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Effect of Using the HEART Score in Patients With Chest Pain in the Emergency Department

A Stepped-Wedge, Cluster Randomized Trial

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Background: The HEART (History, Electrocardiogram, Age, Risk factors, and initial Troponin) score is an easy-to-apply instrument to stratify patients with chest pain according to their short-term risk for major adverse cardiac events (MACEs), but its effect on daily practice is unknown.

Objective: To measure the effect of use of the HEART score on patient outcomes and use of health care resources.

Design: Stepped-wedge, cluster randomized trial. (Clinical Trials.gov: NCT01756846)

Setting: Emergency departments in 9 Dutch hospitals.

Patients: Unselected patients with chest pain presenting at emergency departments in 2013 and 2014.

Intervention: All hospitals started with usual care. Every 6 weeks, 1 hospital was randomly assigned to switch to "HEART care," during which physicians calculated the HEART score to guide patient management.

Measurements: For safety, a noninferiority margin of a 3.0% absolute increase in MACEs within 6 weeks was set. Other outcomes included use of health care resources, quality of life, and cost-effectiveness.

Results: A total of 3648 patients were included (1827 receiving usual care and 1821 receiving HEART care). Six-week incidence of MACEs during HEART care was 1.3% lower than during usual care (upper limit of the 1-sided 95% CI, 2.1% [within the noninferiority margin of 3.0%]). In low-risk patients, incidence of MACEs was 2.0% (95% CI, 1.2% to 3.3%). No statistically significant differences in early discharge, readmissions, recurrent emergency department visits, outpatient visits, or visits to general practitioners were observed.

Limitation: Physicians were hesitant to refrain from admission and diagnostic tests in patients classified as low risk by the HEART score.

Conclusion: Using the HEART score during initial assessment of patients with chest pain is safe, but the effect on health care resources is limited, possibly due to nonadherence to management recommendations.

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Only 20% of patients with chest pain have an acute coronary syndrome that requires prompt admission and treatment. In the remaining 80%, the underlying condition is noncardiac and is usually not life-threatening (1). These patients might be discharged from the emergency department and managed further in an outpatient setting. However, approximately 50% of patients with an acute coronary syndrome do not have classic symptoms, and coronary angiography, the reference standard for investigation, is costly and carries a risk for complications (2). Current management in most Western countries is conservative, with two thirds of patients being admitted and receiving additional testing, which puts a large burden on health care resources and also carries the risk for overdiagnosis and overtreatment (3). Nevertheless, reports indicate that approximately 2% to 6% of patients with an acute coronary syndrome are still being missed in current practice (4, 5).

International guidelines advise the use of risk-stratifying instruments in patients with chest pain because they are superior to clinical assessment alone and their potential effect on patient outcomes (such as safety and length of stay) has been demonstrated (6–12). The HEART score is based on 5 key elements in the initial work-up of patients with chest pain: History, Electrocardiogram (ECG), Age, Risk factors, and Troponin (**Figure 1**, and **Appendix Figure 1**, available at Annals.org) (13). In contrast to other risk scores for chest pain, the HEART score was developed on the basis of clinical experience alone. It provides the physician with a formal recommendation for admission, observation, or discharge in individual patients. The HEART score has shown promising results in external validation studies in various countries and hospital settings (14–21). Still,

See also:

Web-Only
Supplement

Figure 1. HEART score for patients with chest pain.

History (anamnesis)	Highly suspicious	2	
	Moderately suspicious	1	
	Slightly suspicious	0	
ECG	Significant ST-segment deviation	2	
	Nonspecific repolarization disturbance/LBBB/PM	1	
	Normal	0	
Age	≥65 y	2	
	45–65 y	1	
	≤45 y	0	
Risk factors*	≥3 risk factors or history of atherosclerotic disease	2	
	1 or 2 risk factors	1	
	No known risk factors	0	
Troponin	≥3 × normal limit	2	
	1–3 × normal limit	1	
	Normal limit or lower	0	
		Total	

ECG = electrocardiogram; HEART = History, ECG, Age, Risk factors, and initial Troponin; LBBB = left bundle branch block; PM = pacemaker.
* Hypercholesterolemia, hypertension, diabetes mellitus, cigarette smoking, family history of atherosclerotic disease, and obesity (body mass index >30 kg/m^2).

clinicians remain uncertain about safety when using the HEART score in daily practice because its effect has not yet been evaluated.

Our aim was to determine whether use of the HEART score results in reduced burden of care, hospitalizations, and health care costs but no increase in the occurrence of adverse cardiac events.

