

VIEWPOINTS

Typical and Atypical Symptoms of Acute Coronary Syndrome: Time to Retire the Terms?

Holli A. DeVon , PhD, RN; Sahereh Mirzaei, PhD, RN; Jessica Zègre-Hemsey, PhD, RN

ABSTRACT: Studies indicate that symptoms labeled as “atypical” are more common in women evaluated for myocardial infarction (MI) and may contribute to the lower likelihood of a diagnosis and delayed treatment and result in poorer outcomes compared with men with MI. Atypical pain is frequently defined as epigastric or back pain or pain that is described as burning, stabbing, or characteristic of indigestion. Typical symptoms usually include chest, arm, or jaw pain described as dull, heavy, tight, or crushing. In a recent article published in the *Journal of the American Heart Association (JAHA)*, Ferry and colleagues addressed presenting symptoms in men and women diagnosed with MI and reported that typical symptoms in women were more predictive of a diagnosis of MI than for men. A critical question is, are there really typical or atypical symptoms, and if so, who is the reference group? We propose that researchers and clinicians either discontinue using the terms *typical* and *atypical* or provide the reference group to which the terms apply (eg, men versus women). We believe it is past time to standardize the symptom assessment for MI so that proper and rapid diagnostic testing can be undertaken; however, we cannot standardize the symptom experience. When we do this, we are at risk of having study results, such as those of Ferry and colleagues, that vary from prior evidence and could lead to what the authors hope to avoid: disadvantaging women in receiving expeditious diagnostic testing and treatment for acute coronary syndrome.

Key Words: acute coronary syndrome ■ clinical presentation ■ myocardial infarction ■ sex differences ■ symptoms

Symptoms are the trigger that propel individuals with symptoms suspicious of acute coronary syndrome (ACS) to seek emergent care for this potentially life-threatening condition. After 3 decades of research on sex differences in the symptoms of ACS, ample evidence suggests that although sex differences in symptoms exist, they are modest and do not contribute significantly to risk stratification or provide a rationale for diagnostic testing based on sex. In a large prospective study, we found that only 3 of 13 common symptoms were predictive of a diagnosis of ACS versus non-ACS. The predictive value of shoulder pain (odds ratio: 2.53 [95% CI, 1.29–4.96] versus 1.11 [95% CI, 0.67–1.85]) and arm pain (odds ratio: 2.15 [95% CI, 1.10–4.20] versus 1.21 [95% CI, 0.74–1.99]) for women were nearly twice that of men.

Shortness of breath was predictive of a non-ACS diagnosis for men only.¹

Scores of authors have found some sex differences in symptoms of ACS,^{2,3} but small differences were usually based on frequency and distribution of symptoms, not the type of symptom. In many studies, statistical significance was reached when sex differences were as small as a few percentage points. Kahn et al⁴ found, for example, that men reported chest pain more frequently than women (86.3% versus 81%; $P=0.03$). We must distinguish between clinical significance (whether the magnitude of difference is large enough to change clinical care) and statistical significance (which is subject to variability in sampling and measurement) in assessing patients for further intervention. A more critical issue than sex differences in symptoms is likely the

Correspondence to: Holli A. DeVon PhD, RN, FAAN, FAHA, School of Nursing, University of California Los Angeles, 700 Tiverton Ave., Factor Building, Room 2-244, Los Angeles, CA 90095. E-mail: hdevon@sonnet.ucla.edu.

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magnitude of symptom overlap in individuals ruled in and out for ACS. Approximately 10% to 15% of patients presenting to the emergency department (ED) with symptoms suggestive of ACS are actually experiencing ACS,^{5,6} yet the other 85% of patients look so similar that the same diagnostic testing and resources are required to safely rule them out for ACS. Numerous clinical-decision aids to assess risk for ACS in the ED have been validated over the years, some with 100% sensitivity.⁵ Many of these clinical-decision or prediction rules have facilitated transfer of low-risk patients to a chest-pain or clinical-decision unit or early discharge from the ED.⁷

In a recent article published in the *Journal of the American Heart Association (JAHA)*, Ferry et al⁸ addressed presenting symptoms in men and women diagnosed with myocardial infarction (MI) using sex-specific criteria in a substudy of the High-STEACS (High-Sensitivity Troponin in the Evaluation of Patients With Acute Coronary Syndrome) trial. The definition of sex-specific criteria were troponin levels >99th percentile, which are 16 ng/L for women and 34 ng/L for men.⁹ The rationale for the study was that sex-specific thresholds for troponin have identified a population of patients with MI that was previously unrecognized. Therefore, these patients would have been excluded from prior research on sex differences in symptoms. In addition, “atypical” symptom presentations are more common in women than men and may contribute to the lower likelihood of a diagnosis and treatment and result in poorer outcomes compared with men with MI. Atypical pain was defined by Greenslade et al¹⁰ as “epigastric or back pain or pain that was described as burning, stabbing, characteristic of indigestion, or other.” Typical symptoms included “chest, arm, or jaw pain described as dull, heavy, tight, or crushing.” The main study finding was that typical symptoms in women were more predictive of a diagnosis of MI than those in men.

