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Are there disparities in symptom presentation or triage of women and men with chest discomfort at primary care out-of-hours services?

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Are there disparities in symptom presentation or triage of women and men with chest discomfort at primary care out-of-hours services?

Manon G. van der Meer[1], Yolande Appelman[2], Karlijn H.G. Rutten[3], Yolanda van der Graaf[3], Hendrik M. Nathoe[1], Pieter A. Doevendans[1], Michelle Smit[3], Emmy Verheij[3], Anne Botermans[3], Frans H. Rutten[3]

[1] Department of Cardiology, University Medical Center Utrecht, Utrecht University, the Netherlands

[2] Department of Cardiology, Amsterdam Medical Center, VU University, the Netherlands

[3] Julius Center for Health Sciences and Primary Care, University Medical Center, Utrecht University, the Netherlands

Corresponding author:

Frans H. Rutten, MD, PhD

Prof. General practice

Julius Center for Health Sciences and Primary Care

University Medical Center Utrecht, Utrecht University

HP STR 6.131, PO Box 85500, 3508 GA Utrecht

The Netherlands

Phone number: +31 (0)88 75 680 51

Email: f.h.rutten@umcutrecht.nl

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ABSTRACT

Objectives: Previous hospital-based studies suggested delayed recognition of an acute coronary syndrome (ACS) in women. We wanted to assess differences in symptom presentation or triage among women and men who contacted primary care out-of-hours services (OHS) for chest discomfort.

Design: Retrospective observational study.

Setting: Primary care OHS.

Participants: 276 women and 242 men with chest discomfort who contacted a primary care OHS in the Netherlands in 2013 and 2014.

Main outcome measures: Differences between women and men regarding symptom presentation and urgency allocation. The medical diagnosis was retrieved from the patients' general practitioner.

Results: 8.4% women and 14.0% men had an ACS. Differences in symptoms between patients with and without ACS were in general small, for both women and men. The only exception was that radiation of chest pain was more discriminative among men than women.

The duration of telephone calls of women and men with an ACS was shorter than in those without an ACS; 5.22 versus 7.26 minutes, p-value=0.003, and 6.27 versus 7.22 minutes, p=0.087, respectively. Women and men with ACS received equally often a high urgency allocation (95.7% versus 88.2%, p-value=0.331).

Conclusions: Discriminating patients with ACS from those without in patients with chest discomfort who contacted primary care OHS seems equally difficult in women as in men. Women with chest discomfort were not under-triaged compared to men with chest discomfort.

Keywords: gender, primary care out-of-hours service, chest pain, acute coronary syndrome, triage.

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STRENGHTS AND LIMITATIONS OF THIS STUDY

- We could evaluate the initial symptom presentation of women and men with chest discomfort before knowledge of the eventual diagnosis, thus without hindsight bias.
- Symptom presentation may change over the time, notably after repeated, and suggestive questions by multiple health care workers.
- Women with and without ACS, and men with and without ACS should be compared to assess disparities in the diagnostic phase.
- We assessed routine care data and thus could analyse only a restricted number of determinants.
- In 37.7% we did not receive information from the patients' GP to make a diagnosis. This did not bias our results as determinants were similar between participants and non-participants.

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INTRODUCTION

In the Netherlands, patients in general first present to primary care and the general practitioner (GP) decides as a 'gatekeeper' who should be sent to a hospital for further analysis. Chest discomfort, however, is an exception with 80% first contacting the GP and 20% directly calling the ambulance or being self-referrals.(1) Chest discomfort is a common reason for contacting primary care and around one in seven to ten people has an underlying cardiac cause, most often coronary artery disease (CAD), including an acute coronary syndrome (ACS).(1–3) Timely diagnosis of an ACS is of utmost importance, because early medical and interventional treatment can save myocardium ("time is muscle") and lives.(4)

Previous hospital-based studies described a delayed recognition of ACS in women compared to men. (5–8) This delayed recognition of ACS in women has been related to an atypical presentation in women. (9–11) Previous studies also identified that management of chest discomfort by physicians may be influenced by gender of the patient caused by an underestimation of the risk of CAD in women. (12,13) However, this information is selectively retrieved in those with an established ACS and seen at the emergency department for chest pain. Importantly, however, during the diagnostic assessment the clinician is interested in patient characteristics that help to discriminate women with ACS from women without, and similarly for men. Notably in primary care, where electrocardiography and fast results of high-sensitive troponin levels are lacking.

We assessed the triage of women and men presenting with chest discomfort to a primary care out-of-hours service (OHS) and compared sex-stratified those with and without ACS regarding patient characteristics and urgency allocation with telephone triage.

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METHODS

Primary care out-of-hours services

In the Netherlands, primary care OHS cover primary care in 73% of the week hours. The first contact of a patient to a primary care OHS is by telephone and trained triage nurses who are supervised by a GP initially handle these calls. Most Dutch OHS use the "Dutch Triage Standard" (NTS) to triage patients. The NTS started in November 2012 as a decision aid for triage nurses to classify the urgency of the complaint. Based on the initial symptom of the patient, the triage nurse chooses within the NTS system the most appropriate module among 56 NTS modules based on clinical symptoms, and "chest discomfort" is one of them. (14) Based on a decision tree with several hierarchically ordered questions (triage criteria), specified for each module, the NTS generates one out of five urgency levels (U1-U5, Appendix-Table 1). In case of a potential life-threatening situation (U1) an ambulance and/or the GP should arrive at the patient within 15 minutes. U2 means that the patient should be evaluated within 1 hour and in case of U3, the patient should be assessed within three hours. If considered not urgent, the patient should be seen the same day (U4), or a telephone advice is sufficient (U5). The triage nurse, but also the GP on duty can overrule the assigned computer-based urgency if considered necessary.

The routing through each decision tree is the same for women and men. In the module "chest discomfort" (i) severe pain (≥7 on a scale from zero to 10), (ii) radiation of chest pain to arm or neck, (iii) experiencing accompanying shortness of breath, or (iv) symptoms related to activation of the sympathetic nervous system such as sweating, nausea/vomiting, pale face an/or (near) fainting will result in the highest urgency level (U1). The NTS has, however, never been formally validated by correlating the generated urgencies to clinical endpoints. (14)

Study population

This study was carried out in primary care OHS "de Gelderse Vallei" in Ede, the Netherlands. Since 2001, in total 120 GPs provide primary care to a population of around 270,000 people. For the current analysis we used consecutive back-up tapes of telephone contacts classified in the NTS as "chest discomfort" in the months November and December 2013, and January, May, June, and July 2014. We chose these two sets of three consecutive months to be able to neutralize seasonal effects. We

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excluded young adults below the age of 30, repeated contacts, contacts that could not be retrieved from the back-up system, and patients without definitive diagnosis.

The Ethical Committee of the University Medical Center Utrecht and the advisory board of General Practitioners Committee "De Gelderse Vallei" approved the study protocol. The study was carried out according tot the principles of the Declaration of Helsinki and de-identified patient data were used for analysis.

Patient and public involvement

No patients involved.

Data collection

Age, gender, date, time of the telephone contact, presented symptoms and the allocated urgency level were extracted from the electronic "call management system". In some instances, there was a link between the digital record of the GP of the patient and the OHS, and the medical history and drug use of the patient was available during the call. The original telephone calls were retrieved from "Freedom Call Manager", a back-up system containing all telephone calls with the primary care OHS. Research students replayed the telephone calls (MS, EV, AB) and scored them on a standardized case record form (Appendix, Table 2). With the case record form clinical items were registered, such as symptoms, medical history, and the duration of the call. We used the real life telephone calls as source of data giving us the opportunity to evaluate the very initial, 'unbiased' presentation of the patients. As a consequence, we could only analyse information that was discussed during the telephone call.

Medical diagnosis

To retrieve the medical diagnosis related to the primary care OHS contact, we contacted the patient's own GP. They were asked to fill out a case record form with questions about the final medical diagnosis. If this was an ACS, they were asked to classify it in (i) ST-elevation myocardial infarction (STEMI), (ii) non-STEMI, or (iii) unstable angina pectoris (UAP), based on the discharge letter of the hospital admission related to the OHS contact.

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Data analysis

Data were stratified by sex. Continuous variables were expressed as mean (standard deviation), and the duration of the telephone calls as mean (range). Categorical variables were expressed as numbers (percentage). Differences between sexes were assessed with the Student's t- test or Mann-Whitney U test for continuous variables, and the Chi-square test or Fisher's exact test for categorical variables. The five urgency levels were dichotomized in high urgency (U1-2) and low urgency (U3-5) before analysis. We analysed differences in characteristics between participants and patients in whom the medical diagnosis could not be retrieved, to exclude selection bias (Appendix, Table 3). We used multivariable logistic regression analysis to compare the urgency allocations and ACS diagnosis between sexes. We developed two models; a crude model (model 1) and a model adjusted for age (model 2). Results were expressed as odds ratios (OR) with a 95% confidence interval (CI). The retrieved medical diagnoses were categorized. We combined rhythm disorders, heart failure, pericarditis, symptoms related to very high blood pressure, and stable angina pectoris in "other cardiovascular diseases".

The analyses were repeated after adding all potential life-threatening diagnoses to ACS, including pulmonary embolism, pneumothorax, aortic dissection and acute heart failure since a high urgency would be appropriate in all such cases. All data analyses were performed with IBM SPSS version 25.0 for Windows.

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RESULTS

A flowchart of the study population is presented in Figure 1. In 518 patients, the medical diagnosis could be retrieved; 242 men (46.7%) and 276 women (53.3%) of whom (8.4%) women and 34 (14.0%) men had an ACS. There were no differences in sex, age, duration of the telephone calls, and urgency allocation between participants and patients in whom the medical diagnosis could not be retrieved.