METHODS

Study Design

The design of our prospective, stepped-wedge, cluster randomized trial has been previously described (22). This design combines elements of a standard parallel cluster randomized design (the intervention is applied in clusters) and a before–after design (each cluster switches to the intervention) (23). All hospitals (clusters) started with an initial period of usual care. At intervals of 6 weeks ("steps"), each hospital switched in a randomized order to use of the HEART score until all hospitals had crossed over (Appendix Figure 2, available at Annals.org).

Study Population

Nine hospitals in the Netherlands participated, none of which used the HEART score before the start of the trial. All patients aged 18 years or older presenting with chest pain at the emergency department or chest pain unit between 1 July 2013 and 31 August 2014 were eligible. Exclusion criteria were evident ST-segment elevation myocardial infarction, language barrier, recurrent presentation, or inability or unwillingness to give informed consent. Treating physicians informed patients of the study's aim and obtained written consent for the use of data and follow-up. The trial was approved by the Institutional Review Board of University Medical Center Utrecht and subsequently by the boards of the participating hospitals. Most hospitals used a high-sensitivity troponin assay (Appendix Tables 1 and 2, available at Annals.org). None of the hospitals switched the type of assay during the trial.

Usual Care Versus HEART Care

Usual care was defined as daily practice of an attending physician to evaluate patients with chest pain. In this period, physicians in the emergency department assessed risk for acute coronary syndrome based on standard history taking, physical examination, ECG, laboratory tests, or chest radiography and using their clinical expertise, intuition, and national or international clinical guidelines that could include the calculation of risk scores other than the HEART score (24). During usual care, explicit instructions were given not to calculate the HEART score.

"HEART care" consisted of routine initial work-up plus formal calculation of the HEART score in all patients and linking the total HEART score to specific recommendations for further management ("directive use" [25]). A HEART score that is based on a single baseline troponin measurement has been validated. Therefore, the recommendation for patients with a score of 3 or less was reassurance and discharge without further diagnostic testing, including no second troponin measurement. To avoid missed acute coronary syndromes in patients with low HEART scores who were discharged without a representative troponin measurement, a second troponin test was performed the same or next day while the patient was ambulatory. Hospitalization for observation and investigation was recommended for the intermediate-risk group (score of 4 to 6), and prompt invasive treatment was recommended for the high-risk group (score of 7 to 10). In accordance with daily practice, in which physicians are able to pick up specific clues in patients, physicians could overrule the score's recommendation and, for example, admit a patient with a low score. Information about the reason for overruling the recommendation was collected. Nonadherence was defined as admission and additional testing (including a second troponin measurement) in low-risk patients or no further diagnostic testing in high-risk patients. We prepared our participating hospitals before inclusion with presentations during morning meetings and face-to-face instruction of the residents, nurses, and cardiologists. The hospital was informed about the switch to HEART care 1 week in advance with a meeting on case exercises, including calculation of the HEART score.

Figure 2 shows the protocol for usual care versus HEART care.

End Points

Primary Outcome

The primary outcome was safety, defined as occurrence of major adverse cardiac events (MACEs) within 6

weeks, consisting of the following events: ST-segment elevation myocardial infarction, non–ST-segment elevation myocardial infarction, unstable angina, percutaneous coronary intervention, coronary artery bypass grafting, significant stenosis (>50%) treated conservatively, or death due to any cause. To identify MACEs occurring after discharge, all patients were contacted by telephone, by e-mail, or via the patient's general practitioner at 3 months. Any information indicative of a relevant end point was further investigated by consulting electronic hospital medical files and was subsequently reviewed for final classification by 2 independent cardiologists who were blinded to study period and HEART score and who used the definitions in the European guidelines (24, 26). In cases of disagreement, the case was discussed in a consensus meeting with at least 3 participating cardiologists.

Use of Health Care Resources

The number and cause of initial admissions and the number of early discharges from the emergency department (≤4 hours after presentation) as well as readmissions, recurrent emergency department visits, and outpatient clinic visits within 3 months after the initial presentation were recorded for all patients. The number and reason for general practitioner visits were collected during the telephone call with the patient at 3 months.

We decided in advance to collect detailed data on the use of diagnostic procedures in 5 of the 9 participating hospitals, which were chosen on the basis of their differences in size and type (1 academic, 4 nonacademic, 2 small, and 3 large) and their ability to provide high-quality data. The expected number of patients in these hospitals was sufficient to investigate differences in health-related quality of life and costs.

Quality of Life

Quality-of-life data were collected in patients from the same 5 participating hospitals during usual and HEART care, at baseline, and at 2-week and 3-month follow-up using the EuroQol 5-Dimensional (EQ-5D) questionnaire (22).

