



Published in final edited form as:

Circulation. 2018 February 20; 137(8): 781–790. doi:10.1161/CIRCULATIONAHA.117.031650.

Sex Differences in the Presentation and Perception of Symptoms among Young Patients with Myocardial Infarction: Evidence from the VIRGO Study

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Abstract

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 18–55 years hospitalized for AMI at 103 US hospitals participating in the Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients (VIRGO) study. 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

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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 post-market 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.

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 (e.g., epigastric symptoms, palpitations, and pain or discomfort in the jaw, neck, arms, or between the shoulder blades; 61.9% for women vs 54.8% for men, $p<0.001$). In adjusted analyses, women with an ST-elevation AMI were more likely than men to present without chest pain (odds ratio 1.51; 95% confidence interval 1.03–2.22). Compared with men, women were more likely to perceive symptoms as stress/anxiety (20.9% vs 11.8%, $p<0.001$) but less likely to attribute symptoms to muscle pain (15.4% vs 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 as compared 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 compared with men.

Keywords

acute myocardial infarction; care-seeking behavior; delay; medical care; symptoms; women

INTRODUCTION

Young women with heart disease have a higher risk of dying from their acute myocardial infarction (AMI) as compared 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 AMI patients 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 in-hospital 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 AMI patients,⁵ and lack of information on the perception of symptoms and care-seeking behaviors 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 as well as explore how symptom recognition influences patients' care-seeking behaviors and early interactions with healthcare providers.

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 Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients (VIRGO) study.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 18–55 years of age.

METHODS

The VIRGO investigators have an intent to share study data and are investigating mechanisms and funding to make it possible. We are currently working on two 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 18–55 years of age and had increased cardiac biomarker levels, with at least one of these biomarkers >99th 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 symptoms of ischemia or electrocardiogram 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 prior to hospital presentation, perceived cause of symptoms, and prior interactions with the healthcare system for similar symptoms were collected by standardized direct patient interviews administered by trained personnel during the index hospitalization for AMI (see Supplemental Methods for interview questions). The questions were developed based on prior qualitative research conducted in young patients hospitalized with AMI.⁸ Questions included pre-specified 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” 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, 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 (e.g., diabetes), 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, or another cause. Among participants who responded that their doctor suspected heart disease, we asked whether they were tested for a heart problem (e.g., electrocardiogram, 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 codes⁹: metropolitan [population >50,000], micropolitan [population 10,000–49,999], or small town/rural [population <10,000]), marital status (married or living as married vs 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 (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] vs non-ST-segment elevation AMI [NSTEMI]), Killip class (III/IV vs 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.

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 pre-specified subgroups defined by type of AMI and age. All statistical analyses were conducted using SAS version 9.4 (SAS Institute, Cary, North Carolina), 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, 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.

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 ($p<0.001$). Using 3 symptoms as the cut-off based on the distribution of symptoms and clinical input from the investigators, 61.9% of women presented with 3 associated, non-chest pain symptoms compared 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% vs 53.1%, $p<0.001$) and jaw/neck/arms/shoulder pain (67.7% vs 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% vs 46.2%, $p=0.003$), palpitations (21.5% vs 14.6%, $p=0.022$),

and shortness of breath (54.2% vs 46.1%, $p=0.035$) as compared 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 (Supplemental Table 1). Regardless of prior CAD/angina status, women reported more additional symptoms than men (Supplemental Table 2). For those with diabetes, only epigastric symptoms were more common among women compared with men, and no significant difference was observed in the number of associated, non-chest pain symptoms (Supplemental Table 3).

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 as compared with men. Women who had a STEMI had 1.51 (95% CI 1.03–2.22) times the odds of presenting without chest pain as compared 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 non-cardiac conditions, the most prevalent symptom being indigestion or acid reflux in both sexes (Table 4). Compared with men, women were significantly more likely to have perceived their symptoms as due to stress or anxiety (20.9% vs 11.8%, $p<0.001$). Women were less likely to perceive their symptoms as related to muscle pain (15.4% vs 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 due to concerns about a heart problem than women (49.8% vs 41.6%, $p<0.001$), while a greater proportion of women sought care due to concerns about another health problem such as diabetes (16.4% vs 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 vs 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 a high school education, women were more likely to perceive their symptoms as related to stress or anxiety, while men were more likely to seek care because they were worried about a heart problem (Supplemental Tables 4–6). For patients with a high school education or below, women had a longer median time to presentation than men (Supplemental Table 6). Among patients with diabetes, women were more likely to report seeking medical care because they were worried about other health problems such as diabetes, but both women and men with diabetes had a longer median time to hospital presentation than those without diabetes (Supplemental Table 7).

A greater percentage of women sought medical care for similar symptoms prior to being hospitalized for their AMI, as compared with men (29.5% vs 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, as compared 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, compared 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 as well as physician interpretation of the patient's problem and subsequent testing. This may have contributed to the observation that women sought care more frequently for similar symptoms prior to 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 work up 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 45–54 years experienced chest pain. This study also reported that women aged 45–54 years were more likely to present without chest pain compared with 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 46–55 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 45–55 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, as compared 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 work up for ischemic heart disease, particularly 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, particularly 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 one or more 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 reported a higher mean number of associated non-chest pain symptoms. Regardless of AMI subtype, women were significantly more likely to present with epigastric symptoms compared with men. Women with NSTEMI were more likely to present with the symptoms of shortness of breath and palpitations compared with 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. Interestingly, women without chest pain were more likely to have a higher prevalence of diabetes, 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, particularly 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 prior to 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 27–79 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 prior to their hospitalization for AMI compared with 22% of men, yet over half of these women reported that their healthcare provider did not think the symptoms were heart related, as compared with 37% of men. This underscores an important gap in the recognition of heart disease in young patients, particularly 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 prior to 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 While 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 While 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 necessary 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.²⁷ Moreover, women present for treatment later than men.^{13,21,25,27,28} A prior VIRGO analysis found 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 six hours after symptom onset.⁷ It is possible that the delay in treatment found for young women with STEMI may have been partly due to the concomitant presentation of multiple symptoms, the quality of the pain or discomfort, or the order of symptoms described by the patient (e.g., 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 compared to young men. Accordingly, if women present with a myriad of non-chest pain symptoms, especially those women with NSTEMI and without clear electrocardiogram 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 prior to hospital arrival or prior to 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

SOURCES OF FUNDING

VIRGO was supported by grant R01 HL081153-01A1K 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.

