ORIGINAL RESEARCH

Sex-Based Differences in the Performance of the HEART Score in Patients Presenting to the Emergency Department With Acute Chest Pain

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***Background*—**Sex-based differences in clinical presentation, pathophysiology, and outcomes of patients with acute chest pain are increasingly being recognized, but are not implemented in guidelines and clinical prediction tools. We evaluated the performance of the HEART score in women versus men, because sex-based differences may exist among the algorithm's components: history, electrocardiogram, age, risk factors, and admission troponin level.

***Methods and Results*—**The HEART score was retrospectively assessed in 831 women and 1084 men presenting to the emergency department with acute chest pain, assigning patients to the low-, intermediate-, or high-risk category for the occurrence of major adverse cardiac events (MACE) within 6 weeks. MACE, consisting of myocardial infarction, coronary revascularization, and all-cause death, also included events during index visit. Six-week MACE rates were 2 times lower in women than men (10.0% versus 20.8%; $P<0.01$). Despite similar discriminatory accuracy of the HEART score among women and men (c-statistic, 0.80 [0.75–0.84] versus 0.77 [0.74–0.81]; $P=0.43$), 6-week MACE rates were significantly lower in women than men across all HEART risk categories: 2.1% versus 6.5% ($P<0.01$) in the low-risk category, 12.7% versus 21.3% ($P<0.01$) in intermediate-risk category, and 53.1% versus 77.0% ($P=0.02$) in the high-risk category. The HEART score-adjusted risk ratio for men was 1.6 (1.3–2.0; $P<0.01$).

***Conclusions*—**The markedly higher 6-week MACE risk in men across all HEART risk categories should be taken into account when using the HEART score to guide clinical decision making; early discharge with a low-risk HEART score appears less safe for men than women with acute chest pain. **(*J Am Heart Assoc*. 2017;6:e005373. DOI: 10.1161/JAHA.116.005373.)**

Key Words: acute coronary syndrome • decision aids • sex disparities • major adverse cardiac event • risk stratification

In past years, female-specific attention for cardiovascular disease has emerged. The fact that women are underrepresented in clinical studies raises concerns regarding the evidence-based preventive, diagnostic, and therapeutic options for women with cardiovascular disease. Sex-based differences in the clinical presentation, pathophysiological mechanisms, and outcomes of chest pain patients are increasingly being recognized. Compared with men, women with an acute coronary syndrome (ACS) present more frequently with atypical chest pain complaints and a nondiagnostic ECG and less frequently with elevations of troponins.[1–6] Also, women are ≈10 years older and tend to have a higher risk factor burden than men when they experience their first cardiac event.[3,7] These differences may lead to a, possibly falsely, lower perceived risk of ACS in women than men presenting to the emergency department (ED) with chest pain. In addition, the prevalence of myocardial infarction (MI) has increased in midlife women over the past decades, while declining in middle-aged men.[8] However, guideline-directed diagnostic "rule-in" and "rule-out"

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Clinical Perspective

What is New?

- Men assigned to the low-, intermediate-, or high-risk HEART category have a markedly higher 6-week risk of having a major adverse cardiac event compared with women assigned to the same HEART risk category.
- This may be explained by the 2 times higher baseline risk of having a major adverse cardiac event in men than women who present to the emergency department with acute chest pain.
- The HEART score algorithm itself performs equally well among men and women in terms of discriminatory accuracy and calibration.
- Sex is a confounder of the association between the HEART score and major adverse cardiac events.

What are the Clinical Implications?

- The higher 6-week risk of having a major adverse cardiac event in men across all HEART risk categories should be taken into account when using the HEART score to guide clinical decision making.
- Sex-adjusted risk prediction given a HEART score is warranted.
- Early discharge of patients with a low-risk HEART score appears less safe for men than women with acute chest pain.

algorithms for patients presenting to the ED with suspected ACS[9,10] do not consider risk disparities between women and men.

Sensitive cardiac troponin testing is the cornerstone of clinical decision making and management of suspected non-ST-segment elevation MI in the ED.[9,10] Myocardial necrosis can often be confirmed or excluded within 1 to 3 hours,[11,12] but the interpretation of troponin levels depends on clinical context and repeated measurements. The HEART score[13,14] is a simple and effective clinical prediction rule incorporating both clinical context—*H*istory, *E*lectrocardiograph, *A*ge and *R*isk factors—and admission *T*roponin levels. Using solely information collected at time of presentation, the HEART score is able to accurately estimate a patient's short-term cardiac risk, taking into account not only the risk of myocardial infarction during the index visit, but also major adverse cardiac events (MACE) that occur in the first 6 weeks thereafter. The HEART algorithm is able to identify a large group of low-risk patients (40.5%), who are candidates for early discharge from the ED, with a 6-week MACE rate of 2.0%.[15–17]

However, sex-based differences in clinical presentation of chest pain patients may lead to disparities in risk of ACS and adverse outcomes across the individual HEART score components and, consequently, may lead to disparities in the diagnostic (and short-term prognostic) performance of the total HEART score between women and men. We hypothesized that the less-typical clinical presentation of ACS in women might result in underestimation of cardiac risk in women by the HEART score. We therefore studied the clinical performance of the HEART score in men and women with acute chest pain, with focus on the efficiency and safety of rapid identification of patients at low risk of short-term MACE who can be discharged from the ED early.

