to have a history of congestive heart failure, diabetes mellitus, obesity, stroke or transient ischemic attack, chronic kidney disease, and chronic lung disease. Women were less likely to have hypercholesterolemia, STEMI, and stenosis $>50\%$. Similar sex-based patterns were seen among patients presenting with and without chest pain.

Table 1. Patient Characteristics by Sex

| | Overall | | | Among Patients With No Chest Pain | | | Among Patients With Chest Pain | | |
|---|----------------|-------------|--------|-----------------------------------|-------------|-------|--------------------------------|-------------|--------|
| | Women (n=2009) | Men (n=976) | P | Women (n=261) | Men (n=102) | P | Women (n=1748) | Men (n=874) | P |
| Sociodemographic characteristics, % | | | | | | | | | |
| Age range, y | 18–55 | 23–55 | | 27–55 | 29–55 | | 18–55 | 23–55 | |
| Age, mean (SD), y | 47.2 (6.3) | 47.1 (5.9) | 0.726 | 48.6 (5.4) | 47.6 (5.6) | 0.123 | 47.0 (6.4) | 47.0 (6.0) | 0.783 |
| Race | | | | | | | | | |
| White | 72.9 | 81.6 | <0.001 | 78.2 | 75.5 | 0.465 | 72.1 | 82.4 | <0.001 |
| Black | 21.3 | 11.0 | | 14.9 | 13.7 | | 22.3 | 10.7 | |
| Other | 5.7 | 7.4 | | 6.9 | 10.8 | | 5.6 | 7.0 | |
| Hispanic | 7.6 | 8.4 | 0.455 | 5.7 | 6.9 | 0.689 | 7.9 | 8.6 | 0.544 |
| Married | 52.5 | 62.2 | <0.001 | 54.0 | 53.9 | 0.986 | 52.2 | 63.2 | <0.001 |
| Greater than high school education | 56.8 | 56.6 | 0.905 | 62.3 | 51.0 | 0.050 | 56.0 | 57.2 | 0.550 |
| Residence type | | | | | | | | | |
| Metropolitan | 73.7 | 73.2 | 0.885 | 69.8 | 72.0 | 0.303 | 74.3 | 73.3 | 0.577 |
| Micropolitan | 13.3 | 13.1 | | 15.5 | 19.0 | | 13.0 | 12.5 | |
| Small town/rural | 13.0 | 13.7 | | 14.7 | 9.0 | | 12.8 | 14.2 | |
| Work full- or part-time | 56.2 | 71.8 | <0.001 | 52.1 | 67.6 | 0.007 | 56.8 | 72.3 | <0.001 |
| Primary medical insurance: self-pay/none | 21.6 | 24.8 | 0.047 | 21.5 | 21.6 | 0.981 | 21.6 | 25.2 | 0.038 |
| Avoid getting health care due to cost | 35.8 | 33.4 | 0.191 | 33.3 | 30.4 | 0.591 | 36.2 | 33.8 | 0.214 |
| Medical history, % | | | | | | | | | |
| Prior MI, PCI, or CABG | 20.6 | 23.1 | 0.119 | 18.4 | 24.5 | 0.191 | 20.9 | 22.9 | 0.240 |
| Prior angina | 27.4 | 26.1 | 0.470 | 25.3 | 21.6 | 0.457 | 27.7 | 26.7 | 0.577 |
| Congestive heart failure | 5.8 | 2.5 | <0.001 | 5.7 | 4.9 | 0.751 | 5.8 | 2.2 | <0.001 |
| Hypertension | 67.1 | 64.7 | 0.176 | 69.3 | 66.7 | 0.621 | 66.8 | 64.4 | 0.221 |
| Diabetes mellitus | 34.8 | 21.1 | <0.001 | 39.5 | 28.4 | 0.050 | 34.1 | 20.3 | <0.001 |
| Hypercholesterolemia | 66.4 | 72.2 | 0.001 | 65.5 | 75.5 | 0.066 | 66.5 | 71.9 | 0.005 |
| Smoked within past 30 days | 57.7 | 56.6 | 0.578 | 56.7 | 55.9 | 0.887 | 57.8 | 56.7 | 0.579 |
| Obesity (BMI ≥30 kg/m ²) | 55.3 | 47.7 | <0.001 | 53.6 | 38.2 | 0.008 | 55.5 | 48.9 | 0.001 |
| Family history of CAD | 73.8 | 73.1 | 0.657 | 74.3 | 76.5 | 0.672 | 73.7 | 72.7 | 0.553 |
| Prior stroke/TIA | 5.7 | 2.8 | <0.001 | 9.2 | 2.0 | 0.016 | 5.1 | 2.9 | 0.007 |
| Chronic kidney disease | 12.7 | 8.6 | 0.001 | 21.8 | 13.7 | 0.080 | 11.4 | 8.0 | 0.008 |
| Chronic lung disease | 14.2 | 6.4 | <0.001 | 12.6 | 6.9 | 0.114 | 14.4 | 6.3 | <0.001 |
| Clinical characteristics at presentation, % | | | | | | | | | |
| STEMI | 45.9 | 57.7 | <0.001 | 44.8 | 47.1 | 0.701 | 46.1 | 58.9 | <0.001 |
| Ejection fraction <40% | 10.9 | 11.6 | 0.589 | 13.8 | 17.0 | 0.450 | 10.5 | 10.9 | 0.715 |
| Killip class: III/IV | 1.4 | 0.7 | 0.107 | 4.2 | 1.0 | 0.121 | 1.0 | 0.7 | 0.459 |
| Presented during normal business hours | 35.9 | 33.2 | 0.144 | 36.6 | 28.4 | 0.143 | 35.8 | 33.8 | 0.297 |
| Vessel disease (stenosis >50%) | 85.9 | 95.6 | <0.001 | 84.3 | 93.7 | 0.022 | 86.1 | 95.8 | <0.001 |
| Psychosocial factors, % | | | | | | | | | |
| Depression (PHQ-9 score ≥10) | 39.1 | 22.5 | <0.001 | 33.6 | 22.9 | 0.054 | 39.9 | 22.4 | <0.001 |
| Low social support | 21.6 | 22.4 | 0.633 | 19.0 | 30.0 | 0.026 | 22.0 | 21.5 | 0.778 |
| Perception of risk prior to event, % | | | | | | | | | |
| Patient considered himself/herself at risk | 55.1 | 58.8 | 0.059 | 53.1 | 54.5 | 0.814 | 55.4 | 59.3 | 0.061 |
| Healthcare provider told patient he/she was at risk | 48.7 | 52.9 | 0.031 | 48.6 | 57.1 | 0.152 | 48.7 | 52.5 | 0.072 |

BMI indicates body mass index; CABG, coronary artery bypass grafting; CAD, coronary artery disease; MI, myocardial infarction; PCI, percutaneous coronary intervention; PHQ-9, Patient Health Questionnaire-9; STEMI, ST-segment–elevation myocardial infarction; and TIA, transient ischemic attack.