An overview of the baseline characteristics and symptoms of the participants is given in Table 1. In women and men with an ACS compared to those without an ACS, the duration of the telephone calls was less long (women 5.22 vs. 7.26 minutes, p-value=0.003, and men 6.27 vs. 7.22 minutes, p-value=0.087). Women and men with ACS were on average older (women 66.8 vs. 62.8 years, p-value=0.184, and men 68.1 vs. 58.8 years, p-value=0.224) and had more often a history of CVD (women 71.4% vs. 50.4%, p-value=0.066, and men 65.6% vs. 50.3%, p-value=0.113) than those without ACS. In both sexes, patients with ACS experienced more a pressing chest pain than those without ACS. A stabbing pain was less frequent in women and men with ACS than in those without ACS; in women 15.8% vs. 18.8%, p-value=0.073, in men 3.7% vs. 24.0%, p-value=0.014. None of the women and men with ACS experienced right-sided chest pain. Women and men with ACS more often expressed radiation of pain than patients without ACS (women 90.0% vs. 78.6%, p-value=0.227, men 89.3% vs. 64.9%, p-value=0.011). Shortness of breath and nausea/vomiting were similarly distributed among those with and without ACS, but sweating tended to be more present in women and men with ACS compared to those without (women 52.6% vs. 35.5%, p-value=0.138, men 60.7% vs. 43.5%, p-value=0.093).

Medical diagnosis

Men had more often an ACS than women (14.0% vs. 8.4%, p-value=0.038). Of those patients with an ACS, women had relatively more often a NSTEMI than men. Non-specific chest pain/musculoskeletal pain was the most common diagnosis in both sexes (35.9% vs. 40.5%). All other diagnoses were equally distributed among men and women. See Table 2.

Triage

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Both women and men with chest discomfort received often a high urgency allocation (U1, U2) (women 65.6% vs. men 64.9%) and women with an ACS got at least as often a high urgency allocation as men with an ACS (95.7% vs. 88.2%, p-value=0.331); see Table 3. The chance of receiving a high urgency allocation with ACS was not affected by age. When we evaluated the composite of potential life-threatening diagnoses (ACS, pulmonary embolism, pneumothorax, aortic dissection and acute heart failure), comparable high percentages of women and men with a potential life-threatening diagnosis were assigned a high urgency (U1-2); 96.3% vs. 87.9%, p-value=0.241.

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DISCUSSION

In both women and men it is very difficult to differentiate those with ACS from those without in patients with chest discomfort who contact the primary care OHS. In men, stabbing chest pain was significantly more often present in non-ACS patients (2.9% vs. 21.1%, p-value=0.014) while radiation of pain was significantly more often mentioned by men with ACS (73.5% vs. 47.1%, p-value-0.011). 'Classical' symptoms of ACS (oppressing chest pain, with radiation and sweating) were more common in both women and men with ACS as compared to women and men without ACS. Women were not under-triaged, and those with ACS received at least as high urgency allocations as men. Interestingly, women with an ACS had significant shorter telephone call duration than women without an ACS (5.22 vs. 7.26 minutes, p-value=0.003), while in men this difference was smaller and not significant (6.27 vs. 7.22 minutes, p-value=0.087), suggesting that triage nurses were able to recognize an ACS earlier in women than in men. We were unable to adequately assess the predictive value of symptoms in women and men separately with multivariable logistic regression analysis, because of a limited number of events; (23 (8.3%) women and 34 (14.0%) men had an ACS).

Our study has several strengths. Firstly, we had the opportunity to evaluate the very initial symptom presentation of women and men with chest discomfort. This is important, since the presentation may change over time when multiple health care workers repeatedly ask comparable questions. Secondly, by replaying the telephone calls we were not hampered by recall bias of patients. Thirdly, we used data from a primary care OHS that provides out of hours primary care services during 73% of the week-hours for 270,000 people, including rural and city areas, making the study population a good representation of everyday patients seen in primary care.

A limitation of the study was that we were not able to retrieve the medical diagnosis in all 832, but only in 518 (62.3%) patients. This was because some GPs did not provide follow-up data, mainly because they were afraid of violation the privacy of the patient. Selection bias is, however, unlikely because the missing medical diagnoses were not patient driven. Moreover, comparison of the 518 participants with follow-up data and the 314 without a final diagnosis did not show significant differences in important determinants such as age, sex, duration of telephone calls, symptoms and urgency allocation. A second limitation is that we could not present data of patients who immediately

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called an ambulance or went on their own to an emergency department, which is around 20% of those experiencing chest discomfort in the Netherlands.(1) A third limitation was missing data on some determinants, which is rather common in an observational study with real life data. Fourth, a relatively low number of symptoms could univariably be analysed because the Netherlands Triage Standard restricts the number of questions to patients with the aim not to lose too much time with the telephone triage. Fifth, the low number of ACS cases did not allow for multivariable logistic regression analysis in men and women separately. Finally, we do not know whether men and women differ in patient's delay, as we did not assess the durations of symptoms until calling the PC-OHS.

To the best of our knowledge, this is the first study that included the medical diagnosis in the evaluation of triage of patients with chest discomfort who contacted primary care. One Norwegian study showed that 50% of patients who contacted the primary care OHS for chest pain were referred to the hospital, however a final medical diagnosis was lacking. (15) Another study from the Netherlands assessed gender differences in the symptom presentation of patients suspected of an ACS in primary care (from both day care and out-of hours) found no relevant differences between sexes regarding chest pain and autonomic nervous system-associated symptoms, but information on other symptoms or urgency allocation is lacking. (16) They did find, however, a significant longer doctor delay in women than in men with chest discomfort: 45 minutes vs. 33 minutes (p-value=0.01). (16) Our results on the prevalence of ACS in women (8.3%) and men (14.0%) is in line with a previous study performed in German primary care reporting a prevalence of 14% in women and 17% in men in those with acute chest pain. (17)

Studies performed at the emergency department compared men and women with ACS, and concluded that women were more likely to present with dyspnoea instead of chest pain, and with atypical symptoms (e.g. nausea/vomiting, indigestion and palpitations) compared to men.(18,19) This is different to our results, showing no clear difference in symptoms between women and men with ACS. But even more importantly, from the practicing clinician point of view it is not relevant to know if women and men with ACS differ from each other in symptom presentation, the clinician wants to know which symptoms or other patient characteristics help to differentiate (i) women with ACS from women without, and (ii) men with ACS from men without. This is even more relevant for primary care,

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where the GP needs to decide whom to refer and with what urgency, all based on clinical items and very limited access to timely electrocardiography and results of high-sensitive troponin.

Conclusion

Discriminating patients with ACS from those without in patients with chest discomfort who contacted primary care OHS seems equally difficult for women as in men. Women with chest discomfort were not under-triaged compared to men with chest discomfort in the primary care OHS.

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FIGURES

Figure 1: Flowchart of the study population

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TABLES

Table 1: Baseline characteristics of 276 women and 242 men with and without ACS contacting the primary care OHS for chest discomfort

	Women (n=276)			Men (n=242)		
	ACS	No ACS	P-value	ACS	No ACS	P-value
	n = 23 (8.3%)	n = 253 (91.7%)		n=34 (14.0%)	n=208 (86.0%)	
Duration of call, minutes	5.22	7.26	**0.003**	6.27	7.22	0.087
Mean age in years (SD)	66.8 (18.0)	62.8 (15.9)	0.309	68.1 (14.2)	58.8 (16.1)	0.224
History of CVD (n=210)	15 (71.4%)	94 (50.3%)	0.066	21 (65.6%)	80 (50.3%)	0.113
Chest pain (n=455)	22 (95.7%)	215 (87.0%)	0.228	34 (100%)	184 (91.1%)	0.070
Type of chest pain:						
Pressing (n=249)	15 (78.9%)	131 (58.7%)	0.084	18 (64.3%)	85 (46.4%)	0.079
Stabbing (n=90)	3 (15.8%)	42 (18.8%)	0.743	1 (3.7%)	44 (24.0%)	**0.014**
Pain location:						
Left side of the chest (n=107)	4 (36.4%)	44 (23.8%)	0.346	7 (46.7%)	52 (33.1%)	0.291
Right side of the chest (n=32)	0 (0%)	13 (7.0%)	0.363	0 (0%)	19 (12.1%)	0.153
Mid-sternal (n=143)	7 (63.6%)	78 (42.2%)	0.163	7 (46.7%)	51 (32.5%)	0.267
Radiation of the pain to:						
Arm (n=154)	9 (60.0%)	78 (42.4%)	0.186	17 (63.0%)	50 (33.3%)	**0.003**
Back or shoulder (n=124)	8 (66.7%)	73 (51.8%)	0.321	6 (46.2%)	37 (37.0%)	0.523

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Jaw (n=44)	2 (18.2%)	25 (17.6%)	0.961	5 (29.4%)	12 (10.7%)	**0.034**
Any radiation (n=295)	18 (90.0%)	154 (78.6%)	0.227	25 (89.3%)	98 (64.9%)	**0.011**
Additional symptoms:						
Dyspnoea (n=219)	9 (69.2%)	110 (63.2%)	0.664	10 (47.6%)	90 (61.6%)	0.220
Nausea or vomiting (n=141)	5 (45.5%)	75 (39.5%)	0.694	11 (42.3%)	50 (35.2%)	0.489
Sweating (n=166)	10 (52.6%)	72 (35.5%)	0.138	17 (60.7%)	67 (43.5%)	0.093

CVD = cardiovascular disease; (n=): number of patients

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Table 2: Diagnosis of 518 patients who contacted the OHS for chest discomfort, divided in women and men

	Women n= 276 (%)	Men n= 242 (%)	p-value
Acute coronary syndrome	23 (8.4%)	34 (14.0%)	**0.038**
UAP	*8 (34.8%)*	*12 (35.3)*	
NSTEMI	*10 (43.5%)*	*7 (20.6%)*	
STEMI	*3 (13.0%)*	*6 (17.6%)*	
*Non-classified myocardial infarction**	*2 (8.7%)*	*9 (26.5%)*	
Other cardiovascular diseases**	35 (12.7%)	30 (12.4%)	0.922
Gastrointestinal tract disorders	38 (13.8%)	23 (9.5%)	0.133
Respiratory tract disorders	37 (13.4%)	34 (14.0%)	0.832
Psychogenic disorders	25 (9.1%)	12 (5.0%)	0.071
Non-specific chest pain including musculoskeletal pain	99 (35.9%)	98 (40.5%)	0.279
Other diagnoses	19 (6.9%)	11 (4.5%)	0.256