Methods

Study Population

The MINERVA (Determination of *M*icrovesicle content *IN* the *E*mergency *R*oom: diagnostic *V*alue for *A*cute coronary syndromes) study is a prospective, single-center, observational cohort study, involving consecutive patients (>18 years) presenting to the ED with acute chest pain or its equivalents (ie, epigastric, neck, jaw, or arm pain, or discomfort or pressure without an apparent noncardiac source). Patient enrollment took place in the Meander Medical Center (Amersfoort, the Netherlands) from January 2012 to June 2014. Patients who were directly recognized as having an ST-elevation MI were excluded for the lack of diagnostic uncertainty and because of primary percutaneous intervention. Patient evaluation and management were in accord with the European Society of Cardiology guidelines[18] and included serial troponin testing, when needed. Clinical decision making was left to discretion of the attending cardiologist (Figure 1). The MINERVA study has been evaluated and approved by the regional Medical Ethics Committee and conforms to the Declaration of Helsinki. Written informed consent was obtained from all participants. Patients unwilling or unable to give their informed consent were not eligible. Patients were excluded from analysis if the available clinical data were not sufficient to calculate the HEART score, or when the duration of follow-up was less than 6 weeks.

Clinical Data Acquisition

Clinical data, including clinical presentation, medical history, cardiovascular risk factors, ECG, blood biochemical parameters, and the results of additional investigations, were gathered from medical records and were recorded in an online electronic case record form.

HEART Score Assessment

The HEART score algorithm[13] is depicted in Table 1. The HEART score was retrospectively determined based on patient data recorded at time of presentation to the ED. Patients were classified as low risk (0–3 points), intermediate risk (4–6 points), or high risk (7–10 points) according to the total HEART score.