We address several limitations to study methods that may mislead researchers, clinicians, and the public. In the High-STEACS parent study, 16% of men and 12% of women had type 1 MI (myocardial necrosis with troponin levels >99th percentile or myocardial ischemia on the ECG) and the remainder had type 2 (myocardial necrosis caused by increased oxygen demand or decreased supply).⁸ Importantly, patients with ST-segment-elevation MI (STEMI) were excluded from the study. The authors stated that patients with STEMI were not included because symptom differences are less important, as the diagnosis is based primarily on the ECG rather than on other features of the clinical presentation. Although ECG criteria for STEMI account for sex and age differences,¹¹ there are still notable delays in timely reperfusion among women with STEMI compared with men. Jneid et al¹² found that women with STEMI were less likely to receive

fibrinolytic therapy alone, primary PCI, or the combination of fibrinolytic therapy and PCI (5.1% versus 6.2%, 47.3% versus 61.1%, and 3.9% versus 5.8%, respectively; $P < 0.0001$). Women presenting with STEMI were also less likely to achieve timely door-to-needle time (28.3% versus 35.2%; $P = 0.0005$) and timely door-to-balloon time (39.0% versus 44.8%; $P < 0.0001$). Mirzaei et al¹³ found that another factor contributing to women’s less timely reperfusion was longer prehospital delay compared with men. This finding is concerning because ECGs are frequently not obtained within the recommended 10 minutes of arrival, and in one study, women with ischemic-type symptoms had a mean time of 53 minutes from presentation to ECG.¹⁴

It is vitally important to remember that symptoms are cues for patients that a problem exists. Symptoms trigger clinicians to obtain ECGs, which drive subsequent clinical decision-making such as activation of the cardiac catheterization laboratory for emergent percutaneous coronary intervention.¹⁵ Nearly all patients presenting to the ED are undifferentiated. Neither the patient nor the clinician knows what the diagnosis is until testing is complete. Many emergency medical systems now have the capacity to do prehospital ECGs. Nevertheless, we found in our recent study that only 44.6% of patients with ACS arrived at the ED via emergency medical systems. In addition, a minority of patients (24.6%) experienced STEMI, and only 56.3% of patients with STEMI called emergency medical systems. This leaves a large number of patients presenting to the ED without a diagnosis.¹³ In addition, individuals presenting to emergency medical systems with chest pain are significantly more likely to receive prehospital ECG compared with those who have nonchest symptoms. Consequently, despite greater availability of prehospital ECG equipment, if the patient does not report chest pain, then they are disadvantaged from even receiving a prehospital ECG.¹⁶ Including patients with STEMI is vital to determining true differences or similarities in symptoms between female and male patients, particularly because STEMI is a true emergency requiring time-dependent reperfusion therapy.

In the Clinical Perspective section of their article, Ferry et al⁸ state that women with MI are at risk of underdiagnosis and undertreatment if “correct” symptom presentations are not recognized. Researchers, including our team, have spent years attempting to identify sex differences in the symptoms of ACS to provide evidence for clinicians to facilitate expeditious diagnosis and for the public to be able to respond quickly to symptoms. To suggest that there is a “correct” presentation implies there is an “incorrect” symptom presentation, which is not supported by numerous previous studies.^{1,17,18} Assuming a correct presentation can also imply that there is a “standard” symptom presentation, also unsupported by the data to date. The critical question is,

are there really typical or atypical symptoms, and if so, who is the reference group? We propose that researchers and clinicians either discontinue using the terms *typical* and *atypical* or provide the reference group to which the terms apply (eg, men versus women).

Many researchers have reported that upper back pain and fatigue are commonly reported symptoms during ACS, and up to 30% of patients do not experience chest pain.^{19,20} This information is important to consider as we try to differentiate patients who will be ruled in compared with those ruled out for ACS. We found that although chest pain is a sensitive symptom for ACS, it is not very specific (Table).¹ In fact, few other symptoms were sensitive or specific for a diagnosis of ACS. In our multicenter prospective study, we found few symptom differences between patients with and without ACS presenting to the ED.¹³ Ferry et al⁸ defined chest pain as all descriptors of chest symptoms, including pressure or discomfort. Their rationale was that terms other than pain are “functions of sex-related language rather than symptom differences in symptom presentation.” This is an opinion that is counterproductive to science and accurate assessment of symptoms, which are, by definition, subjective and what the patient says they are.

We believe it is past time to standardize the symptom assessment so that proper and rapid diagnostic testing can be undertaken; however, we cannot

standardize the symptom experience. When we do this, we are at risk of having study results such as those of Ferry et al,⁸ that vary from prior evidence and could lead to what the authors hope to avoid: disadvantaging women in receiving expeditious diagnostic testing and treatment for ACS.

ARTICLE INFORMATION

Affiliations

From the School of Nursing, University of California Los Angeles (H.A.D., S.M.); School of Nursing, University of North Carolina, Chapel Hill, NC (J.Z.-H.).

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Table. Sensitivity and Specificity of Symptoms for ACS by Sex¹

Symptom	Female		Male	
	Sensitivity, %	Specificity, %	Sensitivity, %	Specificity, %
Chest pressure	66*	36	63*	41
Shoulder pain	45	67*	29	72*
Sweating	37	70*	33	70*
Palpitation	27	66*	17	77*
Chest discomfort	66*	33	69*	34
Upper back pain	34	64*	14	78*
Shortness of breath	58	39	41	40
Arm pain	49	69*	32	72*
Unusual fatigue	40	54	32	52
Nausea	38	58	30	70*
Lightheaded	40	55	34	58
Chest pain	67*	37	72*	36
Indigestion	30	78*	18	76*

ACS indicates acute coronary syndrome.

*Sensitive and/or specific for a diagnosis of ACS.

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