*UAP: unstable angina pectoris; NSTEMI: Non-ST-elevation myocardial infarction; STEMI: ST-elevation myocardial infarction; * No further information whether it was a STEMI or NSTEMI; ** Including rhythm disorders, heart failure, pericarditis, symptoms related to very high blood pressure, and stable angina pectoris*

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Table 3: Relation between gender and presence/absence of ACS, and urgency level of 518 persons with chest discomfort

		High urgency (U1-2) n=181 (65.6%)	Low urgency (U3-5) n=95 (34.4%)	Crude OR (95%CI)	Adjusted for age OR (95%CI)
Women (n=276)	With ACS	22	1	13.01 (1.73-98.06)	12.50 (1.654-94.48)
	Without ACS	159	94		
		High urgency (U1-2) n=157 (64.9%)	Low urgency (U3-5) n=85 (35.1%)		
Men (n=242)	With ACS	30	4	4.78 (1.63-14.08)	3.90 (1.31-11.66)
	Without ACS	127	81		

U: urgency; OR: odds ratio; CI: confidence interval

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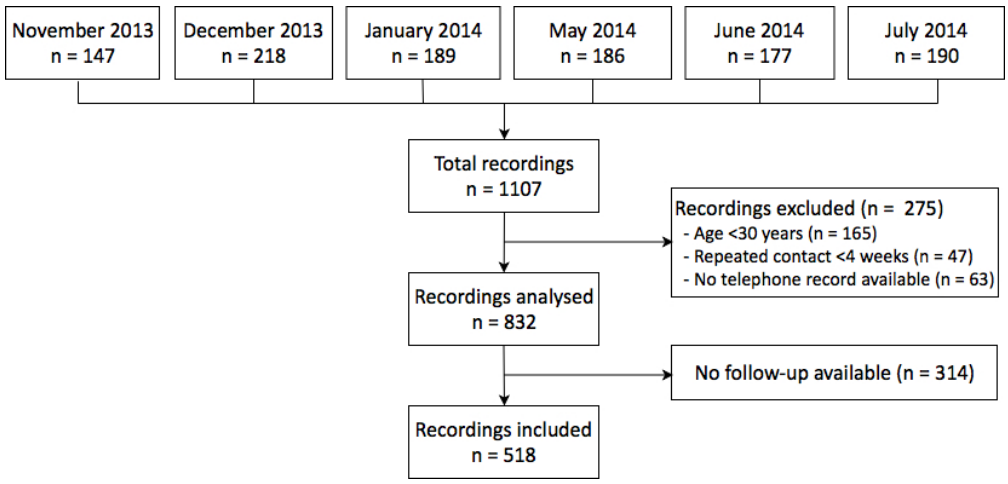

Figure 1: Flowchart of the study population

APPENDIX

Appendix-Table 1: Urgency levels

Urgency level	Implication
U0	Reanimation
U1	Life-threatening, GP/ ambulance should arrive within 15 minutes
U2	Emergency, GP should arrive within 60 minutes
U3	Urgent, consultation by GP within three hours
U4	Routine, consultation by GP the same day
U5	Advise given by triage nurse

U: urgency; GP: general practitioner

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Appendix-Table 2: Items that were registered on a case record form

Duration of the telephone call	Dyspnoea or chest tightness
Was the conversation with the patient or a relative?	Fever, cough or having a cold
Presence of chest pain	Smoking status
Type of pain	History of diabetes mellitus
Location of the chest pain	History of hypertension
Intensity of the pain (score between 0 and 10)	History of hypercholesterolemia
Radiation of the pain	History of cardiovascular disease
Symptoms during rest or during exercise	Complaints similar to previous episodes of cardiac disease
Duration of the symptoms	Family history of cardiovascular disease
Similar symptoms in the last 4 weeks	Family history of sudden cardiac death below the age of 60 years
Nausea or vomiting	Life-threatening disease suspected
Sweating	

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Appendix-Table 3: Participants compared to patients with chest discomfort without a final diagnosis retrieved from the general practitioners

	Participants (n=518)	Non-participants (n=314)	P-value
Duration of call, minutes	7:15	7:19	0.750
Female sex	276 (53.3%)	161 (51.3%)	0.574
Mean age in years (SD)	61.7 (17.1)	61.4 (17.6)	0.769
History of CVD	210 (52.6%)	126 (54.5%)	0.643
Chest pain	455 (89.9%)	281 (90.9%)	0.634
Radiation of chest pain	295 (74.7%)	171 (70.7%)	0.266
Dyspnoea	219 (61.9%)	138 (60.5%)	0.746
Nausea/vomiting	141 (38.3%)	83 (40.3%)	0.624
Sweating	166 (41.1%)	86 (35.0%)	0.120
High urgency allocation (U1-2)	338 (65.3%)	206 (65.6%)	0.917

CVD = cardiovascular disease; (n=): number of patients; U = urgency

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract page 1-2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found page 2
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported page 4
Objectives	3	State specific objectives, including any prespecified hypotheses page 4
Methods		
Study design	4	Present key elements of study design early in the paper page 5-6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection page 5-6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up page 5-7
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed -
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable page 6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group page 6
Bias	9	Describe any efforts to address potential sources of bias page 7
Study size	10	Explain how the study size was arrived at page 5-6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why page 6-7
Statistical methods page 6-7	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses

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Results page 8-9		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed page 8 and flow-chart (Figure 1)
		(b) Give reasons for non-participation at each stage page 8
		(c) Consider use of a flow diagram Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders page 8, Table 1
		(b) Indicate number of participants with missing data for each variable of interest Table 1
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount) -
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time page 8-9, Table 2
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included page 8-9
		(*b*) Report category boundaries when continuous variables were categorized -
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period -
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses -
Discussion		
Key results	18	Summarise key results with reference to study objectives page 10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias page 10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence page 11
Generalisability	21	Discuss the generalisability (external validity) of the study results page 11
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based. No funding was used. We added this to the article on page 13.

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Are there gender disparities in symptom presentation or triage of patients with chest discomfort at primary care out-of-hours services? An observational study

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Are there gender disparities in symptom presentation or triage of patients with chest discomfort at primary care out-of-hours services? An observational study

Manon G. van der Meer[1], Yolande Appelman[2], Karlijn H.G. Rutten[3], Yolanda van der Graaf[3], Hendrik M. Nathoe[1], Pieter A. Doevendans[1], Michelle Smit[3], Emmy Verheij[3], Anne Botermans[3], Frans H. Rutten[3]

[1] Department of Cardiology, University Medical Center Utrecht, Utrecht University, the Netherlands

[2] Department of Cardiology, Amsterdam Medical Center, VU University, the Netherlands

[3] Department of General Practice, Julius Center for Health Sciences and Primary Care, University Medical Center, Utrecht University, the Netherlands

Corresponding author:

Frans H. Rutten, MD, PhD

Prof. General practice

Department of General Practice, Julius Center for Health Sciences and Primary Care

University Medical Center Utrecht, Utrecht University

HP STR 6.131, PO Box 85500, 3508 GA Utrecht

The Netherlands

Phone number: +31 (0)88 75 680 51

Email: f.h.rutten@umcutrecht.nl

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ABSTRACT

Objectives: Previous hospital-based studies have suggested delayed recognition of acute coronary syndrome (ACS) in women. We wanted to assess differences in symptom presentation or triage among women and men who contacted primary care out-of-hours services (OHS) for chest discomfort.

Design: Retrospective observational study.

Setting: Primary care OHS.

Participants: 276 women and 242 men with chest discomfort who contacted a primary care OHS in the Netherlands in 2013 and 2014.

Main outcome measures: Differences between women and men regarding symptom presentation and urgency allocation.

Results: 8.4% women and 14.0% men had ACS. Differences in symptoms between patients with and without ACS were in general small, for both women and men. In women with ACS compared to women without ACS, mean duration of telephone calls was discriminative; 5.22 (SD 2.53) versus 7.26 (SD 3.11) minutes, p-value=0.003. In men radiation of pain (89.3% vs. 54.9%, p-value=0.011) was discriminative for ACS, and stabbing chest pain (3.7% vs. 24.0%, p-value=0.014) for absence of ACS . Women and men with chest discomfort received similar high urgency allocation (crude and adjusted odds ratio after correction for ACS and age; 1.03 (95%CI 0.72-1.48) and 1.04 (95%CI 0.72-1.52), respectively). Women with ACS received a high urgency allocation in 22/23 (95.7%) and men with ACS in 30/34 (88.2%), p-value=0.331.

Conclusions: Discriminating ACS in patients with chest discomfort who contacted primary care OHS is difficult in both women and men. Women and men with chest discomfort received similar high urgency allocation.

Keywords: gender, primary care out-of-hours service, chest pain, acute coronary syndrome, triage.

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STRENGHTS AND LIMITATIONS OF THIS STUDY

- We could evaluate the initial symptom presentation of women and men with chest discomfort before knowledge of the eventual diagnosis, thus without hindsight bias.
- We assessed routine care data and thus could analyse only a restricted number of determinants.
- 37.7% of cases could not be included as participants, since we did not receive information from the patients' GP to make a diagnosis. This did not seem to bias our results because patient characteristics were similar between participants and non-participants.
- Only a small number of patients with chest discomfort actually had an ACS, therefore, no firm conclusions on disparities on symptom presentation between women and men can be made.
- Relative small numbers and missing data prevented us from full multivariable logistic regression analysis.

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INTRODUCTION

In the Netherlands, patients in general first present to primary care and the general practitioner (GP) decides as a 'gatekeeper' who should be sent to a hospital for further analysis. Chest discomfort, however, is an exception with 80% first contacting the GP and 20% directly calling the ambulance or appearing as self-referrals.(1) Chest discomfort is a common reason for contacting primary care and around 10-15% has an underlying cardiac cause, most often coronary artery disease (CAD), including an acute coronary syndrome (ACS).(1–3) Timely diagnosis of an ACS is of utmost importance, because early medical and interventional treatment can save myocardium ("time is muscle") and lives.(4) Previous hospital-based studies described a delayed recognition of ACS in women compared to men. (5–8) This delayed recognition of ACS in women has been related to an atypical presentation in women. (9–11) Previous studies also identified that management of chest discomfort by physicians may be influenced by gender of the patient caused by an underestimation of the risk of CAD in women. (12,13) However, this information is selectively retrieved in those with an established ACS diagnosis and seen at the emergency department for chest pain. Importantly, however, during the diagnostic assessment the clinician is interested in patient characteristics that help to discriminate women with ACS from women without, and similarly for men. Notably in primary care, where electrocardiography and fast results of high-sensitive troponin levels are lacking.