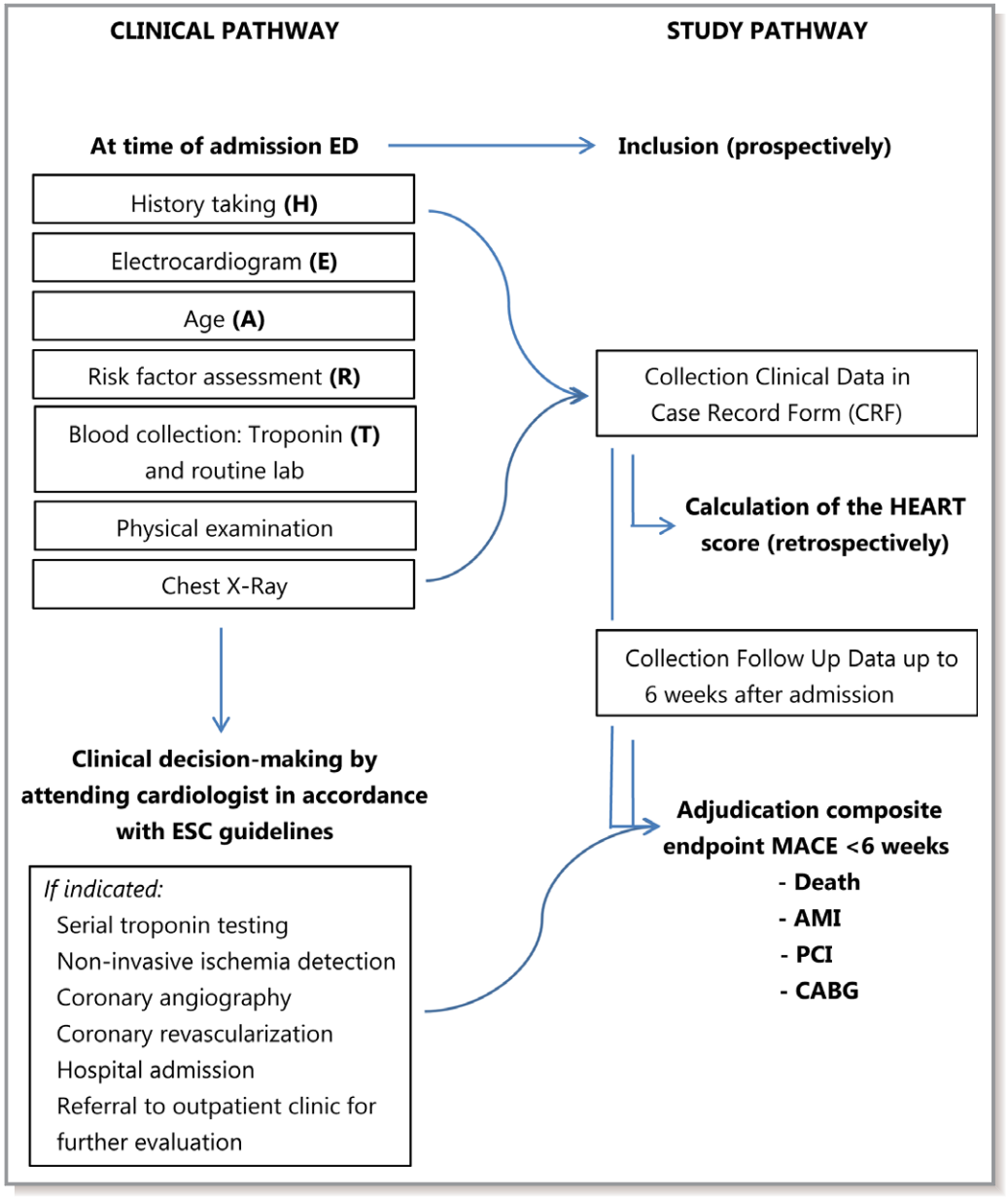

Figure 1. Clinical pathway and study pathway. AMI indicates acute myocardial infarction; CABG, coronary artery bypass grafting; CRF, case record form; ED, emergency department; ESC, European Society of Cardiology; PCI, percutaneous coronary intervention.

History

Patient history was scored as highly suspicious in case of typical chest pain—retrosternal or left-sided chest pain with radiation to jaw, neck, or left arm, induced by exercise or emotional stress, and relieved by rest and/or nitroglycerin—and scored nonsuspicious in case of atypical chest pain—no chest pain, right-sided chest pain, abdominal symptoms, pain that radiated to the back, or pain worsening on inspiration or palpation. Patients presenting with both typical and atypical symptoms were scored moderately suspicious.

ECG

The admission ECG was evaluated by 2 cardiologists. In case of dispute, a third cardiologist has decided. One point was given in case of nonspecific ST-T wave changes, signs of previous MI, or other abnormalities not diagnostic for ischemia, such as left bundle branch block, left ventricular hypertrophy, or pacemaker rhythm. Two points were given if there was significant new ST-segment elevation or -depression suspect for myocardial ischemia, in the absence of left bundle branch block, left ventricular hypertrophy, or use of digoxin.

Table 1. HEART Score Algorithm

HEART Score for Chest Pain Patients at the Emergency Department		
Variable	Description	Score
*H*istory	Highly suspicious	2
	Moderately suspicious	1
	Slightly or nonsuspicious	0
*E*CG	Significant ST-depression	2
	Nonspecific repolarization disturbances	1
	Normal	0
*A*ge	≥65 y	2
	45 to 65 y	1
	≤45 y	0
*R*isk factors	≥3 risk factors*, or history of atherosclerotic disease†	2
	1 or 2 risk factors	1
	No risk factors known	0
*T*roponin	≥3x normal limit	2
	1 to 2x normal limit	1
	≤normal limit	0

Total score: 0 to 10 points. 0 to 3 points, low risk; 4 to 6 points, intermediate risk; 7 to 10 points, high risk.
*Risk factors: hypertension, hypercholesterolemia, diabetes mellitus, family history of premature coronary artery disease, current smoking (or quit smoking <1 month ago), and obesity (body mass index ≥30 kg/m^2).
†History of atherosclerotic disease: previous myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft, stroke, or peripheral artery disease.

Risk factors

Cardiovascular risk factors taken into account were current smoking (or quit <1 month ago), dyslipidemia, hypertension, diabetes mellitus, obesity (body mass index, ≥30 kg/m^2), and history of cardiovascular disease (coronary revascularization, MI, cerebrovascular accident/transient ischemic attack, and/or peripheral artery disease). Dyslipidemia was scored when diagnosed previously by a physician or diagnosed during the index visit, according to the European Society of Cardiology/European Atherosclerosis Society guidelines.[19] Hypertension was scored when reported in the medical history, when diagnosed during the index visit, or when the patient was treated for hypertension.[20] Diabetes mellitus was defined as any type of diabetes mellitus diagnosed previously by a physician or during the index visit.[21]

Troponin

The HEART score only considers admission troponin levels. Troponin levels were measured with the Access AccuTnI+3 Troponin I assay on the UniCel DxI Immunoassay System (Beckmann Coulter, Brea, CA). The cutoff for MI was set at >60 ng/L at the coefficient of variation <10%. The limit of detection was 10 ng/L, and the 99th percentile cut-off point of 42 ng/L.[22]

End Points

The main end point of this study was the primary end point of the HEART score: the occurrence of MACE within 6 weeks of initial ED presentation, including the diagnosis and events during the index visit. The combined end point of MACE consisted of ST-elevation MI, type I non-ST-elevation MI, percutaneous coronary intervention, coronary arterial bypass grafting, and all-cause death. The diagnosis of MI was made according to the third universal definition of myocardial infarction.[23] Diagnoses were adjudicated in retrospect by 2 cardiologists independently (blinded for the assigned HEART scores), taking in consideration all patient information available, including serial troponins and further investigations that were performed during or after the index presentation. In case of disagreement, the panel decided on the final diagnosis. Follow-up information was gathered by mail or telephone interview, and collected data were cross-checked with the patient hospital records.

