ORIGINAL RESEARCH

Presenting Symptoms in Men and Women Diagnosed With Myocardial Infarction Using Sex-Specific Criteria

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***Background*—**Sex-specific criteria are recommended for the diagnosis of myocardial infarction, but the impact of these on presenting characteristics is unknown.

***Methods and Results*—**We evaluated patient-reported symptoms in 1941 patients (39% women) with suspected acute coronary syndrome attending the emergency department in a substudy of a prospective trial. Standardized criteria defined typical and atypical presentations based on pain nature, location, radiation, and additional symptoms. Diagnosis of myocardial infarction was adjudicated using a high-sensitivity cardiac troponin I assay with sex-specific thresholds (>16 ng/L women, >34 ng/L men). Patients identified who were missed by the contemporary assay with a uniform threshold (≥50 ng/L) were reclassified by this approach. Type 1 myocardial infarction was diagnosed in 16% (184/1185) of men and 12% (90/756) of women, with 9 (5%) men and 27 (30%) women reclassified using high-sensitivity cardiac troponin I and sex-specific thresholds. Chest pain was the presenting symptom in 91% (1081/1185) of men and 92% (698/756) of women. Typical symptoms were more common in women than in men with myocardial infarction (77% [69/90] versus 59% [109/184]; P=0.007), and differences were similar in those reclassified (74% [20/27] versus 44% [4/9]; P=0.22). The presence of ≥3 typical features was associated with a positive likelihood ratio for the diagnosis of myocardial infarction in women (positive likelihood ratio, 1.18; 95% CI, 1.03–1.31) but not in men (positive likelihood ratio 1.09; 95% CI, 0.96–1.24).

***Conclusions*—**Typical symptoms are more common and have greater predictive value in women than in men with myocardial infarction whether or not they are diagnosed using sex-specific criteria.

***Clinical Trial Registration*—**URL: http://www.clinicaltrials.gov. Unique identifier NCT01852123. **(*J Am Heart Assoc*. 2019;8: e012307. DOI: 10.1161/JAHA.119.012307.)**

Key Words: acute coronary syndrome • chest pain • chest pain diagnosis • myocardial infarction • sex

An evaluation of clinical symptoms is a major part of the risk stratification of patients presenting to the emergency department with suspected acute coronary syndrome. The accurate interpretation of clinical symptoms has implications for patient triage, treatment, and subsequent management.

The last 2 revisions of the universal definition of myocardial infarction[1,2] recommend the use of sex-specific troponin thresholds for the diagnosis of myocardial infarction. Use of sex-specific thresholds has identified a population of patients with previously unrecognized myocardial infarction.[3] These patients would not have been included in previous study populations investigating sex differences in symptom presentation. Atypical symptom presentations associated with myocardial infarction in women are thought to contribute to lower rates of diagnosis and treatment, and worse outcomes compared with men with myocardial infarction.[4–7] International guidelines reinforce the view that women are more likely to present with atypical symptoms, such as epigastric pain, dyspepsia, or breathlessness.[5,8] It is unknown how identification of these newly identified patients will impact the symptom profile of patients with myocardial infarction.

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Clinical Perspective

What Is New?

- The fourth universal definition of myocardial infarction now recommends the use of sex-specific diagnostic criteria, but the impact of these criteria on the presentation and clinical features of men and women with suspected acute coronary syndrome is unknown.
- Many previous studies have relied on clinician-reported symptoms that may be susceptible to ascertainment bias, whereas we prospectively recorded patient-reported symptoms in 1941 patients with suspected acute coronary syndrome.
- We report that typical symptoms are more common and have greater predictive value in women than in men with myocardial infarction, whether diagnosed using sex-specific or uniform criteria.

What Are the Clinical Implications?

- International guidelines currently state that women with myocardial infarction commonly present with atypical symptoms, which is contrary to evidence supported in this study.
- The accurate interpretation of clinical symptoms has implications for patient triage, treatment, and subsequent management.
- Women with myocardial infarction are at risk of underdiagnosis and undertreatment if correct symptom presentations are not recognized.

While studies reporting sex differences in symptom presentation can boast large study populations,[9–11] they are limited by the use of retrospective data collection from clinical records or registries of patients with confirmed myocardial infarction and therefore are at risk of selection bias. In contrast, studies that evaluated patients with suspected acute coronary syndrome report there are more similarities than differences in symptom presentation between men and women.[12,13] Additionally, studies performed before the third universal definition of myocardial infarction may not be representative of current practice where the use of sex-specific diagnostic thresholds for cardiac troponin are recommended.[1,2]

Women with myocardial infarction are at risk of underdiagnosis and undertreatment if correct symptom presentations are not recognized. Our aim was to prospectively evaluate the frequency and predictive value of patient-reported symptoms in men and women with suspected acute coronary syndrome and to determine whether symptoms differ when the diagnosis of myocardial infarction is based on sex-specific criteria.

Methods

Study Population

Patients with suspected acute coronary syndrome were recruited from the emergency department of the Royal Infirmary of Edinburgh, a tertiary care hospital in Scotland, between June 1, 2013, and March 3, 2017, into a substudy of the High-STEACS (High-Sensitivity Troponin in the Evaluation of Patients with Acute Coronary Syndrome) trial. All patients over 18 years of age in whom the attending clinician requested cardiac troponin for suspected acute coronary syndrome were eligible for inclusion. We did not enroll patients with ST-segment elevation myocardial infarction, those who were unable to provide consent, or those with previous involvement in the trial. This clinical trial and associated substudies were registered (ClinicalTrials.gov number NCT01852123), approved by the National Research Ethics Committee, and conducted in accordance with the Declaration of Helsinki. We do not currently have approval to share the study data set. However, it is our intention to seek additional approvals to share a deidentified data set.

Baseline Characteristics

Patient baseline characteristics, including prior medical history, cardiovascular risk factors, clinical observations, and 12-lead electrocardiography, were obtained from a case record form, and the electronic patient record. Hyperlipidemia and hypertension were defined as a history of the condition, or by the use of lipid-lowering or antihypertensive therapies, respectively. Ischemic heart disease was defined as a history of angina, prior myocardial infarction, or prior coronary revascularization. The criteria used to define ST-segment elevation, ST-segment depression, left bundle branch block, and T-wave inversion were based on international guidelines.[2] Myocardial ischemia was based on a global assessment of the ECG and the presence of any dynamic changes on serial testing.

