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Gender differences in pre-hospital time delay and symptom presentation in patients suspected of acute coronary syndrome in primary care

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Objective. To describe gender differences in pre-hospital delay times and symptom presentation in patients suspected of acute coronary syndrome (ACS) in a primary care setting.

Methods. Over 150 participating GPs included 298 consecutive patients suspected of ACS (52% female, mean age 66 years, 22% eventually diagnosed with ACS according to international guidelines) in a 28-month time period. Data on time from call for help until GP consultation (doctor delay) were prospectively collected, while the time from onset of symptoms until call for help (patient delay) was recorded by the GP at the time of arrival at the patient, together with patient characteristics, including age, sex, previous medical history, chest pain, radiation of chest pain and nausea/sweating.

Results. Median doctor delay was 45 [interquartile range (IQR) 20–55] minutes in women and 33 (IQR 26–72) minutes in men ($P = 0.01$). Median patient delay was 108 (IQR 39–348) minutes in women and 180 (IQR 48–396) minutes in men ($P = 0.20$). Women reported spreading chest pain more often than men (68% versus 57%, $P = 0.06$). Women diagnosed with ACS were older than men (mean 75 years versus 65 years, $P < 0.001$).

Conclusions. In patients suspected of ACS in primary care, no differences were found in patient delay, but doctor delay was longer in women than in men. Symptom presentation was largely similar between men and women, although women tended to report 'spreading' chest pain more often.

Keywords. Acute coronary syndrome, gender differences, primary care, time delay.

Introduction

Coronary heart disease is the second leading cause of death in both men and women in Europe, accounting for 21% and 22% of all deaths, respectively.[1] In the case of acute coronary syndrome [ACS, comprising acute myocardial infarction (AMI) and unstable angina], early recognition is of paramount importance since a timely intervention (e.g. percutaneous coronary intervention, anti-thrombotic therapy or bypass surgery) will reduce the severity of infarction and improve patient outcome. In both primary and secondary care, the early diagnosis of ACS presents a diagnostic challenge for physicians as signs and symptoms of ACS can be atypical and causes of chest pain may vary widely. Biomarkers, especially troponin, have become the cornerstone for the diagnosis of ACS. It is important to measure cardiac biomarkers in the correct time interval because of their specific pattern of rise and fall. For instance, troponin reaches the threshold for AMI 6–9 hours after the onset of symptoms.[2] It is therefore important to establish the time frame in which physicians are confronted with patients suspected of ACS since this influences the choice and interpretation of the biomarker to be measured.

Previous studies on the time delay in ACS have been conducted within a hospital setting, often retrospectively, and typically included patients with confirmed ACS only. Information about time delay in a primary care setting is scarce, as is knowledge of the

delay of those with suspected ACS who are not referred to hospital and/or do not eventually show to have an ACS. It is especially important to determine time delays in patients presenting with ACS in primary care since in many European countries, including the Netherlands, the GP is the first point of contact for patients suspected of ACS.

Some studies suggest that there are gender differences in symptom presentation of ACS. Women have been reported to more often present atypical complaints, such as back pain, neck or jaw pain (without chest pain) and nausea and shortness of breath, while men are more likely to present with chest pain and diaphoresis.[3–7] Other studies, however, could not support these gender differences[8,9] and further research systematically investigating gender differences in the presentation of ACS is needed.[10,11]

We therefore assessed gender differences in pre-hospital delay times and in symptom presentation in suspected ACS patients in the primary care setting.

Methods

The pre-hospital components of delay were divided into patient delay and doctor delay. We defined patient delay as the time from onset of (chest pain) symptoms until the patient's call for help to a GP. We defined doctor delay as the time from the first call for help until the actual GP consultation. Overall delay was defined as the time from symptom onset until the GP consultation. All time intervals were prospectively recorded, from the time of a patient's call for a GP onwards. The GP assistant handling the phone call copied the time of the call for help of the patient (as recorded by the computer) onto a case record form which was given to the participating GP. The GP than recorded the time of chest pain onset as given by the patient and the time of the arrival of the GP at the patient consultation. Also recorded by the GP were patient characteristics (age, sex, previous medical history) and presenting symptoms (presence of chest pain, radiation of pain, nausea/sweating).