Symptom Presentation

Nearly 90% of women and men presented with chest pain, pressure, tightness, or discomfort (87.0% for women and 89.5% for men; Table 2). Overall, women presented with a greater number of additional non-chest pain symptoms than men, including epigastric symptoms (indigestion, nausea, and stomach pain, pressure, burning, or discomfort); pain or discomfort in the jaw, neck, arms, or between the shoulder blades; palpitations; and shortness of breath. The mean number of symptoms was 3.4 ± 2.0 for women and 3.0 ± 1.9 for men ($P < 0.001$). With the use of ≥ 3 symptoms as the cutoff based on the distribution of symptoms and clinical input from the investigators, 61.9% of women presented with ≥ 3 associated, non-chest pain symptoms in comparison with 54.8% of men ($P < 0.001$). There were no significant differences between symptoms reported among women and men presenting without chest pain. Among patients with STEMI, women were significantly more likely than men to report epigastric symptoms (67.1% versus 53.1%, $P < 0.001$) and jaw/neck/arms/shoulder pain (67.7% versus 58.6%, $P = 0.003$); 65.9% of women versus 57.5% of men presented with ≥ 3 additional non-chest pain symptoms ($P = 0.001$). Women

with NSTEMI were significantly more likely to report epigastric symptoms (56.8% versus 46.2%, $P = 0.003$), palpitations (21.5% versus 14.6%, $P = 0.022$), and shortness of breath (54.2% versus 46.1%, $P = 0.035$) in comparison with men with NSTEMI; almost 58.5% of women versus 51.1% of men reported ≥ 3 additional non-chest pain symptoms ($P < 0.001$). Comparisons stratified by symptom duration were generally consistent with the overall results, except there was no sex difference in jaw/neck/arms/shoulder pain for patients with symptoms present for ≤ 1 day, and there were no differences observed for shortness of breath regardless of duration (Table I in the online-only Data Supplement). Regardless of prior CAD/angina status, women reported more additional symptoms than men (Table II in the online-only Data Supplement). For those with diabetes mellitus, only epigastric symptoms were more common among women than among men, and no significant difference was observed in the number of associated, non-chest pain symptoms (Table III in the online-only Data Supplement).

In adjusted analyses of chest pain presentation (Table 3), women aged >45 years had 1.39 (95% confidence interval [CI], 1.01–1.92) times the odds of presenting without chest pain in comparison with men.

Table 2. Symptom Presentation by Sex

| | Overall | | | Among Patients With STEMI | | | Among Patients With NSTEMI | | | Among Patients With No Chest Pain | | |
|--|----------------|-------------|--------|---------------------------|-------------|--------|----------------------------|-------------|--------|-----------------------------------|-------------|-------|
| | Women (n=2009) | Men (n=976) | P* | Women (n=922) | Men (n=563) | P* | Women (n=1087) | Men (n=413) | P* | Women (n=261) | Men (n=102) | P* |
| Individual symptoms, % | | | | | | | | | | | | |
| Chest pain, pressure, tightness, or discomfort | 87.0 | 89.5 | 0.185 | 87.3 | 91.5 | 0.092 | 86.8 | 86.9 | 1 | | | |
| Dizziness | 28.0 | 26.3 | 0.774 | 29.5 | 28.1 | 1 | 26.7 | 23.8 | 0.999 | 21.9 | 22.8 | 1 |
| Epigastric: indigestion, nausea, or stomach pain, pressure, burning, or discomfort | 61.5 | 50.2 | <0.001 | 67.1 | 53.1 | <0.001 | 56.8 | 46.2 | 0.003 | 55.2 | 51.0 | 1 |
| Pain/discomfort in jaw, neck, arms, or between shoulder blades | 64.9 | 58.1 | 0.002 | 67.7 | 58.6 | 0.003 | 62.6 | 57.3 | 0.293 | 55.4 | 48.5 | 1 |
| Palpitations | 18.7 | 12.5 | <0.001 | 15.4 | 11.0 | 0.103 | 21.5 | 14.6 | 0.022 | 8.5 | 11.9 | 1 |
| Shortness of breath | 52.8 | 47.6 | 0.043 | 51.2 | 48.7 | 1 | 54.2 | 46.1 | 0.035 | 41.2 | 42.6 | 1 |
| Sweating | 53.3 | 55.5 | 0.774 | 62.1 | 63.1 | 1 | 45.8 | 45.1 | 1 | 39.2 | 40.6 | 1 |
| Weakness or fatigue | 45.2 | 40.9 | 0.142 | 46.1 | 43.7 | 1 | 44.4 | 37.1 | 0.068 | 31.9 | 32.7 | 1 |
| Confusion | 12.1 | 11.2 | 0.774 | 13.3 | 12.6 | 1 | 11.0 | 9.2 | 0.999 | 10.0 | 4.0 | 0.496 |
| Number of associated, non-chest pain symptoms | | | | | | | | | | | | |
| Mean (SD) | 3.4 (2.0) | 3.0 (1.9) | <0.001 | 3.5 (1.9) | 3.2 (1.9) | 0.001 | 3.2 (2.0) | 2.8 (1.9) | <0.001 | 2.6 (1.7) | 2.5 (1.5) | 0.582 |
| 0 symptoms, % | 5.6 | 6.7 | <0.001 | 4.2 | 5.7 | 0.009 | 6.8 | 8.0 | <0.001 | 4.2 | 4.9 | 0.801 |
| 1–2 symptoms, % | 32.5 | 38.5 | | 29.8 | 36.8 | | 34.7 | 40.9 | | 49.4 | 50 | |
| 3–4 symptoms, % | 33.0 | 33.4 | | 36.2 | 33.6 | | 30.2 | 33.2 | | 31.8 | 34.3 | |
| >4 symptoms, % | 29.0 | 21.4 | | 29.7 | 24.0 | | 28.3 | 17.9 | | 14.6 | 10.8 | |

NSTEMI indicates non-ST-segment-elevation myocardial infarction; and STEMI, ST-segment-elevation myocardial infarction.

*The stepdown Bonferroni method was used to adjust the *P* values for multiple pairwise comparisons.

Table 3. Sex Differences in Presentation Without Chest Pain, Pressure, Tightness, or Discomfort: Overall and Stratified by Age and Final Myocardial Infarction Diagnosis

| | Presentation With No Chest Pain (Women vs. Men) | |
|-----------------|---|-------|
| | Odds Ratio (95% CI)* | P |
| Overall | 1.20 (0.92–1.56) | 0.187 |
| Age | | |
| ≤45 y | 0.86 (0.52–1.43) | 0.564 |
| >45 y | 1.39 (1.01–1.92) | 0.042 |
| Final diagnosis | | |
| NSTEMI | 0.95 (0.65–1.37) | 0.770 |
| STEMI | 1.51 (1.03–2.22) | 0.036 |

CI indicates confidence interval; NSTEMI, non-ST-segment-elevation myocardial infarction; and STEMI, ST-segment-elevation myocardial infarction.

