



# BMJ Open Coronary artery disease prediction in women and men using chest pain characteristics and risk factors: an observational study in outpatient clinics

Floor Groepenhoff <sup>1</sup>, Anouk L M Eikendal,<sup>2</sup> N Charlotte Onland-Moret,<sup>2</sup> Sophie Heleen Bots <sup>3</sup>, Roxana Menken,<sup>4</sup> Igor I Tulevski,<sup>4</sup> Aernout G Somsen,<sup>4</sup> Leonard Hofstra,<sup>4</sup> Hester M den Ruijter<sup>3</sup>

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LH and HMdR contributed equally.

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For numbered affiliations see end of article.

## Correspondence to

Dr Hester M den Ruijter; [h.m.denRuijter-2@umcutrecht.nl](mailto:h.m.denRuijter-2@umcutrecht.nl)

## ABSTRACT

**Objectives** To assess the diagnostic value of non-acute chest pain characteristics for coronary artery disease in women and men referred to outpatient cardiology clinics.

**Design and setting** This is an observational study performed at outpatient cardiology centres of the Netherlands.

**Participants** The study population consisted of 1028 patients with non-acute chest pain (505 women).

**Analysis and results** Twenty-four women (5%) and 75 men (15%) were diagnosed with coronary artery disease by invasive coronary angiography or CT angiography during regular care follow-up. Elastic net regression was performed to assess which chest pain characteristics and risk factors were of diagnostic value. The overall model selected age, provocation by temperature or stress, relief at rest and functional class as determinants and was accurate in both sexes (area under the curve (AUC) of 0.76 (95% CI 0.68 to 0.85) in women and 0.83 (95% CI 0.78 to 0.88) in men). Both sex-specific models selected age, pressuring nature, radiation, duration, frequency, progress, provocation and relief at rest as determinants. The female model additionally selected dyspnoea, body mass index, hypertension and smoking while the male model additionally selected functional class and diabetes. The sex-specific models performed better than the overall model, but more so in women (AUC: 0.89, 95% CI 0.81 to 0.96) than in men (AUC: 0.84, 95% CI 0.73 to 0.90).

**Conclusions** In both sexes, the diagnostic value of non-acute chest pain characteristics and risk factors for coronary artery disease was high. Provocation, relief at rest and functional class of chest pain were the most powerful diagnostic predictors in both women and men. When stratified by sex the performance of the model improved, mostly in women.

## INTRODUCTION

Although women suffering from a myocardial infarction are reported to present with more atypical symptoms than men,<sup>1 2</sup> chest pain remains a major common symptom of coronary artery disease (CAD) in both women and men.<sup>3</sup> The relation between chest pain

## Strengths and limitations of this study

- The study is based on routine care data which enabled us to study a unique representative sample of patients presenting at outpatient cardiology clinics.
- The study had an almost equal number of women and men and could therefore study both sexes with equal power.
- Data were only available as part of routine clinical care and therefore not available for every patient presenting to the clinics with chest pain.

characteristics has been studied quite extensively in patients with acute chest pain,<sup>1–9</sup> yet not comprehensively in patients with non-acute chest pain presenting at outpatient clinics.

Currently, approximately 1% of all patients consulting the general practitioner have chest pain complaints as main reason for their visit.<sup>10</sup> However, only 8%–12% of these patients actually have ischaemic heart disease.<sup>10 11</sup> Forty percent of the patients with chest pain are referred to a cardiologist because of the fear of missing the potentially life-threatening diagnosis of CAD and because of difficulties in estimating the probability of CAD in those patients.<sup>12</sup> In the Netherlands, this results in over 250.000 patients evaluated by a cardiologist for stable angina each year.<sup>13</sup> Furthermore, additional (non-)invasive diagnostic tests are performed based on the cardiologists' estimation of the probability of CAD.<sup>14</sup> For structural evaluation of the coronary arteries, cardiac CT (calcium score with or without angiography) or invasive coronary angiography (CAG) is used. Interestingly, in patients undergoing CAG, no obstructive CAD is found twice as often in women as in men.<sup>15 16</sup> Additionally,



approximately 50% of cardiac CT investigations show a zero calcium score.<sup>17</sup>

