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Are there Symptom Differences in Patients with Coronary Artery Disease Presenting to the Emergency Department Ultimately Diagnosed with or without Acute Coronary Syndrome?

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Background & 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

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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. While 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 as ACS because they may be atypical or similar to those of other non-cardiac 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. Additionally, many studies have assessed symptoms retrospectively from chart reviews, which are limited by the variations and omissions inherent with clinician charting. 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]

Goals of This Investigation

The purpose of this secondary analysis was to compare whether there were differences in symptoms among CAD patients presenting to the ED who were ultimately diagnosed with or without ACS. Several studies have identified gender differences in ACS symptoms, with women being less likely to report chest pain compared to 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 ACS or not, we compared symptoms in men and women and in older and younger subjects.

Study Design

The data for this secondary analysis were obtained from the randomized, controlled PROMOTION clinical trial (Clinical Trial Registration: URL 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 six centers, three in the United States, two in Australia, and one 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 (i.e., not in an institutional setting). Exclusion criteria were: 1) complicating serious comorbidities (i.e., major psychiatric disorder or chronic renal failure), 2) untreated malignancy or neurological 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.

Selection of Participants

The convenience sample from the primary study included 3,522 individuals with a documented history of CAD. Over the two year follow-up period, 565 (16%) patients were admitted to an emergency department (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 since they were comparable with regards to demographics, clinical history, ED usage, and outcomes.[9] The local institutional review board at each site approved the study, and all participants gave informed consent.

Methods of Measurement

During the 2-year follow-up in the PROMOTION trial, emergency Department (ED) visits by participants were identified by: (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 phone number on easy to locate items (e.g., refrigerator magnets, and business cards) and via "reminders" every three months (e.g., post card, and phone call). Those patients who sought care were interviewed by research nurses, usually within days following 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 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 navel. Additionally, participants were given the opportunity to provide symptoms other than the seven suggested. Following an ED admission medical records were reviewed for discharge diagnosis.

Data Analysis

Data at each study site were entered into a specifically designed database which was imported into Statistical Package for Social Sciences (SPSS version 19, 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 standard deviations are presented for continuous variables and proportions for categorical variables. Demographics, clinical history and symptoms were compared between the two groups (non-ACS diagnosis versus ACS). Categorical variables were compared using chi-square tests and continuous variables with independent t-tests. A p-value of < 0.05 was used as the critical value to determine statistical significance for these tests.

Multivariate logistic regression was used to assess whether demographic (i.e., ethnicity, gender, age), clinical history factors (i.e., angina, MI, PCI, coronary artery bypass graft surgery, diabetes, hypercholesterolemia, and hypertension) or symptoms (listed above) were predictive of an ACS diagnosis. Knowing 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) gender and (5) age (<70 years, 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 of the demographic, clinical history and symptoms variables were entered into the model regardless of whether they were statistically significant in the univariate analysis. Presented are adjusted odds ratios, and 95% confidence intervals. A p-value of < 0.05 was used as the critical value to determine statistical significance for variables entered into the multivariate analysis.

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 regards to age, gender, and ethnicity. Clinical differences were found between the groups, with more ACS patients having a history of MI (51% vs 60% p 0.031), percutaneous coronary intervention (PCI) (51% vs 63% p 0.004), diabetes (18% vs 26%, p 0.020) and hypercholesterolemia (60% vs 69% p 0.021) than non ACS patients.

The most frequent symptom for the entire sample was chest pain, occurring in 408 (72%) of the subjects. Table 2 shows the comparison of symptoms between non-ACS and ACS patients. Shortness of breath (33% vs 25%,p 0.028) and dizziness/fainting (11% vs 3%, p 0.001) were more likely in the non-ACS group. Whereas chest pain (65% vs 77%, p 0.002) and arm pain (11% vs 21%, p = 0. 001) were more likely in the ACS group.

Gender

When differences were assessed by gender, 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 gender for the other symptoms (Table 3).