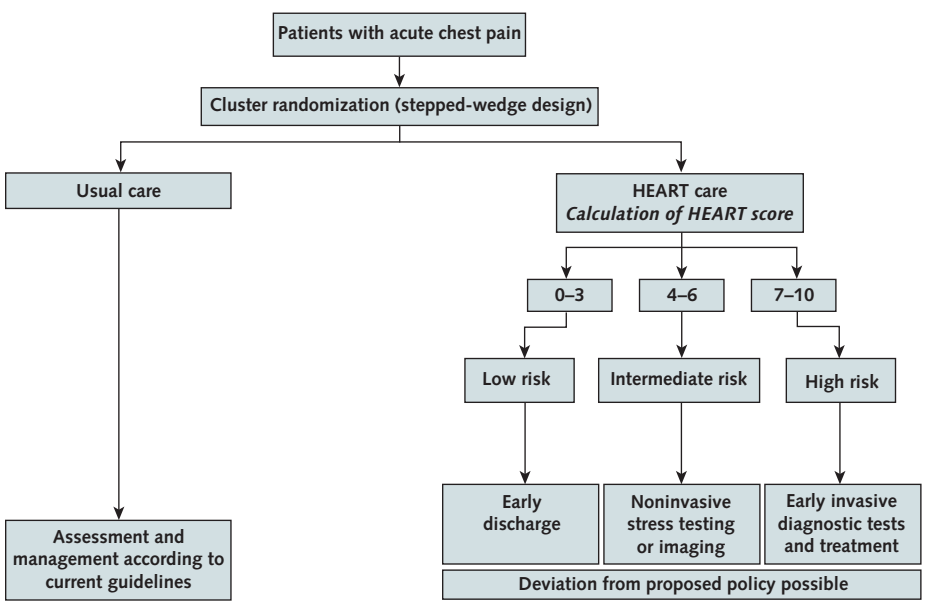
Direct Costs

Health care resource use was extracted from the electronic hospital medical files from 5 participating hospitals. Unit costs (in euros) were determined using the available literature (27).

Statistical Analysis

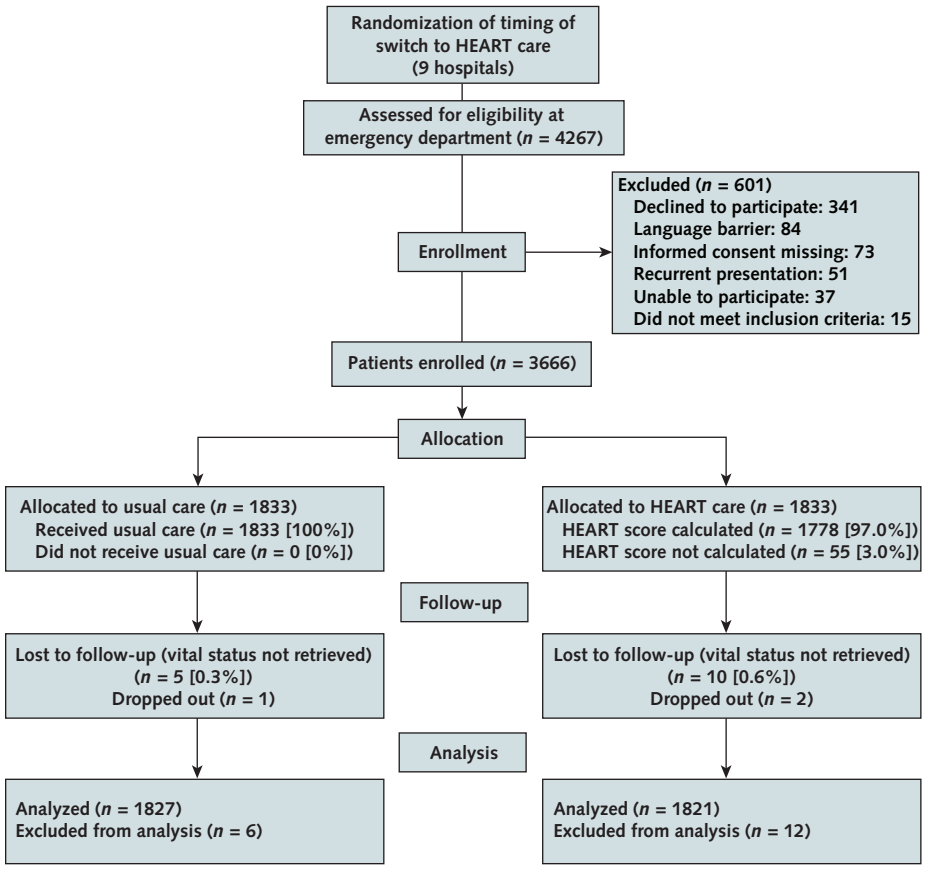
The 6-week cumulative incidence of MACEs was analyzed using generalized linear models. The binomial distribution and the identity link were used to directly estimate absolute differences in MACE incidence between HEART and usual care patients. The generalized estimating equation approach was used to take clustering of MACEs within hospitals into account given the stepped-wedge design (23, 28). Bootstrapping was used to obtain CIs (29). The main model included type of care (usual or HEART), steps (time periods) as a categorical variable, and hospitals as clusters. The difference in MACEs with a 1-sided 95% CI was estimated in order to evaluate noninferiority. The noninferiority margin was prespecified at 3.0%.