The high prevalence of normal imaging results raises the question whether the presence of CAD could be estimated with more certainty to prevent unnecessary imaging. In addition, differences in outcome and clinical presentation between women and men may suggest this estimation should take sex-specific symptoms and risk factors into account. According to the European and Dutch guidelines, chest pain characteristics are an important part of the diagnostic work-up since these are considered helpful in estimating the probability of CAD.<sup>14 18</sup> However, their exact diagnostic value remains unclear.<sup>9 19</sup> Moreover, even though outpatient clinics evaluate the largest proportion of patients with chest pain, most information on diagnostic value of signs and symptoms is derived from hospitals. As such, little is known on the diagnostic value of chest pain characteristics for CAD in men and women with non-acute chest pain visiting outpatient cardiology clinics. Therefore, we evaluated the diagnostic value of non-acute chest pain characteristics in differentiating patients with CAD from patients with no CAD in women and men presenting to outpatient cardiology clinics.

## METHODS

### Study design and population

We retrospectively collected individual patient data records from Dutch outpatient cardiology clinics (Cardiology Centers of the Netherlands). Records contained baseline data from the electronic health records (CardioPortal, Cardiology Centers of the Netherlands proprietary electronic health records). The necessity for informed consent was waived because research within the Cardiology Centers of the Netherlands database does not fall under the Dutch Medical Research Involving Human Subjects Act.<sup>20</sup> Patients visited 1 of the 13 Cardiology Centers of the Netherlands locations between April 2007 and February 2018. We included data from patients referred by their general practitioner because of non-acute chest pain of whom chest pain characteristics were registered in a standardised way using a specified questionnaire. Standard cardiovascular work-up for patients with chest pain consisted of an intake by a nurse who collected information on cardiovascular risk factors (age, sex, history of smoking, history of cardiovascular disease, presence of diabetes mellitus, hypertension, dyslipidaemia, body mass index (BMI) and signs of heart failure) and ischaemia detection by exercise ECG, followed by evaluation by the cardiologist. All data were stored in a systematic manner. Patients were referred for cardiac CT angiography or invasive CAG only if the cardiologist estimated an intermediate or high probability of CAD.<sup>14</sup> If referred for CT, first a non-contrast enhanced cardiac CT was performed to quantify the Agatston coronary artery calcium score.<sup>21</sup> Additional CT angiography was only performed in case of

a positive calcium score. The results of these procedures were reported in the electronic health records.

### Chest pain characteristics

Data records comprising the cardiologist's documented detailed and standardised description of non-acute chest pain characteristics (n=1028) were retrieved from the electronic health records. These contained aspect, localisation, radiation, onset, duration, frequency, progress, provoking and relieving factors and attendant symptoms. The functional degree of chest pain was scored by the cardiologist using the New York Heart Association (NYHA) classification.<sup>22</sup> Based on prior studies, documented characteristics were reclassified into binary or categorical characteristics for analysis.<sup>18</sup> This resulted in categorical characteristics for nature, dynamics (radiation, onset, duration, frequency, progress), coexisting symptoms (vagal complaints and dyspnoea), provocation during exercise, emotional stress, cold or warmth and relief at rest.

### Definition of CAD

The diagnosis of CAD was based on available imaging reports or, if no imaging was performed, on the cardiologist's estimation of CAD. Patients not referred for imaging, because of an estimated low probability of CAD by the cardiologist after standard cardiovascular work-up, were considered to have no CAD. In patients referred for imaging, a significant stenosis (>50%) was considered to indicate CAD.<sup>23</sup> If the significance of a stenosis was not documented, a coronary artery calcium score above 160 was used as a surrogate marker for relevant CAD.<sup>21</sup> Of 238 patients referred for imaging, 28 (11.7%) were excluded from analysis due to missing imaging data.

### Statistical analysis

Baseline characteristics and chest pain characteristics were stratified by sex and presented as mean±SD for continuous variables and numbers (with %) for categorical variables. The presence or absence of any cardiovascular history (eg, previous CAD, cerebrovascular disease and cardiovascular intervention) was combined into one categorical variable for history of cardiovascular disease. Missing values for cardiovascular risk factors were complemented based on medication use if possible. Missing variables were imputed using the *hot.deck* function from the R package *hot.deck*.<sup>24</sup> Information of the number (percentage) of missing variables is listed in online supplementary appendix 1.