*Hierarchical logistic regression models were used to assess the relationship between sex (women vs. men) and presentation without chest pain/discomfort in the overall patient sample and within subgroups defined by age and final myocardial infarction. Models adjusted for age, race, Hispanic ethnicity, education, prior coronary artery disease (myocardial infarction, percutaneous coronary intervention, or coronary artery bypass grafting), history of angina, congestive heart failure, hypertension, diabetes mellitus, hypercholesterolemia, smoking within past 30 days, obesity, family history of coronary artery disease, prior stroke or transient ischemic attack, vessel stenosis >50%, final myocardial infarction diagnosis, and Killip class (I/II, III/IV).

Women who had a STEMI had 1.51 (95% CI, 1.03–2.22) times the odds of presenting without chest pain in comparison with men. The interaction of these variables with sex, however, was not statistically significant ($P=0.137$ for age-by-sex; $P=0.150$ for AMI diagnosis-by-sex).

More than half of patients initially attributed their index AMI symptoms to noncardiac conditions, the most prevalent symptom being indigestion or acid reflux in both sexes (Table 4). In comparison with men, women were significantly more likely to have perceived their symptoms as attributable to stress or anxiety (20.9% versus 11.8%, $P<0.001$). Women were less likely to perceive their symptoms as related to muscle pain (15.4% versus 21.2%, $P=0.029$). Almost two-thirds of both women and men reported that persistent symptoms were the reason they decided to seek medical care, and over half responded that they sought care because the pain was too bad to ignore. A greater proportion of men decided to seek medical care because of concerns about a heart problem than women (49.8% versus 41.6%, $P<0.001$), whereas a greater proportion of women sought care because of concerns about another health problem such as diabetes mellitus (16.4% versus 11.8%, $P=0.004$). Women had a longer median time from symptom onset to hospital presentation than men (3.2 [interquartile range, 0.8–21.2] hours versus 2.4 [interquartile range, 0.7–13.0] hours, $P<0.004$). In comparisons stratified by symptom duration and among those with prior CAD/angina or greater than

Table 4. Patient Response to Symptoms

| | Women (n=2009) | Men (n=976) | P* |
|---|----------------|----------------|--------|
| Patient did not perceive cause of symptoms to be heart-related, % | 54.7 | 52.3 | 0.379 |
| Perceived reason, % | | | |
| Indigestion or acid reflux | 42.8 | 49.4 | 0.076 |
| Muscle pain | 15.4 | 21.2 | 0.029 |
| Stress/anxiety | 20.9 | 11.8 | <0.001 |
| Stomach illness or flu | 11.6 | 9.8 | 0.592 |
| Asthma | 10.7 | 8.0 | 0.281 |
| Fatigue | 5.9 | 5.7 | 0.856 |
| Diabetes mellitus | 4.5 | 2.0 | 0.076 |
| Other cause | 8.9 | 6.3 | 0.281 |
| Decision to seek medical care, % | | | |
| Symptoms would not go away | 64.4 | 62.5 | 0.582 |
| Pain too bad to ignore | 59.8 | 56.3 | 0.290 |
| Worried about heart problem | 41.6 | 49.8 | <0.001 |
| Family/friend told me to get help | 25.8 | 26.5 | 0.698 |
| Worried about other health problems (eg, diabetes mellitus) | 16.4 | 11.8 | 0.004 |
| Other | 1.1 | 0.5 | 0.345 |
| Time to hospital presentation, % | | | |
| ≤2 h | 32.9 | 38.1 | 0.002 |
| >2–6 h | 15.2 | 18.5 | |
| >6 h | 38.7 | 31.8 | |
| Median time (IQR), h | 3.2 (0.8–21.2) | 2.4 (0.7–13.0) | 0.004 |

IQR indicates interquartile range.

*The stepdown Bonferroni method was used to adjust the P values for multiple pairwise comparisons.

a high school education, women were more likely to perceive their symptoms as related to stress or anxiety, whereas men were more likely to seek care because they were worried about a heart problem (Tables IV to VI in the online-only Data Supplement). For patients with a high school education or below, women had a longer median time to presentation than men (Table VI in the online-only Data Supplement). Among patients with diabetes mellitus, women were more likely to report seeking medical care because they were worried about other health problems such as diabetes mellitus, but both women and men with diabetes mellitus had a longer median time to hospital presentation than those without diabetes mellitus (Table VII in the online-only Data Supplement).

A greater percentage of women sought medical care for similar symptoms before being hospitalized for their AMI, in comparison with men (29.5% versus

22.1%, $P < 0.001$; Table 5). However, over half of women (53.4%) reported that their provider did not think these symptoms were heart-related, in comparison with 36.7% of men ($P < 0.001$). During these healthcare encounters, symptoms of both women and men were most often attributed to gastric conditions and stress/anxiety. There was no sex difference in the reported receipt of cardiac testing among those with suspected heart disease.

DISCUSSION

Our findings represent the largest study of symptom presentation, perception of symptoms, and care-seeking behaviors for young patients based on direct patient interviews conducted during the index AMI admission. Chest pain, described as pain, pressure, tightness, or discomfort, was the predominant symptom for women and men (87% versus 89.5%). Young women presented more often with NSTEMI and reported more additional non-chest pain symptoms, such as epigastric symptoms, palpitations, and shortness of breath, in comparison with similarly aged men. The clustering of multiple associated non-chest pain symptoms for young women, particularly among those presenting with NSTEMI, may influence an individual's perception and care-seeking behaviors, and physician interpretation of the patient's problem and subsequent testing as well. This may have contributed to the observation that women sought care more frequently for similar

symptoms before hospitalization than men, but they were less likely to be told the symptoms may be related to heart disease. If symptoms were perceived as heart-related, which may possibly reflect physician feedback or individual initiative, we found no difference in the workup for heart disease.

Consistent with prior studies, we found that the vast majority of young women and men presented with traditional chest pain symptoms.^{4,5,11,12} A prior medical chart review found that 81.5% of women and 85% of men aged <45 years and 78.4% of women and 84.3% of men aged 45 to 54 years experienced chest pain. This study also reported that women aged 45 to 54 years were more likely to present without chest pain than men (odds ratio, 1.26; 95% CI, 1.22–1.30). To be consistent with this approach, we conducted post hoc analyses stratified by age and found that women aged 46 to 55 years in VIRGO were more likely to present without chest pain, but there was no comparable association for those aged ≤ 45 years. A second study of 305 women and 710 men aged ≤ 55 years found that 86.3% of men and 81.0% of women presented with chest pain based on a symptom survey administered during the index hospitalization. They noted that women were more likely to present with other additional symptoms such as weakness or back, shoulder, or neck pain in comparison with men. In our study based on detailed in-person patient interviews, we also found that chest pain, described as pain, pressure, tightness, or discomfort, was the most commonly reported symptom for both women and men, but women reported a greater number of additional non-chest pain symptoms. The presentation of multiple non-chest pain symptoms may influence the decision of the physician on initiating a workup for ischemic heart disease, in particular if chest pain or the various ways chest pressure is described is not the primary or most emphasized symptom at the time of clinical presentation. In light of our findings and those of others, physicians should listen carefully and consider the diagnosis of heart disease in young patients, in particular those with multiple cardiac risk factors who mention chest pain, pressure, tightness, or discomfort in a history. Most of the young patients in VIRGO had ≥ 1 traditional cardiac risk factors, and care providers should take this into consideration while evaluating symptoms in these patients to determine whether additional diagnostic evaluations for heart disease are indicated.

