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Original Contribution

Are there symptom differences in patients with coronary artery disease presenting to the ED ultimately diagnosed with or without ACS?☆

Michele M. Pelter PhD, RN[a,*], Barbara Riegel DNSc, RN[b], Sharon McKinley PhD, RN[c], Debra K. Moser DNSc, RN[d], Lynn V. Doering DNSc, RN[e], Hendrika Meischke PhD[f], Patricia Davidson RN, PhD[g], Heather Baker RN, MA[h], Wei Yang MD, PhD[i], Kathleen Dracup DNSc, RN[j]

[a]*Orvis School of Nursing, University of Nevada, Reno, Mail Stop 134, Reno, NV 89557, USA*
[b]*School of Nursing, University of Pennsylvania, Philadelphia, PA 19104-4217, USA*
[c]*Faculty of Nursing Midwifery and Health, University of Technology Sydney and Northern Sydney Central Coast Health, St Leonards NSW 2065*
[d]*College of Nursing, University of Kentucky, Lexington, KY 40536-0232, USA*
[e]*School of Nursing, University of California, Los Angeles, CA 90024, USA*
[f]*Department of Health Services, University of Washington, Seattle, WA 98195, USA*
[g]*Curtin University, Broadway, NSW 2007, Australia*
[h]*University of Auckland, Auckland 1142, New Zealand*
[i]*Nevada Center for Health Statistics and Informatics, University of Nevada, Reno, NV 89557-0038, USA*
[j]*School of Nursing, University of California, San Francisco, CA 94143, USA*

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Abstract

Objectives: Symptoms are compared among patients with coronary artery disease (CAD) admitted to the emergency department with or without acute coronary syndrome (ACS). Sex and age are also assessed.

Methods: A secondary analysis from the PROMOTION (Patient Response tO Myocardial Infarction fOllowing a Teaching Intervention Offered by Nurses) trial, an multicenter randomized controlled trial, was conducted.

Results: Of 3522 patients with CAD, at 2 years, 565 (16%) presented to the emergency department, 234 (41%) with non-ACS and 331 (59%) with ACS. Shortness of breath (33% vs 25%, $P = .028$) or dizziness (11% vs 3%, $P = .001$) were more common in non-ACS. Chest pain (65% vs 77%, $P = .002$) or arm pain (9% vs 21%, $P = .001$) were more common in ACS. In men without ACS, dizziness was more common (11% vs 2%; $P = .001$). Men with ACS were more likely to have chest pain (78% vs 64%; $P = .003$); both men and women with ACS more often had arm pain (men, 19% vs 10% [$P = .019$]; women, 26% vs 13% [$P = .023$]). In

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* Corresponding author. Tel.: +1 775 682 7161; fax: +1 775 784 4262.
E-mail address: mpelter@unr.edu (M.M. Pelter).

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multivariate analysis, patients with shortness of breath (odds ratio [OR], 0.617 [confidence interval [CI], 0.410-0.929]; P = .021) or dizziness (OR, .0311 [CI, 0.136-0.708]; P = .005) were more likely to have non-ACS. Patients with prior percutaneous coronary intervention (OR, 1.592 [CI, 1.087-2.332]; P = .017), chest pain (OR, 1.579 [CI, 1.051-2.375]; P = .028), or arm pain (OR, 1.751 [CI, 1.013-3.025]; P <.042) were more likely to have ACS.

Conclusions: In patients with CAD, shortness of breath and dizziness are more common in non-ACS, whereas prior percutaneous coronary intervention and chest or arm pain are important factors to include during ACS triage.

1. Background and significance

Despite a decline in cardiovascular mortality, coronary artery disease (CAD) remains the leading cause of morbidity and mortality in both men and women worldwide. In the United States, more than 830 000 adults present to acute care facilities each year for treatment of acute coronary syndrome (ACS) [1]. Recurrent ischemia among the ACS population is a common problem. Although the estimated annual incidence of new myocardial infarction (MI) is 610 000, it is estimated that 325 000 people with a history of ACS will have a recurrent MI [2]. Symptoms are most often the initial clinical feature of ACS, yet symptoms can be difficult for clinicians to recognize them as ACS because they may be atypical or similar to those of other noncardiac diagnoses.