Symptom Characterization

Patients were interviewed in the emergency department. The presenting symptoms as reported by the patient were documented on a data collection form (Figure S1) by a research nurse from the trial team blinded to the troponin concentration. If patients reported >1 symptom (eg, chest pain and dyspnea), both symptoms were recorded as a presenting symptom. Presenting symptoms were then classified as typical or atypical, as described by Greenslade and colleagues.[14] Typical pain was classified in patients reporting the presence of chest, arm, or jaw pain with descriptors of

dull, heavy, tight, pressure, ache, squeezing, crushing, or gripping. Atypical pain was classified in patients reporting epigastric or back pain or pain that was burning, stabbing, indigestion-like, or any other pain description or presentation.[14] Guidelines also state that radiation of pain and the presence of associated symptoms form part of a typical presentation[8]; therefore the presence of radiation (right arm, left arm, neck, jaw, back) and presence of any associated feature (nausea, vomiting, sweating, dyspnea, palpitations) was also documented.

High-Sensitivity Cardiac Troponin I Assay

The Abbott ARCHITECT$_{STAT}$ high-sensitivity cardiac troponin I assay (Abbott Laboratories, Abbott Park, IL) is a 2-step chemoluminescent assay with a limit of detection of 1.2 ng/L and coefficient of variation of <10% at 6 ng/L.[15] Assay performance has been independently validated under routine laboratory working conditions, with a reported interlaboratory coefficient of variation of 12.6% at 3.5 ng/L across 33 instruments.[16] The upper reference limit 99th percentiles were determined in 4590 samples from healthy individuals as 16 ng/L for women and 34 ng/L in men,[17] and from December 10, 2013, onwards these thresholds were used in clinical practice.

Diagnostic Adjudication

The final diagnosis was adjudicated independently by 2 physicians (A.A./K.L.), with consensus from a third physician (A.S.) where there was discrepancy following review of all clinical information, both noninvasive and invasive investigations, and outcomes from presentation to 30 days. All patients with cardiac troponin I concentrations above the sex-specific 99th percentile were adjudicated and classified as having type 1 myocardial infarction, type 2 myocardial infarction, or myocardial injury, in accordance with the third universal definition of myocardial infarction as previously reported.[16] Type 1 myocardial infarction was defined as myocardial necrosis (any high-sensitivity cardiac troponin I concentration above the 99th percentile with a rise and/or fall in concentration where serial testing was performed) in the context of a presentation with symptoms suggestive of acute coronary syndrome or evidence of myocardial ischemia on the ECG or subsequent invasive or noninvasive testing. Patients with myocardial necrosis and symptoms or signs of myocardial ischemia due to increased oxygen demand or decreased supply (eg, tachyarrhythmia, hypotension, or anemia) secondary to an alternative pathology were classified as type 2 myocardial infarction. Myocardial injury was defined if high-sensitivity cardiac troponin I concentrations were above the 99th percentile in the absence of any clinical features of myocardial ischemia. Agreement for a diagnosis of type 1 myocardial infarction was good (κ=0.77; 95% CI, 0.69–0.84).

Participants diagnosed with myocardial injury identified by the high-sensitivity assay with sex-specific thresholds (>16 ng/L for women and >34 ng/L for men) who would have been unrecognized with the previous generation of contemporary cardiac troponin I assays (those with high-sensitivity troponin I concentrations of 17–49 ng/L for women and 35–49 ng/L for men) were "reclassified." Identification of this group of patients permits exploration of a previously unstudied group of patients because of the limitations of previous assay technology.

Statistical Analysis

Baseline characteristics are summarized as mean (SD) or median (interquartile range) as appropriate. We compared presenting chest pain characteristics of men and women for the whole population, for those with type 1 myocardial infarction, and for those with type 2 myocardial infarction, using chi-squared tests for categorical data. Likelihood ratios (LRs) with 95% CIs were calculated to assess the predictive value of typical symptom characteristics (pain nature, pain location, radiation, additional features) for the diagnosis of type 1 myocardial infarction in men and women. An LR summarizes how many times more likely patients with a particular symptom feature are to have a diagnosis of type 1 myocardial infarction than those without the feature. An LR of >1 indicates that the feature is associated with the presence of type 1 myocardial infarction, and <1 indicates that the feature is associated with the absence of type 1 myocardial infarction. Multivariate logistic regression modeling was then used to calculate odds ratios with 95% CIs for the number of typical features present based on the following categorization. Symptom presentations were categorized as having between 0 and 4 typical features on the basis of the pain nature (dull, heavy, tight, pressure, ache, squeezing, crushing, or gripping), location (central, left, or right chest; arm; or jaw), radiation (right arm, left arm, neck, jaw, back, other), and the presence of associated symptoms (nausea, vomiting, sweating, dyspnea, palpitations, other). This model was adjusted for age, history of ischemic heart disease, diabetes mellitus, hypertension, smoking (current or ex-smoker), ischemia on the presenting 12-lead ECG and an atypical feature variable (in either nature or location). All analyses were performed using R (Version 3.2.2).

Results

Baseline Characteristics

We recruited a total study population of 1941 patients (39% women) with suspected acute coronary syndrome (756

women, 62.8±14.0 years; 1185 men, 60.7±14.3 years; Table 1). A total of 388 (20%) patients (152/756 women and 236/1185 men) had a troponin concentration above the upper reference limit. The adjudicated diagnosis was type 1 myocardial infarction in 11.9% (90/756) of women and 15.5% (184/1185) of men. Men with suspected acute coronary syndrome had a higher burden of established cardiovascular risk factors than women, including higher rates of diabetes mellitus, hyperlipidemia, known ischemic heart disease, and cigarette smoking. A positive family history was more common among women. However, the frequency of cardiovascular risk factors was similar in men and women with a diagnosis of type 1 myocardial infarction, with only previous coronary artery bypass grafting and cigarette smoking more common in men than women (Table S1).