The present study forms part of a large diagnostic accuracy study in suspected ACS patients. The design of this study was presented in detail elsewhere.[12] In short, consecutive patients suspected of ACS by the participating GP were included. Presenting symptoms could be chest pain, dyspnoea or any other symptom, such as collaps or transpiration that could prompt a GP to suspect an ACS, importantly, including patients with a low suspicion. Three out-of-hours GP services (one urban and two semi-urban) in the region of Utrecht, The Netherlands, participated in the study, and 25 GPs from group practices recruited patients during daytime hours on week days during a 28-month time period. We excluded patients with complaints lasting >24 hours and patients who required instant hospital referral, as judged by the GP, to prevent any delay with questions as part of our study.

An expert panel consisting of two cardiologists and one GP established the final diagnosis in each patient. For all patients, whether they were referred to the hospital or not, an electrocardiogram (ECG) and biomarker levels (troponin, CK and CK-MB) were obtained within 12–36 hours after the onset of symptoms. Either in the emergency departments of the participating hospitals in referred cases, or at the patient's home, by trained GP laboratory personnel. The panel used all available patient information, including signs and symptoms, ECG and biomarker levels, specialist letters in those who had been referred to hospital and follow-up results (obtained from the GP records) up to 1 month after the event. ACS (comprising AMI and unstable angina) was defined in accordance with guidelines from the European Society of Cardiology and the American College of Cardiology.[13,14] AMI was diagnosed based on the presence of symptoms suggestive of cardiac ischaemia in combination with a rise of a cardiac biomarker, preferably troponin, above the decision limit for AMI with or without typical ECG changes indicative of myocardial ischaemia. Unstable angina was diagnosed when there were typical symptoms and ECG changes indicating cardiac ischaemia, without the elevation of cardiac biomarkers above the decision limit.

Importantly, the main outcome of the original study was the added value of a bedside test for a new cardiac biomarker to detect ACS and the power calculation was based on that outcome.[12] Delay was a secondary outcome of the study, and because of the lack of a power calculation for delay, the provided *P* values should be interpreted carefully.

Data analyses

We examined the differences in median time delay between men and women suspected of ACS using the Mann–Whitney *U*-test. Gender differences in patient characteristics and symptom characteristics were compared using the chi-square or Fisher's exact test (categorical variables) and *t*-test (continuous variables). We performed a subgroup analysis in patients with an established diagnosis of ACS. A stratified analysis according to age was also performed. Due to lack of power, we refrained from performing a multivariate analysis. SPSS version 16.0 (SPSS, Inc., Chicago, IL, USA) was used for all statistical analyses.

Results

Participating GPs in 3 out-of-hours GP services and 9 GP group practices (n = 166) included 298 patients suspected of ACS in the study. We excluded 38 patients (11%). Of these, 12 refused informed consent,

23 had symptoms suggestive of ACS for >24 hours and 3 patients had an undetermined final diagnosis (due to logistical problems, these last three patients were not visited at home for testing of cardiac biomarkers and ECG). The baseline characteristics of the patients and their symptoms are presented in Table 1. There were 155 (52%) females and the mean age of the participants was 66 years (SD 14). The panel established ACS in 66 (22%) patients: 38 (13%) men and 28 (9%) women.

Time delay

Median patient delay in patients suspected of ACS was 108 [interquartile range (IQR) 39–348] minutes in women and 180 (IQR 48–396) minutes in men ($P = 0.20$). Also, doctor delay in women suspected of ACS was longer than in men: 45 (IQR 26–72) minutes compared with 33 (IQR 20–55) minutes ($P = 0.01$). Overall, pre-hospital delay in women suspected of ACS was 168 (IQR 90-408) minutes, in men this was 228 (IQR 90–480) minutes (Fig. 1).

A stratified analyses according to patient age (cut-off 65 years) was also performed, showing that for patients under 65 doctor delay in women was 36 (IQR 26–61) minutes compared with 30 (IQR 18–42) minutes in men ($P = 0.06$) and in patients over 65 doctors delay in women was 45 (IQR 25–79) minutes compared with 35 (IQR 22–67) minutes in men over 65 years ($P = 0.20$).