Prior research is limited in that many studies have assessed symptom differences in patients with and without a history of CAD [3-7]. This former group is of particular interest because recurrent ischemia is of concern; however, many of these patients who present to the emergency department (ED) have ACS ruled out. In addition, many studies have assessed symptoms retrospectively from medical record reviews, which are limited by the variations and omissions inherent with clinician medical recording. In this study, we report on data obtained prospectively from subjects enrolled in a large clinical trial assessing the value of an educational intervention to reduce prehospital delay in a group of patients with a history of CAD [8,9].

2. Goals of this investigation

The purpose of this secondary analysis was to compare whether there were differences in symptoms among patients with CAD presenting to the ED who were ultimately diagnosed with or without ACS. Several studies have identified sex differences in ACS symptoms, with women being less likely to report chest pain compared with men [3,10-17]. Age has also been identified as an important variable in symptom presentation for ACS, with older adults reporting symptoms less often [18-20]. Therefore, in addition to assessing differences in presenting symptoms in those diagnosed with or without ACS, we compared symptoms in men and women and in older and younger subjects.

3. Study design

The data for this secondary analysis were obtained from the randomized, controlled PROMOTION (Patient Response tO Myocardial Infarction fOllowing a Teaching Intervention Offered by Nurses) clinical trial (clinical trial registration: http://clinicaltrials.gov/ct2/show/NCT00734760#NCT00734760) [8]. Briefly, the PROMOTION trial tested whether an educational and counseling intervention could reduce prehospital delay in response to symptoms suggestive of ACS [9]. Between 2001 and 2004, participants were enrolled from a total of 6 centers, 3 in the United States, 2 in Australia, and 1 in New Zealand. The institutional review board at each site approved the study. Patients were eligible for the trial if they had a prior diagnosis of CAD, confirmed by their physician and/or medical record, and lived independently (ie, not in an institutional setting). Exclusion criteria were as follows: (1) complicating serious comorbidities (ie, major psychiatric disorder or chronic renal failure), (2) untreated malignancy or neurologic disorder that impaired cognition, (3) inability to understand spoken English or unable to respond to English language questionnaires, and (4) major and uncorrected hearing loss.

4. Selection of participants

The convenience sample from the primary study included 3522 individuals with a documented history of CAD. During the 2 year follow-up period, 565 (16%) patients were admitted to an ED for symptoms suggestive of ACS. These 565 patients are the focus of this report. We combined the experimental and control groups for this secondary analysis because they were comparable with regard to demographics, clinical history, ED use, and outcomes [9]. The local institutional review board at each site approved the study, and all participants gave informed consent.

5. Methods of measurement

During the 2-year follow-up in the PROMOTION trial, ED visits by participants were identified by the following: (1) participants reported an ED visit by calling the research office using a toll-free telephone number, (2) routine

review of hospital medical records for ED admission, and (3) participants reported an ED visit during a routine telephone follow-up call done as part of the protocol [21]. To increase the likelihood that participants would contact the study personnel regarding an ED visit, we provided them with the study telephone number on easy-to-locate items (eg, refrigerator magnets and business cards) and via "reminders" every 3 months (eg, postcard and telephone call). Those patients who sought care were interviewed by research nurses, usually within days after hospital discharge, to identify specific symptoms that prompted them to seek care.

Symptoms were measured using a scripted telephone interview tool designed by the investigators, based on symptoms used in the Rapid Early Action for Coronary Treatment (REACT) trial [22]. Six symptoms were suggested to patients: (1) chest pain, discomfort, or pressure; (2) left arm pain or discomfort; (3) shortness of breath; (4) diaphoresis; (5) upset stomach; and (6) discomfort in the area between the breastbone and the navel. In addition, participants were given the opportunity to provide symptoms other than the 7 suggested. After an ED admission, medical records were reviewed for discharge diagnosis.

6. Data analysis

Data at each study site were entered into a specifically designed database that was imported into Statistical Package for Social Sciences (version 19; SPSS, Chicago, IL) and then merged for analysis. Descriptive statistics were used to characterize study participants and check for data accuracy, and histograms were used to check the normality of distributions of continuous variables. For sample characteristics, means and SDs are presented for continuous variables and proportions for categorical variables. Demographics, clinical history, and symptoms were compared between the 2 groups (non-ACS diagnosis vs ACS). Categorical variables were compared using χ^2 tests and continuous variables using independent t tests. A P value of less than .05 was used as the critical value to determine statistical significance for these tests.