Statistical Analysis

All baseline continuous variables were non-normally distributed and are therefore presented as medians with interquartile range. Comparisons of continuous variables between the sexes were performed with the nonparametric Kruskal–Wallis test. Baseline categorical variables and the binomial proportions of 6-week MACE occurrence are presented as percentages. Comparisons between the sexes were performed with Pearson's chi-squared tests or Fisher Exact tests in case of low expected numbers per cell. Poisson regression models with robust SEs were used to estimate risk ratios (RRs) for the binary outcome 6-week MACE in (1) men versus women, (2) in men versus women within the HEART risk categories, and (3) in men versus women, adjusted for the HEART score.

The key role of the HEART score is to identify patients at low risk for MACE. Therefore, we assessed the diagnostic accuracy of the "low-risk" category (HEART score 0–3) versus the "non-low-risk" categories (intermediate- and high-risk category, HEART score 4–10) by calculating the sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV) from 2×2 tables. Test characteristics were calculated separately for women and men. The discriminative value of the total HEART score was determined by the area under the receiver operating characteristics curve (AUC), indicating the probability that 2 patients (1 with and 1 without MACE within 6 weeks) were classified correctly. Receiver operating characteristics curves were obtained for women

and men separately, and the difference between the 2 AUCs was tested using the method of DeLong. Calibration plots were constructed for the HEART score in women and men separately. Calibration, that is, whether or not the actual observed event rates correspond to the predicted event rates, was tested using the Hosmer–Lemeshow test for goodness of fit.

Furthermore, we examined whether sex modified the association between the HEART score and the outcome 6-week MACE in a logistic regression model using a multiplicative interaction term (HEART score×sex). Univariable logistic regression was performed in men and women separately in order to obtain sex-specific odds ratios and 95% CIs of the HEART score (per 1 point increase) for 6-week MACE. In addition, we examined whether sex modified the association between the individual HEART score components and the outcome 6-week MACE using multiplicative interaction terms. The interaction terms were tested (1) univariably, in a logistic regression model containing only sex and the respective HEART component (plus interaction term), and (2) multivariably, in a logistic regression model containing sex and all 5 HEART score components (plus the interaction term). Because the comparisons between 2 groups for the trichotomous scores require 2 statistical tests, a P value for interaction below 0.05/2=0.025 was considered significant, according to the Bonferroni principle. Sex-specific odds ratios and 95% CIs of the associations between the individual HEART score components and 6-week MACE were obtained from multivariable logistic regression models in women and men separately. The models contained all 5 HEART score components. For each HEART component, score 0 was chosen as the reference category.

All statistical analyses were performed using the R software package (version 3.1.2 GUI 1.65; R Foundation for Statistical Computing, Vienna, Austria). A P value of <0.05 was considered statistically significant.

Results

Study Population

Between 2012 and 2014, 2013 consecutive patients participated in the MINERVA study. In 62 patients (3.1%), we were unsuccessful to gather 6-week follow-up data. These patients were excluded because of loss to follow-up/missing primary end point. In another 36 patients (1.8%), data were insufficient to calculate the HEART score (n=13, no admission ECG was stored in electronic patient record; n=23, incomplete information on risk factor profile). Eventually, 1915 patients remained for analysis: 831 women and 1084 men. Baseline characteristics are depicted in Table 2.

Clinical Outcome: 6-Week Risk of MACE

A total of 83 (10.0%) women and 225 (20.8%) men were diagnosed with a MACE within 6 weeks of the initial presentation. The P value for the difference between the sexes was <0.01. The 6-week risk of MACE was thus 2 times higher in men than women (RR, 2.1; 95% CI, 1.6–2.6; P<0.01). Both the 6-week risk of acute MI (7.6% versus 15.7%; P<0.01) and the 6-week risk of coronary revascularization (6.6% versus 15.7%; P<0.01) were twice as low in women as compared with men. Ten patients died: 4 women (0.5%) and 6 men (0.6%; P>0.99. Table 3 gives an overview of the contribution of adverse events that occurred during the index visit and adverse events that occurred postdischarge to the primary end point of MACE within 6 weeks.

Assigned HEART Scores

Of the 1915 patients, 702 (36.7%) were classified as low risk (HEART score 0–3), 1094 (57.1%) were classified as intermediate risk (HEART score 4–6), and 119 (6.2%) were classified as high risk (HEART score 7–10). A larger proportion of women than men was assigned to the low-risk category, (40.2% versus 33.9%; P<0.01), whereas men were more likely to be assigned to the high-risk category (8.0% versus 3.9%; P<0.01). None of the women had a HEART score above 8.

Occurrence of MACE Across Risk Score Categories

Within each HEART risk category, the 6-week risk of MACE was significantly lower in women than men. Event rates for women and men were, respectively, 2.1% versus 6.5% (P<0.01) in the low-risk category, 12.7% versus 21.3% (P<0.01) in the intermediate-risk category, and 53.1% versus 77.0% (P=0.02) in the high-risk category (Figure 2). Hence, compared with women, men had a 3.1 times higher risk of MACE (RR, 3.1; 95% CI, 1.4–7.1; P<0.01) given a low-risk HEART score, a 1.7 times higher risk of MACE (RR, 1.7; 95% CI, 1.3–2.2; P<0.01) given an intermediate-risk HEART score, and a 1.4 times higher risk of MACE (RR, 1.4; 95% CI, 1.0–2.0; P<0.01) given a high-risk HEART score. Adjusted for the HEART score, the RR for having a MACE within 6 weeks for men compared with women was 1.6 (95% CI, 1.3–2.0; P<0.01).