Symptom Characteristics

Chest pain was the most common presenting symptom, reported by 92% (698/756) of women and 91% (1081/1185) of men with suspected acute coronary syndrome (P=0.439; Table 2). Pain with typical nature descriptors, the presence of radiation, and the presence of additional symptoms were all more common in women with suspected acute coronary syndrome (P<0.04 for all; Table 2). Women, compared with men, more often reported palpitations as a presenting symptom (11% versus 7%; Table S2). Women were also more likely to report that their pain radiated to the left arm (36% versus 31%), the back (31% versus 17%), or to the neck or jaw (28% versus 20%) than were men, and were more likely to report associated nausea (34% versus 22%; Table S2).

Chest pain remained the most common presenting symptom for women and men with a diagnosis of type 1 myocardial infarction (93% and 93%; P=1.00; Table 2). The frequency of typical and atypical features of chest pain in women and men with and without an adjudicated diagnosis of type 1 myocardial infarction is illustrated in Figure 1. Women with type 1 myocardial infarction reported pain with more typical nature features than did men (81% versus 64%; P=0.005; Table 2), and pain was classified overall as typical more commonly in women (77% versus 59%; P=0.007; Table 2).

The adjudicated diagnosis was type 2 myocardial infarction in 5.1% (39/756) of women and 3.2% (38/1185) of men (Table 1). Chest pain remained the most common presenting symptom for women and men with type 2 myocardial infarction (82% and 87%, respectively) but was less common than in those with type 1 myocardial infarction (Table S3). Overall, patients with type 2 myocardial infarction were less likely to have typical chest pain location (82% versus 91%; P=0.04), less likely to have radiating pain (49% versus 67%; P=0.006), and more likely to present with palpitations (19% versus 4%; P<0.001) when compared with patients with type 1

Table 1. Baseline Characteristics of Study Population

	Suspected Acute Coronary Syndrome (n=1941)		
	Men	Women	*P* Value
No. of participants, n (%)	1185 (61)	756 (39)	<0.001
Age, y, mean (SD)	60.7 (14.3)	62.8 (14.0)	0.002
Past medical history			
Smoking, n (%)	725 (61.2)	379 (50.1)	<0.001
Diabetes mellitus, n (%)	198 (16.7)	89 (11.8)	0.003
Hypertension, n (%)	472 (39.8)	301 (39.8)	1.00
Hyperlipidemia, n (%)	510 (43.0)	258 (34.1)	<0.001
Family history, n (%)	534 (45.1)	393 (52.0)	0.003
Angina, n (%)	381 (32.2)	203 (26.9)	0.015
Myocardial infarction, n (%)	327 (27.6)	134 (17.7)	<0.001
Previous PCI, n (%)	265 (22.4)	101 (13.4)	<0.001
Ischemic heart disease, n (%)	500 (42.2)	259 (34.3)	0.001
Previous CABG, n (%)	103 (8.7)	14 (1.9)	<0.001
Heart failure, n (%)	43 (3.6)	23 (3.0)	0.571
Cerebrovascular disease, n (%)	81 (6.8)	39 (5.2)	0.162
Peripheral vascular disease, n (%)	28 (2.4)	11 (1.5)	0.221
Medications at presentation			
Aspirin, n (%)	440 (37.1)	215 (28.4)	<0.001
Clopidogrel, n (%)	171 (14.4)	79 (10.4)	0.013
Prasugrel, n (%)	9 (0.8)	2 (0.3)	0.269
Ticagrelor, n (%)	1 (0.1)	1 (0.1)	1.00
Warfarin, n (%)	71 (6.0)	35 (4.6)	0.236
Beta-blocker, n (%)	336 (28.4)	186 (24.6)	0.078
ACE inhibitor or ARB, n (%)	389 (32.8)	195 (25.8)	0.001
Calcium-channel blocker, n (%)	158 (13.3)	84 (11.1)	0.169
Nitrate, n (%)	243 (20.5)	126 (16.7)	0.041
Nicorandil, n (%)	63 (5.3)	28 (3.7)	0.126
Diuretic, n (%)	168 (14.2)	128 (16.9)	0.114
PPI, n (%)	370 (31.2)	268 (35.4)	0.06
Statin, n (%)	555 (46.8)	270 (35.7)	<0.001
NOAC, n (%)	12 (1.0)	13 (1.7)	0.254
ECG			
Myocardial ischemia	143 (12.1)	74 (9.8)	0.139
ST-segment elevation	50 (4.2)	8 (1.1)	<0.001
ST-segment depression	74 (6.2)	38 (5.0)	0.306
Left bundle branch block	47 (4.0)	29 (3.8)	0.981
T-wave inversion	181 (15.3)	120 (15.9)	0.771

Continued

Table 1. Continued

	Suspected Acute Coronary Syndrome (n=1941)		
	Men	Women	*P* Value
Physiological parameters			
Heart rate, bpm, mean (SD)	75 (20)	78 (20)	0.001
Systolic BP, mm Hg, mean (SD)	137 (26)	140 (29)	0.04
High-sensitivity cardiac troponin I concentration			
At presentation, ng/L, median (IQR)	4 (2–13)	2 (1–7)	<0.001
At peak, ng/L, median (IQR)	5 (2–20)	3 (1–9)	<0.001
Adjudicated diagnosis			
Type 1 myocardial infarction, n (%)	184 (15.5)	90 (11.9)	0.03
Type 2 myocardial infarction, n (%)	38 (3.2)	39 (5.1)	
Myocardial injury, n (%)	13 (1.1)	18 (2.4)	
Unable to classify, n (%)	1 (0.1)	5 (0.7)	

Presented as mean (SD), median (interquartile range [IQR]), or number (%). ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BP, blood pressure; CABG, coronary artery bypass grafting; NOAC, novel oral anticoagulants; PCI, percutaneous coronary intervention; PPI, proton pump inhibitor.

myocardial infarction (Table S3). Consistent with our findings in those with type 1 myocardial infarction, typical symptom features (pain with typical nature descriptors, the presence of radiation, and the presence of additional symptoms) were more frequently reported in women than in men with type 2 myocardial infarction.

