Sex Differences in Symptom Complexity and Door-to-Balloon Time in Patients With ST-Elevation Myocardial Infarction

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Abstract

Greater symptom complexity in women, compared with men, could slow ST-elevation AMI (STEMI) recognition and delay door-to-balloon (D2B) times. We sought to determine sex differences in symptom complexity and their relation to D2B times in 1677 young and older patients with STEMI using data from the VIRGO and SILVER-AMI studies. Symptom complexity was defined by the number of symptom patterns or phenotypes and average number of symptoms. The numbers of symptom phenotypes were compared in women and men using Monte Carlo permutation testing. Groups were also compared using generalized linear regression and logistic regression. The number of symptom phenotypes (244 vs. 171, p=0.02), mean number of symptoms (4.7 vs. 4.2, p<0.001), and mean D2B time (114.6 vs 97.8 minutes, p=0.004) were greater in young women as compared with young men but were not significantly different in older women as compared with older men. Regression analysis did not show a relationship between symptom complexity and D2B time overall, although chest pain was a significant predictor of D2B times, and young women were more likely to report symptoms other than chest pain. Of STEMI patients, 36% did not receive PCI, which was associated with presentation delay > 6

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hours. In STEMI patients with either D2B time 90 minutes or no PCI, women had significantly more symptom phenotypes overall and in VIRGO but not in SILVER-AMI. In conclusion, markers of symptom complexity were not associated with D2B time overall but a greater number of symptom phenotypes in young women was associated with prolonged D2B time or no PCI. In addition, greater frequency of non-chest pain symptoms in young women may have also slowed the recognition of STEMI and D2B times in young women. Further research on symptoms clusters is needed to improve the recognition of STEMIs to improve the D2B times in young women.

Keywords

Introduction

Studies have consistently shown that average door-to-balloon times are longer in women, which has implications for their outcomes.[1–6] A possible reason for the longer door-to-balloon times in women may be related to symptom presentation. Women are marginally less likely to have chest pain and more likely to have atypical symptoms,[7–10] which may obscure the initial diagnosis, causing delays in the door-to-balloon time. Two recent studies examined sex differences in symptom patterns, or symptom phenotypes, in young and older patients with acute myocardial infarction (AMI),[11,12] but these studies did not assess whether greater symptom complexity was associated with longer door-to-balloon times. If symptom complexity makes AMI recognition more difficult,[13] it could have a detrimental effect on door-to-balloon times in patients with STEMI. Accordingly, the aim of this study is to examine how symptom complexity affects door-to-balloon times, whether that relationship varies by sex, and whether symptom complexity explains door-to-balloon times sex differences.

Methods

The study population included young patients with AMI from the VIRGO study[14] and older patients with AMI from the SILVER-AMI study.[15] Patients enrolled in both studies met the criteria for the Third Universal Definition of AMI.[16] Patients were enrolled in both studies at the time of hospitalization and underwent comprehensive, structured interviews at baseline by local research coordinators. Further abstraction of medical records was performed by the Yale Coordinating Center for in-depth chart review. The Institutional Review Boards at each institution approved both studies and all participants provided informed consent.

The VIRGO study is the largest prospective observational study of young women and men with AMI in the US.[14] The VIRGO study prospectively collected information on 3501 young women and men (18–55 years) hospitalized for AMI in 103 hospitals in the United States and 24 hospitals in Spain between August 2009 and January 2012. The VIRGO study focused on the characteristics of young women with AMI and therefore enrolled patients using a 2:1 female-to-male enrollment ratio.

The SILVER-AMI study is a large prospective study of older patients (75 years old) with AMI.[15] The SILVER-AMI study prospectively collected information on 3041 participants from 94 hospitals between January 2013 and June 2018.

In the VIRGO and SILVER-AMI studies, each patient was interviewed by a trained local research coordinator who specifically asked and systematically recorded the patient's presenting symptoms. The symptoms that were recorded for each study are listed in Table 1. Most of the symptoms were identical for the two studies and for symptoms that were different, we matched symptoms by performing additional searches of transcribed symptoms to create the comparable symptoms between the two studies (Table 1). Having matched the symptoms between the two studies, the data from both studies were unified for further analysis.