We assessed the triage of women and men presenting with chest discomfort to a primary care out-of-hours service (OHS) to answer the following question: are there gender disparities in symptom presentation or triage in patients presenting with chest discomfort to a primary OHS?.

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METHODS

Primary care out-of-hours services

In the Netherlands, primary care OHS covers primary care in 73% of the hours of the week. The first contact of a patient to a primary care OHS is by telephone and trained triage nurses who are supervised by a GP initially handle these calls. Most Dutch OHS use the "Dutch Triage Standard" (NTS) to triage patients. The NTS started in November 2012 as a decision aid for triage nurses to classify the urgency of the complaint. Based on the initial symptom of the patient, the triage nurse chooses within the NTS system the most appropriate module among 56 NTS modules based on clinical symptoms, and "chest discomfort" is one of them. (14) Based on a decision tree with several hierarchically ordered questions (triage criteria), specified for each module, the NTS generates one out of five urgency levels (U1-U5, Appendix-Table 1). In case of a potential life-threatening situation (U1) an ambulance and/or the GP should arrive at the patient's location within 15 minutes. U2 means that the patient should be evaluated within 1 hour and in case of U3, the patient should be assessed within three hours. If considered not urgent, the patient should be seen the same day (U4), unless a telephone advice is sufficient (U5). The triage nurse, but also the GP on duty can overrule the assigned computer-based urgency if considered necessary.

The routing through each decision tree is the same for women and men. In the module "chest discomfort" (i) severe pain (≥7 on a scale from zero to 10), (ii) radiation of chest pain to arm or neck, (iii) experiencing accompanying shortness of breath, or (iv) symptoms related to activation of the sympathetic nervous system such as sweating, nausea/vomiting, pale face an/or (near) fainting will result in the highest urgency level (U1). The NTS has, however, never been formally validated by correlating the generated urgencies to clinical endpoints. (14)

Study population

This study was carried out in primary care OHS "de Gelderse Vallei" in Ede, the Netherlands. Since 2001, in total 120 GPs provide primary care to a population of around 270,000 people. For the current analysis we used consecutive back-up tapes of telephone contacts classified in the NTS as "chest discomfort" in the months November and December 2013, and January, May, June, and July 2014. We chose these two sets of three consecutive months to be able to neutralize seasonal effects. We

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excluded young adults below the age of 30, repeated contacts, contacts that could not be retrieved from the back-up system, and patients without definitive diagnosis.

The Ethical Committee of the University Medical Center Utrecht and the advisory board of General Practitioners Committee "De Gelderse Vallei" approved the study protocol. The study was carried out according tot the principles of the Declaration of Helsinki and de-identified patient data were used for analysis.

Patient and public involvement

Patients and the public were not involved in the design or planning of the study.

Data collection

Age, gender, date, time of the telephone contact, presented symptoms and the allocated urgency level were extracted from the electronic "call management system". In some instances, there was a link between the digital record of the GP of the patient and the OHS, and the medical history and drug use of the patient were available during the call. The original telephone calls were retrieved from "Freedom Call Manager", a back-up system containing all telephone calls with the primary care OHS. Research students replayed the telephone calls (MS, EV, AB) and scored them on a standardized case record form (Appendix, Table 2). With the case record form clinical items were registered, such as symptoms, medical history, and the duration of the call. We used the real life telephone calls as source of data giving us the opportunity to evaluate the very initial, 'unbiased' presentation of the patients. As a consequence, we could only analyse information that was discussed during the telephone call.

Medical diagnosis

To retrieve the medical diagnosis related to the primary care OHS contact, we contacted the patient's own GP. They were asked to fill out a case record form with questions about the final medical diagnosis. If this was an ACS, they were asked to classify it in (i) ST-elevation myocardial infarction (STEMI), (ii) non-STEMI, or (iii) unstable angina pectoris (UAP), based on the discharge letter of the hospital admission related to the OHS contact.

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Data analysis

Data were stratified by sex. Continuous variables were expressed as mean (standard deviation), and the duration of the telephone calls as mean (standard deviation). Categorical variables were expressed as numbers (percentage). Differences between sexes were assessed with the Student's t-test or Mann-Whitney U test for continuous variables, and the Chi-square test or Fisher's exact test for categorical variables. The five urgency levels were dichotomized in high urgency (U1-2) and low urgency (U3-5) before analysis. We analysed differences in characteristics between participants and patients in whom the medical diagnosis could not be retrieved, to exclude selection bias (Appendix, Table 3). We used multivariable logistic regression analysis with urgency allocation (high vs. low) as the outcome to assess differences between women and men with chest discomfort, after adjustment for the diagnosis ACS and age. Results were expressed as odds ratios (OR) with a 95% confidence interval (CI). The retrieved medical diagnoses were categorized. We combined rhythm disorders, heart failure, pericarditis, symptoms related to very high blood pressure, and stable angina pectoris in "other cardiovascular diseases". All data analyses were performed with IBM SPSS version 25.0 for Windows.

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RESULTS

A flowchart of the study population is presented in Figure 1. In 518 patients, the medical diagnosis could be retrieved; there were 242 men (46.7%) and 276 women (53.3%) of whom 22 (8.4%) women and 34 (14.0%) men had an ACS. There were no differences in sex, age, duration of the telephone calls, and urgency allocation between participants and patients in whom the medical diagnosis could not be retrieved.

An overview of the baseline characteristics and symptoms of the participants is given in Table 1. In women with an ACS compared to those without an ACS, the duration of the telephone calls was less long (5.22 (SD 2.53) vs. 7.26 (SD 3.11) minutes, p-value=0.003). In men this difference was non-significant (6.27 (SD 2.59) vs. 7.22 (SD 2.51) minutes, p-value=0.087). In both sexes, patients with ACS experienced a pressing chest pain more often than those without ACS. A stabbing pain was less frequent in men with ACS than in those without ACS; 3.7% vs. 24.0%, p-value=0.014. None of the women and men with ACS experienced right-sided chest pain. Men with ACS more often expressed radiation of pain than patients without ACS (men 89.3% vs. 64.9%, p-value=0.011). Shortness of breath, nausea/vomiting and sweating were similarly distributed among those with and without ACS.

Triage

Both women and men with chest discomfort received most often a high urgency allocation (U1, U2) (women 65.6% vs. men 64.9%). Also in those with an ACS, women and men received as often a high urgency allocation (95.7% vs. 88.2%, p-value=0.331). See Table 2. Urgency allocation between women and men remained the same after adjustment for ACS and age (crude OR 1.03 (95%CI 0.72-1.48) and adjusted OR 1.04 (95%CI 0.72-1.52), see Table 3.

Medical diagnosis

Men more often had an ACS than women (14.0% vs. 8.4%, p-value=0.038). Of those patients with an ACS, women relatively more often had a NSTEMI than men. Musculoskeletal pain was the most common diagnosis in both sexes (35.9% vs. 40.5%). All other diagnoses were equally distributed among men and women. See Table 4.

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DISCUSSION

In both women and men it is very difficult to differentiate those with ACS from those without in patients with chest discomfort who contact the primary care OHS. In men, stabbing chest pain was significantly more often present in non-ACS patients (2.9% vs. 21.1%, p-value=0.014), while radiation of pain was significantly more often mentioned by men with ACS (73.5% vs. 47.1%, p-value-0.011). 'Classical' symptoms of ACS (oppressing chest pain, with radiation and sweating) were more common in both women and men with ACS as compared to women and men without ACS. Women were not under-triaged, and those with ACS received at least as high urgency allocations as men. Interestingly, women with an ACS had significant shorter telephone call duration than women without an ACS (5.22 vs. 7.26 minutes, p-value=0.003), while in men this difference was smaller and not significant (6.27 vs. 7.22 minutes, p-value=0.087), suggesting that triage nurses were able to recognize an ACS earlier in women than in men. We were unable to adequately assess the predictive value of symptoms in women and men separately with multivariable logistic regression analysis, because of a limited number of events; (23 (8.3%) women and 34 (14.0%) men had an ACS).

Our study has several strengths. Firstly, we had the opportunity to evaluate the very initial symptom presentation of women and men with chest discomfort. This is important, since the presentation may change over time when multiple health care workers repeatedly ask comparable questions. Secondly, by replaying the telephone calls we were not hampered by recall bias of patients. Thirdly, we used data from a primary care OHS that provides out of hours primary care services during 73% of the week-hours for 270,000 people, including rural and city areas, making the study population a good representation of everyday patients seen in primary care.

A limitation of the study was that we were not able to retrieve the medical diagnosis in all 832, but only in 518 (62.3%) patients. This was because some GPs did not provide follow-up data, mainly because they were afraid of violation the privacy of the patient. Selection bias is, however, unlikely because the missing medical diagnoses were not patient driven. Moreover, comparison of the 518 participants with follow-up data and the 314 without a final diagnosis did not show significant differences in important determinants such as age, sex, duration of telephone calls, symptoms and urgency allocation. A second limitation is that we could not present data of patients who immediately

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called an ambulance or went on their own to an emergency department, which is around 20% of those experiencing chest discomfort in the Netherlands.(1) A third limitation was missing data on some determinants, which is rather common in an observational study with real life data. Fourth, a relatively low number of symptoms could univariably be analysed because the Netherlands Triage Standard restricts the number of questions to patients with the aim not to lose too much time with the telephone triage. Fifth, missing values on symptoms prevented us from full multivariable analysis with urgency allocation (high vs. low) as the outcome, and the low number of ACS cases let us decide to refrain from multivariable logistic regression analysis considering symptoms and with ACS (yes/no) as the outcome ACS. Moreover, the low number of patients with ACS did lead to large confidence intervals of ORs in the logistic regression analysis. Finally, we do not know whether men and women differ in patient's delay, as we did not assess the durations of symptoms until calling the PC-OHS.