In a subgroup analysis in patients who were diagnosed with ACS patient delay in women was 84 (IQR 40–210) minutes compared with 180 (34–330) minutes in men ($P = 0.33$). Doctor delay in women was 44 (IQR 25–90) minutes in women and 30 (IQR 15–58) minutes in men ($P = 0.04$). Overall pre-hospital delay in this subgroup was 150 (102–240) minutes in women and 222 (IQR 72–366) minutes in men.

The majority of patients (209, 70%) was seen by the GP within6 hours after onset of symptoms.

Patient characteristics and symptom presentation

Women suspected of ACS in primary care had a mean age of 63 (SD 14) years compared with a mean age of 68 (SD 13) years for men ($P < 0.001$). Women were less likely to smoke than men (16% versus 31%, $P < 0.01$). Diabetes tended to be more prevalent in women than men (26% presence in women versus 20% in men, $P = 0.20$). Other risk factors for coronary heart disease such as hypertension, hyperlipidaemia and a previous history of coronary heart disease did not differ appreciably between men and women. Women reported radiation of chest pain more often than men (68% versus 57%, $P = 0.06$). Other symptoms, such as the presence of chest pain and nausea/sweating, did not differ between men and women. There were no differences in the time of presentation (morning, afternoon/evening or night) between men and women and also the management decision of the GP (hospital referral or not) was similar for both sexes.

TABLE 1 *Patient and symptom characteristics according to gender of patients suspected of acute coronary syndrome (%)*

Patient characteristics (%)	Study participants suspected of ACS by GP			
	Overall % ($N = 298$)	Men ($n = 143$)	Women ($n = 155$)	P value
Age (mean, years)	66 (SD 14)	63 (SD 13)	68 (SD 14)	<0.001
History of AMI, bypass, PCI, angina pectoris	36	37	36	0.81
Current smoker	23	31	16	<0.003
Diabetes	23	20	26	0.20
Hypertension	49	45	52	0.20
Hyperlipidaemia	31	32	30	0.74
Presence of cardiovascular risk factors[a]	79	76	82	0.23
Symptom characteristics (%)				
Chest pain	93	91	96	0.12
Radiation of pain	63	58	68	0.06
Nausea/sweating	58	59	57	0.77
Time of presentation (%)				
Morning (6.00 a.m. to 11.59 a.m.)	16	15	18	0.10
Afternoon/evening (12.00 a.m. to 11.59 p.m.)	22	26	18	0.43
Night (12.00 p.m. to 5.59 a.m.)	62	59	64	0.43
Weekend[b]	34	34	34	0.99
Referred to hospital (%)	73	76	71	0.38
Outcome acute coronary syndrome (%)	22	27	18	0.08
Unstable angina pectoris	21	18	25	0.88
Non-ST myocardial infarction	52	53	50	0.18
ST myocardial infarction	27	29	25	0.25

PCI, percutaneous coronary intervention; ST refers to ECG pattern in which electric activity is denoted with PQRST for different phases in each complex.

[a]Current smoker, diabetes, hypertension and hypercholesterolaemia.

[b]Friday 00:00 p.m. to Sunday 00:00 p.m. In total, 66% of the participants were seen not within the weekend.