First, we tested which chest pain characteristics distinguished CAD from no CAD cases using a t-test for continuous variables and a  $\chi^2$  test for categorical variables. Second, to build the most optimal model to discriminate between CAD and no CAD, elastic net penalised logistic regression was performed. Elastic net was chosen as this is a dimensionality reduction method that can select important predictors in situations where there are a lot of predictors and a relatively modest number of events.<sup>25</sup> As

predictors, both cardiovascular risk factors and chest pain characteristics were included. In total, 18 possible predictors were included in the multivariable elastic net analysis: seven known cardiovascular risk factors (age, BMI, hypertension, dyslipidaemia, diabetes mellitus, smoking status, cardiovascular history) and 11 chest pain characteristics (pressuring nature, radiation, onset, duration, frequency, progress, provocation during stress or extreme temperature, relief at rest, accompanying complaints, dyspnoea, NYHA class). We built the elastic net model with R package *glmnet*<sup>26</sup> by using 66% of the data defined as training set and 33% as testing set (randomly selected). The optimal penalisation proportion  $\alpha$  was determined with 10-fold cross-validation. The tuning parameter  $\lambda$  was determined by choosing the largest  $\lambda$  one SD away from the  $\lambda$  resulting in the minimal deviance of the model (minimiser  $\lambda$ ). This tuning parameter would result in a sparse model. A sex-specific model for both women and men was fitted to evaluate possible sex differences in selected or relevance of variables as a subgroup analysis. Due to the decrease in power in the sex-specific elastic net regression, we determined the tuning parameter  $\lambda$  as the minimiser  $\lambda$  resulting in a less sparse model with which we minimised the deviance and were able to include more variables in the model.

Receiver operating characteristic curves were constructed and areas under the curve (AUC) were calculated to estimate the performance of the model for women and men separately using the R package *ROCR*.<sup>27</sup>  $P_{2\text{-sided}} < 0.05$  was considered statistically significant. All statistical analyses were performed using RStudio V.3.5.2 (www.r-project.org).<sup>28</sup> FG had full access to all the data in the study and took responsibility for the integrity of the data and the accuracy of the statistical analysis.

### Patient and public involvement

No patients were involved in the design of the study.

## RESULTS

### Baseline characteristics

Baseline characteristics of the study population are shown in table 1. The total study population comprised 1028 patients of which 505 (49%) were women. On average, women were 2 years older than men (58 years vs 56 years,  $p=0.009$ ). In women, a history of cardiovascular disease (8.3% in women vs 13.8% in men,  $p=0.007$ ) and antihypertensive medication use (66.1% vs 72.8%,  $p=0.04$ ) were less common than in men. The prevalence of all other cardiovascular risk factors was similar for women and men (table 1).

After their visit to the cardiology clinic, 238 patients (23% of all patients, 44% women) were referred for cardiac CT (angiography) or invasive CAG. Of these 238 referred patients, 99 were diagnosed with CAD (42% of all patients, 24% women) (figure 1). Detailed baseline characteristics of patients with CAD compared with

patients without CAD are listed in online supplementary appendix 2.

### Discriminating chest pain characteristics for CAD

Table 2 shows the prevalence of chest pain characteristics for women and men stratified by the presence of CAD. In both women and men daily occurring and short-lasting chest pain were more prevalent in the presence of CAD as compared with no CAD. In women with CAD, daily occurring chest pain was prevalent in 63% vs 33% without CAD ( $p=0.005$ ). Daily occurring chest pain was common in 51% of men with CAD versus 28% of men without CAD ( $p<0.001$ ). Women with CAD reported short-lasting chest pain in 96% as compared with 76% without CAD ( $p<0.05$ ). For short-lasting chest pain, the prevalence was 93% in men with CAD versus 72% of men with no CAD ( $p<0.001$ ). In addition, complaints were more often provoked by emotional or physical stress or extreme temperature and alleviated in rest in patients with CAD as compared with patients without CAD. Provocation was prevalent in women in 75% of CAD cases versus 42% of no CAD cases ( $p=0.003$ ), and in 88% of men with CAD as compared with 44% of men without CAD ( $p<0.001$ ). Relief of chest pain complaints at rest was common in 75% in women with CAD versus 39% in women without CAD ( $p=0.001$ ). In men, complaints alleviated at rest in 83% with CAD and in 37% of men without CAD ( $p<0.001$ ). The functional class of chest pain was higher in CAD than in no CAD cases in both women and men: NYHA class II or higher in 54% of women and 76% of men with CAD as compared with 30% of women ( $p=0.025$ ) and 23% of men ( $p<0.001$ ) without CAD. In men, but not in women, pressuring nature (96% vs 72%,  $p<0.01$ ), non-acute onset (51% vs 37%,  $p=0.04$ ) and progressive complaints (53% vs 22%,  $p<0.001$ ) accompanied by dyspnoea (20% vs 9%,  $p<0.01$ ) were discriminating CAD cases from those without CAD.