Regarding the identification of patients who can be discharged early, the NPV (1-event rate) of a low-risk HEART score (0–3 points, proposed policy: early discharge) versus a nonlow HEART score (4–10 points) was 97.9% in women versus 93.5% in men. The higher NPV in women was counterbalanced by a lower PPV of 15.3% in women versus

Table 2. Baseline Characteristics

	Women	Men	*P* Value	No. of Missing Values (%)
n	831	1084		
Age, y (median [IQR])	63.0 [53.0, 74.0]	61.0 [52.0, 71.0]	0.04	…
BMI, kg/m^2 (median [IQR])	26.1 [23.5, 29.6]	26.9 [24.8, 29.7]	<0.01	18 (0.9)
Obesity, % (BMI >30)	24.2	23.1	0.62	18 (0.9)
SBP, mm Hg (median [IQR])	149.0 [130.0, 168.0]	142.0 [128.0, 160.0]	<0.01	33 (1.7)
DBP, mm Hg (median [IQR])	77.0 [70.0, 85.0]	80.0 [70.0, 90.0]	<0.01	33 (1.7)
Diabetes mellitus, %	12.6	17.3	<0.01	…
Hypertension, %	46.6	48.3	0.47	…
Hypercholesterolemia, %	30.3	31.4	0.66	4 (0.2)
Smoking, %	26.8	28.4	0.46	4 (0.2)
Family history CAD, %	31.3	31.7	0.92	46 (2.4)
History of MI, %	14.1	26.0	<0.01	2 (0.1)
History of PCI, %	13.4	29.9	<0.01	1 (0.05)
History of CABG, %	2.9	10.8	<0.01	1 (0.05)
History of stroke, %	2.7	2.7	>0.99	1 (0.05)
History of PAD, %	3.4	4.8	0.154	1 (0.05)
Renal impairment, %	21.1	13.3	<0.01	17 (0.9)
Moderate (GFR 30–60), %	19.4	11.6	<0.01	17 (0.9)
Severe (GFR <30), %	1.7	1.7	>0.99	17 (0.9)
Aspirin, %	31.9	42.1	<0.01	…
Clopidogrel, %	5.9	9.4	<0.01	…
Other antiplatelet agents, %	2.6	4.5	0.04	…
Beta-blocker, %	33.6	39.5	<0.01	…
ACE inhibitor, %	19.6	26.8	<0.01	…
AT-II antagonist, %	32.6	39.0	<0.01	…
Statins, %	34.4	46.5	<0.01	…

BMI indicates body mass index; CABG, coronary artery bypass grafting; CAD, coronary artery disease; DBP, diastolic blood pressure; GFR, glomerular filtration rate; IQR, interquartile range; MI, myocardial infarction; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; SBP, systolic blood pressure.

a PPV of 28.1% in men (Table 4). Importantly, no deaths occurred in the low-risk HEART score group, and no MACE occurred in patients with an assigned HEART score of 0 or 1 (concerning 7.1% of women and 5.5% of men). Further details on the suboutcomes of MACE occurring in the HEART risk groups are provided in Table 5.

Table 3. Clinical Outcome: 6-Week Risk of MACE and the Contribution of Events During Index Visit and Events Postdischarge

	Women			Men		
	Total	Index Visit	Postdischarge	Total	Index Visit	Postdischarge
No. of Patients at Risk	831	831	830	1084	1084	1081
MACE, n (%)	83 (10.0)	73 (8.8)	16 (1.9)	225 (20.8)	188 (17.3)	52 (4.8)
Death, n (%)	4 (0.5)	1 (0.1)	3 (0.4)	6 (0.6)	3 (0.3)	3 (0.3)
MI, n (%)	63 (7.6)	62 (7.5)	1 (0.1)	170 (15.7)	161 (14.9)	9 (0.8)
CR, n (%)	55 (6.6)	42 (5.1)	13 (1.6)	169 (15.6)	121 (11.1)	48 (4.4)

CR indicates coronary revascularization; MACE, major adverse cardiac events (combination of MI, coronary revascularization and death); MI, myocardial infarction.

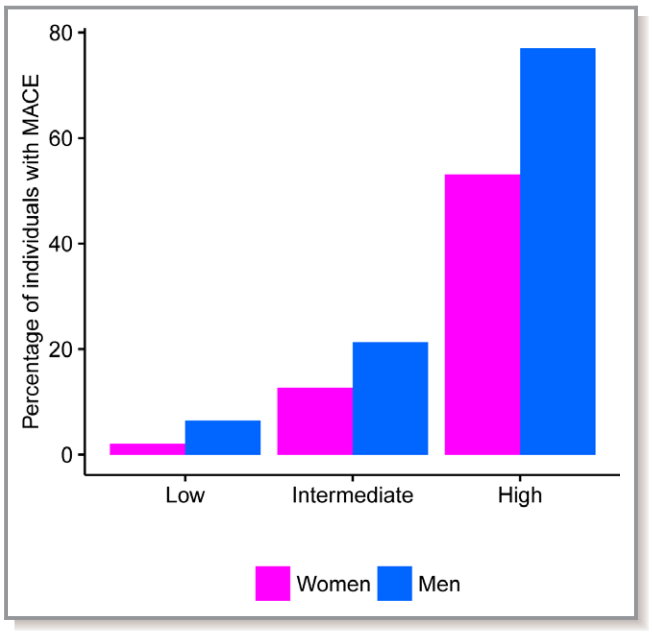

Figure 2. Percentage of men and women within the HEART score risk categories with MACE within 6 weeks from inclusion. MACE indicates major adverse cardiac events.