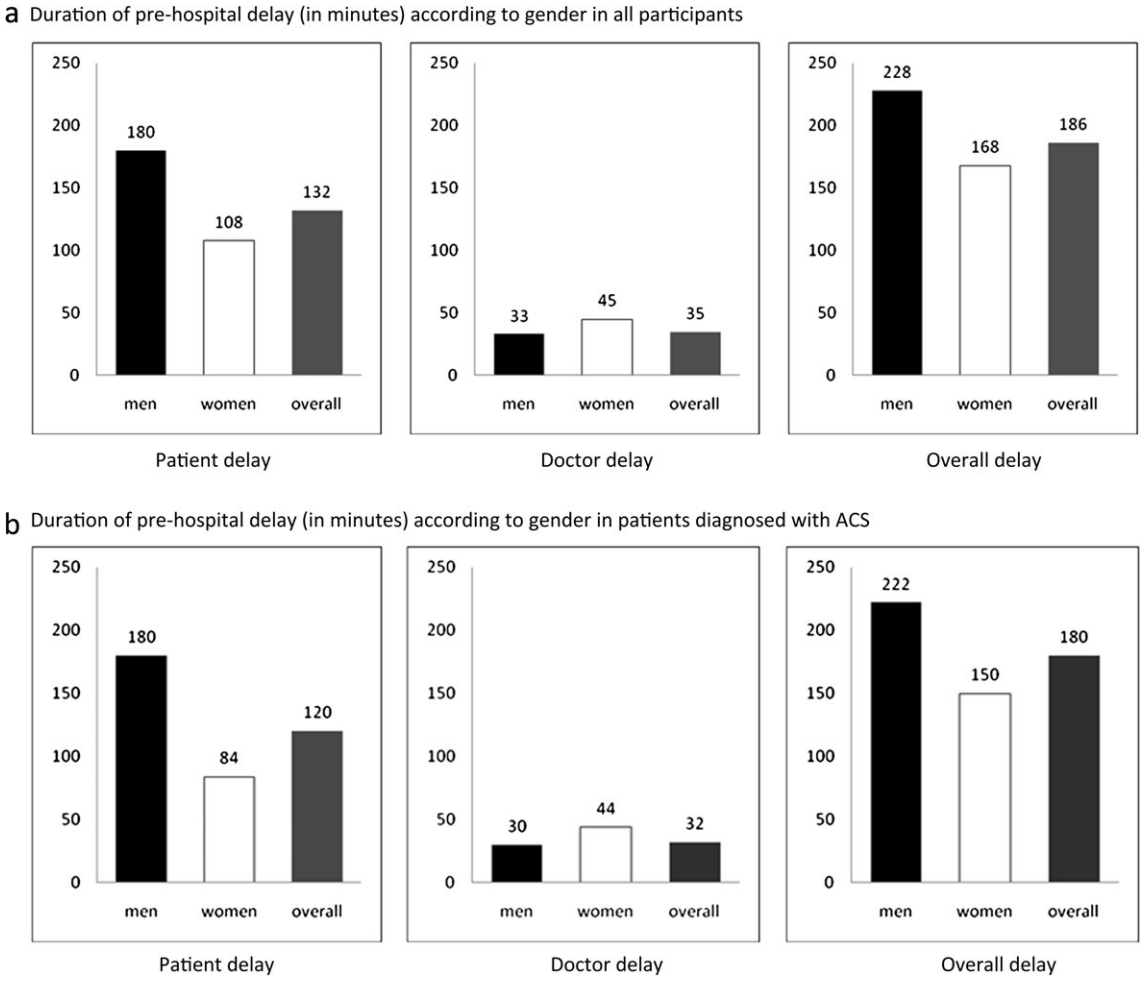

FIGURE 1 *(**a**) Duration of pre-hospital delay (in minutes) according to gender in all participants. (**b**) Duration of pre-hospital delay (in minutes) according to gender in patients diagnosed with ACS*

In a subgroup analysis of patients diagnosed with ACS (n = 66), the women (n = 28) were again significantly older than the men [n = 38, mean age 75 (SD 14) years and 65 (SD 13) years, respectively, $P < 0.001$]. Although more women tended to have had a previous history of coronary heart disease (46% of women versus 37% of men, respectively) and also suffered from diabetes more often (39% versus 24%), these differences were not statistically significant. Overall, however, women suspected of ACS by the GP suffered cardiovascular risk factors more often than men (93% versus 74%, $P < 0.05$). Again, no gender differences were found for time of presentation (morning, afternoon, evening or weekend compared to working days) and men and women were similarly referred to hospital by the GP.

Discussion

Doctor delay, defined as the time from the patients call for help until the actual GP consultation, was >10 minutes longer in women suspected of ACS than in men (median doctor delay 45 and 33 minutes, P = 0.01). Stratified by age, there still is a trend towards a longer doctor delay in women (P = 0.06). The overall delay time, from start of symptoms until the actual GP consultation, was similar (median overall delay 168 and 228 minutes, respectively, P = 0.40). In the subgroup of patients that was eventually diagnosed with ACS, we found similar results. Regarding symptom presentation of ACS, women tended to report spreading chest pain more often than men (P = 0.06), but other symptoms such as the presence of chest pain or nausea/sweating were similar in both sexes.