Figure 2. Study protocol for usual care versus HEART care.



HEART = History, Electrocardiogram, Age, Risk factors, and initial Troponin.

Figure 3. Study flow diagram.



HEART = History, Electrocardiogram, Age, Risk factors, and initial Troponin.

In a sensitivity analysis, we further adjusted for the following prognostic factors: age, sex, any cardiovascular history, and risk factors for cardiovascular disease. Four prespecified subgroups were investigated to determine whether the effect of HEART care on MACEs differed: men versus women, older versus younger than 75 years, diabetic versus nondiabetic patients, and white versus other race. Appendix 1 (available at Annals.org) provides information on changes in this subgroup analysis. The same modeling approach was applied for other binary outcomes to estimate absolute differences in health care use. The generalized estimating equation models were performed using the XT and XTGEE routines in Stata, version 13.1 (StataCorp), with use of their bootstrap procedure to obtain robust estimates of SEs. More details on the statistical analysis and deviations from the protocol can be found in Appendix 2 (available at Annals.org).

Sample Size

We expected the incidence of MACEs to be similar between HEART and usual care. Specifically, on the basis of clinical judgment and literature, the difference in MACE incidence between HEART and usual care should not exceed 3.0% (noninferiority margin) (13–17). The proportion of MACEs expected during usual care was 17%, and the between-hospital variation in incidence of MACEs was estimated at 16% to 18%. Based on these numbers, a 1-sided α level of 5%, and a power of 80%, the required total sample size for a stepped-wedge design with 10 clusters was calculated as 6600 (22).

Cost-Effectiveness Analysis

Differences in health-related quality of life at baseline, 2 weeks, and 3 months were assessed with the EQ-5D questionnaire. Costs per patient were calculated according to Dutch guidelines for pharmacoeconomic analyses (27). Bootstrapping (n = 2500) was used to obtain 95% CIs around differences in quality-of-life estimates and costs. A cost-effectiveness analysis was performed; more detail is provided in Appendix 3 (available at Annals.org) and in our published study protocol (22).

Role of the Funding Source

A research grant was obtained from the Netherlands Organisation for Health Research and Development as part of the Effectiveness Program. The study sponsor had no role in the design of the study; collection, analysis, or interpretation of the data; writing of

the report; or the decision to submit the manuscript for publication.

RESULTS

Study Population

A total of 3666 patients met our inclusion criteria and agreed to participate (Figure 3). Three patients withdrew from the study within 6 weeks, and 15 (0.4%) were lost to follow-up. A total of 3648 patients were included in the analysis (1827 receiving usual care and 1821 receiving HEART care). The mean age of patients was 62 years, and 54% were male (Table 1). A low HEART score (0 to 3) was calculated in 715 (39%) patients, an intermediate score (4 to 6) was calculated in 861 (47%) patients, and a high score (7 to 10) was calculated in 190 (11%) patients. The score was not calculated in 55 (3%) patients during the HEART care period.

Safety

The 6-week cumulative incidence of MACEs was 18.9% during HEART care and 22.2% during usual care. The difference in MACE incidence (HEART care minus usual care) after adjustment for time steps and clustering was −1.3%, with a 1-sided 95% upper confidence limit of 2.1% (within the prespecified noninferiority margin of 3.0%) (Appendix Figure 3, available at Annals.org). Adjustment for known prognostic factors did not meaningfully change the estimate of treatment effect (<10% change in odds ratio). None of the prespecified subgroup analyses of women, elderly patients, and diabetic patients showed a statistically significantly different effect of HEART care with respect to incidence of MACEs (data not shown). The additional analysis comparing usual versus HEART care stratified by time period did not indicate heterogeneity of the odds ratio across time periods (Breslow–Day test $P = 0.34$) (Appendix Table 3, available at Annals.org).

Five (0.3%) deaths occurred during HEART care, and 9 (0.5%) occurred during usual care. Further details on MACE components are provided in Table 2. The incidence of MACEs in low-risk patients was 2.0% (95% CI, 1.2% to 3.3%), with 1 death of unknown cause occurring 4 weeks after initial presentation. This patient presented with atypical symptoms and ECG, and 2 troponin measurements were normal; the HEART score was calculated as 3 but should have been 4 because the patient was older than 65 years and was known to have had a stroke. Appendix Table 4 (available at Annals.org) shows detailed information on MACEs in low-risk patients. The non-MACE group consisted of 2900 (80%) patients, with a final diagnosis on initial presentation of stable angina in 231 patients, rhythm disorders in 208 patients, heart failure in 37 patients, pericarditis in 58 patients, and nonspecific or noncardiac chest pain in 2366 patients.