Diagnostic Performance of Pain Characteristics

Typical pain nature symptoms were predictive of type 1 myocardial infarction in women (LR+, 1.18; 95% CI, 1.04–1.31) but not men (LR+, 0.97; 95% CI, 0.86–1.09; Figure 2). Conversely, radiation of pain was predictive of myocardial infarction in men (LR+, 1.39; 95% CI, 1.22–1.56) but not women (LR+, 1.13; 95% CI, 0.97–1.28). In women, the combination of ≥3 typical features (pain nature, pain location, radiation, associated symptoms) was associated with a significant positive LR for the diagnosis of type 1 myocardial infarction (LR+, 1.18; 95% CI, 1.03–1.31), but this relationship was not present in men (LR+, 1.09; 95% CI, 0.96–1.24).

Using logistic regression modeling, odds ratios were calculated for combinations of typical features to predict a diagnosis of type 1 myocardial infarction compared with 0 or 1 feature being present (0 and 1 were combined because of low numbers). Each subsequent addition of a typical feature increased the odds of type 1 myocardial infarction in women, but symptoms had no associated predictive value in men (Table 3). This association remained even after adjusting for baseline characteristics including age and comorbidity.

Sex-Specific Diagnostic Thresholds

The use of a high-sensitivity cardiac troponin I assay and sex-specific diagnostic thresholds increased the number of patients diagnosed with type 1 myocardial infarction by 30%

Table 2. Presenting Symptom Features of the Study Population

	Suspected Acute Coronary Syndrome			Type 1 Myocardial Infarction		
	Men (n=1185)	Women (n=756)	*P* Value	Men (n=184)	Women (n=90)	*P* Value
Presenting symptom						
Chest pain, n (%)	1081 (91.2)	698 (92.3)	0.439	171 (92.9)	84 (93.3)	1.00
Symptom feature						
Typical nature,* n (%)	772 (65.1)	532 (70.4)	0.019	117 (63.6)	73 (81.1)	0.005
Typical location,† n (%)	1068 (90.1)	683 (90.3)	0.937	165 (89.7)	84 (93.3)	0.445
Radiation (any), n (%)	586 (49.5)	491 (64.9)	<0.001	119 (64.7)	65 (72.2)	0.266
Additional symptoms, n (%)	657 (55.4)	456 (60.3)	0.038	94 (51.1)	56 (62.2)	0.107
Symptom classification						
Typical pain‡	719 (61)	489 (65)	0.084	109 (59)	69 (77)	0.007
Atypical pain§	466 (39)	267 (35)		75 (41)	21 (23)	

Symptoms compared between men and women using chi-squared tests for categorical data.
*Typical nature is pain with descriptors of dull, heavy, tight, pressure, ache, squeezing, crushing, or gripping.
†Typical location is chest (left, right, or center), arm, or jaw. Location data missing in 6.6% of patients with chest pain.
‡Typical pain classified in any patient who described pain of chest, arm, or jaw, with descriptors of dull, heavy, tight, pressure, ache, squeezing, crushing, or gripping.
§Atypical pain classified in any patient who described epigastric or back pain or pain that was burning, stabbing, indigestion-like, or any other pain description or presentation.

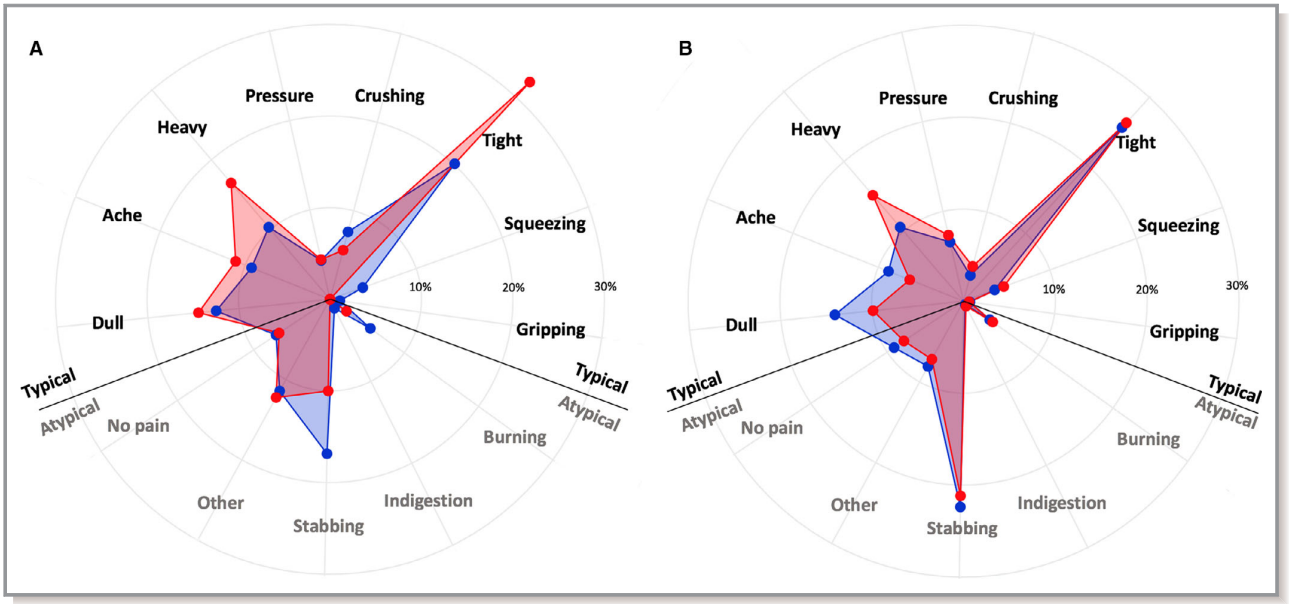

Figure 1. Radar plot showing frequency of typical and atypical pain descriptors. Frequency of typical and atypical descriptors of pain, stratified by sex, in those with myocardial infarction (**A**, n=274) and without myocardial infarction (**B**, n=1667). Men are represented in blue; women are represented in red.

(27/90) in women and 4.9% (9/184) in men (P<0.001). The symptoms reported by patients reclassified using this approach were similar to those identified by the contemporary assay with a uniform threshold (Table S4).