Multivariate logistic regression was used to assess whether demographics (ie, ethnicity, sex, age), clinical history factors (ie, angina, MI, percutaneous coronary intervention [PCI], coronary artery bypass graft surgery, diabetes, hypercholesterolemia, and hypertension), or symptoms (listed previously) were predictive of an ACS diagnosis. Knowing that there may be interactions between important variables, we tested interactions using the following variables: (1) chest pain at presentation, (2) history of MI, (3) history of PCI, (4) sex, and (5) age (<70 or ≥70 years) to determine if any of these variables showed a significant interaction. Each of these variables was tested individually for interactions. The interaction analysis did not show any statistically significant associations. Therefore, all demographic, clinical history, and symptom variables were entered into the model regardless of whether they were statistically significant in the univariate analysis. Presented are adjusted odds ratios (ORs) and 95% confidence intervals (CIs). A P value of less than .05 was used as the critical value to determine statistical significance for variables entered into the multivariate analysis.

7. Results

A total of 565 patients, all with a history of CAD, were admitted to the ED for symptoms suggestive of ACS. Of these, 234 (41%) had non-ACS and 331 (59%) had confirmed ACS. Overall, the mean (SD) age of the patients was 67 (±11) years, 367 (65%) were male, 509 (90%) were white, and 356 (65%) were married or living with a significant other. Comparisons of demographic and clinical variables comparing patients with non-ACS to those with ACS are shown in Table 1. The groups were similar with regard to age, sex, and ethnicity. Clinical differences were found between the groups, with more patients with ACS having a history of MI (51% vs 60%, $P = .031$), PCI (51% vs 63%, $P = .004$), diabetes (18% vs 26%, $P = .020$), and hypercholesterolemia (60% vs 69%, $P = .021$) than patients with non-ACS.

The most frequent symptom for the entire sample was chest pain, occurring in 408 (72%) of the patients. Table 2 shows the comparison of symptoms between patients with non-ACS and patients with ACS. Shortness of breath (33% vs 25%, $P = .028$) and dizziness/fainting (11% vs 3%, $P = .001$) were more likely in the non-ACS group, whereas chest pain (65% vs 77%, $P = .002$) and arm pain (11% vs 21%, $P = .001$) were more likely in the ACS group.

Table 1 Demographics and medical history by diagnosis (n = 565)

Characteristic	Non-ACS (n = 234), n (%)	ACS (n = 331), n (%)	P
Age (y), mean ± SD	68 ± 12	68 ± 12	.892
Sex: men	146 (62)	221 (67)	.283
Ethnicity: white	208 (90)	301 (91)	.422
Medical history			
Angina	152 (65)	240 (73)	.055
MI	120 (51)	200 (60)	.031
Cardiac surgery	92 (40)	145 (44)	.287
PCI	119 (51)	208 (63)	.004
Diabetes	42 (18)	87 (26)	.020
Hypercholesterolemia	140 (60)	229 (69)	.021
Hypertension	136 (58)	207 (63)	.290

Table 2 Comparison of symptoms by diagnosis (n = 565)

Symptom	No ACS (n = 234), n (%)	ACS (n = 331), n (%)	*P*
Chest pain	153 (65)	255 (77)	.002
Shortness of breath	77 (33)	81 (25)	.028
Arm pain	25 (11)	69 (21)	.001
Diaphoresis	34 (15)	35 (11)	.157
Discomfort between breastbone and navel	13 (6)	11 (3)	.195
Upset stomach	36 (15)	40 (12)	.257
Other symptoms patient identified			
Jaw/Throat pain	13 (6)	23 (7)	.504
Palpitations/Tachycardia	15 (6)	11 (3)	.085
Back/Shoulder pain	10 (4)	19 (6)	.436
Dizzy/Fainting	25 (11)	9 (3)	.001

7.1. Sex

When differences were assessed by sex, dizziness was more common in men without ACS (11% vs 2%, $P = .001$). Men with ACS were more likely to have chest pain (64% vs 78%, $P = .003$). Both men and women with ACS more often had arm pain (men, 19% vs 10% [$P = .019$]; women, 26% vs 13% [$P = .023$]). There were no differences by sex for the other symptoms (Table 3).