### Multivariable analysis by elastic net penalised regression

In our elastic net analysis including both women and men the optimal model retained 4 out of 18 predictors with non-zero coefficients ( $\alpha=0.68$ ;  $\lambda=1$  SD from the minimiser  $\lambda$ ); age, provocation during stress or extreme temperature, relief at rest and NYHA class. The model distinguished women and men with CAD from those without CAD with an AUC of 0.82 (95% CI 0.75 to 0.88). The AUC was 0.76 for women (95% CI 0.68 to 0.85) and 0.83 (95% CI 0.78 to 0.88) for men.

When we analysed women separately, there were no predictors in the model. Therefore, we decided to use  $\lambda$ =the minimiser  $\lambda$  for the sex-specific analyses. In men, 10 clinical symptoms and risk factors with non-zero coefficients were retained in the model ( $\alpha=0.70$ ,  $\lambda$ =the minimiser  $\lambda$ ; age, pressuring nature, radiation, duration, frequency, progress, provocation during stress or extreme temperature, relief at rest, NYHA class and diabetes mellitus). The model achieved an AUC of 0.84 (95% CI 0.73 to 0.90) in men (table 3). In women, this elastic net

**Table 1** Characteristics of study population presenting at the outpatient cardiology clinics with chest pain complaints

Demographic characteristics	Women	Men	P value	Total population
n	505	523		1028
Age (years), mean (SD)	58 (13)	56 (13)	0.009	57 (13)
Current cigarette smoking status, yes (%)	227 (48)	239 (48)	0.929	466 (48)
Diabetes mellitus, yes (%)	38 (8)	50 (10)	0.271	88 (9)
Hypertension, yes (%)	170 (34)	171 (33)	0.912	341 (33)
Dyslipidaemia, yes (%)	83 (17)	101 (20)	0.233	184 (18)
Cardiovascular history, yes (%)	42 (8)	72 (14)	0.007	114 (11)
Antihypertensive medication, yes (%)	289 (66)	300 (73)	0.042	589 (69)
Statin use, yes (%)	160 (37)	216 (52)	<0.001	376 (44)
<b>Anthropometric characteristics</b>				
BMI (kg/m <sup>2</sup> ), mean (SD)	26 (4.5)	26 (3.8)	0.005	26 (4.2)
SBP (mm Hg), mean (SD)	139 (21.3)	140 (18.5)	0.347	140 (20.0)
DBP (mm Hg), mean (SD)	83 (11.1)	83 (10.8)	0.536	83 (11.0)
<b>Chest pain-specific characteristics</b>				
Pressing nature, yes (%)	411 (81)	402 (77)	0.088	813 (79)
Radiation, yes (%)	223 (44)	175 (34)	0.001	398 (39)
Acute onset, yes (%)	298 (59)	309 (59)	1	607 (59)
Short duration, yes (%)	391 (77)	394 (75)	0.474	785 (76)
Daily frequency, yes (%)	173 (34)	169 (32)	0.552	342 (33)
Progressive complaints, yes (%)	141 (28)	147 (28)	1	288 (28)
Provocation of complaints by stress/ temperature, yes (%)	234 (46)	274 (52)	0.06	508 (49)
Relief at rest, yes (%)	214 (42)	243 (47)	0.209	457 (45)
Vegetative symptoms, yes (%)	81 (16)	62 (12)	0.065	143 (14)
Dyspnoea, yes (%)	78 (15)	61 (12)	0.093	139 (14)
NYHA class II or higher, yes (%)	166 (33)	171 (33)	1	337 (33)

BMI, body mass index; DBP, diastolic blood pressure; NYHA, New York Heart Association; SBP, systolic blood pressure.

regression resulted in a model with 12 clinical symptoms and risk factors with non-zero coefficients ( $\alpha=0.51$ ,  $\lambda$ =the minimiser  $\lambda$ ; age, pressing nature, radiation, duration, frequency, progress, provocation during stress or extreme temperature, relief at rest, dyspnoea, BMI, hypertension, smoking status). The model achieved an AUC of 0.89 (95% CI 0.81 to 0.96).