To the best of our knowledge, this is the first study that included the medical diagnosis in the evaluation of triage of patients with chest discomfort who contacted primary care. One Norwegian study showed that 50% of patients who contacted the primary care OHS for chest pain were referred to the hospital, however a final medical diagnosis was lacking. (15) Another study from the Netherlands assessed gender differences in the symptom presentation of patients suspected of an ACS in primary care (from both day care and out-of hours) found no relevant differences between sexes regarding chest pain and autonomic nervous system-associated symptoms, but information on other symptoms or urgency allocation is lacking. (16) They did find, however, a significant longer doctor delay in women than in men with chest discomfort: 45 minutes vs. 33 minutes (p-value=0.01). (16) Our results on the prevalence of ACS in women (8.3%) and men (14.0%) is in line with a previous study performed in German primary care reporting a prevalence of 14% in women and 17% in men in those with acute chest pain. (17)

Multiple previous studies compared symptoms of women and men with ACS, and only one single study compared symptoms similarly as we did; comparing women with and without ACS, and men with and without ACS. In this study, executed among 736 patients seen in four emergency departments, the authors concluded that there were more similarities than differences in symptom predictors of ACS for women and men. (18) As said, most studies performed at the emergency

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department compared men and women with ACS, and concluded that women were more likely to present with dyspnoea instead of chest pain, and with atypical symptoms (e.g. nausea/vomiting, indigestion and palpitations) compared to men.(19,20) This is different to our results, showing no clear difference in symptoms between women and men with ACS. But even more importantly, from the practicing clinician point of view it is not relevant to know if women and men with ACS differ from each other in symptom presentation, the clinician wants to know which symptoms or other patient characteristics help to differentiate (i) women with ACS from women without, and (ii) men with ACS from men without. This is even more relevant for primary care, where the GP needs to decide whom to refer and with what urgency, all based on clinical items and very limited access to timely electrocardiography and results of high-sensitive troponin.

Conclusion

Discriminating patients with ACS from those without in patients with chest discomfort who contacted primary care OHS seems equally difficult for women as in men. Women and men with chest discomfort received similar high urgency allocation.

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Patient consent for publication: Not required.

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FIGURES

Figure 1: Flowchart of the study population

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TABLES

Table 1: Baseline characteristics of 276 women and 242 men with and without ACS contacting the primary care OHS for chest discomfort

	Women (n=276)			Men (n=242)		
	ACS	No ACS	P-value	ACS	No ACS	P-value
	n = 23 (8.3%)	n = 253 (91.7%)		n=34 (14.0%)	n=208 (86.0%)	
Mean duration of call, minutes (SD)	5.22 (2.53)	7.26 (3.11)	**0.003**	6.27 (2.59)	7.22 (2.51)	0.087
Mean age in years (SD)	66.8 (18.0)	62.8 (15.9)	0.309	68.1 (14.2)	58.8 (16.1)	0.224
History of CVD (n=210)	15 (71.4%)	94 (50.3%)	0.066	21 (65.6%)	80 (50.3%)	0.113
Chest pain (n=455)	22 (95.7%)	215 (87.0%)	0.228	34 (100%)	184 (91.1%)	0.070
Type of chest pain:						
Pressing (n=249)	15 (78.9%)	131 (58.7%)	0.084	18 (64.3%)	85 (46.4%)	0.079
Stabbing (n=90)	3 (15.8%)	42 (18.8%)	0.743	1 (3.7%)	44 (24.0%)	**0.014**
Pain location:						
Left side of the chest (n=107)	4 (36.4%)	44 (23.8%)	0.346	7 (46.7%)	52 (33.1%)	0.291
Right side of the chest (n=32)	0 (0%)	13 (7.0%)	0.363	0 (0%)	19 (12.1%)	0.153
Mid-sternal (n=143)	7 (63.6%)	78 (42.2%)	0.163	7 (46.7%)	51 (32.5%)	0.267
Radiation of the pain to:						
Arm (n=154)	9 (60.0%)	78 (42.4%)	0.186	17 (63.0%)	50 (33.3%)	**0.003**

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Back or shoulder (n=124)	8 (66.7%)	73 (51.8%)	0.321	6 (46.2%)	37 (37.0%)	0.523
Jaw (n=44)	2 (18.2%)	25 (17.6%)	0.961	5 (29.4%)	12 (10.7%)	**0.034**
Any radiation (n=295)	18 (90.0%)	154 (78.6%)	0.227	25 (89.3%)	98 (64.9%)	**0.011**
Additional symptoms:						
Dyspnoea (n=219)	9 (69.2%)	110 (63.2%)	0.664	10 (47.6%)	90 (61.6%)	0.220
Nausea or vomiting (n=141)	5 (45.5%)	75 (39.5%)	0.694	11 (42.3%)	50 (35.2%)	0.489
Sweating (n=166)	10 (52.6%)	72 (35.5%)	0.138	17 (60.7%)	67 (43.5%)	0.093

CVD = cardiovascular disease; (n=): number of patients

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Table 2: Urgency allocation in women and men with chest discomfort, and selectively in those with ACS

	High urgency (n= 338)	Low urgency (n=180)	OR (95%CI)	P-value
All patients with chest discomfort (n=518)				
Women (%)	181 (65.6%)	95 (34.4%)	1.03 (0.72-1.48)	0.867
Men (%)	157 (64.3%)	85 (35.1%)		
Patients with ACS diagnosis (n=57)	**High urgency (n=52)**	**Low urgency (n=5)**		
Women (%)	22 (95.7%)	1 (4.3)	2.93 (0.31-28.09)	0.331
Men (%)	30 (88.2%)	4 (11.8)		

High urgency: U1 or U2; Low urgency: U3 or U4 or U5; CI: confidence interval; OR: odds ratio

Table 3: Crude and adjusted odds ratios of women versus men for urgency allocation in 518 persons with chest discomfort

	High vs. low urgency Crude OR (95%CI)
Women vs. men	1.03 (0.72-1.48)
ACS vs. no ACS	6.36 (2.49-16.24)
Age per year	1.02 (1.01-1.03)
	High vs. low urgency Adjusted OR (95%CI)
Women vs. men adjusted for ACS	1.11 (0.77-1.61)
Women vs. men adjusted for ACS and age	1.04 (0.72-1.52)

High urgency: U1 or U2, low urgency: U3 or U4 or U5, CI: confidence interval; OR: odds ratio

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Table 4: Diagnosis of 518 patients who contacted the OHS for chest discomfort, divided in women and men

	Women n= 276 (%)	Men n= 242 (%)	p-value
Acute coronary syndrome	23 (8.4%)	34 (14.0%)	**0.038**
UAP	*8 (34.8%)*	*12 (35.3)*	
NSTEMI	*10 (43.5%)*	*7 (20.6%)*	
STEMI	*3 (13.0%)*	*6 (17.6%)*	
*Non-classified myocardial infarction**	*2 (8.7%)*	*9 (26.5%)*	
Other cardiovascular diseases**	35 (12.7%)	30 (12.4%)	0.922
Gastrointestinal tract disorders	38 (13.8%)	23 (9.5%)	0.133
Respiratory tract disorders	37 (13.4%)	34 (14.0%)	0.832
Psychogenic disorders	25 (9.1%)	12 (5.0%)	0.071
Non-specific chest pain including musculoskeletal pain	99 (35.9%)	98 (40.5%)	0.279
Other diagnoses	19 (6.9%)	11 (4.5%)	0.256

*UAP: unstable angina pectoris; NSTEMI: Non-ST-elevation myocardial infarction; STEMI: ST-elevation myocardial infarction; * No further information whether it was a STEMI or NSTEMI; ** Including rhythm disorders, heart failure, pericarditis, symptoms related to very high blood pressure, and stable angina pectoris*

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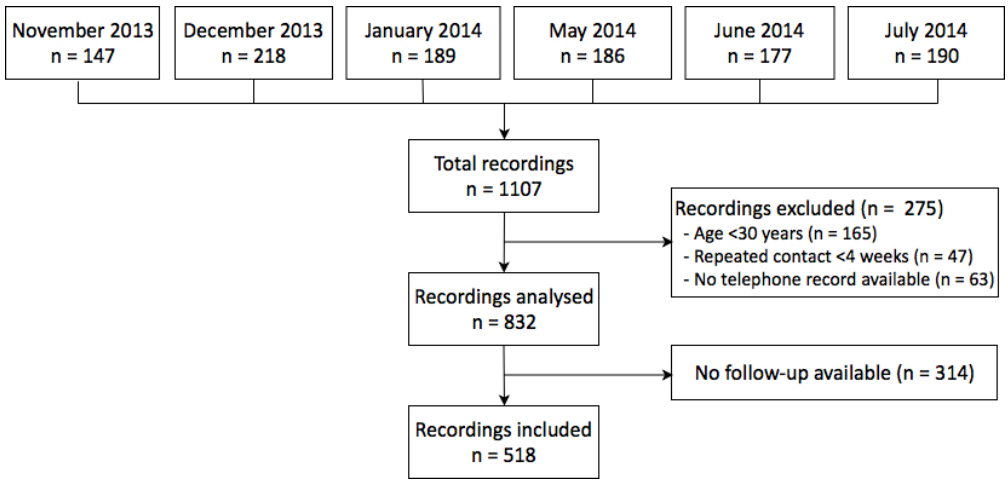

Figure 1: Flowchart of the study population

APPENDIX

Appendix-Table 1: Urgency levels

Urgency level	Implication
U0	Reanimation
U1	Life-threatening, GP/ ambulance should arrive within 15 minutes
U2	Emergency, GP should arrive within 60 minutes
U3	Urgent, consultation by GP within three hours
U4	Routine, consultation by GP the same day
U5	Advise given by triage nurse

U: urgency; GP: general practitioner

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Appendix-Table 2: Items that were registered on a case record form