7.2. Age

Because the median age of the sample was 70 years, we divided the sample into 2 groups, those younger than 70 years and those 70 years or older, and assessed symptom differences by comparing the age groups to whether they were diagnosed with non-ACS or ACS (Table 4). Chest pain (82% vs 72%, $P = .025$), diaphoresis (17% vs 4%, $P = .001$), and upset stomach (17% vs 7%, $P = .009$) occurred less frequently in patients 70 years or older who were diagnosed with ACS. Diaphoresis was also less common in those 70 years or older who were ultimately diagnosed with non-ACS (20% vs 10%, $P = .038$). The remaining symptoms were not statistically different when comparing age by diagnosis.

7.3. Multivariate analysis

Multivariate logistic regression was done to determine which demographics, clinical factors, or symptoms were associated with ACS (Table 5). As mentioned in the "Data analysis" section, we tested for interactions by sex and age (<70 or ≥70 years) to determine if these variables were associated with any of the variables entered into the model and found none. Patients with shortness of breath (OR, 0.617 [CI, 0.410-0.929]; $P = .021$) or dizziness (OR, 0.311 [CI, 0.136-0.708]; $P = .005$) were more likely to have a non-ACS diagnosis, whereas those with prior PCI (OR, 1.592 [CI, 1.087-2.332]; $P = .017$), chest pain (OR, 1.579 [CI, 1.051-2.375]; $P = .028$), or arm pain (OR, 1.751 [CI, 1.013-3.025]; $P < .042$) were more likely to have an ACS diagnosis.

8. Limitations

This study was a secondary analysis; therefore, limitations inherent in this design must be taken into consideration. For example, in the primary study, we did not collect information about current medications. This variable may have helped us explain the association of hypercholesterolemia with an ACS diagnosis, if patients were not prescribed this medication.

Although our sample was interviewed as soon as possible after the ED admission, participants were asked about their symptoms after discharge. It is possible that patients may not have been able to recall all of their symptoms. We used a standardized script and procedure to obtain symptoms, which did include an "other symptom" category. However, additional symptoms as well as information about quality or intensity of symptoms would have been valuable. Lastly,

Table 3 Comparison of symptoms during diagnosis and sex (n = 565)

Symptom	Male (n = 367), n (%)			Female (n = 198), n (%)		
	Non-ACS	ACS	*P*	Non-ACS	ACS	*P*
Chest pain	93 (64)	172 (78)	.003	60 (68)	83 (76)	.256
Shortness of breath	43 (30)	51 (23)	.171	34 (39)	30 (27)	.089
Arm pain	14 (10)	41 (19)	.019	11 (13)	28 (26)	.023
Diaphoresis	25 (17)	24 (11)	.084	9 (10)	11 (10)	.958
Discomfort between breastbone and navel	6 (4)	6 (3)	.462	7 (8)	5 (5)	.318
Upset stomach	21 (14)	23 (10)	.251	15 (17)	17 (16)	.763
Other symptoms patient identified						
Jaw/Throat pain	6 (4)	12 (5)	.566	7 (8)	11 (10)	.619
Palpitations/Tachycardia	8 (6)	6 (3)	.176	7 (8)	5 (5)	.318
Back/Shoulder pain	5 (3)	10 (5)	.602	5 (6)	9 (8)	.495
Dizzy/Fainting	16 (11)	5 (2)	.001	9 (10)	4 (4)	.063

Table 4 Comparison of symptoms by diagnosis and age, with age groups divided into those younger than 70 years and those 70 years or older (n = 565)

Symptom	Non-ACS (n = 234), n (%)			ACS (n = 331), n (%)		
	<70 (n = 113)	≥70 (n = 121)	*P*	<70 (n = 168)	≥70 (n = 163)	*P*
Chest pain	80 (71)	73 (60)	.093	138 (82)	117 (72)	.025
Shortness of breath	36 (32)	41 (34)	.742	44 (26)	37 (23)	.460
Arm pain	16 (14)	9 (7)	.096	36 (21)	33 (20)	.791
Diaphoresis	22 (20)	12 (10)	.038	28 (17)	7 (4)	.001
Discomfort between breastbone and navel	6 (5)	7 (6)	.874	4 (2)	7 (4)	.332
Upset stomach	20 (18)	16 (13)	.343	28 (17)	12 (7)	.009
Other symptoms patient identified						
Jaw/Throat pain	6 (5)	7 (6)	.874	11 (7)	12 (7)	.771
Palpitations/Tachycardia	6 (5)	9 (7)	.507	5 (3)	6 (4)	.721
Back/Shoulder pain	5 (4)	5 (4)	.912	8 (5)	11 (7)	.437
Dizzy/Fainting	11 (10)	14 (11)	.650	3 (2)	6 (4)	.289

we combined some symptoms due to low numbers to include them in the analysis (eg, right and left arm pain was combined into "arm pain"; numbness, tingling, and weakness were combined into the category "other"); had we had a larger sample, analysis of these specific symptoms might have been useful.