Use of Health Care Resources

No major differences between HEART care and usual care were observed (Table 3). The proportion of patients with early discharge from the emergency department (≤4 hours) was slightly higher during HEART care (34.8% vs 30.9%, leading to a difference after adjustment for clustering and time steps of 0.7% [CI, −5.6% to 7.0%]). There was no difference in median length of stay (4 hours) at the emergency department. Among low-risk patients, 648 (91%) were discharged from the emergency department after initial presentation, although 232 of these patients (36%) were discharged only after prolonged observation. Of the 67 low-risk patients admitted to the hospital, 42 received a final diagnosis of nonspecific chest pain, 18 received a noncardiac diagnosis (such as cholangitis), and 7 were diagnosed with cardiac ischemia. During HEART care, outpatient clinic visits (both cardiology and other medical specialties) increased (69.6% vs. 59.8%, leading to a difference after adjustment for time steps and clustering of −0.9% [CI, −11.3% to 9.5%]). In addition, a small decrease in the proportion of patients who underwent exercise stress ECG, nuclear imaging, and coronary an-

Table 1. Patient Characteristics at Baseline

Characteristic	Usual Care (n = 1827)	HEART Care (n = 1821)
Demographic		
Male, *n (%)*	1005 (55)	975 (54)
Mean age (SD), *y*	62 (14)	62 (14)
Vital signs at presentation		
Mean blood pressure (SD), *mm Hg*		
Systolic	143 (24)	144 (24)
Diastolic	81 (13)	81 (13)
Mean heart rate (SD), *beats/min*	74 (17)	73 (15)
Killip class I, *n (%)*	1809 (99)	1796 (99)
Cardiac risk factors, *n (%)*		
Diabetes mellitus	301 (16)	285 (16)
Obesity (body mass index >30 kg/m^2)	253 (14)	327 (18)
Hypercholesterolemia	683 (37)	585 (32)
Hypertension	926 (51)	879 (48)
Positive family history	599 (33)	651 (36)
Current smoking	444 (24)	452 (25)
History of cardiovascular disease, *n (%)*	670 (37)	596 (33)
Acute myocardial infarction	351 (19)	288 (16)
Percutaneous coronary intervention	416 (23)	344 (19)
Coronary artery bypass grafting	162 (9)	131 (7)
Cerebrovascular accident or transient ischemic attack	131 (7)	101 (6)
Peripheral artery disease	77 (4)	69 (4)
Laboratory results at presentation		
Mean creatinine level (SD)		
μmol/L	82 (31)	80 (33)
mg/dL	0.9 (0.4)	0.9 (0.4)
Medication at presentation, *n (%)*		
Aspirin	671 (37)	621 (34)
$P2Y_{12}$ inhibitor (clopidogrel)	132 (7)	109 (6)
Vitamin K antagonists (coumarin)	190 (10)	168 (9)
Other (dipyridamole, ticagrelor, and direct oral anticoagulants)	84 (5)	69 (4)
HEART score, *n (%)*		
0–3 (low risk)	–	715 (39)
4–6 (intermediate risk)	–	861 (47)
7–10 (high risk)	–	190 (11)
Missing	–	55 (3)

HEART = History, Electrocardiogram, Age, Risk factors, and initial Troponin.

Table 2. Comparison of 6-Week Incidence of MACE and Its Components Between Usual Care and HEART Care*

Variable	Usual Care (*n* = 1827)	HEART Care (*n* = 1821)	HEART Score 0–3 (*n* = 715)†	HEART Score 4–6 (*n* = 861)	HEART Score 7–10 (*n* = 190)	HEART Score Missing (*n* = 55)
Patients with MACE	405 (22.2)	345 (18.9)	14 (2.0)	175 (20.3)	140 (73.7)	16 (29.1)
MACE components‡						
Death	9 (0.5)	5 (0.3)	1 (0.1)	2 (0.2)	2 (1.1)	0 (0)
Cardiovascular	6	1	0	0	1	0
Noncardiovascular	0	1	0	0	1	0
Unknown cause§	3	3	1	2	0	0
Total cardiac ischemia	400 (21.9)	329 (18.1)	10 (1.4)	162 (18.8)	143 (75.3)	14 (25.4)
Unstable angina	157	105	6	70	25	4
Non–ST-segment elevation myocardial infarction	214	211	4	91	107	9
ST-segment elevation myocardial infarction	29	13	0	1	11	1
Total significant stenosis	290 (15.9)	247 (13.6)	10 (1.4)	117 (13.6)	102 (11.8)	16 (29.1)
Managed conservatively	39	41	1	27	13	0
Percutaneous coronary intervention	208	158	7	70	66	13
Coronary artery bypass grafting	43	48	2	20	23	3
Total MACEs	699	581	21	281	247	30