Duration of the telephone call	Dyspnoea or chest tightness
Was the conversation with the patient or a relative?	Fever, cough or having a cold
Presence of chest pain	Smoking status
Type of pain	History of diabetes mellitus
Location of the chest pain	History of hypertension
Intensity of the pain (score between 0 and 10)	History of hypercholesterolemia
Radiation of the pain	History of cardiovascular disease
Symptoms during rest or during exercise	Complaints similar to previous episodes of cardiac disease
Duration of the symptoms	Family history of cardiovascular disease
Similar symptoms in the last 4 weeks	Family history of sudden cardiac death below the age of 60 years
Nausea or vomiting	Life-threatening disease suspected
Sweating	

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Appendix-Table 3: Participants compared to patients with chest discomfort without a final diagnosis retrieved from the general practitioners

	Participants (n=518)	Non-participants (n=314)	P-value
Duration of call, minutes	7:15	7:19	0.750
Female sex	276 (53.3%)	161 (51.3%)	0.574
Mean age in years (SD)	61.7 (17.1)	61.4 (17.6)	0.769
History of CVD	210 (52.6%)	126 (54.5%)	0.643
Chest pain	455 (89.9%)	281 (90.9%)	0.634
Radiation of chest pain	295 (74.7%)	171 (70.7%)	0.266
Dyspnoea	219 (61.9%)	138 (60.5%)	0.746
Nausea/vomiting	141 (38.3%)	83 (40.3%)	0.624
Sweating	166 (41.1%)	86 (35.0%)	0.120
High urgency allocation (U1-2)	338 (65.3%)	206 (65.6%)	0.917

CVD = cardiovascular disease; (n=): number of patients; U = urgency

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract page 1-2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found page 2
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported page 4
Objectives	3	State specific objectives, including any prespecified hypotheses page 4
Methods		
Study design	4	Present key elements of study design early in the paper page 5-6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection page 5-6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up page 5-7
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed -
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable page 6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group page 6
Bias	9	Describe any efforts to address potential sources of bias page 7
Study size	10	Explain how the study size was arrived at page 5-6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why page 6-7
Statistical methods page 6-7	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses

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Results page 8-9		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed page 8 and flow-chart (Figure 1)
		(b) Give reasons for non-participation at each stage page 8
		(c) Consider use of a flow diagram Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders page 8, Table 1
		(b) Indicate number of participants with missing data for each variable of interest Table 1
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount) -
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time page 8-9, Table 2
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included page 8-9
		(*b*) Report category boundaries when continuous variables were categorized -
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period -
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses -
Discussion		
Key results	18	Summarise key results with reference to study objectives page 10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias page 10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence page 11
Generalisability	21	Discuss the generalisability (external validity) of the study results page 11
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based. No funding was used. We added this to the article on page 13.

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Are there gender disparities in symptom presentation or triage of patients with chest discomfort at primary care out-of-hours services? An observational study

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Keywords:	gender, primary care out-of-hours service, chest pain, acute coronary syndrome, triage

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Are there gender disparities in symptom presentation or triage of patients with chest discomfort at primary care out-of-hours services? An observational study

Manon G. van der Meer[1], Yolande Appelman[2], Karlijn H.G. Rutten[3], Yolanda van der Graaf[3], Hendrik M. Nathoe[1], Pieter A. Doevendans[1], Michelle Smit[3], Emmy Verheij[3], Anne Botermans[3], Frans H. Rutten[3]

[1] Department of Cardiology, University Medical Center Utrecht, Utrecht University, the Netherlands

[2] Department of Cardiology, Amsterdam Medical Center, VU University, the Netherlands

[3] Department of General Practice, Julius Center for Health Sciences and Primary Care, University Medical Center, Utrecht University, the Netherlands

Corresponding author:

Frans H. Rutten, MD, PhD

Prof. General practice

Department of General Practice, Julius Center for Health Sciences and Primary Care

University Medical Center Utrecht, Utrecht University

HP STR 6.131, PO Box 85500, 3508 GA Utrecht

The Netherlands

Phone number: +31 (0)88 75 680 51

Email: f.h.rutten@umcutrecht.nl

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ABSTRACT

Objectives: Previous hospital-based studies have suggested delayed recognition of acute coronary syndrome (ACS) in women. We wanted to assess differences in symptom presentation or triage among women and men who contacted primary care out-of-hours services (OHS) for chest discomfort.

Design: Retrospective observational study.

Setting: Primary care OHS.

Participants: 276 women and 242 men with chest discomfort who contacted a primary care OHS in the Netherlands in 2013 and 2014.

Main outcome measures: Differences between women and men regarding symptom presentation and urgency allocation.

Results: 8.4% women and 14.0% men had ACS. Differences in symptoms between patients with and without ACS were in general small, for both women and men. In women with ACS compared to women without ACS, mean duration of telephone calls was discriminative; 5.22 (SD 2.53) versus 7.26 (SD 3.11) minutes, p-value=0.003. In men radiation of pain (89.3% vs. 54.9%, p-value=0.011) was discriminative for ACS, and stabbing chest pain (3.7% vs. 24.0%, p-value=0.014) for absence of ACS . Women and men with chest discomfort received similar high urgency allocation (crude and adjusted odds ratio after correction for ACS and age; 1.03 (95%CI 0.72-1.48) and 1.04 (95%CI 0.72-1.52), respectively). Women with ACS received a high urgency allocation in 22/23 (95.7%) and men with ACS in 30/34 (88.2%), p-value=0.331.

Conclusions: Discriminating ACS in patients with chest discomfort who contacted primary care OHS is difficult in both women and men. Women and men with chest discomfort received similar high urgency allocation.

Keywords: gender, primary care out-of-hours service, chest pain, acute coronary syndrome, triage.

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STRENGHTS AND LIMITATIONS OF THIS STUDY

- We could evaluate the initial symptom presentation of women and men with chest discomfort before knowledge of the eventual diagnosis, thus without hindsight bias.
- We assessed routine care data and thus could analyse only a restricted number of determinants.
- 37.7% of cases could not be included as participants, since we did not receive information from the patients' GP to make a diagnosis. This did not seem to bias our results because patient characteristics were similar between participants and non-participants.
- Only a small number of patients with chest discomfort actually had an ACS, therefore, no firm conclusions on disparities on symptom presentation between women and men can be made.
- Relative small numbers and missing data prevented us from full multivariable logistic regression analysis.

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INTRODUCTION

In the Netherlands, patients in general first present to primary care and the general practitioner (GP) decides as a 'gatekeeper' who should be sent to a hospital for further analysis. Chest discomfort, however, is an exception with 80% first contacting the GP and 20% directly calling the ambulance or appearing as self-referrals.(1) Chest discomfort is a common reason for contacting primary care and around 10-15% has an underlying cardiac cause, most often coronary artery disease (CAD), including an acute coronary syndrome (ACS).(1–3) Timely diagnosis of an ACS is of utmost importance, because early medical and interventional treatment can save myocardium ("time is muscle") and lives.(4) Previous hospital-based studies described a delayed recognition of ACS in women compared to men. (5–8) This delayed recognition of ACS in women has been related to an atypical presentation in women. (9–11) Previous studies also identified that management of chest discomfort by physicians may be influenced by gender of the patient caused by an underestimation of the risk of CAD in women. (12,13) However, this information is selectively retrieved in those with an established ACS diagnosis and seen at the emergency department for chest pain. Importantly, however, during the diagnostic assessment the clinician is interested in patient characteristics that help to discriminate women with ACS from women without, and similarly for men. Notably in primary care, where electrocardiography and fast results of high-sensitive troponin levels are lacking.

We assessed the triage of women and men presenting with chest discomfort to a primary care out-of-hours service (OHS) to answer the following question: are there gender disparities in symptom presentation or triage in patients presenting with chest discomfort to a primary OHS?.

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METHODS

Primary care out-of-hours services

In the Netherlands, primary care OHS covers primary care in 73% of the hours of the week. The first contact of a patient to a primary care OHS is by telephone and trained triage nurses who are supervised by a GP initially handle these calls. Most Dutch OHS use the "Netherlands Triage Standard" (NTS) to triage patients. The NTS started in November 2012 as a decision aid for triage nurses to classify the urgency of the complaint. Based on the initial symptom of the patient, the triage nurse chooses within the NTS system the most appropriate module among 56 NTS modules based on clinical symptoms, and "chest discomfort" is one of them. (14) Based on a decision tree with several hierarchically ordered questions (triage criteria), specified for each module, the NTS generates one out of five urgency levels (U1-U5, Appendix-Table 1). In case of a potential life-threatening situation (U1) an ambulance and/or the GP should arrive at the patient's location within 15 minutes. U2 means that the patient should be evaluated within 1 hour and in case of U3, the patient should be assessed within three hours. If considered not urgent, the patient should be seen the same day (U4), unless a telephone advice is sufficient (U5). The triage nurse, but also the GP on duty can overrule the assigned computer-based urgency if considered necessary.

The routing through each decision tree is the same for women and men. In the module "chest discomfort" (i) severe pain (≥7 on a scale from zero to 10), (ii) radiation of chest pain to arm or neck, (iii) experiencing accompanying shortness of breath, or (iv) symptoms related to activation of the sympathetic nervous system such as sweating, nausea/vomiting, pale face an/or (near) fainting will result in the highest urgency level (U1). The NTS has, however, never been formally validated by correlating the generated urgencies to clinical endpoints. (14)

Study population

This study was carried out in primary care OHS "de Gelderse Vallei" in Ede, the Netherlands. Since 2001, in total 120 GPs provide primary care to a population of around 270,000 people. For the current analysis we used consecutive back-up tapes of telephone contacts classified in the NTS as "chest discomfort" in the months November and December 2013, and January, May, June, and July 2014. We chose these two sets of three consecutive months to be able to neutralize seasonal effects. We

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excluded young adults below the age of 30, repeated contacts, contacts that could not be retrieved from the back-up system, and patients without definitive diagnosis.

The Ethical Committee of the University Medical Center Utrecht and the advisory board of General Practitioners Committee "De Gelderse Vallei" approved the study protocol. The study was carried out according tot the principles of the Declaration of Helsinki and de-identified patient data were used for analysis.