Patients who presented with STEMI and received emergency PCI within 12 hours of presentation were defined as the D2B Sample for both study populations.

Symptoms obtained by standardized interviews in both studies were analyzed by combining the symptoms in individual patients into combinations, or symptom phenotypes, as in the two prior studies.[11,12] In both the VIRGO and SILVER-AMI studies, trained personnel conducted review of the medical charts during the index AMI admission to record sociodemographic factors and medical history, including cardiac risk factors, co-morbid conditions, AMI type, presentation delay, and door-to-balloon time.

In both the VIRGO and SILVER-AMI studies, there were unequal numbers of women and men, which could bias the comparison of the number of phenotypes in women and men by affecting to ability to detect rare symptom phenotypes in a smaller group of patients. To overcome this source of potential bias, we used Monte Carlo permutation testing as the primary method for analyzing the differences in the number of symptom phenotypes between women and men.

For Monte Carlo permutation analysis, patients' sexes were randomly permuted to generate 99,999 data sets reflecting the null hypothesis that any difference in the number of phenotypes was due to the unequal sample sizes for women and men rather than the effect of sex. This analysis created an empirical distribution of the differences between women and men in the number of phenotypes for significance testing. The median of the empirical distribution was interpreted as an estimate of the difference in the number of phenotypes between women and men that would have been expected due to differences in the sample sizes alone and the P value was the proportion of the empirical distribution showing differences as large or larger than the differences between sexes observed in the original VIRGO or SILVER-AMI data.

Comparisons of door-to-balloon times were performed between young and older patients from the two study populations and between women and men in each study. Since the observed door-to-balloon times were best described by an inverse Gaussian distribution (rather than normal or gamma), the effects of sex, study, number of symptoms, individual symptoms, and other factors on door-to-balloon time were analyzed via generalized linear regression, using the identity link and an inverse Gaussian distribution. The effects of sex

and study on symptom counts were analyzed via negative binominal regression, and the effects of sex and study on the presence of individual symptoms were analyzed via logistic regression. In each of these regression analyses, sex and study were allowed to interact.

Since number of symptom phenotypes is a property of a group rather than an individual, it was not possible to analyze the effect of the number of symptom phenotypes using door-to-balloon time as a patient-level continuous variable, so we divided patients into subgroups according to whether the reported door-to-balloon time was < 90 minutes or 90 minutes. We arbitrarily chose a 90-minute cutoff given that 90 minutes is a commonly used threshold for door-to-balloon time. We also compared patients with door-to-balloon time < 90 minutes with patients with door-to-balloon time 90 minutes combined with STEMI patients who did not receive PCI. The resulting groups were compared using the methods described above (but using logistic regression to model door-to-balloon time subgroups rather than a generalized linear model of the door-to-balloon time itself).

As these analyses are exploratory in nature, a two-sided significance threshold of .05 was used throughout, except for the comparisons of frequencies of individual symptoms; here, the Hochberg procedure was used to maintain an overall type 1 error rate of .05 across the 40 comparisons (10 symptoms × [2 comparisons of sex within study + 2 comparisons of study within sex]). Mean values were reported ± standard deviations and median values were reported with interquartile ranges (IQRs). Model comparisons were based on the Akaike information criterion as modified for finite samples (AICC), which balances model fit with parsimony by penalizing models with more parameters.[17] All analyses were conducted using SAS/STAT software, version 15.2 (SAS Institute, Inc, Cary, NC).

Results

There were 3501 patients in the VIRGO study (2349 women and 1152 men) and 3041 patients (1346 women and 1645 men) in the SILVER-AMI study, for a total of 6542 AMI patients. STEMI was diagnosed in 1811 (52%) of the VIRGO patients and 797 (26%) of the SILVER-AMI patients. The D2B Sample (STEMI patients receiving emergency PCI within 12 hours of arrival) consisted of 1167 VIRGO patients (717 women and 450 men) and 510 SILVER-AMI patients (228 women and 282 men) for a total of 1677 patients (Figure 1).