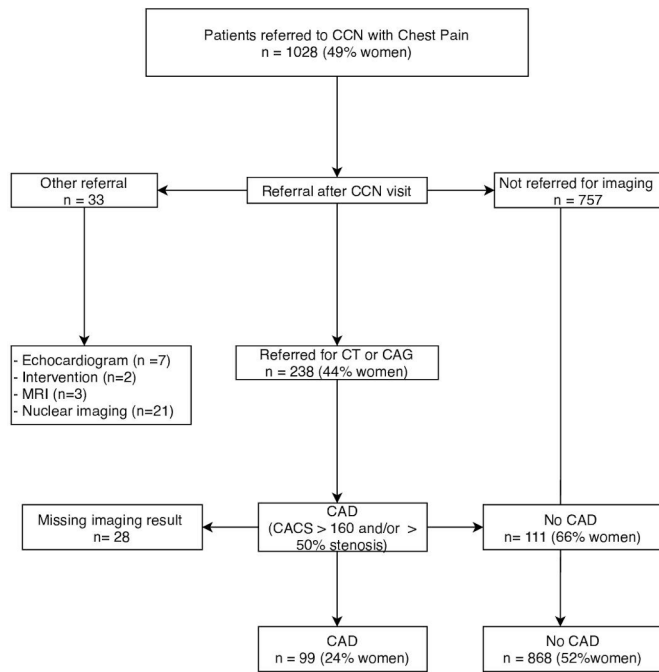
As described above, the overall model including both sexes achieved an AUC of 0.76 (95% CI 0.68 to 0.85) in women and 0.83 (95% CI 0.78 to 0.88) in men. Comparison of the performance of the overall model to that of the sex-specific models showed an improved performance in women (AUC 0.89, 95% CI 0.81 to 0.96) and only minimal improvement in men (AUC 0.83, 95% CI 0.73 to 0.90).

## DISCUSSION

This study shows that characteristics of non-acute chest pain are useful in identification of CAD in both women and men referred to outpatient cardiology clinics. In fact,

their diagnostic value appears to be reasonably high. Additionally, if presenting with non-acute chest pain, women and men with CAD present quite similar with regard to chest pain characteristics. However, small differences between women and men were observed with respect to the selected characteristics in the sex-specific models and their diagnostic performance. In women, dyspnoea, BMI, hypertension and smoking were stronger predictors of the presence of CAD as compared with men. In men, functional class and history of diabetes were more important than in women. The performance of chest pain characteristics in diagnosing CAD improved when stratified by sex. This improvement was mostly seen in women in whom a separate model might be more appropriate than a model using data derived from both sexes.

Our analysis is based on routine care data of patients presenting at the outpatient cardiology clinic undergoing extensive standardised cardiovascular work-up. This provided us with a unique representative sample of the general population who present to outpatient cardiology



**Figure 1** Flow chart study results. CACS, coronary artery calcium score; CAD, coronary artery disease; CAG, coronary angiography; CCN, Cardiology Centers of the Netherlands.

clinics with non-acute chest pain, without any selection bias that may occur in cohort studies in whom many patients may not participate due to their poor quality of life.<sup>29</sup> Second, our study contained an almost equal number of women and men, which enabled us to study both women and men with equal power.

In the primary care setting, Bösner *et al*<sup>19</sup> assessed sex differences in clinical characteristics of chest pain. The researchers observed some chest pain characteristics, for example, pain worsening with exercise, to be equally relevant for men and women. Yet, in women, prolonged

**Table 3** Sex-stratified elastic net results of clinical characteristics and chest pain-specific characteristics for CAD

	Women	Men
	Penalised coefficient	Penalised coefficient
Age	0.0208	0.0250
Pressuring nature	0.0336	0.5203
Radiation	-0.0452	0.0252
Duration	0.1245	0.1475
Frequency	0.0868	0.1364
Progressive complaints	0.1168	0.0226
Provocative complaints	0.2205	0.5002
Relief at rest	0.3624	0.5569
NYHA class		1.0619
History of diabetes		0.4927
Dyspnoea	0.0118	
BMI	-0.0169	
History of hypertension	0.0467	
Smoking status	-0.0708	
AUC (95% CI)	0.89 (0.81 to 0.96)	0.84 (0.73 to 0.90)