Discrimination and Calibration

The overall discriminatory accuracy of the HEART score for the occurrence of MACE within 6 weeks did not significantly differ between the sexes (AUC, 0.80 [95% CI, 0.75–0.84] in women versus 0.77 [95% CI, 0.74–0.81] in men; *P*=0.43). In addition, there was no evidence that the HEART score had poor calibration in either women or men. The Hosmer–Lemeshow test *P* values were >0.99 and *P*=0.25, respectively.

Interaction Analysis: Does Sex Affect the Associations of the HEART Score or the Algorithm's 5 Individual Components With 6-Week MACE?

Male sex remained a significant predictor of 6-week MACE (OR, 1.95 [95% CI, 1.46–2.63]; *P*<0.01), when adjusted for the HEART score. Furthermore, higher HEART scores were associated with higher odds of having a MACE within 6 weeks in both women (OR, [per 1-point increase in HEART score] 2.40 [95% CI, 1.99–2.95]; *P*<0.01) and men (OR, 2.10 [95% CI, 1.87–2.37]; *P*<0.01), with a nonsignificant interaction between sex and the total HEART score for the outcome of 6-week MACE (*P* interaction=0.25). Thus, male sex and higher HEART scores were independent predictors of MACE.

The associations between the individual HEART score components and 6-week MACE are presented in Table 6, stratified by sex. In brief, higher scores on the items *H*istory, *E*CG, and *T*roponin, that is, an increase from 0 points to 1 or 2 points, were associated with higher odds of having a MACE within 6 weeks. This was similarly true for women and men (no significant interactions in univariable and multivariable analysis). Regarding *A*ge, however, higher scores were not related to 6-week MACE in women, whereas in men both *A*ge scores 1 (45–65 years) and 2 (>65 years) were associated with higher odds of having a MACE within 6 weeks as compared with *A*ge score 0 (<45 years). This sex difference for *A*ge was not statistically significant in univariable interaction analysis (*P*=0.04) or in a multivariable model containing all 5 HEART score components (*P* interaction=0.16).

Table 4. Diagnostic Test Characteristics of a Low HEART Score vs Nonlow HEART Score in Men and Women

	Women	Men
All patients, n	831	1084
NPV	97.9 (95.7–99.2)	93.5 (90.4–95.8)
PPV	15.3 (12.2–18.8)	28.1 (24.8–31.5)
Sensitivity	91.6 (83.4–96.5)	89.3 (84.5–93.0)
Specificity	43.7 (40.1–47.4)	40.0 (36.08–43.4)

Low HEART score, 0 to 3 points; nonlow HEART score, 4 to 10 points (intermediate- and high-risk category). NPV indicates negative predictive value; PPV, positive predictive value.

Table 5. Six-Week Risk of MACE per HEART Risk Category by Sex

	Women	Men	
	831	1084	*P* Value
MACE % (n/n)			
Low	2.1 (7/334)	6.5 (24/368)	<0.01
Intermediate	12.7 (59/465)	21.3 (134/629)	<0.01
High	53.1 (17/32)	77.0 (67/87)	0.02
Death % (n/n)			
Low	0.0 (0/334)	0.0 (0/368)	>0.99
Intermediate	0.9 (4/465)	0.3 (2/629)	0.41
High	0.0 (0/32)	4.6 (4/87)	0.57
MI % (n/n)			
Low	0.9 (3/334)	3.3 (12/368)	0.06
Intermediate	9.2 (43/465)	14.8 (93/629)	0.02
High	53.1 (17/32)	74.7 (65/87)	0.04
CR % (n/n)			
Low	1.8 (6/334)	6.0 (22/368)	<0.01
Intermediate	8.0 (37/465)	16.9 (106/629)	<0.01
High	37.5 (12/32)	47.1 (41/87)	0.69

Low-risk category: 0 to 3 points; intermediate-risk category: 4 to 6 points; high-risk category: 7 to 10 points. CR indicates coronary revascularization; MACE, major adverse cardiovascular events (combination of MI, coronary revascularization, and death); MI, myocardial infarction.