Baseline demographic characteristics of patients in the D2B Samples from both studies are shown in Table 2. Older patients were more likely to live alone, and young patients were more likely to have a presentation delay; otherwise, the subgroups were similar.

In the D2B Sample of the VIRGO study, there were 244 symptom phenotypes in women and 171 symptom phenotypes in men. The difference of 73 symptom phenotypes was significantly greater than the difference of 52 that would have been expected if the difference was merely due to differences in sample size (p=0.02).

In the D2B Sample of the SILVER-AMI study, there were 122 symptom phenotypes in women and 144 symptom phenotypes in men. The difference of 22 symptom phenotypes was not significantly different from the difference of 20 that would have been expected if the difference was merely due to differences in sample size (p=0.60).

The 10 top-ranked symptom phenotype subgroups from both studies are listed in Table 3. For the VIRGO D2B Sample patients, the symptom phenotypes were more broadly distributed, as only 21% of the women had one of the top 10 symptom phenotypes, as compared to 29% in men (p=0.002). The top 10 symptom phenotypes tended to be more complicated descriptions of symptoms for young women than for other subgroups, as shown in Table 3. For the SILVER-AMI D2B Sample patients, the proportion of women and men with one of the top 10 symptom phenotypes was not significantly different (34% in women versus 37% in men, p=0.47).

In the D2B Sample of the VIRGO study, the mean number of symptoms in women was 4.7 ± 2.1 in women as compared with 4.2 ± 2.0 in men (p<0.0001). In the D2B Sample of the SILVER-AMI study, the difference in mean number of symptoms in women and men was not statistically significant (3.5 ± 1.9 vs 3.2 ± 1.9, p=0.08). The mean number of symptoms was significantly greater in VIRGO than in SILVER-AMI in both women and men (p<0.0001).

Neither the main effect of sex nor that of study was statistically significant in a generalized linear model containing only these predictors of door-to-balloon times, although their interaction was statistically significant (p=0.02). Examining the simple effects of sex within study, we found that in the VIRGO study, the door-to-balloon time was significantly longer in women (mean=114.6 ± 93.5, median=86.0, IQR=79.5 minutes) than men (mean=97.8 ± 78.4, median=77.5, IQR=62.0 minutes, p=0.004), while in the SILVER-AMI study, the door-to-balloon time was not significantly different between women (mean=106.6 ± 96.2, median=76.0, IQR=73.0 minutes) and men (mean=109.2 ± 103.4, median=77.5, IQR=69.0 minutes, p=0.7116).

Adding the number of symptoms or number of symptoms other than chest pain did not yield significant effects or improve the model, regardless of whether these variables were treated as linear or categorical predictors.

When chest pain was added to the model, the interaction of sex and study became nonsignificant, effectively being replaced by an interaction of study and chest pain (p=0.008), likely because chest pain was more likely to occur in VIRGO women as compared with SILVER-AMI patients. The pattern of simple effects of chest pain on door-to-balloon time within study mirrored that of sex within study in the previous model: significantly longer in those without chest pain (mean=130.8 ± 119.7, median=91.0, IQR=80.0 minutes) than those with chest pain (mean=105.6 ± 83.8, median=82.0, IQR=67.0 minutes, p=0.03) in VIRGO but not in SILVER-AMI (without chest pain: mean=97.2 ± 58.4, median=79.5, IQR=73.0 minutes; with chest pain: mean=110.6 ± 107.5, median=76.0, IQR=70.0 minutes; p=0.11).

A model including sex, study, and delayed presentation (≥6 hours) produced a main effect for delay (with delay: mean=123.4 ± 100.7, median=92.0, IQR=90.5 minutes; without delay: mean=102.9 ± 88.4, median=78.0, IQR=65.0 minutes; p=0.004) with the sex by study interaction becoming marginal (p=0.06), while a model including sex, study, and history of diabetes produced a main effect for diabetes (with diabetes: mean=125.1 ± 108.4,

median=94.0, IQR=82.0 minutes; without diabetes: mean=102.3 ± 85.0, median=78.0, IQR=60.0 minutes; p=0.005) and retained the sex by study interaction (p=0.02). Including both presentation delay and history of diabetes produced the best model AICC among those we examined, though only delay (p=0.02) and the sex by study interaction (p=0.03) remained significant (diabetes main effect p=0.11). Adding chest pain, the number of symptoms, or number of symptoms other than chest pain to this model did not yield significant effects or improve the model.