AUC, area under the curve; BMI, body mass index; CAD, coronary artery disease; NYHA, New York Heart Association.

duration of chest pain was positively associated with CAD, whereas in men shorter duration showed a positive association with CAD. These chest pain characteristics are different from those reported in our study, namely dyspnoea in women and functional class in men. This difference might be due to the dissimilarity in domain as the women and men presented at outpatient cardiology clinics were already referred by their general practitioner. In an additional study, the researchers observed

**Table 2** Relation between chest pain characteristics and CAD

	Women			Men		
	CAD (n=24)	No CAD (n=448)	P value	CAD (n=75)	No CAD (n=420)	P value
Pressing nature, yes (%)	22 (91.7)	361 (80.6)	0.278	72 (96.0)	303 (72.1)	<0.001
Radiation, yes (%)	8 (33.3)	198 (44.2)	0.404	32 (42.7)	129 (30.7)	0.057
Acute onset, yes (%)	13 (54.2)	270 (60.3)	0.704	37 (49.3)	264 (62.9)	0.037
Short duration, yes (%)	23 (95.8)	341 (76.1)	0.046	70 (93.3)	301 (71.7)	<0.001
Daily frequency, yes (%)	15 (62.5)	146 (32.6)	0.005	38 (50.7)	117 (27.9)	<0.001
Progressive, yes (%)	10 (41.7)	118 (26.3)	0.159	40 (53.3)	94 (22.4)	<0.001
Provocation, yes (%)	18 (75.0)	190 (42.4)	0.003	66 (88.0)	184 (43.8)	<0.001
Relief at rest, yes (%)	18 (75.0)	173 (38.6)	0.001	62 (82.7)	155 (36.9)	<0.001
Vegetative symptoms, yes (%)	2 (8.3)	71 (15.8)	0.483	7 (9.3)	51 (12.1)	0.616
Dyspnoea, yes (%)	6 (25.0)	66 (14.7)	0.284	15 (20.0)	39 (9.3)	0.011
NYHA class II or higher, yes (%)	13 (54.2)	135 (30.1)	0.025	57 (76.0)	97 (23.1)	<0.001

CAD, coronary artery disease; NYHA, New York Heart Association.



a combination of clinical characteristics and symptoms in patients presenting with chest pain to be helpful in diagnosing coronary heart disease.<sup>30</sup> Their results support the high diagnostic value of chest pain characteristics in differentiating patients with CAD from patients with no CAD that we observed in both sexes as well as the small sex differences in associated chest pain characteristics with CAD. This suggests that using a sex-stratified method may improve the diagnostic approach within these patients.

Several studies performed at the emergency department showed a similar high diagnostic value of clinical symptoms and cardiovascular risk factors for CAD in patients presenting with chest pain.<sup>6 7 9</sup> They showed women and men to present quite similar if presenting with chest pain.<sup>7</sup> Moreover, Ferry *et al*<sup>6</sup> reported that in patients diagnosed with myocardial infarction, typical symptoms were more prevalent and had a higher predictive value in women than in men. In line with our findings and the aforementioned findings in primary care, van der Meer *et al*<sup>8</sup> and Gimenez *et al*<sup>7</sup> also only found small sex differences in chest pain characteristics associated with CAD.

Interestingly, even though pressuring nature of chest pain is often seen as one of the most typical and suspect characteristics in the evaluation of chest pain, this characteristic was not retained in the overall elastic net model. This is similar to a previous report.<sup>9</sup> Although pressuring nature was differentiating between CAD and no CAD in both men and women in our univariable analysis, it shrunk to zero in our most optimal elastic net model. This could be a result of the correlation of pressuring nature with other chest pain characteristics retained in the model that had a stronger association with CAD, as the elastic net analysis is designed to create a model with a high diagnostic accuracy with fewest variables. Radiation was not significantly different between women and men with and without CAD in our univariable analyses, as was also shown in earlier research.<sup>30</sup>

Our study shows that chest pain characteristics have diagnostic value in women and men presenting with non-acute chest pain at outpatient cardiology clinics. Our results were comparable to the acute setting at the emergency department, and also to the primary care setting. This implies that these easy-to-obtain chest pain characteristics are equally predictive in high<sup>7 9</sup> as well as in low-risk<sup>19</sup> populations. These insights obtained from different clinical settings enable both the general practitioner and the cardiologist to improve the identification of women and men at risk for CAD. This knowledge, when brought to practice, may lower the currently rising costs of healthcare due to unnecessary cardiac work-up and imaging. Besides reducing healthcare costs, it may improve patient care since less imaging reduces the amount of radiation used and the burden of an unnecessary examination.