Consistent with studies of older patients, we found that women in VIRGO were more likely to present with NSTEMI, and women with STEMI were more likely to present without chest pain than men.^{4,13} Our study extends prior work by providing detailed symptom presentation information obtained by direct patient interview and comparing symptom presentation patterns by sex and AMI type. For both STEMI and NSTEMI, women re-

Table 5. Sought Care for Similar Symptoms Before Hospitalization

| | Women (n=2009) | Men (n=976) | P* |
|---|----------------|-------------|--------|
| Sought medical care for similar symptoms, % | 29.5 | 22.1 | <0.001 |
| Provider did not think symptoms were heart-related, % | 53.4 | 36.7 | <0.001 |
| Perceived cause of symptom, % | | | |
| Indigestion or acid reflux | 29.1 | 40.5 | 0.401 |
| Stress/anxiety | 25.0 | 15.2 | 0.401 |
| Muscle pain | 13.3 | 15.2 | 1 |
| Asthma | 14.9 | 10.1 | 1 |
| Stomach illness or flu | 5.1 | 3.8 | 1 |
| Diabetes mellitus | 5.7 | 2.5 | 1 |
| Fatigue | 5.1 | 0.0 | 0.401 |
| Other | 7.3 | 3.8 | 1 |
| Among those with suspected symptoms of heart disease, % | | | |
| Tested for a heart condition | 89.1 | 89.0 | 0.589 |
| Test showed evidence of a heart condition | 57.4 | 56.6 | 0.268 |

*The stepdown Bonferroni method was used to adjust the P values for multiple pairwise comparisons.

ported a higher mean number of associated non-chest pain symptoms. Regardless of AMI subtype, women were significantly more likely to present with epigastric symptoms than men. Women with NSTEMI were more likely to present with the symptoms of shortness of breath and palpitations than men. The greater likelihood for young women to present with NSTEMI, present without chest pain, and have a cluster of associated symptoms may add to the complexity of diagnosing AMI in young women who are generally considered low-risk for cardiac events. It is interesting to note that women without chest pain were more likely to have a higher prevalence of diabetes mellitus, prior stroke or transient ischemic attack, chronic kidney disease, and chronic lung disease than women presenting with chest pain. Thus, young women who present with comorbid conditions along the vascular pathway and atypical symptoms may warrant further testing and careful consideration for cardiac risk even in the absence of traditional chest pain, in particular if they have a family history of heart disease.

The presence of prodromal symptoms in women has been noted in qualitative and quantitative studies, but the findings reflect patients with AMI that are generally older than the VIRGO participants.^{8,14–18} Common prodromal symptoms include unusual fatigue, shortness of breath, and pain in the shoulder and upper back, and symptoms have varied in terms of progression patterns and duration.^{5,8,15} We also noted non-chest pain symptoms that differed for young women and men, and we found young women who sought care before their hospitalization for similar symptoms were less likely to be told their symptoms might be related to their heart. A qualitative study that enrolled women aged 27 to 79 years noted that, despite numerous symptoms and visits with clinicians, most women were not diagnosed with coronary heart disease before their AMI.¹⁹ Moreover, during the infarction, women with typical symptoms were more readily diagnosed than women reporting atypical symptoms. A review found that individuals who experienced cardiac-related prodromal symptoms, such as chest, arm, or back discomfort or pain, were more likely to report the same or similar symptoms during their acute presentation,¹⁸ highlighting the need to recognize prodromal symptoms before they lead to larger acute events. Nearly 30% of women in our study sought care for similar symptoms before their hospitalization for AMI in comparison with 22% of men, yet over half of these women reported that their healthcare provider did not think the symptoms were heart-related, in comparison with 37% of men. This underscores an important gap in the recognition of heart disease in young patients, in particular young women who are typically thought to be a low-risk population.

Over 40% of patients in our cohort reported that they did not consider themselves at risk before their

AMI. Many patients also initially misattributed their symptoms to causes other than the heart. Prior studies have indicated that such misattribution could be related to lack of knowledge about symptoms or symptoms presenting in a way that is unexpected.⁸ Although most individuals are knowledgeable about chest pain as a symptom of AMI, many are less familiar with the many symptoms or chest sensations other than chest pain.^{20–22} Perception of risk may be particularly important for this relatively young population. Pooled survey data from the 2006 and 2009 American Heart Association National Women's Surveys revealed that only 55% of women were aware that heart disease is the leading cause of death in women, 47% considered themselves well informed about heart disease in women, and 50% reported a doctor discussing heart disease with them.²² Although nearly 60% of women identified chest pain as a symptom of AMI, few identified less traditional symptoms such as fatigue (7%), nausea (15%), and shortness of breath (34%). Awareness was even lower for women younger than 55 years of age. Knowledge of cardiac risk does not necessarily translate to personal risk,²³ and to date, interventions to increase awareness of risk have had limited success in decreasing the time from symptom onset to presentation.²⁴ Competing responsibilities, embarrassment or fear of bothering others, and a desire to wait until symptoms subside have been noted as reasons to delay seeking care.^{20,21,25} Our findings demonstrate that even in this young cohort, we need to increase awareness of potential symptoms of AMI for women and men.

Sex differences in the prompt recognition of and presentation for cardiac symptoms can adversely affect the appropriate triage, receipt of diagnostic testing, and timely receipt of therapies after AMI, particularly for patients with STEMI.^{21,26,27} Prior studies have reported that more than half of patients with AMI presented to the hospital more than 2 hours after symptom onset,²⁵ with a longer onset time reported for those without chest pain⁴ and those with diabetes mellitus.²⁷ Moreover, women present for treatment later than men.^{13,21,25,27,28} A prior VIRGO analysis found that young women who received reperfusion therapy were more likely than men to present with no symptoms or atypical chest pain, and these women were more likely to present more than 6 hours after symptom onset.⁷ It is possible that the delay in treatment found for young women with STEMI may have been partly attributable to the concomitant presentation of multiple symptoms, the quality of the pain or discomfort, or the order of symptoms described by the patient (eg, chest pain not the first or most prominent symptom reported). Given the young age of participants in VIRGO, the pretest probability of AMI at the time of triage may be low, particularly for

young women in comparison with young men. Accordingly, if women present with a myriad of non-chest pain symptoms, especially those women with NSTEMI and without clear ECG changes, the reporting of epigastric symptoms, anxiety, and fatigue, which are not uncommon in this age group, may complicate the initial assessment of AMI. As a result, it is important to elicit all symptoms at the time of clinical presentation and prioritize potential heart disease if chest pain, pressure, tightness, or discomfort is mentioned as one of multiple symptoms.