Further analysis of the number of symptom phenotypes in subgroups using door-to-balloon time as a dichotomous variable was unrevealing overall. No significant differences were found between study or sexes in the number of symptom phenotypes, the mean number of symptoms, or the main effects of the logistic regression model.

STEMI patients who received PCI were significantly less likely to have a presentation delay compared with STEMI patients who did not receive PCI (30.4% vs. 35.2%, p=0.04). Because presentation delay was associated with both whether patients received PCI and door-to-balloon times in the logistic regression model, we combined STEMI patients with no PCI with STEMI patients with door-to-balloon times   90 minutes. In this combined subgroup, women had significantly more symptom phenotypes than men (232 vs. 166, difference of 66 compared with expected difference of 40, p=0.01) and in VIRGO (198 vs. 109, difference of 89 compared with expected difference of 53, p<0.001), but not in SILVER-AMI (85 vs. 94, difference of −9 compared with expected difference of −6, p=0.68).

The frequencies of individual symptoms in patients in the D2B Sample from both studies are listed in Table 4. Chest pain was the dominant symptom in the D2B Sample of both studies for both women and men. In the D2B Sample, chest pain was more common in VIRGO women and men as compared with SILVER-AMI women and men and not significantly different between sexes within either study. Nausea/vomiting was more likely to occur in women as compared with men in VIRGO and in the VIRGO study patients as compared with the SILVER-AMI study patients. Radiating or other pain were more likely to occur in women as compared with men in both studies and in men in VIRGO as compared with men in SILVER-AMI. Confusion was more likely to occur in women in the VIRGO study than in the SILVER-AMI study, while anxiety/stress/agitation was more likely to occur in men in the SILVER-AMI study than in the VIRGO study. Chest pain, dyspnea, diaphoresis, and weakness/fatigue were more likely to occur in VIRGO study patients as compared with SILVER-AMI study patients but were not significantly different between sexes within each study. Other than chest pain, other presenting symptoms did not predict door-to-balloon time, whether analyzing using door-to-balloon time as a continuous variable, or as a dichotomous variable using the 90-minute cutoff.

Discussion

Combining data from both the VIRGO and SILVER-AMI studies allowed this detailed evaluation of the relationship of symptoms and symptom complexity with door-to-balloon times in young and older patients with STEMI. Our analysis showed significantly more

symptom phenotypes and more symptoms on average in the young women as compared with men in the VIRGO study. Young women in the VIRGO study had symptom combinations that were more broadly distributed over a larger number of symptom phenotype subgroups. Our analysis also showed a significant delay in the door-to-balloon times in the young women from the VIRGO study.

In contrast to the young VIRGO cohort, there was no significant difference between women and men in the older SILVER-AMI cohort in the number of symptom phenotypes, the distribution of symptom phenotypes, or average number of symptoms, and there was also no difference between women and men in door-to-balloon times in the older cohort. The findings in the D2B Sample of the SILVER-AMI cohort contrast with the prior study of the entire SILVER-AMI cohort, where there were more symptom phenotypes and more symptoms on average in women as compared with men.

The generalized linear model showed a significant interaction between sex and study as predictors of door-to-balloon times. Chest pain replaced sex as a significant predictor of door-to-balloon times and lack of chest pain correlated with longer door-to-balloon times in the VIRGO patients but not SILVER-AMI patients.

The relative lack of chest pain and the distracting effect of numerous other symptoms may have obscured the STEMI diagnosis in young women, leading to a delay in door-to-balloon time. It is important to note, however, that chest pain was a cardinal symptom in young women (occurring in 88%) and chest pain occurred more commonly in young women than in older women. It was likely the compounding effect of age and symptom recognition that caused the delay in door-to-balloon time in younger women. Multiple prior studies have shown prolonged door-to-balloon times in women,[1–6] which may mostly affect young women where young age and relative lack of chest pain may work together to make the STEMI diagnosis seem less probable.