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CLINICAL PERSPECTIVE

What Is New?

- Sex differences in symptom presentation for acute myocardial infarction (AMI) 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 AMI.
- 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 as compared with men.
- Among patients who sought care for symptoms prior to 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 AMI.
- Presentation with multiple non-chest pain symptoms may influence the decision to initiate a work up 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 VIRGO had 1 traditional cardiac risk factors; 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.

Patient Characteristics by Sex

Table 1

	Overall		Among Patients with No Chest Pain		Among Patients with Chest Pain		p
	Women (n=2009)	Men (n=976)	Women (n=261)	Men (n=102)	Women (n=1748)	Men (n=874)	
Sociodemographic Characteristics, %							
Age range, years	18–55 47.2 (6.3)	23–55 47.1 (5.9)	27–55 48.6 (5.4)	29–55 47.6 (5.6)	18–55 47.0 (6.4)	23–55 47.0 (6.0)	0.783
Age, mean (SD), years	72.9	81.6 <0.001	78.2	75.5 0.465	72.1	82.4 <0.001	
Race							
White	21.3	11.0	14.9	13.7	22.3	10.7	
Black	5.7	7.4	6.9	10.8	5.6	7.0	
Other	7.6	8.4 0.455	5.7	6.9 0.689	7.9	8.6 0.544	
Hispanic	52.5	62.2 <0.001	54.0	53.9 0.986	52.2	63.2 <0.001	
Married	56.8	56.6 0.905	62.3	51.0 0.050	56.0	57.2 0.550	
Greater than high school education							
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 healthcare 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	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	

	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
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

Abbreviations: BMI, 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; SD, standard deviation; STEMI, ST-elevation myocardial infarction; TIA, transient ischemic attack.

Symptom Presentation by Sex

Table 2

	Overall		Among Patients with STEMI		Among Patients with NSTEMI		Among Patients with No Chest Pain		* p
	Women (n=2009)	Men (n=976)	Women (n=922)	Men (n=563)	Women (n=1087)	Men (n=413)	Women (n=261)	Men (n=102)	
Individual Symptoms, %									
Chest pain, pressure, tightness, or discomfort	87.0	89.5	87.3	91.5	86.8	86.9	21.9	22.8	1
Dizziness	28.0	26.3	29.5	28.1	26.7	23.8	21.9	22.8	1
Epigastric: indigestion, nausea, or stomach pain, pressure, burning, or discomfort	61.5	50.2	67.1	53.1	56.8	46.2	55.2	51.0	1
Pain/discomfort in jaw, neck, arms, or between shoulder blades	64.9	58.1	67.7	58.6	62.6	57.3	55.4	48.5	1
Palpitations	18.7	12.5	15.4	11.0	21.5	14.6	8.5	11.9	1
Shortness of breath	52.8	47.6	51.2	48.7	54.2	46.1	41.2	42.6	1
Sweating	53.3	55.5	62.1	63.1	45.8	45.1	39.2	40.6	1
Weakness or fatigue	45.2	40.9	46.1	43.7	44.4	37.1	31.9	32.7	1
Confusion	12.1	11.2	13.3	12.6	11.0	9.2	10.0	4.0	0.496
Number of Associated, Non-Chest Pain Symptoms									
Mean (SD)	3.4 (2.0)	3.0 (1.9)	3.5 (1.9)	3.2 (1.9)	3.2 (2.0)	2.8 (1.9)	2.6 (1.7)	2.5 (1.5)	0.582
0 symptoms	5.6	6.7	4.2	5.7	6.8	8.0	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	

Abbreviations: SD, standard deviation; NSTEMI, non-ST-elevation myocardial infarction; STEMI, ST-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)*	<i>P</i>
Overall	1.20 (0.92–1.56)	0.187
Age		
45y	0.86 (0.52–1.43)	0.564
>45y	1.39 (1.01–1.92)	0.042
Final Diagnosis		
NSTEMI	0.95 (0.65–1.37)	0.77
STEMI	1.51 (1.03–2.22)	0.036

Abbreviations: CI, confidence interval; NSTEMI, non-ST-elevation myocardial infarction; STEMI, ST-elevation myocardial infarction

* Hierarchical logistic regression models were used to assess the relationship between sex (women versus 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, 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).

Table 4

Patient Response to Symptoms

	Women (n=2009)	Men (n=976)	<i>p</i> [*]
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	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 (e.g., diabetes)	16.4	11.8	0.004
Other	1.1	0.5	0.345
Time to hospital presentation, %			
2 hours	32.9	38.1	0.002
>2–6 hours	15.2	18.5	
>6 hours	38.7	31.8	
Median time (IQR), hours	3.2 (0.8–21.2)	2.4 (0.7–13.0)	0.004

Abbreviations: IQR, interquartile range.

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

Table 5

Sought Care for Similar Symptoms Prior to Hospitalization

	Women (n=2009)	Men (n=976)	<i>p</i> [*]
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	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.

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