Our study has several limitations. Patients who died before hospital arrival or before consent were not included in the study, and therefore, there is potential survival bias. We did not interview providers about their perceptions or impressions of symptoms, but we collected detailed information on the patient perception of symptom recognition and interactions with the healthcare system, including whether cardiac testing had or had not been initiated. We were unable to ascertain the first or primary symptom the patient provided to the care providers at the time of presentation, and we are missing data on time of symptom onset for 12% of the patients. Finally, although recall bias is possible, we minimized this concern by conducting the interviews during the index hospitalization, shortly after the AMI event.

Based on direct patient interviews with 2985 young patients hospitalized with AMI, the presentation of young women and men with heart disease was similar, with nearly 90% of women and men presenting with chest pain, pressure, tightness, or discomfort. Women presented with a greater number of non-chest pain symptoms, and although the total number of additional symptoms may not be noteworthy, the presentation of chest pain within the context of multiple symptoms may influence the prompt recognition of heart disease and initial actions on the part of providers. Our results highlight the challenge for providers to identify heart disease in this young cohort traditionally considered low-risk, even though they may have multiple risk factors and often have a family history of heart disease.

ARTICLE INFORMATION

Received September 26, 2017; accepted December 11, 2017.

The online-only Data Supplement is available with this article at <http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIRCULATIONAHA.117.031650/-/DC1>.

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Sources of Funding

VIRGO was supported by grant R01 HL081153 from the National Heart, Lung, and Blood Institute. The funding organization had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

Disclosures

Dr Krumholz is a recipient of research agreements from Medtronic and from Johnson & Johnson (Janssen), through Yale, to develop methods of clinical trial data sharing; is the recipient of a grant from Medtronic and the Food and Drug Administration, through Yale, to develop methods for postmarket surveillance of medical devices; works under contract with the Centers for Medicare & Medicaid Services to develop and maintain performance measures that are publicly reported; chairs a cardiac scientific advisory board for UnitedHealth; is a participant/participant representative of the IBM Watson Health Life Sciences Board; is a member of the advisory board for Element Science and the physician advisory board for Aetna; and is the founder of Hugo, a personal health information platform.

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Sex Differences in the Presentation and Perception of Symptoms Among Young Patients With Myocardial Infarction: Evidence from the VIRGO Study (Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients)

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Circulation. 2018;137:781-790

doi: 10.1161/CIRCULATIONAHA.117.031650

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://circ.ahajournals.org/content/137/8/781>

Data Supplement (unedited) at:

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SUPPLEMENTAL MATERIAL

Supplemental Methods. VIRGO Presenting Symptoms/Perceived Risk Interview Questions

Supplemental Table 1. Symptom Presentation by Sex and Symptom Duration

Supplemental Table 2. Symptom Presentation by Sex and Prior Coronary Artery Disease

Supplemental Table 3. Symptom Presentation by Sex and Diabetes Status

Supplemental Table 4. Patient Response to Symptoms by Sex and Symptom Duration

Supplemental Table 5. Patient Response to Symptoms by Sex and Prior Coronary Artery Disease

Supplemental Table 6. Patient Response to Symptoms by Sex and Education

Supplemental Table 7. Patient Response to Symptoms by Sex and Diabetes Status

Supplemental Methods. VIRGO Presenting Symptoms/Perceived Risk Interview Questions

1. What symptoms were you having before you came to the hospital? **[Check all that apply.]**

- Chest pain, pressure, tightness or discomfort
- Dizziness
- Indigestion or stomach pain, pressure, burning or discomfort
- Nausea
- Pain or discomfort in jaw, neck, arms or between your shoulder blades
- Palpitations
- Shortness of breath
- Sweating
- Weakness or fatigue
- Confusion
- Other symptom _____

2. Why did you decide to get help for these symptoms? **[Check all that apply.]**

- Symptoms would not go away
- Pain too bad to ignore
- Worried about heart problem
- Worried about other health problems (e.g., diabetes)
- Family / friend told me to get help
- Other _____

3. When you were first having these symptoms, did you think that something was wrong with your heart?

- Yes No Don't Know

[If No] What did you think was causing these symptoms? **[Check all that apply]**

- Indigestion or acid reflux
- Stomach illness or flu
- Muscle pain
- Fatigue
- Stress / anxiety
- Asthma
- Diabetes
- Other cause _____

4. Were you having any of these symptoms (or not feeling well) for more than a day prior to seeking medical care?

- Yes No

[If Yes] How long were you having these symptoms (or not feeling well)?

___ (days) ___ (months)

What were the reason(s) that you decided to wait before seeking medical care?
[Check all that apply.]

- Didn't have time to go to the doctor
- Symptoms did not seem bad enough for emergency care
- Symptoms would come and go over time (not persistent)
- Symptoms were different than expected for a heart problem
- Took medication for symptoms (e.g., antacids, over the counter meds)
- Transportation – waited for someone to drive me to office/hospital
- Health insurance concerns
- Embarrassment or fear
- Other _____
- Don't know

5. Did you visit your doctor for any of these symptoms before this hospitalization?

- Yes
- You never had these symptoms before
- You never visited your doctor for these symptoms
- Don't know

[If Yes] How many times have you seen your doctor for these symptoms?

_____ Don't Know

Did you see your doctor in the week before going to the hospital for any of these symptoms?

- Yes
- No
- Don't Know

Did your doctor ever tell you that your symptoms might be related to a heart problem?

- Yes
- No
- Don't Know

[If No] What did they think caused these symptoms?

- Indigestion or acid reflux
- Stomach illness or flu
- Muscle pain
- Fatigue
- Stress / anxiety
- Asthma
- Diabetes
- Other cause _____

Were you tested for a heart problem (e.g., ECG, stress test)?

Yes No Don't Know

[If Yes] Did the tests show that you were having a problem with your heart?

Yes No Don't Know

6. Where did you first go for help? **[Check all that apply.]**

- Went directly to the Emergency Room (ER)
- Called 9-1-1
- Went to my primary health care provider
- Went to a walk-in clinic
- Other _____

7. When you first went for help, did the health care providers think that you were having a problem with your heart?

Yes No

[If No] What did they think was wrong?