Age

Because the median age of the sample was 70 years old we divided the sample into two groups those <70 years, or ≥70 years and assessed symptoms differences 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 ACS patients ≥ 70 years. Diaphoresis was also less common in those ≥ 70 years old who were ultimately diagnosed with non-ACS (20% vs. 10%; p = 0.038). The remaining symptoms were not statistically different when comparing age by diagnosis.

Multivariate Analysis

Multivariate logistic regression was done to determine which demographic, clinical factors or symptoms were associated with ACS (Table 5). As mentioned in the data analysis section, we tested for interactions by gender and age (<70 years, 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 . 617 [CI .410 – .929], p .021) or dizziness (OR . 311 [CI .136 – .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.

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.

While our sample was interviewed as soon as possible following the ED admission, participants were asked about their symptoms following discharge. It is possible 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, we combined some symptoms due to low numbers in order to include them in the analysis (e.g., right and left arm pain was combined into `arm pain', numbness, tingling, and weakness was 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.

Discussion

This study is unique in that a group of patients with known CAD were prospectively followed and assessed for ED visits over a two-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 demographic, clinical history and 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.

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). The fact 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, even though 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 ACS patients.

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 two 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 a respiratory conditions or arrhythmia; however, we did not collect this data during the ED admission and therefore cannot definitively know the source of these symptoms.

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 following stent placement is not uncommon, 11% to 19%[25] for drug eluting stents and 18% to 23% with bare metal stents.[26] Based upon this finding, clinicians should ask patients specifically about prior PCI during the triage process since 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.

Gender

When symptoms were analyzed by univariate analysis, both men and women who experienced arm pain were more likely to have ACS as compared to 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 gender differences in two other classic symptoms (i.e., diaphoresis, 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 the multivariate logistic regression analysis, gender 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. While there was a trend for more dizziness/fainting to occur in non-ACS women as compared to women with ACS the difference was not statistically significant. Interestingly, in the multivariate analysis patients who experienced the symptom of dizziness/fainting were 3 times more likely to have a non-ACS diagnosis. This suggests this symptom might be helpful to assess for during the triage process when ruling out ACS. When gender was tested for as an interaction using this symptom (dizziness/fainting) in the multivariate analysis it was not statistically significant. There were no differences between men and women in other atypical symptoms (i.e., 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.

Age

Prior investigations have reported that typical symptoms (i.e., chest pain, diaphoresis, or shortness of breath) are less frequent in older versus younger ACS patients.[6, 20, 23] Our results are consistent with these studies with regards 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 to younger patients (7% versus 17%), which 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. 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.[20] Worth noting, was that the older patients in their study were less likely to be referred for angiography as compared to 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 who are ≥ 70 years of age who are indeed experiencing ACS. Based on 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 occurring should be discussed with CAD patients during patient education.

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. While 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 for 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 other potentially important demographic, and clinical factors associated with future ACS events.

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Table 1

Demographics and medical history by diagnosis (n = 565).

Characteristic	Non-ACS (n = 234) n (%)	ACS (n = 331) n (%)	p
Age, years (mean, SD)	68 ± 12	68 ± 12	.892
Gender			
Men	146 (62)	221 (67)	0.283
Ethnicity			
White	208 (90)	301 (91)	0.422
Medical History			
Angina	152 (65)	240 (73)	0.055
MI	120 (51)	200 (60)	0.031
Cardiac Surgery	92 (40)	145 (44)	0.287
PCI	119 (51)	208 (63)	0.004
Diabetes	42 (18)	87 (26)	0.020
Hypercholesterolemia	140 (60)	229 (69)	0.021
Hypertension	136 (58)	207 (63)	0.290

ACS = acute coronary syndrome, MI = myocardial infarction, PCI = percutaneous coronary intervention