Patient and public involvement

Patients and the public were not involved in the design or planning of the study.

Data collection

Age, gender, date, time of the telephone contact, presented symptoms and the allocated urgency level were extracted from the electronic "call management system". In some instances, there was a link between the digital record of the GP of the patient and the OHS, and the medical history and drug use of the patient were available during the call. The original telephone calls were retrieved from "Freedom Call Manager", a back-up system containing all telephone calls with the primary care OHS. Research students replayed the telephone calls (MS, EV, AB) and scored them on a standardized case record form (Appendix, Table 2). With the case record form clinical items were registered, such as symptoms, pain characteristics, medical history, and the duration of the call. We used the real life telephone calls as source of data giving us the opportunity to evaluate the very initial, 'unbiased' presentation of the patients. As a consequence, we could only analyse information that was discussed during the telephone call.

Medical diagnosis

To retrieve the medical diagnosis related to the primary care OHS contact, we contacted the patient's own GP. They were asked to fill out a case record form with questions about the final medical diagnosis. If this was an ACS, they were asked to classify it in (i) ST-elevation myocardial infarction (STEMI), (ii) non-STEMI, or (iii) unstable angina pectoris (UAP), based on the discharge letter of the hospital admission related to the OHS contact.

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Data analysis

Data were stratified by sex. Continuous variables were expressed as mean (standard deviation), and the duration of the telephone calls as mean (standard deviation). Categorical variables were expressed as numbers (percentage). Differences between sexes were assessed with the Student's t-test or Mann-Whitney U test for continuous variables, and the Chi-square test or Fisher's exact test for categorical variables. The five urgency levels were dichotomized in high urgency (U1-2) and low urgency (U3-5) before analysis. We analysed differences in characteristics between participants and patients in whom the medical diagnosis could not be retrieved, to exclude selection bias (Appendix, Table 3). We used both univariable and multivariable logistic regression analysis with urgency allocation (high vs. low) as the outcome to assess differences between women and men with chest discomfort. For multivariable analysis, after adjustment for the diagnosis ACS and age. Results were expressed as odds ratios (OR) with a 95% confidence interval (CI). The retrieved medical diagnoses were categorized. We combined rhythm disorders, heart failure, pericarditis, symptoms related to very high blood pressure, and stable angina pectoris in "other cardiovascular diseases". All data analyses were performed with IBM SPSS version 25.0 for Windows.

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RESULTS

A flowchart of the study population is presented in Figure 1. In 518 patients, the medical diagnosis could be retrieved; there were 242 men (46.7%) and 276 women (53.3%) of whom 22 (8.4%) women and 34 (14.0%) men had an ACS. There were no differences in sex, age, duration of the telephone calls, and urgency allocation between participants and patients in whom the medical diagnosis could not be retrieved.

An overview of the baseline characteristics and symptoms of the participants is given in Table 1. In women with an ACS compared to those without an ACS, the duration of the telephone calls was less long (5.22 (SD 2.53) vs. 7.26 (SD 3.11) minutes, p-value=0.003). In men this difference was non-significant (6.27 (SD 2.59) vs. 7.22 (SD 2.51) minutes, p-value=0.087). In both sexes, patients with ACS experienced a pressing chest pain more often than those without ACS. A stabbing pain was less frequent in men with ACS than in those without ACS; 3.7% vs. 24.0%, p-value=0.014. None of the women and men with ACS experienced right-sided chest pain. Men with ACS more often expressed radiation of pain than patients without ACS (men 89.3% vs. 64.9%, p-value=0.011). Shortness of breath, nausea/vomiting and sweating were similarly distributed among those with and without ACS.

Triage

Both women and men with chest discomfort received most often a high urgency allocation (U1, U2) (women 65.6% vs. men 64.9%). Also in those with an ACS, women and men received as often a high urgency allocation (95.7% vs. 88.2%, p-value=0.331). See Table 2. Men and women with ACS received more often a high urgency allocation than those who showed not to have an ACS (crude OR 6.36, 95%CI 2.49-16.24). Urgency allocation between women and men remained the same after adjustment for ACS and age (crude OR 1.03 (95%CI 0.72-1.48) and adjusted OR 1.04 (95%CI 0.72-1.52), see Table 3.

Medical diagnosis

Men more often had an ACS than women (14.0% vs. 8.4%, p-value=0.038). The distribution of unstable angina, NSTEMI, STEMI and 'non-classified myocardial infarction' are presented in Table 4. Men had more often 'non-classified myocardial infarction' (26.5% vs. 8.9%). Musculoskeletal pain was

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the most common diagnosis in both sexes (35.9% vs. 40.5%). All other diagnoses were equally distributed among men and women. See Table 4.

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DISCUSSION

In both women and men it is very difficult to differentiate those with ACS from those without in patients with chest discomfort who contact the primary care OHS. In men, stabbing chest pain was significantly more often present in non-ACS patients (2.9% vs. 21.1%, p-value=0.014), while radiation of pain was significantly more often mentioned by men with ACS (73.5% vs. 47.1%, p-value-0.011). 'Classical' symptoms of ACS (oppressing chest pain, with radiation and sweating) were more common in both women and men with ACS as compared to women and men without ACS. Women were not under-triaged, and those with ACS received at least as high urgency allocations as men. Interestingly, women with an ACS had significant shorter telephone call duration than women without an ACS (5.22 vs. 7.26 minutes, p-value=0.003), while in men this difference was smaller and not significant (6.27 vs. 7.22 minutes, p-value=0.087), suggesting that triage nurses were able to recognize an ACS earlier in women than in men. We were unable to adequately assess the predictive value of symptoms in women and men separately with multivariable logistic regression analysis, because of a limited number of events; (23 (8.3%) women and 34 (14.0%) men had an ACS).

To the best of our knowledge, this is the first study that included the medical diagnosis in the evaluation of triage of patients with chest discomfort who contacted primary care. One Norwegian study showed that 50% of patients who contacted the primary care OHS for chest pain were referred to the hospital, however a final medical diagnosis was lacking. (15) Another study from the Netherlands assessed gender differences in the symptom presentation of patients suspected of an ACS in primary care (from both day care and out-of hours) found no relevant differences between sexes regarding chest pain and autonomic nervous system-associated symptoms, but information on other symptoms or urgency allocation is lacking. (16) They did find, however, a significant longer doctor delay in women than in men with chest discomfort: 45 minutes vs. 33 minutes (p-value=0.01). (16) Our results on the prevalence of ACS in women (8.3%) and men (14.0%) is in line with a previous study performed in German primary care reporting a prevalence of 14% in women and 17% in men in those with acute chest pain. (17)

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Multiple previous studies compared symptoms of women and men with ACS, and only one single study compared symptoms similarly as we did; comparing women with and without ACS, and men with and without ACS. In this study, executed among 736 patients seen in four emergency departments, the authors concluded that there were more similarities than differences in symptom predictors of ACS for women and men. (18) As said, most studies performed at the emergency department compared men and women with ACS, and concluded that women were more likely to present with dyspnoea instead of chest pain, and with atypical symptoms (e.g. nausea/vomiting, indigestion and palpitations) compared to men.(19,20) This is different to our results, showing no clear difference in symptoms between women and men with ACS. But even more importantly, from the practicing clinician point of view it is not relevant to know if women and men with ACS differ from each other in symptom presentation, the clinician wants to know which symptoms or other patient characteristics help to differentiate (i) women with ACS from women without, and (ii) men with ACS from men without. This is even more relevant for primary care, where the GP needs to decide whom to refer and with what urgency, all based on clinical items and very limited access to timely electrocardiography and results of high-sensitive troponin.

Our study has several strengths. Firstly, we had the opportunity to evaluate the very initial symptom presentation of women and men with chest discomfort. This is important, since the presentation may change over time when multiple health care workers repeatedly ask comparable questions. Secondly, by replaying the telephone calls we were not hampered by recall bias of patients. Thirdly, we used data from a primary care OHS that provides out of hours primary care services during 73% of the week-hours for 270,000 people, including rural and city areas, making the study population a good representation of everyday patients seen in primary care.

A limitation of the study was that we were not able to retrieve the medical diagnosis in all 832, but only in 518 (62.3%) patients. This was because some GPs did not provide follow-up data, mainly because they were afraid of violation the privacy of the patient. Selection bias is, however, unlikely because the missing medical diagnoses were not patient driven. Moreover, comparison of the

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518 participants with follow-up data and the 314 without a final diagnosis did not show significant differences in important determinants such as age, sex, duration of telephone calls, symptoms and urgency allocation. A second limitation is that we could not present data of patients who immediately called an ambulance or went on their own to an emergency department, which is around 20% of those experiencing chest discomfort in the Netherlands.(1) A third limitation was missing data on some determinants, which is rather common in an observational study with real life data. Fourth, a relatively low number of symptoms could univariably be analysed because the NTS restricts the number of questions to patients with the aim not to lose too much time with the telephone triage. Since this is not part of the NTS, risk factors for ischaemic heart disease and co morbidities could not be evaluated. Fifth, missing values on symptoms prevented us from full multivariable analysis with urgency allocation (high vs. low) as the outcome, and the low number of ACS cases let us decide to refrain from multivariable logistic regression analysis comparing symptoms with ACS (yes/no) as the outcome ACS. Moreover, the low number of patients with ACS did lead to large confidence intervals of ORs in the logistic regression analysis. Finally, we do not know whether men and women differ in patient's delay, as we did not assess the durations of symptoms until calling the PC-OHS.

Conclusion

Discriminating patients with ACS from those without in patients with chest discomfort who contacted primary care OHS seems equally difficult for women as in men. Women and men with chest discomfort received similar high urgency allocation.

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Data sharing statement: Data are housed at the University of Utrecht and requests for data analyses may be sent to Frans H. Rutten, the corresponding author.

Patient consent for publication: Not required.