- Acid reflux
- Stomach illness or flu
- Asthma
- Other chronic condition (i.e. diabetes)
- Other _____

8. When you got to the hospital, did you think you waited a long time before you were seen by a doctor?

Yes No

[If Yes] Roughly how long did you wait? _____ hours _____ minutes

What were the reasons you waited? **[Check all that apply.]**

- Triage nurse / care provider did not think symptoms were urgent
- The emergency room was crowded
- Other people were seen ahead of me
- Waited for tests or results
- There were not any beds – waited to be transferred to a floor in the hospital
- Other _____

9. Did you take aspirin before seeking medical attention?

Yes No Don't Remember Don't Know

[If No] Why didn't you take aspirin?

- Aspirin was not available at the time
- Allergic to aspirin
- Did not know that I should take aspirin
- Other (specify) _____
- Don't know

10. Prior to your recent hospital stay, did you consider yourself at risk for heart disease or a heart problem?

Yes No

11. Prior to your recent hospital stay, did any of your healthcare providers ever tell you that you were at risk for heart disease or a heart problem?

Yes No Don't Know

12. Did a doctor ever talk to you about heart disease and talk about things that you could do to take care of your heart?

Yes No Don't Know

Supplemental Table 1. Symptom Presentation by Sex and Symptom Duration

| | Among Patients with | | | Among Patients with | | |
|--|-------------------------|----------------|------------|-------------------------|----------------|------------|
| | Symptom Duration >1 Day | | | Symptom Duration ≤1 Day | | |
| | Women (n=1099) | Men (n=477) | <i>p</i> * | Women (n=910) | Men (n=499) | <i>p</i> * |
| Individual Symptoms, % | | | | | | |
| Chest pain, pressure, tightness, or discomfort | 87.3 | 89.3 | 1 | 86.7 | 89.8 | 0.550 |
| Dizziness | 29.4 | 28.1 | 1 | 26.3 | 24.5 | 1 |
| Epigastric: indigestion, nausea, or stomach pain, pressure, burning, or discomfort | 62.8 | 50.3 | <0.001 | 60.0 | 50.1 | 0.003 |
| Pain/discomfort in jaw, neck, arms, or between shoulder blades | 67.8 | 59.5 | 0.013 | 61.5 | 56.6 | 0.524 |
| Palpitations | 20.4 | 14.7 | 0.053 | 16.6 | 10.4 | 0.013 |
| Shortness of breath | 56.6 | 50.5 | 0.157 | 48.3 | 44.8 | 0.826 |
| Sweating | 51.0 | 52.2 | 1 | 56.1 | 58.6 | 1 |
| Weakness or fatigue | 48.2 | 45.1 | 1 | 41.5 | 36.9 | 0.550 |
| Confusion | 13.4 | 11.5 | 1 | 10.6 | 10.8 | 1 |
| Number of Associated, Non- Chest Pain Symptoms | | | | | | |
| Mean (SD) | 3.5 (2.0) | 3.1 (1.9) | <0.001 | 3.2 (2.0) | 2.9 (1.9) | 0.009 |
| Median (IQR) | 3 (2-5) | 3 (2-4) | <0.001 | 3 (2-5) | 3 (2-4) | 0.009 |
| 0 symptoms | 3.9 | 6.1 | 0.009 | 7.7 | 7.2 | 0.006 |

| | | | | |
|--------------|------|------|------|------|
| 1-2 symptoms | 31.8 | 37.1 | 33.2 | 39.9 |
| 3-4 symptoms | 33.5 | 32.9 | 32.3 | 33.9 |
| >4 symptoms | 30.8 | 23.9 | 26.8 | 19.0 |

Abbreviations: IQR, interquartile range; SD, standard deviation.

*The stepdown Bonferroni method was used to adjust the p values for multiple pairwise comparisons.

Supplemental Table 2. Symptom Presentation by Sex and Prior Coronary Artery Disease*

| | Among Patients with | | | Among Patients with | | |
|--|---------------------|----------------|-----------------------|---------------------|----------------|-----------------------|
| | Prior CAD | | | No Prior CAD | | |
| | Women (n=625) | Men (n=294) | <i>p</i> [†] | Women (n=1384) | Men (n=682) | <i>p</i> [†] |
| Individual Symptoms, % | | | | | | |
| Chest pain, pressure, tightness, or discomfort | 87.8 | 90.1 | 1 | 86.6 | 89.3 | 0.426 |
| Dizziness | 31.8 | 27.6 | 1 | 26.2 | 25.7 | 1 |
| Epigastric: indigestion, nausea, or stomach pain, pressure, burning, or discomfort | 63.0 | 56.8 | 0.494 | 60.8 | 47.4 | <0.001 |
| Pain/discomfort in jaw, neck, arms, or between shoulder blades | 66.6 | 63.1 | 1 | 64.2 | 55.9 | 0.002 |
| Palpitations | 22.9 | 16.7 | 0.260 | 16.8 | 10.7 | 0.002 |
| Shortness of breath | 61.9 | 50.5 | 0.010 | 48.7 | 46.3 | 1 |
| Sweating | 53.6 | 55.3 | 1 | 53.1 | 55.6 | 1 |
| Weakness or fatigue | 47.5 | 44.7 | 1 | 44.1 | 39.3 | 0.225 |
| Confusion | 14.6 | 11.9 | 1 | 11.0 | 10.9 | 1 |
| Number of Associated, Non- Chest Pain Symptoms | | | | | | |
| Mean (SD) | 3.6 (2.1) | 3.3 (1.9) | 0.013 | 3.2 (1.9) | 2.9 (1.9) | <0.001 |
| Median (IQR) | 4 (2-5) | 3 (2-4) | 0.011 | 3 (2-5) | 3 (1-4) | <0.001 |
| 0 symptoms | 5.6 | 4.4 | 0.005 | 5.6 | 7.6 | 0.004 |

| | | | | |
|--------------|------|------|------|------|
| 1-2 symptoms | 27.8 | 37.8 | 34.5 | 38.9 |
| 3-4 symptoms | 32.2 | 33.0 | 33.3 | 33.6 |
| >4 symptoms | 34.4 | 24.8 | 26.5 | 19.9 |

Abbreviations: CAD, coronary artery disease; IQR, interquartile range; SD, standard deviation.

*Coronary artery disease includes a history of myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting, or angina.

†The stepdown Bonferroni method was used to adjust the p values for multiple pairwise comparisons.