HEART = History, Electrocardiogram, Age, Risk factors, and initial Troponin; MACE = major adverse cardiac event.
* Values are numbers (percentages).
† For more information on these patients, see **Appendix Table 4** (available at Annals.org).
‡ Totals of MACE components exceed total MACEs because a patient can have >1 component.
§ Includes presumed acute cardiac death at home (no autopsy performed).

giography was observed during HEART care (**Appendix Table 5**, available at Annals.org).

Quality of Life, Costs, and Cost-Effectiveness Analysis

Quality-of-life scores on the EQ-5D at baseline, 2 weeks, and 3 months were 0.71, 0.73, and 0.77, respectively, for HEART care and 0.70, 0.71, and 0.73 for usual care (**Appendix Table 6**, available at Annals.org). Health outcomes over the 3 months after initial presentation, expressed as quality-adjusted life-years (QALYs) per patient, were 0.17 for both HEART care and usual care. The QALYs calculated using visual analogue scale scores were lower, but the difference was similar (data not shown). Mean direct health care costs per patient were €3061 (CI, €2623 to €3527) and €3258 (CI, €2827 to €3762) for HEART and usual care, respectively (difference, −€197 [CI, −€876 to €450]). With regard to health outcomes as well as health care costs, HEART care was superior to usual care (in health economic terms, HEART care dominated usual care). However, differences in health outcomes and costs were small, with substantial uncertainty remaining. The probability that HEART care dominated usual care was 71%, and the probability that HEART care was cost-effective at a willingness-to-pay threshold of €20 000 per QALY was 99% (**Appendix Table 7**, available at Annals.org).

Adherence

Nonadherence occurred in 313 of 1766 (18%) patients (291 of 715 [41%] low-risk patients and 22 of 190 [12%] high-risk patients) (**Appendix Table 8**, available at Annals.org). Nonadherence in low-risk patients consisted of prolonged observation or hospitalization after presentation at the emergency department in 234 of 291 (80%) patients, a second troponin measurement in 170 of 291 (58%) patients, or stress bicycle testing in 52 of 291 (18%) patients. The reason for nonadherence was not given for 161 (55%) low-risk patients and was given as intuition for 70 (24%) patients, an alternative diagnosis being more probable for 33 (11%) patients, and logistics for 27 (9%) patients.

DISCUSSION

In this stepped-wedge, cluster randomized trial comparing use of the HEART score versus usual care in patients with chest pain, noninferiority for the safety outcome (MACE) was demonstrated, with a difference in incidence of −1.3% in favor of HEART care and a 1-sided 95% upper confidence limit of 2.1% (within the noninferiority margin of 3.0%). Major adverse cardiac events occurred in 2.0% (CI, 1.2% to 3.3%) of low-risk patients (HEART score of 0 to 3). Use of health care resources was typically lower during HEART care, but absolute differences were small, and no statistically significant differences were found after adjustment for clustering and time steps. The combination of equal safety, small improvements in quality of life, and lower costs resulted in a likelihood of 99% that HEART care would be cost-effective. Extrapolation of the findings of our cost-effectiveness analysis (including nonadherence) suggests that HEART care could lead to annual savings of €40 million in the Netherlands.

The findings on safety are consistent with several previous studies of the HEART score, in which MACE incidence in low-risk patients ranged from 0.6% to 1.7% (13–21). False-negative rates of 1% or 2% have been considered acceptable for clinicians assessing patients with chest pain (30, 31). Advantages of the HEART score are its simplicity (5 items) and the fact that it was developed specifically for patients with chest pain presenting at the emergency department. Furthermore, it identifies the largest proportion (up to 40%) of patients as low risk and eligible for early discharge from the emergency department, with 99% (CI, 97% to 100%) sensitivity for acute coronary syndrome (15, 17–19, 32).

Nonadherence occurred in 18% of our low-risk patients, which is similar to nonadherence rates found by Mahler and colleagues (29% of low-risk patients in a single-center randomized trial [33]).