Table 6. HEART Score's 5 Components: the Adjusted Predictive Value for 6-Week MACE per Component in Men and Women

	Women		Men	
	831		1084	
N	OR (95% CI)	% Patients*	OR (95% CI)	% Patients*
History				
Score 0	Ref	24.4	Ref	22.4
Score 1	3.7 (1.5–10.8)	67.9	2.1 (1.2–4.0)	64.2
Score 2	12.9 (4.3–43.2)	7.7	11.7 (6.0–23.8)	13.4
ECG				
Score 0	Ref	69.2	Ref	64.7
Score 1	1.6 (0.8–2.8)	28.8	1.6 (1.0–2.4)	31.5
Score 2	3.9 (0.9–15.2)	2.0	4.4 (1.8–10.3)	3.8
Age				
Score 0	Ref	11.4	Ref	11.6
Score 1	0.8 (0.3–2.5)	40.6	2.1 (1.0–5.1)	44.7
Score 2	1.2 (0.5–3.5)	48.0	2.2 (1.0–5.3)	43.6
Risk factors				
Score 0	Ref	16.4	Ref	13.5
Score 1	0.9 (0.4–2.3)	45.7	2.0 (1.0–4.2)	32.4
Score 2	1.9 (0.8–5.0)	37.9	1.4 (0.7–2.9)	54.2
Troponin				
Score 0	Ref	92.4	Ref	88.1
Score 1	24.5 (10.0–62.7)	3.6	12.9 (6.5–27.2)	4.8
Score 2	57.3 (22.3–163.3)	4.0	59.1 (26.3–158.5)	7.1

Adjusted odds ratios (OR) and 95% CI of the individual HEART score components for the outcome 6-week major adverse cardiac events (MACE) were derived from multivariable logistic regression models in men and women separately. The models included all HEART score variables. Score 0 of each component was chosen as the reference category.
*Percentage of men/women with score 0, 1, or 2 in the corresponding component of the HEART score. No $P<0.025$ were observed per category in univariable or multivariable interaction testing HEART-item×sex for outcome 6-week MACE.

Furthermore, both in women and men, higher *Ri*sk factor scores were not significantly associated with the odds of 6-week MACE.

Discussion

Here, we demonstrate that there are distinct sex-based differences in the 6-week risk of MACE across the individual HEART score risk categories among patients presenting to the ED with suspected ACS. In contrast to our expectation, women who were assigned to the low-, intermediate-, or high-risk category had a markedly lower 6-week risk of MACE as compared with men who were assigned to the same HEART risk category. With regard to clinical decision making, early discharge of patients with a low-risk HEART score (0–3) appears to be less safe for men than women, with a 6-week MACE risk of 6.5% in men versus 2.1% in women.

To our knowledge, this is the first sex-stratified analysis of the clinical performance of the HEART score. The HEART score was developed from a clinical perspective, based on factors important for clinical decision making and medical literature.[13] Besides, the HEART score was designed to be easy to use. Hence, the HEART score was not developed using logistic regression modeling upon a real-life database. Although male sex was reported to be a statistically significant predictor of MACE occurrence in previous HEART score validation studies, the HEART algorithm maintained similar discriminatory accuracy among men and women.[14,24,25] In the prospective multicenter HEART score validation study, for example, Backus et al[25] reported 6-week MACE rates of 11.4% (116 of 1016) in women and 21.2% (291 of 1372) in men, with AUCs of 0.82 and 0.83, respectively. This is in line with both the 2.1 times higher baseline risk of MACE among men and the lack of sex differences in diagnostic accuracy of the HEART score we observed in the MINERVA cohort.

However, the similar AUCs of the HEART score in women and men only reflect the equal ability of the HEART score to

distinguish between women with and without MACE within 6 weeks, and to distinguish between men with and without MACE within 6 weeks (ie, do cases have higher HEART scores than noncases). Hence, irrespective of how well the height of assigned HEART scores of diseased women correspond to the height of assigned HEART scores of diseased men. There was no evidence that the HEART score had poor calibration in either women or men, indicating that the predicted risk of MACE given a HEART score (0–10) may well reflect the actual proportion patients with MACE assigned to that specific HEART score in both sexes. Importantly, these general measures of model accuracy overlook the distinct discrepancy in 6-week MACE risk between women and men across all HEART risk categories, whereas it has considerable implications for decision making in the ED.

From the interaction analysis, it appears that the HEART score has just as strong of a relationship with MACE in women as in men. Furthermore, we observed only subtle and nonsignificant sex-based differences in the strength of the relationships between the individual HEART score components—history, ECG, age, risk factors, and admission troponin level—and the occurrence of MACE within 6 weeks. Interestingly, previous studies suggest that women with ACS present more frequently with atypical chest pain complaints, and less frequently with elevations of troponins as compared with men with ACS,[5,6,26] though we observed no significant sex differences in the predictive value of the HEART score components *H*istory and *T*roponin for the occurrence of MACE.

The present finding that male sex is an independent and strong risk factor for the occurrence of adverse coronary events is consistent with results from 2 previous population-based, prospective studies.[27,28] These large registries reported roughly 2-fold higher risks of incident MI (Albrektsen et al) and incident coronary heart disease (Jousilathi et al) in men than women, after adjustment for established risk factors. Our findings add to these population-based data that also in symptomatic individuals (presenting to the ED with suspected ACS) a clear sex-based risk disparity exists, regardless of established risk factors and clinical presentation. Likewise, men presenting to the ED with symptoms suggestive of ACS in the ROMICAT-II trial[29] had higher ACS rates than women (12% versus 3%) and more obstructive coronary disease (17% versus 5%) as determined by coronary computed tomography angiography. This lower burden of obstructive coronary artery disease in women with chest pain complaints may explain the considerably lower MACE rates in women than men in the current study: Revascularization of epicardial coronary stenosis is an important driver of the primary end point of the HEART score, whereas more female-specific pathophysiology of ischemic heart disease (microvascular dysfunction, endothelial dysfunction, and vasomotor abnormalities[30]) is overlooked.