Supplemental Table 3. Symptom Presentation by Sex and Diabetes Status

| | Among Patients with | | | Among Patients | | |
|--|---------------------|----------------|------------|-------------------|----------------|------------|
| | Diabetes | | | Without Diabetes | | |
| | Women (n=699) | Men (n=206) | <i>p</i> * | Women (n=1310) | Men (n=770) | <i>p</i> * |
| Individual Symptoms, % | | | | | | |
| Chest pain, pressure, tightness, or discomfort | 85.3 | 85.9 | 1 | 87.9 | 90.5 | 0.282 |
| Dizziness | 26.4 | 24.4 | 1 | 28.9 | 26.8 | 0.665 |
| Epigastric: indigestion, nausea, or stomach pain, pressure, burning, or discomfort | 60.9 | 48.5 | 0.014 | 61.8 | 50.6 | <0.001 |
| Pain/discomfort in jaw, neck, arms, or between shoulder blades | 62.5 | 62.4 | 1 | 66.3 | 56.9 | <0.001 |
| Palpitations | 18.1 | 12.7 | 0.567 | 19.0 | 12.5 | <0.001 |
| Shortness of breath | 54.9 | 54.1 | 1 | 51.8 | 45.8 | 0.055 |
| Sweating | 50.0 | 46.8 | 1 | 55.0 | 57.8 | 0.665 |
| Weakness or fatigue | 44.8 | 44.9 | 1 | 45.3 | 39.9 | 0.075 |
| Confusion | 13.3 | 11.2 | 1 | 11.5 | 11.2 | 0.845 |
| Number of Associated, Non- Chest Pain Symptoms | | | | | | |
| Mean (SD) | 3.3 (2.0) | 3.0 (1.9) | 0.088 | 3.4 (2.0) | 3.0 (1.9) | <0.001 |
| Median (IQR) | 3 (2-5) | 3 (2-4) | 0.094 | 3 (2-5) | 3 (2-4) | <0.001 |
| 0 symptoms | 4.9 | 6.8 | 0.317 | 6.0 | 6.6 | <0.001 |

| | | | | |
|--------------|------|------|------|------|
| 1-2 symptoms | 34.3 | 35.9 | 31.5 | 39.2 |
| 3-4 symptoms | 34.2 | 36.4 | 32.3 | 32.6 |
| >4 symptoms | 26.6 | 20.9 | 30.2 | 21.6 |

Abbreviations: IQR, interquartile range; SD, standard deviation.

*The stepdown Bonferroni method was used to adjust the p values for multiple pairwise comparisons.

Supplemental Table 4. Patient Response to Symptoms by Sex and Symptom Duration

| | Among Patients with Symptom Duration >1 Day | | | Among Patients with Symptom Duration ≤1 Day | | |
|--|--|---------|------------|--|---------|------------|
| | Women | Men | <i>p</i> * | Women | Men | <i>p</i> * |
| | (n=1099) | (n=477) | | (n=910) | (n=499) | |
| Patient did not perceive cause of symptoms to be heart related, % | 57.1 | 55.1 | 0.130 | 51.8 | 49.5 | 0.815 |
| Perceived reason | | | | | | |
| Indigestion or acid reflux | 44.3 | 50.2 | 0.457 | 40.8 | 48.6 | 0.224 |
| Muscle pain | 16.4 | 23.2 | 0.119 | 14.0 | 19.0 | 0.239 |
| Stress / anxiety | 22.6 | 12.9 | 0.007 | 18.7 | 10.5 | 0.036 |
| Stomach illness or flu | 12.3 | 8.4 | 0.457 | 10.6 | 11.3 | 1 |
| Asthma | 14.3 | 9.5 | 0.300 | 5.9 | 6.5 | 1 |
| Fatigue | 8.1 | 5.3 | 0.457 | 3.0 | 6.1 | 0.224 |
| Diabetes | 4.5 | 2.7 | 0.457 | 4.5 | 1.2 | 0.130 |
| Other cause | 4.9 | 4.6 | 0.812 | 14.2 | 8.1 | 0.118 |
| Decision to seek medical care, % | | | | | | |
| Symptoms would not go away | 67.5 | 64.8 | 0.866 | 60.7 | 60.1 | 1 |

| | | | | | | |
|---|----------------|----------------|-------|---------------|---------------|-------|
| Pain too bad to ignore | 62.6 | 59.1 | 0.766 | 56.3 | 53.5 | 1 |
| Worried about heart problem | 42.5 | 47.8 | 0.257 | 40.5 | 51.7 | 0.002 |
| Family / friend told me to get help | 26.8 | 29.4 | 0.866 | 24.6 | 23.6 | 1 |
| Worried about other health problems (e.g., diabetes) | 18.3 | 11.3 | 0.004 | 14.2 | 12.2 | 1 |
| Other | 1.3 | 0.8 | 0.866 | 0.9 | 0.2 | 1 |
| Time to hospital presentation, % | | | | | | |
| ≤2 hours | 25.5 | 27.0 | 0.113 | 41.9 | 48.7 | 0.002 |
| >2-6 hours | 12.0 | 14.7 | | 19.1 | 22.2 | |
| >6 hours | 52.0 | 45.7 | | 22.7 | 18.4 | |
| Median time (IQR), hours | 8.7 (1.0-46.4) | 5.5 (1.0-36.0) | 0.070 | 1.7 (0.5-7.9) | 1.6 (0.6-4.8) | 0.286 |

Abbreviations: CAD, coronary artery disease; IQR, interquartile range.

*The stepdown Bonferroni method was used to adjust the p values for multiple pairwise comparisons.

Supplemental Table 5. Patient Response to Symptoms by Sex and Prior Coronary Artery Disease*

| | Among Patients with | | | Among Patients with | | |
|--|---------------------|----------------|-----------------------|---------------------|----------------|-----------------------|
| | Prior CAD | | | No Prior CAD | | |
| | Women (n=625) | Men (n=294) | <i>p</i> [†] | Women (n=1384) | Men (n=682) | <i>p</i> [†] |
| Patient did not perceive cause of symptoms to be heart related, % | 39.7 | 36.7 | 0.417 | 61.5 | 58.9 | 0.417 |
| Perceived reason | | | | | | |
| Indigestion or acid reflux | 39.1 | 50.9 | 0.268 | 43.8 | 49.0 | 0.430 |
| Muscle pain | 14.1 | 18.5 | 1 | 15.7 | 21.9 | 0.049 |
| Stress / anxiety | 23.4 | 10.2 | 0.030 | 20.2 | 12.2 | 0.004 |
| Stomach illness or flu | 13.7 | 7.4 | 0.541 | 10.9 | 10.4 | 1 |
| Asthma | 9.7 | 6.5 | 1 | 11.0 | 8.5 | 0.632 |
| Fatigue | 6.9 | 6.5 | 1 | 5.6 | 5.5 | 1 |
| Diabetes | 5.6 | 4.6 | 1 | 4.1 | 1.2 | 0.049 |
| Other cause | 8.5 | 4.6 | 1 | 9.0 | 6.7 | 0.632 |
| Decision to seek medical care, % | | | | | | |
| Symptoms would not go away | 64.2 | 62.6 | 0.748 | 64.5 | 62.3 | 1 |

| | | | | | | |
|--|----------------|----------------|--------|----------------|----------------|--------|
| Pain too bad to ignore | 60.5 | 57.5 | 0.748 | 59.4 | 55.7 | 0.854 |
| Worried about heart problem | 54.2 | 63.9 | 0.037 | 35.9 | 43.7 | 0.014 |
| Family / friend told me to get help | 22.7 | 23.8 | 0.748 | 27.2 | 27.6 | 1 |
| Worried about other health problems (e.g., diabetes) | 17.6 | 10.9 | 0.058 | 15.9 | 12.2 | 0.306 |
| Other | 1.1 | 0.0 | 0.265 | 1.1 | 0.7 | 1 |
| Time to hospital presentation, % | | | | | | |
| ≤2 hours | 33.8 | 36.1 | 0.0498 | 32.5 | 39.0 | <0.001 |
| >2-6 hours | 17.1 | 20.4 | | 14.4 | 17.7 | |
| >6 hours | 36.8 | 27.9 | | 39.6 | 33.4 | |
| Median time (IQR), hours | 2.6 (0.7-19.1) | 2.4 (0.7-11.5) | 0.323 | 3.6 (0.8-22.2) | 2.4 (0.7-13.7) | 0.004 |

Abbreviations: CAD, coronary artery disease; IQR, interquartile range.