The longer doctor delay we observed in women is not easy to explain since we also found that men and women are equally likely to present with chest pain and that women more often have radiation of chest pain (considered a typical symptom). One explanation may be the misconception, shared by both patients and physicians, that women are at a lower risk for developing coronary heart disease than men. An experimental case study found that physicians assigned women to a lower risk category for coronary vascular

disease than men, despite a similar calculated risk.[15] Also, in two reviews for gender differences in ACS presentation, women were found to experience chest pain less often than men[11,10] and present with more atypical complaints,[11] which would indeed explain a longer delay in the diagnosis. Nevertheless, these findings were not supported by our study.

While we found a longer doctor delay in women than in men, *overall* pre-hospital delay was similar. One previous hospital-based study reported that women with AMI delayed longer than men in calling for help after the start of symptoms (76 minutes for women and 65 minutes for men),[9] but other studies on pre-hospital delay yielded opposite results: women arrived 10–45 minutes later in hospital than men.[16–18] These studies, however, included only patients with proven myocardial infarction and were all performed in a hospital setting. The 'conflicting' results could therefore be caused by a different setting and patient type. It has been shown that the more serious the ACS (for instance, ST-elevation myocardial infarction patients compared with unstable angina patients) the shorter the pre-hospital delay time.[19,20] In our study, more low-risk patients were included as patients at high risk of ACS are more likely to contact the emergency room or cardiologist directly, thereby bypassing the GP.

Our study illustrates that delay times in a primary care setting differ from those found in a hospital setting. It is especially difficult to assess patients with a low suspicion of ACS in primary care, and the lack of diagnostic facilities makes it difficult for the GP to accurately diagnose or exclude ACS.[21] More diagnostic certainty is needed and biomarker testing may play an important part, also in primary care, in the diagnosis of ACS in the future.

Some methodological issues need to be addressed. One of the weaknesses of our study is the small number of patients included in the study and the even smaller number of patients diagnosed with ACS. Thus, the findings of the subgroup analysis in diagnosed ACS patients should be viewed with caution. The patients that required instant hospital referral according to the participating GP are not included in our study because this would lead to an unacceptable delay in patients requiring instant medical attention. We also excluded patients with complaints lasting >24 hours since in this study we simultaneously evaluated and early biomarker for ACS that had to be measured within 24 hours. However, the most challenging group of patients are those presenting within 24 hours because this is the time interval in which most complications of ACS occur. Regarding gender differences in symptom presentation, it is a drawback that on the case record form that was used, symptoms were not separately specified, but clustered into broad categories. We therefore neither had information on the exact location of the chest pain or the radiation pattern nor we assess the type of chest pain (e.g. sharp pain, pressure, tightness).

A major strength of our study is that the data on time delay were prospectively recorded by the participating GPs, as opposed to many other studies in which these time delays were obtained by interviewing of the patient after the event, or retrospective chart review, with possible recall bias and missing information. The only retrospective timing in our study is the time from symptoms to the call for the GP because the patient was asked for this time period when the GP attended the patient. This was inevitable due to the design of the study, and it is important to realize that at the point of time the patient was asked for the delay, he/she did not yet know the outcome, and 'selective memory' would affect to the same extend patients who eventually showed to have an ACS as those who did not. Also, the patients that we included in our study (suspected of ACS) are highly representative of the actual patient spectrum that the GP will encounter. Most studies included only patients diagnosed with ACS, but in actual clinical practice, GPs will not know whether or not a patient is suffering ACS. We deliberately included patients from this diagnostically challenging domain since this is most in accordance with clinical practice.

Conclusion

In patients suspected of ACS in a primary care setting, we found a longer doctor delay in women than in men, while presenting symptoms of ACS are similar. Women suspected of and diagnosed with ACS were older than men. Both physicians and patients should be aware that women are not at a lower risk for developing ACS: they just do so at an older age. Women with symptoms suggestive of ACS should therefore be just as rapidly evaluated by the GP as their male counterparts and if necessary a prompt hospital referral for additional diagnostic testing and adequate treatment should be ascertained.

Declaration

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