Following the conclusion that men have a higher baseline risk of MACE than women, it is important to appreciate that the prevalence of disease affects the predictive values of any test. Higher prevalence leads to lower NPV and higher PPV when the sensitivity and specificity of the test remain constant. On the basis of the HEART score's equal diagnostic accuracy (ie, in terms of AUC) in the 2 sexes, the lack of poor calibration, and the nonsignificant interaction between sex and the HEART score, it seems reasonable to assume that the HEART score predicts the risk of MACE equally well in men and women. The lower NPV and higher PPV of the HEART score in men compared with women might therefore just be explained by men's 2 times higher baseline risk of MACE. Sex-adjusted prediction of 6-week MACE risk given a HEART score is warranted, and sex-specific definitions of the low-, intermediate-, and high-risk HEART categories should be considered.

Importantly, early discharge from the hospital with a low HEART score (0–3)—as proposed in the current protocol—may be safe for women, but appears less safe for men, who have a considerable risk of MACE within 6 weeks. The NPV of 93.5% among men with a low-risk HEART score is substantially lower than the NPV of 99% that is considered acceptable to safely rule out ACS and to consider early discharge from the hospital.[31] To a lesser extent, this also holds true for the NPV of 97.7% for a low-risk HEART score in women. The lower 6-week risk of MACE in women compared with men was driven by lower rates of MI and coronary revascularization. No deaths occurred in the low-risk categories. Lowering the cut-off value to define men as low-risk patients (eg, from score 3 to 2) will reduce the rate of missed events, but will also considerably reduce the number of patients identified as low risk and thus lower the efficacy and usefulness of the HEART score. Ma et al recently assessed the validity of such a modified HEART score with a low-risk group of 0 to 2 points for both men and women in a Chinese chest pain cohort: Only 6.8% of patients were assigned to the low-risk category, with an event rate of 1.1%.[32] Mahler et al added a repeated troponin measurement at 3 hours to the HEART score (HEART Pathway) to increase the NPV. They were able to identify 39.7% of patients for early discharge (HEART score 0–3 and negative serial troponins) with an NPV of 100% and a PPV of 10.7%.[33] The drawback of this approach is that it requires serial troponin testing.

Strengths of our study include the large cohort size and the real-world setting of recruiting chest pain patients with maximum diagnostic uncertainty (exclusion of clear-cut ST-elevation MI). In addition, the HEART score does not only consider the risk of having an MI at time of presentation to the ED, but also takes into account the risk of adverse events occurring shortly after hospital discharge. This combination of diagnostic and (short-term) prognostic elements results in risk prediction that is relevant for decision making at the ED:

Which patients have a low risk of MACE within 6 weeks and can therefore safely be discharged for deferred further evaluation at the outpatient clinic?

Several important limitations need to be mentioned as well. First, HEART scores were assessed retrospectively and separately for the 5 components per patient, whereas in clinical practice a physician will score all components at once at time of presentation to the ED. Second, the diagnoses of ACS and MACE were adjudicated by a panel of experts using all available information rather than a standardized diagnostic pathway. This will lead to an incorporation bias, because information related to, for instance, history, ECG, cardiac troponin levels, as well as results of ischemia detection and coronary angiography is necessarily incorporated in the primary end point, but also guides the need for further diagnostic testing and subsequent coronary revascularization. This may lead to underestimation of disease prevalence in patients with low risk of epicardial coronary artery disease and low troponins (predominantly women) in whom, in clinical practice, less additional diagnostic tests will be performed. However, it is unlikely that the observed sex-based differences fully can be explained by differences in diagnostic sensitivity. Third, the overall diagnostic performance of the HEART score in our study was slightly lower than previously reported.[15]

In conclusion, the 6-week risk of MACE was substantially lower in women than in men across all HEART risk categories. This may be explained by the 2.1 times higher baseline risk of MACE in men compared with women, given that the HEART algorithm appears to predict MACE equally well in men and women—evidenced by the similar overall diagnostic accuracy between the sexes, the lack of poor calibration of the HEART score in either women or men, and nonsignificant interaction between sex and the HEART score for MACE. Sex-adjusted prediction of 6-week MACE risk given a HEART score is warranted, because the higher event rates in men should be taken into account when using the HEART score to guide clinical decision making in patients with acute chest pain. Furthermore, sex-specific definitions of the low-, intermediate-, and high-risk HEART categories should be considered. Regarding the rapid rule out of MACE in patients with a low-risk HEART score, early discharge appears to be safe in women, but less safe in men. Our findings underscore the importance of risk score validation studies to report event rates for the relevant subgroups across all of the score's risk categories. Or at least for the risk categories that have implications for clinical decision making.

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Disclosures

None.

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