Within the outpatient clinics assessed in this study, CT or CAG is the preferred method for the evaluation of CAD. However, non-invasive stress imaging is also recommended and frequently performed for the evaluation of

CAD in patients presenting with chest pain in current clinical care.<sup>14</sup> To improve the diagnostic approach in patients presenting with chest pain beyond the evaluation of anatomical CAD by CT or CAG, it would be interesting to evaluate whether clinical characteristics could add to the evaluation of ischaemia in patients presenting with chest pain as well and could be useful to improve patient selection for non-invasive stress imaging.

### Limitations

As our study was based on data of electronic health records, data were only available if documented as part of routine clinical care. This may have resulted in some limitations of this study. First, chest pain characteristics were collected as part of the regular diagnostic work-up using a specific questionnaire and not available for every patient presenting with chest pain. Hence, missing data with respect to the chest pain characteristics may have caused bias. Cardiologists may have only recorded chest pain characteristics when chest pain was the prevailing complaint. As such, our conclusion may not be applicable to patients who present with mild dyspnoea and chest discomfort. Also, some chest pain characteristics (eg, vagal symptoms) were not reported enough to be studied. Furthermore, not all patients in our study were referred for diagnostic imaging, and we have assumed that these non-referred women and men were free from CAD which may not have been the case. This may have resulted in misclassification of patients.<sup>4</sup> This misclassification of CAD may have resulted in an underestimation of the diagnostic value of chest pain characteristics for CAD. As such, the diagnostic value of chest pain characteristics may in fact even be higher than reported in this study.

At last, since our data were collected during clinical care and were not available for patients who were referred back to their general practitioner, we did not have access to long-term follow-up information nor were we allowed to contact patients to obtain this information. As a result, our study was limited to diagnostic research evaluating the absence or presence of obstructive CAD as assessed by CT and/or CAG. Our data did not enable us to expand our research to the diagnostic value of chest pain-specific characteristics for coronary microvascular disease or assessment of their prognostic value within patients presenting with chest pain with(out) CAD presenting to the outpatient clinics. Future studies are needed for us to elucidate the prognostic value of chest pain-specific characteristics for cardiac events within all patients presenting with chest pain.

### CONCLUSION

In both men and women, the diagnostic value of non-acute chest pain characteristics and risk factors in differentiating CAD from no CAD was high. Provocation by temperature or stress, relief at rest and functional class of chest pain were most powerful in diagnosing CAD. Furthermore, when presenting with non-acute chest pain,

women and men with CAD present quite similar with regard to chest pain characteristics. Nonetheless, our data do show small sex differences regarding chest pain characteristics and stratified by sex the performance of the model improved, mostly in women. These results might suggest the need for a sex-specific model in diagnosing CAD and a possibility to improve referral for cardiac imaging of women and men at the outpatient clinic with non-acute chest pain.

#### Author affiliations

<sup>1</sup>Department of Clinical Chemistry and Hematology, University Medical Center Utrecht, Utrecht, The Netherlands

<sup>2</sup>Department of Epidemiology, Julius Center for Health Sciences and Primary Care, Utrecht, The Netherlands

<sup>3</sup>Laboratory of Experimental Cardiology, University Medical Center Utrecht, Utrecht, The Netherlands

<sup>4</sup>Cardiology Centers of the Netherlands, Utrecht, The Netherlands

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**Contributors** FG undertook the writing of the paper, developed the analysis plan and analysed the data. ALME guided the writing of the paper and the statistical analysis of the results. NCOM guided the statistical analysis of the results and made substantial improvements to the paper. SHB contributed to the data management and made substantial improvements to the paper. RM, IIT and AGS made substantial improvements to the paper. LH and HMdR supervised the study, contributed to the data analysis plan and made substantial improvements to the paper. All authors have read and given final approval of the submitted manuscript.

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#### ORCID iDs

Floor Groepenhoff <http://orcid.org/0000-0002-1583-701X>

Sophie Heleen Bots <http://orcid.org/0000-0002-4483-5582>

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