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)	0.002
Shortness of Breath	77 (33)	81 (25)	0.028
Arm Pain	25 (11)	69 (21)	0.001
Diaphoresis	34 (15)	35 (11)	0.157
Discomfort b/w Breastbone & Navel	13 (6)	11 (3)	0.195
Upset Stomach	36 (15)	40 (12)	0.257
Other Patient Identified			
Jaw/Throat Pain	13 (6)	23 (7)	0.504
Palpitations/Tachycardia	15 (6)	11 (3)	0.085
Back/Shoulder Pain	10 (4)	19 (6)	0.436
Dizzy/Fainting	25 (11)	9 (3)	0.001

Table 3

Comparison of symptoms by diagnosis gender (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)	0.003	60 (68)	83 (76)	0.256
Shortness of Breath	43 (30)	51 (23)	0.171	34 (39)	30(27)	0.089
Arm Pain	14 (10)	41 (19)	0.019	11 (13)	28 (26)	0.023
Diaphoresis	25 (17)	24 (11)	0.084	9 (10)	11 (10)	0.958
Discomfort b/w Breastbone & Navel	6 (4)	6 (3)	0.462	7 (8)	5 (5)	0.318
Upset Stomach	21 (14)	23 (10)	0.251	15 (17)	17 (16)	0.763
Other Patient Identified						
Jaw/Throat Pain	6 (4)	12 (5)	0.566	7(8)	11 (10)	0.619
Palpitations/Tachycardia	8 (6)	6 (3)	0.176	7 (8)	5 (5)	0.318
Back/Shoulder Pain	5 (3)	10 (5)	0.602	5 (6)	9 (8)	0.495
Dizzy/Fainting	16 (11)	5 (2)	0.001	9 (10)	4 (4)	0.063

Table 4

Comparison of symptoms by diagnosis and age, with age groups divided into those < 70 years to those ≥ 70 years of age (n = 565).

Symptom	**Non-ACS (n = 234) n (%)**			**ACS (n = 331) n (%)**		
	n (%)			**n (%)**		
	<70	**≥ 70**	**p**	**<70**	**≥ 70**	**p**
	n = 113	**n= 121**		**n = 168**	**n = 163**	
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 b/w Breastbone & Navel	6 (5)	7 (6)	.874	4 (2)	7 (4)	.332
Upset Stomach	20 (18)	16 (13)	.343	28 (17)	12 (7)	.009
Other 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

Table 5

Multivariate logistic regression analysis assessing demographics, clinical history and symptoms associated with a diagnosis of acute coronary syndrome (n = 565). Interactions were also tested assessing gender (male versus female) and age (< 70 years versus > 70 years); no significant interactions were found.

Characteristic	B	Odds Ratio	95% CI	p
Age	.005	1.005	.989–1.022	.556
Gender	−.094	.910	.613– 1.351	.641
Ethnicity	−.442	.643	.354 – 1.165	.145
Clinical History				
Angina	.131	1.140	.767 – 1.694	.518
MI	.372	1.450	1.003 – 2.096	.048
Cardiac Surgery	.214	1.239	.836 – 1.836	.286
PCI	.465	1.592	1.087 – 2.332	.017
Diabetes	.462	1.587	1.007 – 2.499	.046
Hypercholesterolemia	.371	1.449	.977 – 2.148	.065
Hypertension	.071	1.073	.726 – 1.588	.723
Symptoms				
Chest Pain	.457	1.579	1.051 – 2.375	.028
Shortness of Breath	−.482	.617	.410 – .929	.021
Arm Pain	.664	1.943	1.149 – 3.288	.013
Diaphoresis	−.246	.782	.445 – 1.372	.391
Discomfort b/w Breastbone & Navel	−.354	.702	.294 – 1.680	.427
Upset Stomach	−.170	.844	.495 – 1.440	.533
Other Patient Identified				
Jaw/Throat Pain	−.080	.923	.429 – 1.983	.837
Palpitations/Tachycardia	−.645	.525	.223 – 1.234	.139
Back/Shoulder Pain	.199	1.220	.535 – 2.784	.363
Dizzy/Fainting	−1.169	.311	.136 – .708	.005

CI - Confidence Interval, ACS = acute coronary syndrome, MI = myocardial infarction, PCI = percutaneous coronary intervention;