In addition to study and chest pain, a prolonged presentation time of >6 hours and a history of diabetes mellitus were also associated with prolonged door-to-balloon times in the best fitting logistic regression model. Presentation delay may have affected the door-to-balloon time, or alternatively, presentation delay and door-to-balloon time may have both been affected by another factor, such as initial recognition of STEMI. Diabetes may have affected the perception and description of symptoms or may have been a marker for peripheral vascular disease that may have delayed door-to-balloon times.

Young women had greater symptom complexity as shown by a greater number of symptom phenotypes, but the number of symptom phenotypes in subgroups could not be used in the predictive model of door-to-balloon time. To analyze the number of symptom phenotypes and door-to-balloon time, we compared the number of symptom phenotypes in subgroups divided by a 90-minute door-to-balloon cutoff. This analysis did not show a difference between door-to-balloon time subgroups in the number of symptom phenotypes. By combining the subgroup of patients with door-to-balloon times   90 minutes with STEMI patients with no PCI, however, we were able to show that women had significantly more symptom phenotypes than men overall and, in the VIRGO patients, but not in the

SILVER-AMI patients, which was consistent with our overall comparison of symptom phenotypes in women and men. This finding suggests that symptom complexity could have either prolonged door-to-balloon time or reduced the chances of receiving PCI in young women with STEMI, possibly due to presentation delay.

Comparisons of the young VIRGO patients and the older SILVER-AMI patients also revealed interesting differences in the frequencies of several of the individual symptoms of AMI. Five out of 10 symptoms were more frequently reported in the young VIRGO patients, as compared with the older SILVER-AMI patients. Nausea/vomiting and diaphoresis were markedly more common in the young cohort as compared with the older cohort.

Our finding have implications for the rapid diagnosis of STEMI and efforts to improve door-to-balloon times, which may improve the outcomes of patients with STEMI.[18–21] Studies have shown that expert clinicians use a diagnostic process that requires an initial step of recognizing diagnostic possibilities before proceeding to diagnostic confirmation through testing.[13,22–25] For STEMI, rapid recognition leads to diagnostic confirmation by electrocardiogram and studies have shown that the time to obtaining a confirming electrocardiogram is a key determinant of door-to-balloon time.[26–30] Prior studies of the VIRGO patients showed that absence of prehospital electrocardiograms and female sex were associated with prolonged door-to-balloon times, also suggesting that the lack of initial recognition of STEMI in young women contributes to prolonged door-to-balloon times.[5,6]

Our study has recognized limitations. The VIRGO study enrolled patients from August 2008 to January 2012 and the SILVER-AMI study enrolled patients from January 2013 to June 2018. The discordant timeframes could affect door-to-balloon times, however both studies occurred after a major nationwide initiative to address door-to-balloon times and nationally recorded door-to-balloon times were relatively stable during the two study timeframes.[21,26,27] Furthermore, the study's different timeframes would not affect inter-study comparisons between women and men. Also, the two studies used an age cutoff to define their study populations which limited the ability to use age as a continuous variable in the multivariable analysis, although the study was used as a dichotomous variable, which reflected age. Finally, our study design allowed analysis of symptoms and symptom combinations but lacked specific information about how patients would have ranked the relative severity or importance of symptoms. Despite these limitations, the VIRGO and SILVER-AMI studies provided a useful opportunity to evaluate symptom combinations in young and older STEMI patients and the relationship of symptom complexity to door-to-balloon times.

In summary, door-to-balloon times were longer in young women as compared with young men, but not in older women as compared with older men and young women had more symptom phenotypes and more symptoms on the average than men. Chest pain was a significant predictor of door-to-balloon times, and young women were significantly more likely to report symptoms other than chest pain. Clearly, symptom presentation compounded by young age affects door-to-balloon times in young women. These findings may have implications for recognizing STEMI in young women more quickly and reliably, which may improve the door-to-balloon times in women.