*Coronary artery disease includes a history of myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting, or angina.

†The stepdown Bonferroni method was used to adjust the p values for multiple pairwise comparisons.

Supplemental Table 6. Patient Response to Symptoms by Sex and Education

| | Among Patients with >High School Education | | | Among Patients with High School Education or Below | | |
|--|---|---------|------------|--|---------|------------|
| | Women | Men | <i>p</i> * | Women | Men | <i>p</i> * |
| | (n=1132) | (n=547) | | (n=877) | (n=429) | |
| Patient did not perceive cause of symptoms to be heart related, % | 55.8 | 52.7 | 0.417 | 53.2 | 51.7 | 0.550 |
| Perceived reason | | | | | | |
| Indigestion or acid reflux | 41.1 | 46.5 | 0.502 | 45.0 | 53.2 | 0.266 |
| Muscle pain | 16.9 | 24.3 | 0.055 | 13.3 | 17.1 | 0.724 |
| Stress / anxiety | 21.0 | 12.5 | 0.015 | 20.8 | 10.8 | 0.010 |
| Stomach illness or flu | 12.8 | 12.8 | 1 | 9.9 | 5.9 | 0.400 |
| Asthma | 10.9 | 7.3 | 0.430 | 10.5 | 9.0 | 1 |
| Fatigue | 6.2 | 6.6 | 1 | 5.6 | 4.5 | 1 |
| Diabetes | 4.3 | 2.4 | 0.509 | 4.7 | 1.4 | 0.193 |
| Other cause | 9.7 | 4.5 | 0.055 | 7.9 | 8.6 | 1 |
| Decision to seek medical care, % | | | | | | |

| | | | | | | |
|---|----------------|----------------|-------|----------------|----------------|-------|
| Symptoms would not go away | 65.5 | 64.9 | 1 | 62.9 | 59.2 | 0.819 |
| Pain too bad to ignore | 58.7 | 54.1 | 0.494 | 61.1 | 59.0 | 0.819 |
| Worried about heart problem | 42.8 | 53.0 | 0.002 | 40.1 | 45.7 | 0.326 |
| Family / friend told me to get help | 25.3 | 24.9 | 1 | 26.5 | 28.4 | 0.819 |
| Worried about other health problems (e.g., diabetes) | 16.9 | 10.4 | 0.009 | 15.8 | 13.5 | 0.819 |
| Other | 1.1 | 0.2 | 0.494 | 1.1 | 0.9 | 0.819 |
| Time to hospital presentation, % | | | | | | |
| ≤2 hours | 35.0 | 39.3 | 0.039 | 30.2 | 36.6 | 0.006 |
| >2-6 hours | 15.0 | 18.1 | | 15.5 | 19.1 | |
| >6 hours | 37.1 | 31.8 | | 40.8 | 31.7 | |
| Median time (IQR), hours | 2.7 (0.7-19.7) | 2.3 (0.7-12.0) | 0.064 | 3.9 (0.8-23.7) | 2.6 (0.8-14.0) | 0.020 |

Abbreviations: IQR, interquartile range.

*The stepdown Bonferroni method was used to adjust the p values for multiple pairwise comparisons.

Supplemental Table 7. Patient Response to Symptoms by Sex and Diabetes Status

| | Among Patients with Diabetes | | | Among Patients Without Diabetes | | |
|--|------------------------------|---------|------------|---------------------------------|---------|------------|
| | Women | Men | <i>p</i> * | Women | Men | <i>p</i> * |
| | (n=699) | (n=206) | | (n=1310) | (n=770) | |
| Patient did not perceive cause of symptoms to be heart related, % | 57.5 | 53.4 | 0.604 | 53.2 | 51.9 | 0.519 |
| Perceived reason | | | | | | |
| Indigestion or acid reflux | 40.3 | 52.7 | 0.137 | 44.2 | 48.5 | 0.671 |
| Muscle pain | 12.2 | 15.5 | 1 | 17.2 | 22.8 | 0.176 |
| Stress / anxiety | 18.9 | 8.2 | 0.059 | 22.1 | 12.8 | <0.001 |
| Stomach illness or flu | 12.7 | 10.9 | 1 | 10.9 | 9.5 | 1 |
| Asthma | 11.2 | 10.9 | 1 | 10.5 | 7.3 | 0.384 |
| Fatigue | 5.5 | 6.4 | 1 | 6.2 | 5.5 | 1 |
| Diabetes | 10.9 | 7.3 | 1 | 0.7 | 0.5 | 1 |
| Other cause | 9.0 | 8.2 | 1 | 8.9 | 5.8 | 0.364 |
| Decision to seek medical care, % | | | | | | |
| Symptoms would not go away | 63.2 | 65.5 | 1 | 65.0 | 61.6 | 0.444 |
| Pain too bad to ignore | 59.1 | 56.3 | 1 | 60.1 | 56.2 | 0.429 |

| | | | | | | |
|---|----------------|----------------|-------|----------------|----------------|--------|
| Worried about heart problem | 42.2 | 49.0 | 0.678 | 41.3 | 50.0 | <0.001 |
| Family / friend told me to get help | 26.3 | 22.8 | 1 | 25.5 | 27.4 | 0.467 |
| Worried about other health problems (e.g., diabetes) | 22.2 | 12.6 | 0.045 | 13.4 | 11.6 | 0.467 |
| Other | 0.9 | 0.5 | 1 | 1.2 | 0.5 | 0.444 |
| Time to hospital presentation, % | | | | | | |
| ≤2 hours | 28.2 | 28.6 | 0.931 | 35.4 | 40.6 | <0.001 |
| >2-6 hours | 15.6 | 16.0 | | 15.0 | 19.2 | |
| >6 hours | 44.9 | 42.7 | | 35.4 | 28.8 | |
| Median time (IQR), hours | 4.9 (1.0-25.7) | 4.8 (0.9-34.2) | 0.935 | 2.6 (0.7-18.1) | 2.1 (0.7-10.0) | 0.016 |

Abbreviations: IQR, interquartile range.

*The stepdown Bonferroni method was used to adjust the p values for multiple pairwise comparisons.