Discussion

Clinical symptoms are a major part of risk stratification for patients presenting to the emergency department with suspected acute coronary syndrome. The subject of sex differences in presenting symptoms of acute coronary syndromes has led to multiple review articles and research studies addressing this issue without resolution.[7,9–13,18–22] International guidelines continue to state that atypical symptom presentations are more common in women than in men.[5,8]

We aimed to establish the presenting symptoms of patients with myocardial infarction in an emergency department setting, using sex-specific diagnostic criteria and direct

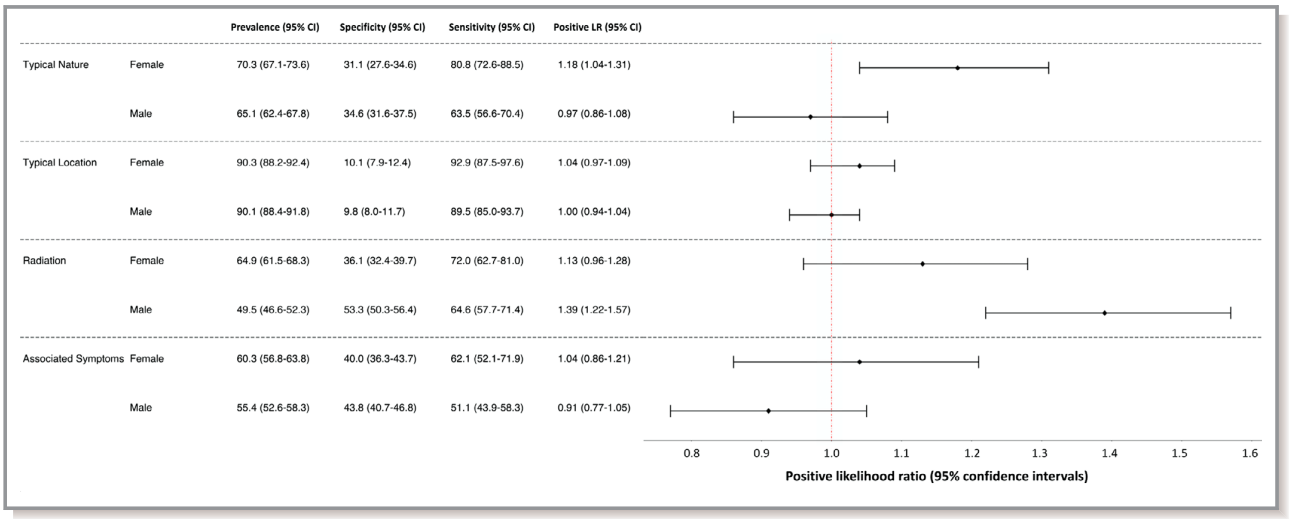

Figure 2. Positive likelihood ratios for the diagnosis of type 1 myocardial infarction of typical clinical features in men and women. Forest plot of the positive likelihood ratios and 95% CIs of 4 clinical features (pain nature, pain location, radiation, associated symptoms) in predicting the diagnosis of myocardial infarction.

Table 3. Logistic Regression Model Evaluating Typicality of Symptoms to Predict the Diagnosis of Myocardial Infarction

	OR in Men (95% CI)	OR in Women (95% CI)
Unadjusted		
Number of typical features		
0 or 1	1.0 (reference)	1.0 (reference)
2	1.1 (0.6–1.8)	3.6 (1.0–23.0)
3	1.2 (0.7–2.1)	5.1 (1.5–31.6)
4	1.4 (0.8–2.5)	5.3 (1.5–33.3)
Adjusted*		
Number of typical features		
0 or 1	1.0 (reference)	1.0 (reference)
2	1.1 (0.6–2.0)	4.0 (1.0–26.1)
3	1.5 (0.9–2.7)	5.9 (1.6–38.0)
4	1.8 (0.9–3.6)	6.9 (1.8–45.3)

Results are odds ratios (ORs) and 95% CIs. Typical features refer to the nature, location, or radiation of pain and any associated features. Scores of 0 and 1 were combined because of low numbers.
*Model adjusted for age, history of ischemic heart disease, diabetes mellitus, hypertension, smoking (current or ex-smoker), ischemia on presentation ECG, and the presence of any atypical feature.

patient interview at the time of presentation. We report 2 major findings. First, women with type 1 myocardial infarction reported more typical symptoms than did men. Second, while individual typical pain features had a similar likelihood for predicting type 1 myocardial infarction in women and men, the cumulative effect of between 1 and 4 typical pain features predicted a diagnosis of type 1 myocardial infarction more strongly in women than in men even after adjusting for baseline characteristics including age and comorbidity.

Our study has several strengths. We used a prospective cohort of patients with diagnosis of myocardial infarction informed by the independent adjudication of 2 cardiologists. Diagnosis was based on a high-sensitivity cardiac troponin I assay with sex-specific diagnostic thresholds as recommended by the latest international guidelines.[1,2] Data on the presenting symptoms were collected prospectively through direct patient interview, by an independent research team, at the time of presentation in the emergency department, and before the patient was informed of his or her diagnosis. Symptoms were classified using standardized definitions of typical and atypical pain.[14]

Our findings add to those from previous studies undertaken in an emergency department population.[12,13,20–22] All disagree with the contention in clinical guidelines that atypical symptom presentations occur more commonly in women. Milner and colleagues observed that typical symptoms were more common in women, and these symptoms were more predictive of myocardial infarction in women in a population of patients with suspected acute coronary syndrome in a US emergency department.[22] By enrolling patients with suspected acute coronary syndrome before the initial diagnosis, we reduce the risk of selection bias that may compromise findings in cohorts enrolled once the diagnosis of myocardial infarction is confirmed. Studies that rely on patient registries or populations with confirmed myocardial infarction risk excluding many symptom presentations. Furthermore, studies performed before the third universal definition of myocardial infarction[2] may not be representative of current practice in which the use of sex-specific diagnostic thresholds are recommended.