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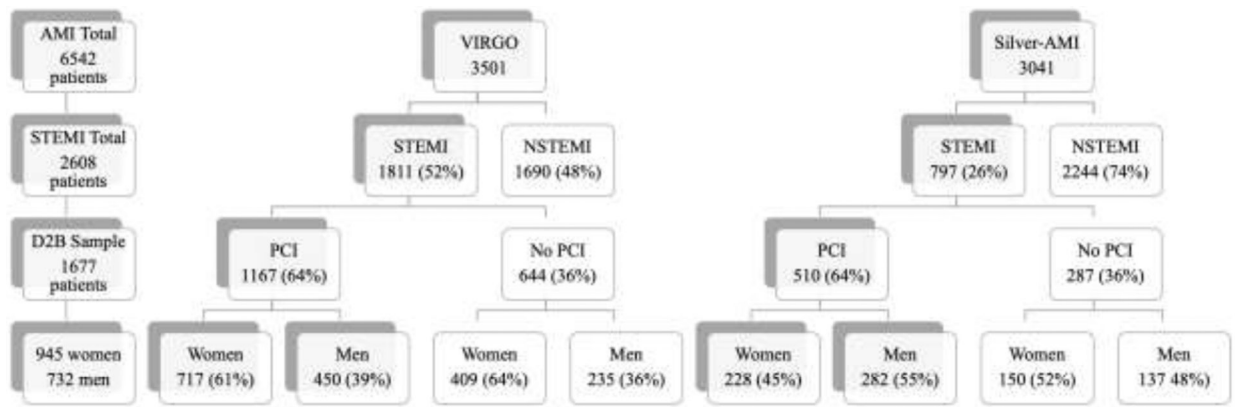
Figure 1.
Flow chart showing selection of study patients from VIRGO and SILVER-AMI. AMI=acute myocardial infarction, STEMI=ST-elevation myocardial infarction, NSTEMI=non-ST-elevation myocardial infarction, D2B=door-to-balloon, PCI=percutaneous coronary intervention.

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Table 1.

Symptoms recorded in VIRGO and SILVER-AMI and Matched Symptoms

VIRGO	SILVER-AMI	Matched Symptoms
Chest pain	Chest pain	Chest pain
Dizziness	Light-headed	Dizziness/Lightheadedness
Indigestion	Indigestion/epigastric pain	Indigestion/epigastric pain
Nausea	Nausea/vomiting/belching	Nausea/vomiting/belching
Other pain/discomfort	Radiation	Radiating or other pain
Palpitations	Anxiety/stress/agitation	Anxiety/agitation/palpitations
Shortness of breath	Dyspnea	Dyspnea
Sweating	Diaphoresis	Diaphoresis
Weakness/fatigue	Weakness/fatigue	Weakness/fatigue
Confusion	Confusion	Confusion

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Table 2.

Demographic Characteristics of Patients in the D2B Sample from the VIRGO and SILVER-AMI Studies.

	VIRGO D2B Sample (1167)		SILVER-AMI D2B Sample (510)	
	Women (717, 61%)	Men (450, 39%)	Women (228, 45%)	Men (282, 55%)
Age in years (mean ±SD)	46.9 ± 6.2	47.0 ± 5.8	82.3 ± 5.2	80.7 ± 4.8
Race				
White	578 (81%)	379 (84%)	200 (88%)	258 (92%)
Black	108 (15%)	41 (9%)	25 (11%)	11 (4%)
Other	31 (4%)	30 (7%)	3 (1%)	13 (5%)
Hispanic	36 (5%)	36 (8%)	2 (1%)	14 (5%)
Education				
Less than high school	153 (21%)	60 (13%)	27 (12%)	33 (12%)
High school graduate or GED	413 (58%)	268 (60%)	115 (50%)	113 (40%)
Two-year or four-year college degree	111 (16%)	81 (18%)	66 (29%)	87 (31%)
Graduate or post-graduate degree	40 (6%)	41 (9%)	19 (8%)	49 (17%)
Married or living as married/living with partner	394 (55%)	282 (63%)	76 (33%)	203 (72%)
Living alone	82 (11%)	77 (17%)	104 (46%)	81 (29%)
Presentation delay of 6 hours or more	242 (34%)	110 (25%)	32 (14%)	36 (13%)
Diabetes	223 (31%)	66 (15%)	61 (27%)	75 (27%)

Table 3.