This study included individuals willing to sit through a 40-minute educational session and participate in follow-up for 2 years. Most participants were white, thus limiting our ability to analyze racial/ethnic group differences.

9. Discussion

This study is unique in that a group of patients with known CAD were prospectively followed up and assessed for ED visits during a 2-year period. Overall, we found that a higher percentage of patients with ACS experienced chest or arm pain, whereas, shortness of breath or dizziness/fainting were more common in non-ACS. Logistic regression analysis indicated that prior PCI, chest pain, or arm pain were associated with ACS when controlling for demographics, clinical history, and

Table 5 Multivariate logistic regression analysis assessing demographics, clinical history, and symptoms associated with a diagnosis of ACS (n = 565)

Characteristic	*B*	OR	95% CI	*P*
Age	0.005	1.005	0.989-1.022	.556
Sex	−0.094	0.910	0.613-1.351	.641
Ethnicity	−0.442	0.643	0.354-1.165	.145
Clinical history				
Angina	0.131	1.140	0.767-1.694	.518
MI	0.372	1.450	1.003-2.096	.048
Cardiac surgery	0.214	1.239	0.836-1.836	.286
PCI	0.465	1.592	1.087-2.332	.017
Diabetes	0.462	1.587	1.007-2.499	.046
Hypercholesterolemia	0.371	1.449	0.977-2.148	.065
Hypertension	0.071	1.073	0.726-1.588	.723
Symptoms				
Chest pain	0.457	1.579	1.051-2.375	.028
Shortness of breath	−0.482	0.617	0.410-0.929	.021
Arm pain	0.664	1.943	1.149-3.288	.013
Diaphoresis	−0.246	0.782	0.445-1.372	.391
Discomfort between breastbone and navel	−0.354	0.702	0.294-1.680	.427
Upset stomach	−0.170	0.844	0.495-1.440	.533
Others that patients identified				
Jaw/Throat pain	−0.080	0.923	0.429-1.983	.837
Palpitations/Tachycardia	−0.645	0.525	0.223-1.234	.139
Back/Shoulder pain	0.199	1.220	0.535-2.784	.363
Dizzy/Fainting	−1.169	0.311	0.136-0.708	.005

Interactions were also tested assessing sex (male vs female) and age (<70 years vs >70 years); no significant interactions were found.

other common symptoms associated with ACS. Conversely, patients with non-ACS were more likely to experience the symptoms of shortness of breath or dizziness/fainting.

9.1. Symptoms

Chest pain has been reported in numerous investigations as the most common symptom in ACS [3-7,15,18,20,23]. Similar to these investigations, we found that a higher proportion of those with confirmed ACS had this symptom. This symptom remained associated with ACS in the multivariate analysis. However, chest pain was common in a high percentage of the patients included in our study (65% non-ACS, 77% ACS). That so many patients, both non-ACS and ACS, experienced this symptom highlights the insensitivity of this symptom. Chest pain is clearly an important symptom of ACS, but it is common in patients with non-ACS as well.

Patients with arm pain were nearly twice as likely to have ACS. Arm pain appears to be helpful in diagnosing ACS, although less than one-quarter of the sample experienced this symptom. This proportion is similar to prior studies [5,7,18,23,24], suggesting that arm pain should be specifically asked about because of its diagnostic significance in a substantial minority of patients with ACS.

When only symptoms were analyzed by univariate analysis, patients who experienced shortness of breath or fainting/dizziness were more likely to have a non-ACS diagnosis, which is in contrast to other reports [4,6,7]. These 2 symptoms were also associated with non-ACS when demographics, clinical history, and other symptoms were accounted for. This is counterintuitive because one might expect these symptoms as a result of altered cardiac output during acute ischemia. One possibility is that these symptoms were caused by respiratory conditions or arrhythmia; however, we did not collect these data during the ED admission and, therefore, cannot definitively know the source of these symptoms.