In our study we adjudicated the diagnosis of myocardial infarction using sex-specific thresholds. We observed that 1 in 3 women with a diagnosis of type 1 myocardial infarction were only identified using a high-sensitivity cardiac troponin I assay with sex-specific thresholds. This approach is now endorsed by the fourth universal definition of myocardial infarction[1] and will substantially increase the number of women diagnosed with myocardial infarction. Interestingly, women reclassified by this approach were as likely to present with typical chest pain as those identified using a conventional assay with a uniform diagnostic threshold for both men and women.

We used the standardized definition of typical and atypical symptoms offered by Greenslade and colleagues[14] to classify patient presentations into these categories. Many previous studies did not use standardized definitions and have categorized the presenting symptom differently with terms such as *chest discomfort* and *chest pressure* considered to be distinct from chest pain. This may account for our high percentage of patients presenting with chest pain, as we have considered all such terms to indicate the presence of chest pain, agreeing with Kreatsoulas and colleagues[23] that these terms are a function of sex-related language rather than differences in symptom presentation. Abstracting symptom presentation from medical records may further dilute such terms, as they are translated into medical terminology at the discretion of the attending clinician. A term such as *chest discomfort* may be translated into the absence of chest pain, rendering the presentation atypical.

We view patient-reported data collection as the gold standard and superior to that gained from medical record review. Data were collected during the emergency department attendance, minimizing the risk of recall bias, and before the clinical diagnosis; therefore, reporting was not influenced by lay interpretation of the usual symptoms associated with myocardial infarction. Clinician-patient interactions as the focus of an observation study revealed clinicians actively restructuring patient accounts until they fit diagnostic criteria that the clinician felt applicable.[24] By using patient-reported data, accounts of symptom presentation remain as intended by the source and are not limited to predetermined answers prompting particular responses as in a questionnaire format.

The increased reporting of associated symptoms in women has been widely documented[7,9,20,22,25] and confirmed in our patient population, with radiation to the back, nausea, and palpitations described more commonly among women. As 93% of women with myocardial infarction presented with chest pain, these symptoms occurred as additional symptoms and not primary presenting symptoms. The presence of these additional symptoms in women may cloud their symptom presentation, influence clinician interpretation of symptoms,[7] and provide the basis for the atypical symptom message to gain dominance.

The limited predictive value of chest pain characteristics in the absence of other diagnostic information such as ECG has been confirmed by several studies[12,26,27] and could be responsible for delays in diagnosis. The predictive value of the combined presence of multiple typical pain features renders a typical pain presentation in women more diagnostically valuable than in men. The assessment of patients using symptom clusters may be more clinically relevant than focusing on symptoms in isolation, as this is often how patients present. Typical symptom clusters in women should therefore provoke high suspicion of myocardial infarction. Recognition of the clinical significance of such symptom clusters may in part address the disparity in treatment and outcomes experienced by women.[20]

The National Institute for Health and Care Excellence guidelines in the United Kingdom state that men and women with suspected acute coronary syndrome should not be assessed differently[28]; this should be extended to international guidelines, with a stronger message of the clinical value of typical symptoms in women. It may be time to reflect on the usefulness of the terms *typical* and *atypical* and acknowledge that both men and women with acute coronary syndrome present with an array of symptoms.[25]

There are some limitations of our study that may affect the generalizability of our findings. We enrolled patients presenting to a single tertiary care hospital in Scotland. However, our study population consists of patients who self-presented or were referred from primary care practitioners to our institution, rather than those transferred from other acute care hospitals; we therefore believe our findings are generalizable to most acute secondary and tertiary care centers. Participants were identified at the time cardiac troponin I testing was ordered in the emergency department. It is possible that physician bias may have influenced the selection of patients who underwent troponin testing and that those with less typical symptoms may not have been tested. However, it is widely accepted that troponin testing is overused in this setting, and that our approach will have ensured that a broad spectrum of participants was identified. Recruitment was restricted to those patients presenting between 8 AM and 3 PM, but we do not anticipate that patients presenting outside of this time period would be likely to present with different symptoms. Furthermore, our study was performed in consenting patients and therefore reflects the presenting symptoms of only those who are able to provide informed consent. Patients presenting by ambulance with ST-segment–elevation myocardial infarction bypass the emergency department to facilitate timely coronary revascularization, and therefore these patients were not recruited. A recent study reported sex differences in the presenting symptoms of patients with ST-segment–elevation myocardial infarction, though it should be noted that only 24% of the study population were women.[29] However, we would argue that symptom differences in this subgroup are less important, as the diagnosis here is based primarily on the ECG rather than on other features of the clinical presentation. Finally, we have not taken into account the effect that ethnicity may have on symptom presentation. In Scotland, 96% of the population are classified as white,[30] and this may limit the generalizability of our findings to other, more ethnically diverse populations.

Conclusions

Women more frequently describe pain of a typical nature than do men, and typical symptoms are more predictive of a diagnosis of myocardial infarction in women than in men. We advocate that guidelines and educational material be updated to minimize the risk of underdiagnosis and treatment of women with myocardial infarction.

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SUPPLEMENTAL MATERIAL

Table S1. Characteristics of the type 1 myocardial infarction population.