Top Ten Symptom Phenotypes in Women and Men in the D2B Samples from the VIRGO and SILVER-AMI Studies.

	VIRGO Study				SILVER-AMI Study			
	Women (%)		Men (%)		Women (%)		Men (%)	
1	chest pain	1.7	chest pain	1.3	chest pain, radiation	1.3	chest pain	2.0
2	chest pain, nausea/vomiting/belching, radiation, diaphoresis	1.3	chest pain, diaphoresis	1.1	chest pain	0.7	chest pain, radiation	0.9
3	chest pain, radiation, diaphoresis	1.0	chest pain, radiation	1.1	chest pain, dyspnea	0.5	no symptoms reported	0.7
4	chest pain, radiation	0.8	chest pain, radiation, diaphoresis	1.0	no symptoms reported	0.4	chest pain, diaphoresis	0.7
5	chest pain, dyspnea, diaphoresis	0.7	chest pain, nausea/vomiting/belching, radiation, diaphoresis	0.7	chest pain, radiation, dyspnea, diaphoresis	0.4	chest pain, radiation, diaphoresis	0.4
6	chest pain, nausea/vomiting/belching, diaphoresis	0.7	chest pain, dyspnea	0.7	chest pain, nausea/vomiting/belching, radiation	0.4	chest pain, radiation, dyspnea	0.4
7	chest pain, nausea/vomiting/belching, radiation, dyspnea, diaphoresis	0.7	chest pain, radiation, dyspnea, diaphoresis	0.6	chest pain, radiation, dyspnea	0.4	chest pain, indigestion/epigastric pain	0.4
8	Chest pain, light-headed, nausea/vomiting/belching, radiation, dyspnea, Diaphoresis, weakness/fatigue	0.7	chest pain, radiation, dyspnea	0.5	Radiation, diaphoresis	0.2	chest pain, dyspnea	0.3
9	chest pain, indigestion/epigastricPain, nausea/vomiting/belching, radiation, dyspnea, diaphoresis, weakness/fatigue	0.7	chest pain, nausea/vomiting/belching, diaphoresis	0.5	indigestion/epigastricpain, nausea/vomiting/belching	0.2	radiation	0.2
10	chest pain, light-headed, indigestion/epigastric Pain, nausea/vomiting/belching, radiation, anxiety/stress/agitation, Dyspnea, diaphoresis, weakness/fatigue	0.7	chest pain, diaphoresis, weakness/fatigue	0.4	chest pain, diaphoresis	0.2	chest pain, weakness/fatigue	0.2

Table 4.

Frequencies of Individual Symptoms in Patients from the D2B Samples of the VIRGO and SILVER-AMI Studies. Adjustment for multiple comparisons was made with the Hochberg procedure to preserve an overall two-sided type 1 error rate of .05.

Symptom	VIRGO		SILVER-AMI	
	Women	Men	Women	Men
Chest Pain	88.3[‡]	92.4[‡]	79.4[‡]	82.6[‡]
Dizziness/Lightheadedness	31.7	28.9	22.4	22.3
Indigestion/epigastric pain	32.6	29.1	26.3	24.1
Nausea/Vomiting	57.5[*‡]	38.2[*‡]	36.8[‡]	25.2[‡]
Radiating or other pain	66.8[*]	56.2[*‡]	59.6[*]	44.0[*‡]
Anxiety/agitation/palpitations	16.5	10.9[‡]	19.7	19.1[‡]
Dyspnea	48.0[‡]	47.6[‡]	33.8[‡]	35.8[‡]
Diaphoresis	66.2[‡]	65.1[‡]	33.8[‡]	38.3[‡]
Weakness/Fatigue	47.4[‡]	40.7[‡]	29.8[‡]	24.8[‡]
Confusion	12.6[‡]	12.7	4.4[‡]	6.0

[*] Significant (Hochberg-adjusted p<0.05) between sexes within study

[‡] Significant (Hochberg-adjusted p<0.05) between studies within sex