This trial has several strengths. It was a high-impact trial that included patients in a multicenter collaboration with several types of hospitals, making our results highly generalizable. Furthermore, this pragmatic trial reflects the current real-life effect of implementation of the HEART score, taking into account possible intended and unintended effects of its use. In addition, we had complete follow-up in almost all patients (99.9%). Another strength of our study is its stepped-wedge design (34). This enabled a within-hospital comparison of HEART care versus usual care, which may be less confounded than a comparison between hospitals in a standard, parallel, cluster randomized trial. We ensured that no HEART scores were calculated during usual care. Finally, unstable angina and all revascularization procedures were included in our definition of MACE so as to capture all clinically relevant end points. Excluding unstable angina and elective revascularization would have decreased the incidence of MACEs in low-risk patients from 2.0% to 1.0%.

Several limitations must be considered. First, inclusion of patients during HEART care versus usual care may have differed because we observed small differences in baseline characteristics between study periods. We saw small changes in estimates when taking the effect of time steps into account, but further adjustment for other known prognostic factors of MACEs did not have an effect. Second, we did not reach the number of patients in our initial sample size calculations. This was not due to early termination or interim analyses but to 2 external causes: withdrawal of 1 large hospital 1 week before the start of the trial and the time constraints of obtaining informed consent. Also, the stepped-wedge design results in a fixed number and length of steps, reducing flexibility to add clusters or lengthen the inclusion period. Despite the lower number of inclusions, our study was still able to show noninferiority. In hindsight, the effect of within-cluster correlation was overestimated, with a very low intraclass correlation coefficient of 0.0055 (35, 36).

There are several possible reasons for the limited effect on health care use we observed. First, physicians calculated the score but did not always adhere to its recommendation. Because this was a pragmatic trial assessing a decision-support tool, deviating from the score was part of the intervention. In particular, we observed nonadherence of 41% in the low-risk group. A possible explanation for this is the difficulty in changing

Table 3. Use of Health Care Resources Within 3 Months of Initial Presentation

Variable	Usual Care (*n* = 1827)	HEART Care (*n* = 1821)	HEART Score 0–3 (*n* = 715)	HEART Score 4–6 (*n* = 861)	HEART Score 7–10 (*n* = 190)	HEART Score Missing (*n* = 55)
Initial presentation at ED						
Not admitted, *n (%)*	1199 (66)	1263 (69)	648 (91)	556 (65)	29 (15)	30 (55)
Prompt discharge (≤4 h), *n (%)**	564 (47)	633 (50)	416 (64)	190 (34)	9 (31)	18 (60)
Prolonged observation in ED/chest pain unit, *n (%)*	635 (53)	630 (50)	232 (36)	366 (66)	20 (69)	12 (40)
Median length of stay in ED (IQR), *h:min*	3:57 (2:30–5:57)	3:55 (2:35–5:44)	3:16 (2:21–4:43)	4:40 (2:56–6:20)	3:32 (2:16–5:51)	2:57 (2:17–5:11)
Admitted to hospital, *n (%)*	628 (34)	558 (31)	67 (9)	305 (35)	161 (85)	25 (45)
Admitted to critical care unit/intensive care unit after ED, *n (%)*	296 (47)	223 (40)	25 (37)	104 (34)	81 (50)	13 (50)
Median length of stay (IQR), *d*	4 (2–6)	3 (2–6)	2 (2–3)	3 (2–5)	4 (3–8)	4 (2–7)
Total days, *n*	3365	3085	193	1521	1228	143
Days in critical care unit/intensive care unit	1032	880	44	360	435	41
≥1 recurrent visit to ED, *n (%)*	266 (15)	277 (15)	72 (10)	151 (18)	46 (24)	8 (15)
Total visits, *n*	382	380	110	200	59	11
Final diagnosis of cardiac ischemia, *n*	80	79	11	49	18	1
≥1 readmission, nonelective, *n (%)*	221 (12)	193 (11)	49 (10)	104 (12)	37 (19)	3 (5)
Total readmissions, *n*	296	261	59	145	51	6
Median length of stay (IQR), *d*	2 (0–6)	2 (0–6)	2 (0–4)	2 (0–7)	2 (0–7)	2 (0–4)
≥1 outpatient clinic visit, *n (%)*	1093 (60)	1267 (70)	381 (53)	686 (80)	165 (87)	35 (64)
Total visits, *n*	2730	3203	848	1823	443	89
Cardiology	1505	1779	417	1034	267	61
Other specialty	1225	1424	431	789	176	28
≥1 new visit to general practitioner for cardiac reason, *n (%)*†	195 (11)	213 (12)	86 (12)	102 (12)	18 (9)	7 (13)

ED = emergency department; HEART = History, Electrocardiogram, Age, Risk factors, and initial Troponin; IQR = interquartile range. * Initial work-up consisted of history, physical examination, first troponin measurement, and electrocardiography without further testing (e.g., second troponin measurement or stress testing).
† Information was obtained via the 3-mo telephone call. Answers were missing for 367 (20%) patients in the usual care group and 378 (20%) in the HEART care group because we were unable to contact 20% of all patients and hospital medical files do not record information on general practitioner visits.

behavior. In addition, there may have been concern about the safety of the score. Studies showed rates of misdiagnosis of up to 6% in patients with chest pain, and the estimated incidence of unexpected sudden death is 0.05% to 0.1% (5, 37). Accepting this inevitable risk is becoming more difficult in our increasingly risk-averse society and poses a dilemma for physicians and patients, fueling the need for more testing and monitoring (38).