	Type 1 myocardial infarction (n=274)	
	Men	**Women**
No. of participants, n (%)	184 (15.5)	90 (11.9)
Age (years), mean (SD)	66.1 (13.1)	72.1 (12.8)
Past medical history		
Smoking, n (%)	127 (69)	47 (52.2)
Diabetes mellitus, n (%)	39 (21.2)	18 (20.0)
Hypertension, n (%)	92 (50.0)	44 (48.9)
Hyperlipidaemia, n (%)	81 (44.0)	37 (41.1)
Family history, n (%)	85 (46.2)	47 (52.2)
Angina, n (%)	68 (37.0)	32 (35.6)
Myocardial infarction, n (%)	53 (28.8)	24 (26.7)
Previous PCI, n (%)	41 (22.3)	14 (15.6)
Ischemic heart disease, n (%)	82 (44.6)	42 (46.7)
Previous CABG, n (%)	22 (12.0)	1 (1.1)
Heart failure, n (%)	6 (3.3)	2 (2.2)
Cerebrovascular disease, n (%)	14 (7.6)	5 (5.6)
Peripheral Vascular Disease, n (%)	5 (2.7)	3 (3.3)
Medications at presentation		
Aspirin, n (%)	76 (41.3)	30 (33.3)
Clopidogrel, n (%)	25 (13.6)	11 (12.2)
Prasugrel, n (%)	2 (1.1)	0 (0.0)
Ticagrelor, n (%)	1 (0.5)	0 (0.0)
Warfarin, n (%)	11 (6.0)	3 (3.3)
Betablocker, n (%)	56 (30.4)	24 (26.7)
ACE inhibitor or ARB, n (%)	58 (31.5)	32 (35.6)
Ca-channel blocker, n (%)	27 (14.7)	17 (18.9)
Nitrate, n (%)	49 (26.6)	16 (17.8)
Nicorandil, n (%)	9 (4.9)	0 (0.0)
Diuretic, n (%)	31 (16.8)	20 (22.2)
PPI, n (%)	58 (31.5)	41 (45.6)
Statin, n (%)	85 (46.2)	37 (41.1)
NOAC, n (%)	0 (0.0)	1 (1.1)
Electrocardiogram		
Myocardial ischaemia	61 (33.2)	20 (22.2)
ST-segment elevation	11 (6.0)	2 (2.2)
ST-segment depression	34 (18.5)	8 (8.9)
Left bundle branch block	10 (5.4)	6 (6.7)
T-wave inversion	57 (31.0)	26 (28.9)
Physiological parameters		
Heart rate (bpm), mean (SD)	72 (20)	77 (18)

Systolic BP (mmHg), mean (SD)	137 (29)	141 (26)
High-sensitivity cTnI concentration		
At presentation, ng/L [median, IQR]	94 [3-421]	48 [18-273]
At peak, ng/L [median, IQR]	705 [148-3012]	164 [38-1178]

Presented as mean (SD), median (inter-quartile range), or number (%). Abbreviations: ACE = angiotensin converting enzyme; ARB = angiotensin receptor blockers; CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention; PPI = Proton Pump Inhibitor; NOAC = novel oral anti-coagulants; BP = blood pressure.

Table S2. Presenting symptom characteristics stratified by diagnosis.

	Suspected acute coronary syndrome		Type 1 myocardial infarction	
	Men (n=1,185)	**Women (n=756)**	**Men (n=184)**	**Women (n=90)**
Presenting symptom*				
Chest pain, n (%)	1081 (91.2)	698 (92.3)	171 (92.9)	84 (93.3)
Dyspnoea, n (%)	331 (27.9)	216 (28.6)	58 (31.5)	35 (38.9)
Palpitation, n (%)	86 (7.3)	81 (10.7)	3 (1.6)	8 (8.9)
Syncope, n (%)	22 (1.9)	8 (1.1)	1 (0.5)	1 (1.1)
Other, n (%)	123 (10.4)	65 (8.6)	15 (8.2)	6 (6.7)
Radiation				
Left arm, n (%)	368 (31.1)	271 (35.8)	89 (48.4)	44 (48.9)
Right arm, n (%)	138 (11.6)	87 (11.5)	50 (27.2)	21 (23.3)
Neck/jaw, n (%)	234 (19.7)	212 (28.0)	41 (22.3)	29 (32.2)
Back, n (%)	196 (16.5)	237 (31.3)	29 (15.8)	25 (27.8)
Other, n (%)	81 (6.8)	55 (7.3)	9 (4.9)	8 (8.9)
Additional symptoms				
Nausea, n (%)	262 (22.1)	257 (34.0)	35 (19.0)	30 (33.3)
Vomiting, n (%)	41 (3.5)	34 (4.5)	6 (3.3)	3 (3.3)
Sweating, n (%)	371 (31.3)	229 (30.3)	58 (31.5)	29 (32.2)
Shortness of breath, n (%)	225 (19.0)	126 (16.7)	28 (15.2)	21 (23.3)
Palpitations, n (%)	38 (3.2)	29 (3.8)	3 (1.6)	4 (4.4)
Other, n (%)	54 (4.6)	35 (4.6)	7 (3.8)	1 (1.1)
Symptom feature				
Typical nature†, n (%)	772 (65.1)	532 (70.4)	117 (63.6)	73 (81.1)
Typical location‡, n (%)	1068 (90.1)	683 (90.3)	165 (89.7)	84 (93.3)
Radiation (any), n (%)	586 (49.5)	491 (64.9)	119 (64.7)	65 (72.2)
Additional symptoms, n (%)	657 (55.4)	456 (60.3)	94 (51.1)	56 (62.2)
Symptom classification				
Typical pain§	719 (61)	489 (65)	109 (59)	69 (77)
Atypical pain‖	466 (39)	267 (35)	75 (41)	21 (23)

* Patient reporting more than one symptom were counted for all symptoms reported

† Typical nature is pain with descriptors of dull, heavy, tight, pressure, ache, squeezing, crushing or gripping

‡ Typical location is chest, arm or jaw

§ Typical pain classified in any patient who described pain of chest, arm or jaw, with descriptors of dull, heavy, tight, pressure, ache, squeezing, crushing or gripping.

‖ Atypical pain classified in any patient who described epigastric or back pain, or pain that was burning, stabbing, indigestion like, or any other pain description, or presentation.

Table S3. Comparison of symptom features in all men and women with a diagnosis of type 1 and type 2 myocardial infarction stratified by sex.