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FIGURES

Figure 1: Flowchart of the study population

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TABLES

Table 1: Baseline characteristics of 276 women and 242 men with and without ACS contacting the primary care OHS for chest discomfort

	Women (n=276)			Men (n=242)		
	ACS	No ACS	P-value	ACS	No ACS	P-value
	n = 23 (8.3%)	n = 253 (91.7%)		n=34 (14.0%)	n=208 (86.0%)	
Mean duration of call, minutes (SD)	5.22 (2.53)	7.26 (3.11)	**0.003**	6.27 (2.59)	7.22 (2.51)	0.087
Mean age in years (SD)	66.8 (18.0)	62.8 (15.9)	0.309	68.1 (14.2)	58.8 (16.1)	0.224
History of CVD (n=210)	15 (71.4%)	94 (50.3%)	0.066	21 (65.6%)	80 (50.3%)	0.113
Chest pain (n=455)	22 (95.7%)	215 (87.0%)	0.228	34 (100%)	184 (91.1%)	0.070
Type of chest pain:						
Pressing (n=249)	15 (78.9%)	131 (58.7%)	0.084	18 (64.3%)	85 (46.4%)	0.079
Stabbing (n=90)	3 (15.8%)	42 (18.8%)	0.743	1 (3.7%)	44 (24.0%)	**0.014**
Pain location:						
Left side of the chest (n=107)	4 (36.4%)	44 (23.8%)	0.346	7 (46.7%)	52 (33.1%)	0.291
Right side of the chest (n=32)	0 (0%)	13 (7.0%)	0.363	0 (0%)	19 (12.1%)	0.153
Mid-sternal (n=143)	7 (63.6%)	78 (42.2%)	0.163	7 (46.7%)	51 (32.5%)	0.267
Radiation of the pain to:						
Arm (n=154)	9 (60.0%)	78 (42.4%)	0.186	17 (63.0%)	50 (33.3%)	**0.003**

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Back or shoulder (n=124)	8 (66.7%)	73 (51.8%)	0.321	6 (46.2%)	37 (37.0%)	0.523
Jaw (n=44)	2 (18.2%)	25 (17.6%)	0.961	5 (29.4%)	12 (10.7%)	**0.034**
Any radiation (n=295)	18 (90.0%)	154 (78.6%)	0.227	25 (89.3%)	98 (64.9%)	**0.011**
Additional symptoms:						
Dyspnoea (n=219)	9 (69.2%)	110 (63.2%)	0.664	10 (47.6%)	90 (61.6%)	0.220
Nausea or vomiting (n=141)	5 (45.5%)	75 (39.5%)	0.694	11 (42.3%)	50 (35.2%)	0.489
Sweating (n=166)	10 (52.6%)	72 (35.5%)	0.138	17 (60.7%)	67 (43.5%)	0.093

CVD = cardiovascular disease; (n=): number of patients

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Table 2: Urgency allocation in women and men with chest discomfort, and selectively in those with ACS

	High urgency (n= 338)	Low urgency (n=180)	OR (95%CI)	P-value
All patients with chest discomfort (n=518)				
Women (%)	181 (65.6%)	95 (34.4%)	1.03 (0.72-1.48)	0.867
Men (%)	157 (64.3%)	85 (35.1%)		
Patients with ACS diagnosis (n=57)	**High urgency (n=52)**	**Low urgency (n=5)**		
Women (%)	22 (95.7%)	1 (4.3)	2.93 (0.31-28.09)	0.331
Men (%)	30 (88.2%)	4 (11.8)		

High urgency: U1 or U2; Low urgency: U3 or U4 or U5; CI: confidence interval; OR: odds ratio

Table 3: Crude and adjusted odds ratios of women versus men for urgency allocation in 518 persons with chest discomfort

	High vs. low urgency Crude OR (95%CI)
Women vs. men	1.03 (0.72-1.48)
ACS vs. no ACS	6.36 (2.49-16.24)
Age per year	1.02 (1.01-1.03)
	High vs. low urgency Adjusted OR (95%CI)
Women vs. men adjusted for ACS	1.11 (0.77-1.61)
Women vs. men adjusted for ACS and age	1.04 (0.72-1.52)

High urgency: U1 or U2, low urgency: U3 or U4 or U5, CI: confidence interval; OR: odds ratio

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Table 4: Diagnosis of 518 patients who contacted the OHS for chest discomfort, divided in women and men

	Women n= 276 (%)	Men n= 242 (%)	p-value
Acute coronary syndrome	23 (8.4%)	34 (14.0%)	**0.038**
UAP	*8 (34.8%)*	*12 (35.3)*	
NSTEMI	*10 (43.5%)*	*7 (20.6%)*	
STEMI	*3 (13.0%)*	*6 (17.6%)*	
*Non-classified myocardial infarction**	*2 (8.7%)*	*9 (26.5%)*	
Other cardiovascular diseases**	35 (12.7%)	30 (12.4%)	0.922
Gastrointestinal tract disorders	38 (13.8%)	23 (9.5%)	0.133
Respiratory tract disorders	37 (13.4%)	34 (14.0%)	0.832
Psychogenic disorders	25 (9.1%)	12 (5.0%)	0.071
Non-specific chest pain including musculoskeletal pain	99 (35.9%)	98 (40.5%)	0.279
Other diagnoses	19 (6.9%)	11 (4.5%)	0.256

*UAP: unstable angina pectoris; NSTEMI: Non-ST-elevation myocardial infarction; STEMI: ST-elevation myocardial infarction; * No further information whether it was a STEMI or NSTEMI; ** Including rhythm disorders, heart failure, pericarditis, symptoms related to very high blood pressure, and stable angina pectoris*

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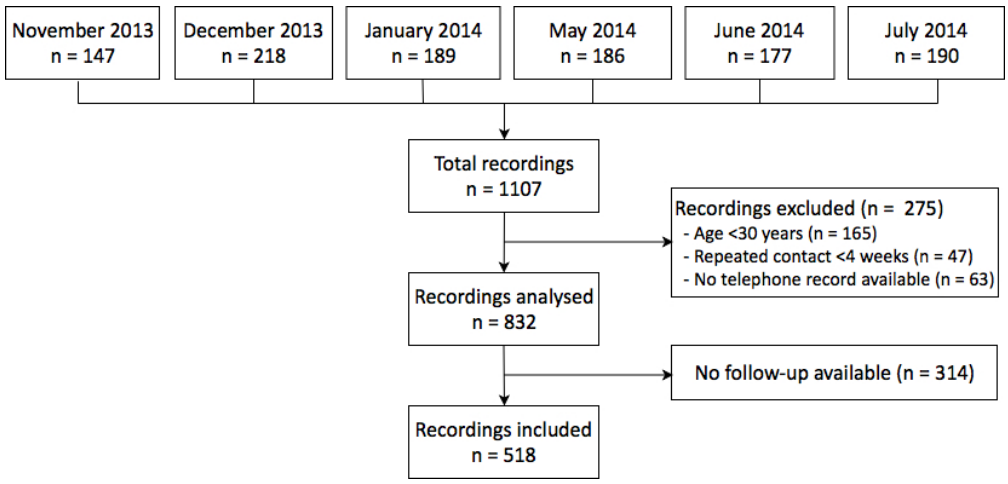

Figure 1: Flowchart of the study population

APPENDIX

Appendix-Table 1: Urgency levels

Urgency level	Implication
U0	Reanimation
U1	Life-threatening, GP/ ambulance should arrive within 15 minutes
U2	Emergency, GP should arrive within 60 minutes
U3	Urgent, consultation by GP within three hours
U4	Routine, consultation by GP the same day
U5	Advise given by triage nurse

U: urgency; GP: general practitioner

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Appendix-Table 2: Items that were registered on a case record form

Duration of the telephone call	Dyspnoea or chest tightness
Was the conversation with the patient or a relative?	Fever, cough or having a cold
Presence of chest pain	Smoking status
Type of pain	History of diabetes mellitus
Location of the chest pain	History of hypertension
Intensity of the pain (score between 0 and 10)	History of hypercholesterolemia
Radiation of the pain	History of cardiovascular disease
Symptoms during rest or during exercise	Complaints similar to previous episodes of cardiac disease
Duration of the symptoms	Family history of cardiovascular disease
Similar symptoms in the last 4 weeks	Family history of sudden cardiac death below the age of 60 years
Nausea or vomiting	Life-threatening disease suspected
Sweating	

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Appendix-Table 3: Participants compared to patients with chest discomfort without a final diagnosis retrieved from the general practitioners

	Participants (n=518)	Non-participants (n=314)	P-value
Duration of call, minutes	7:15	7:19	0.750
Female sex	276 (53.3%)	161 (51.3%)	0.574
Mean age in years (SD)	61.7 (17.1)	61.4 (17.6)	0.769
History of CVD	210 (52.6%)	126 (54.5%)	0.643
Chest pain	455 (89.9%)	281 (90.9%)	0.634
Radiation of chest pain	295 (74.7%)	171 (70.7%)	0.266
Dyspnoea	219 (61.9%)	138 (60.5%)	0.746
Nausea/vomiting	141 (38.3%)	83 (40.3%)	0.624
Sweating	166 (41.1%)	86 (35.0%)	0.120
High urgency allocation (U1-2)	338 (65.3%)	206 (65.6%)	0.917

CVD = cardiovascular disease; (n=): number of patients; U = urgency

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract page 1-2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found page 2
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported page 4
Objectives	3	State specific objectives, including any prespecified hypotheses page 4
Methods		
Study design	4	Present key elements of study design early in the paper page 5-6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection page 5-6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up page 5-7
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed -
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable page 6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group page 6
Bias	9	Describe any efforts to address potential sources of bias page 7
Study size	10	Explain how the study size was arrived at page 5-6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why page 6-7
Statistical methods page 6-7	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses

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Results page 8-9		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed page 8 and flow-chart (Figure 1)
		(b) Give reasons for non-participation at each stage page 8
		(c) Consider use of a flow diagram Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders page 8, Table 1
		(b) Indicate number of participants with missing data for each variable of interest Table 1
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount) -
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time page 8-9, Table 2
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included page 8-9
		(*b*) Report category boundaries when continuous variables were categorized -
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period -
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses -
Discussion		
Key results	18	Summarise key results with reference to study objectives page 10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias page 10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence page 11
Generalisability	21	Discuss the generalisability (external validity) of the study results page 11
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based. No funding was used. We added this to the article on page 13.

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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