9.2. Clinical history

In our study, the only clinical feature that was associated with ACS was prior PCI; these patients had a 61% higher risk for ACS. Restenosis after stent placement is not uncommon, 11% to 19% [25] for drug-eluting stents and 18% to 23% with bare-metal stents [26]. Based on this finding, clinicians should ask patients specifically about prior PCI during the triage process because this could promptly identify high-risk patients. Patients treated with PCI should also be educated about the possibility of restenosis, to include common ACS symptoms and the importance of seeking care promptly if symptoms occur.

9.3. Sex

When symptoms were analyzed by univariate analysis, both men and women who experienced arm pain were more likely to have ACS as compared with their counterparts diagnosed with non-ACS. Men with ACS who complain of chest pain were more likely to have ACS; however, this was not the case among the women in our sample. Of note, we did not find sex differences in 2 other classic symptoms (ie, diaphoresis and shortness of breath), which is similar to a current study [27] but varies from others [6,11,18,24]. This might be explained by the fact that our sample included only patients with known CAD, whereas many previous studies included patients with a first-time diagnosis of CAD. Importantly, in multivariate logistic regression analysis, sex was not associated with ACS and was not a significant interaction when tested against the other variable included in the model.

Dizziness/Fainting occurred more often in men with a non-ACS diagnosis. Although there was a trend for more dizziness/fainting to occur in women with non-ACS as compared with women with ACS, the difference was not statistically significant. Interestingly, in multivariate analysis, patients who experienced the symptom of dizziness/fainting were 3 times more likely to have a non-ACS diagnosis. This suggests that this symptom might be helpful in the assessment during the triage process when ruling out ACS. When sex was tested for as an interaction using this symptom (dizziness/fainting) in multivariate analysis, it was not statistically significant. There were no differences between men and women in other atypical symptoms (ie, jaw/throat pain, palpitations, or back/shoulder pain). However, we had small numbers of patients with atypical symptoms, so these results should be interpreted with caution.

9.4. Age

Prior investigations have reported that typical symptoms (ie, chest pain, diaphoresis, or shortness of breath) are less frequent in older vs younger patients with ACS [6,20,23]. Our results are consistent with these studies with regard to chest pain and arm pain but not for shortness of breath. We also found that older patients with ACS were less likely to experience an upset stomach as compared with younger patients (7% vs 17%), which is in contrast to the one study that reported this symptom [23]. In the multivariate logistic regression analysis, age was not associated with ACS and was not a significant interaction when tested against the other variable included in the model. Overall, our findings support what others have found: older patients are less likely to experience typical symptoms of ACS. Soiza et al [20] reported that older patients who had fewer typical ACS symptoms than a younger group of patients were more likely to have recurrent MI or die within 2 weeks of hospital discharge for ACS. Worth noting was that the older patients in their study were less likely to be referred for angiography as compared with younger patients. Interestingly, the older patients in their study who were referred for angiography were less likely to have a PCI procedure because their CAD

was not amenable to PCI or surgery. The study by Soiza et al [20] highlights the importance of advanced age as a predictor for future ACS events.

Clinicians should use careful and thoughtful evaluation in older patients at risk for ACS and appreciate that symptoms including chest pain, diaphoresis, and stomach upset may be less common among patients 70 years or older who are indeed experiencing ACS. Based on the results from the current study and others, it is clear that classic symptoms of ACS occur less often in older patients. This is an important factor for clinicians to consider, and the possibility of this occurrence should be discussed with patients with CAD during patient education.

10. Conclusions

The results of this study highlight the challenges that clinicians face when evaluating and deciding on treatment options for patients with symptoms suggestive of ACS. Although few of the typical symptoms were helpful, prior PCI, chest pain, and arm pain are important factors that should be included in the ACS triage process. Shortness of breath or dizziness/fainting is more common in non-ACS and may be helpful when triaging patients with suspected ACS. Because symptoms are an important part of a patient's decision to seek treatment of ACS, they must remain an essential part of patient education. However, education should be a thoughtful process tailored for individual patients, to include not only possible symptoms but also other potentially important demographics and clinical factors associated with future ACS events.

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