	Type 1 myocardial infarction			Type 2 myocardial infarction			p-value (All Type 1 vs Type 2)
	All patients (n=274)	Men (n=184)	Women (n=90)	All patients (n=77)	Men (n=38)	Women (n=39)	
Presenting symptom*							
Chest pain, n (%)	255 (93)	171 (93)	84 (93)	65 (84)	33 (87)	32 (82)	0.03
Dyspnoea, n (%)	93 (34)	58 (32)	35 (39)	30 (39)	16 (45)	14 (36)	0.50
Palpitation, n (%)	11 (4)	3 (2)	8 (9)	15 (19)	6 (16)	9 (23)	<0.001
Syncope, n (%)	2 (1)	1 (1)	1 (1)	6 (8)	4 (11)	2 (5)	0.001
Other, n (%)	21 (7)	15 (8)	6 (7)	4 (5)	1 (3)	3 (8)	0.62
Symptom feature							
Typical nature†, n (%)	190 (69)	117 (64)	73 (81)	51 (66)	23 (61)	28 (72)	0.70
Typical location‡, n (%)	249 (91)	165 (90)	84 (93)	63 (82)	31 (82)	32 (82)	0.04
Radiation (any), n (%)	184 (67)	119 (65)	65 (72)	38 (49)	17 (45)	21 (54)	0.006
Associated symptoms, n (%)	150 (55)	94 (51)	56 (62)	44 (57)	21 (55)	23 (59)	0.81
Symptom classification							
Typical pain§	178 (65)	109 (59)	69 (77)	45 (58)	21 (55)	24 (62)	0.36
Atypical pain‖	96 (35)	75 (41)	21 (23)	32 (42)	17 (45)	15 (38)	

* Patient reporting more than one symptom were counted for all symptoms reported

† Typical nature is pain with descriptors of dull, heavy, tight, pressure, ache, squeezing, crushing or gripping

‡ Typical location is chest, arm or jaw

§ Typical pain classified in any patient who described pain of chest, arm or jaw, with descriptors of dull, heavy, tight, pressure, ache, squeezing, crushing or gripping.

‖ Atypical pain classified in any patient who described epigastric or back pain, or pain that was burning, stabbing, indigestion like, or any other pain description, or presentation.

Table S4. Comparison of symptom features in all men and women with a diagnosis of type 1 myocardial infarction and those reclassified using a high-sensitivity cardiac troponin test and sex-specific diagnostic thresholds.

	Patient reported symptoms in those with type 1 myocardial infarction					
	Men			Women		
	All (n=184)	Reclassified by hs-cTnI assay[#] (n=9)	Identified by c-TnI assay (n=175)	All (n=90)	Reclassified by hs-cTnI assay[#] (n=27)	Identified by c-TnI assay (n=63)
Presenting symptom[*]						
Chest pain, n (%)	171 (93)	9 (100)	162 (93)	84 (93)	24 (89)	60 (95)
Dyspnoea, n (%)	58 (32)	5 (56)	53 (30)	35 (39)	8 (30)	27 (43)
Palpitation, n (%)	3 (2)	0 (0)	3 (2)	8 (9)	3 (11)	5 (8)
Syncope, n (%)	1 (1)	0 (0)	1 (1)	1 (1)	0 (0)	1 (2)
Other, n (%)	15 (8)	1 (11)	14 (8)	6 (7)	2 (7)	4 (6)
Symptom feature						
Typical nature[†], n (%)	117 (64)	4 (44)	113 (65)	73 (81)	21 (78)	52 (83)
Typical location [‡],n (%)	165 (90)	9 (100)	156 (89)	84 (93)	25 (93)	59 (94)
Radiation, n (%)	119 (65)	4 (44)	115 (66)	65 (72)	17 (63)	48 (76)
Additional symptoms, n (%)	94 (51)	4 (44)	90 (51)	56 (62)	17 (63)	39 (62)
Symptom classification						
Typical pain, [§] n (%)	109 (59)	4 (44)	105 (60)	69 (77)	20 (74)	49 (78)
Atypical pain, [‖] n (%)	75 (41)	5 (56)	70 (40)	21 (23)	7 (26)	14 (22)

[*] Patient reporting more than one symptom were counted for all symptoms reported

[†] Typical nature is pain with descriptors of dull, heavy, tight, pressure, ache, squeezing, crushing or gripping

[‡] Typical location is chest, arm or jaw

[§] Typical pain classified in any patient who described pain of chest, arm or jaw, with descriptors of dull, heavy, tight, pressure, ache, squeezing, crushing or gripping.

[‖] Atypical pain classified in any patient who described epigastric or back pain, or pain that was burning, stabbing, indigestion like, or any other pain description, or presentation

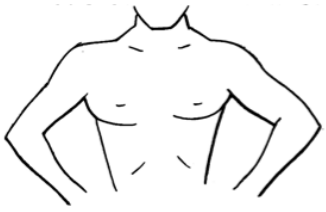
[#] Participants diagnosed with myocardial injury identified by the high sensitivity assay with sex-specific thresholds (>16ng/L for women and >34ng/L for men) who would have been unrecognised with the previous generation of contemporary cardiac troponin I assays (those with high-sensitivity troponin I concentrations of 17-49ng/L for women and 35-49ng/L for men) were “reclassified”.

Figure S1. HighSTEACS suspected acute coronary syndrome symptom checklist.

Presenting symptom									
Chest pain	☐	SOB	☐	Palpitations	☐	Collapse	☐	Other_____	☐

Quality, severity and duration of pain						
Nature of pain		**Radiation**		**Associated symptoms**		**Severity and duration**
Tight	☐	Left arm	☐	Nausea/Vomiting	☐	pain score/10 _____
Dull	☐	Right arm	☐	Sweating	☐	Duration of pain _____minutes
Squeezing	☐	Back	☐	Palpitations	☐	No. of episodes in 24hr_____
Gripping	☐	Jaw/neck	☐	SOB	☐	
Ache	☐	Other_____	☐	Collapse	☐	
Crushing	☐			Other_____	☐	
Heavy	☐					
Pressure	☐					
Sharp	☐					
Stabbing	☐					
Hot	☐					
Burning	☐					
Indigestion	☐					
Other_____	☐					

Pain characteristics	
Worse on changing position for example sitting up or turning to the side	Yes/ No
Worse on palpation	Yes/ No
Worse on exertion (e.g. climbing stairs)	Yes/ No
Better with rest	Yes/ No
Better with nitrates	Yes/ No
Worse on changing position for example sitting up or turning to the side	Yes/ No
Is the pain intermittent/discrete/continuous?	
If previous myocardial infarction or known angina: similar / worse / different / na	

Location		
Central Chest	Yes/ No	Mark with an 'X' areas where pain is present
Left chest	Yes/ No	
Right chest	Yes/ No	
Arm	Yes/ No	
Jaw	Yes/ No	
Epigastric	Yes/ No	
Abdominal	Yes/ No	
Other_____	Yes/No	