We conclude that the HEART score is an accurate risk-stratification instrument and is safe to use when assessing patients with chest pain in the emergency department. Hesitance to refrain from admission and testing in patients with low scores could explain the small effect on health care costs. Such barriers should be addressed for patient management to better adhere to directive use of the HEART score.

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Appendix 1: Differences in Outcomes Between Study Protocol and ClinicalTrials.gov

After publishing the study protocol in 2013, we made several changes in outcomes and the statistical analysis plan, including the following:

Use of health care resources: We included the variables "revisit at the ED" and "outpatient clinic visits" to our list of outcomes measured for use of health care resources to have a more complete view of use of health care resources.

Quality of life and indirect costs: We did not include the Short Form-36 Health Survey and iMTA Productivity Cost Questionnaire in the current cost-effectiveness analysis.

Subgroup analysis: We could not perform the subgroup analysis of ethnicity because too many values were missing and the vast majority (>90%) of patients were white. We changed the cutoff for older age to older than 75 years instead of a median age of 62 years as mentioned in our study protocol to address the difference in elderly and younger patients because we believe that age 62 years is still young.

Appendix 2: Statistical Analysis

The 6-week cumulative incidence of MACEs was analyzed using generalized linear models. The binomial distribution and the identity link were used to directly estimate absolute differences in MACE incidence between HEART care and usual care patients. Because a stepped-wedge design is a type of cluster trial, we used the generalized estimating equation approach to take clustering of MACEs within hospitals into account using the exchangeable correlation structure (23, 28). Generalized estimating equation models tend to underestimate SEs if the number of clusters (9 in our case)

is limited (29). Therefore, we used a stratified bootstrap procedure (500 bootstraps) as implemented in Stata procedure XTGEE to obtain CIs with better coverage (29). The main model included type of care (usual or HEART), steps (time periods) as a categorical variable, and hospitals as clusters. The difference in MACE incidence with a 1-sided 95% CI was estimated in order to evaluate noninferiority of this main safety outcome. The noninferiority margin was prespecified at 3.0% (absolute difference in MACE incidence between HEART and usual care <3.0%). In a sensitivity analysis, we further adjusted for the following known prognostic factors that could be potential confounders: age, sex, any cardiovascular history, and risk factors for cardiovascular disease.

Four prespecified subgroups were investigated to determine whether the effect of HEART care differed with respect to MACE incidence: men versus women, older versus younger than 75 years, diabetic versus nondiabetic patients, and white versus other race. We changed the cutoff for older age from 62 to 75 years to better represent elderly patients. Furthermore, the race subgroup was dropped because this information was missing in 30% of patients and 98% of the remaining patients were white. Subgroups were examined by performing a formal test of interaction by adding the subgroup-by-treatment interaction to the model. No adjustment for multiple comparison was done because of the limited number of subgroups and their prespecified nature.

The same modeling approach was applied for other binary outcomes to estimate absolute differences and 2-sided 95% CIs in the use of health care between HEART and usual care: proportion of initially admitted patients, proportion of patients with early discharge, proportion of readmitted patients, proportion of patients with a revisit to the emergency department, proportion of patients with 1 or more outpatient clinic visits, and proportion of patients undergoing specific diagnostic tests. The 95% CI around the absolute risk for MACEs in patients with a low HEART score was estimated using the method of Wilson. We also performed a stratified analysis comparing the incidence of MACEs between HEART versus usual care within each time period. A formal test for homogeneity of the odds ratio across time periods (Breslow–Day test) was performed. Finally, we performed a stratified analysis comparing the incidence of MACEs between HEART versus usual care, stratified by hospital and overall (**Appendix Table 9**).

The generalized estimating equation models were performed using the XT and XTGEE routines in Stata, version 13.1, with use of their bootstrap procedures to obtain robust estimates of their SEs.

Appendix 3: Cost-Effectiveness Analysis

Detailed information on quality of life and costs was collected in 5 of the 9 participating hospitals (2 academic and 3 general). The costs for health care resource use were calculated based on Dutch guidelines and cost tables for the corresponding hospitals. Different costs were used for the academic and general hospitals, and costs were adjusted for inflation by using the consumer price indices provided by Statistics Netherlands (39). For each participant in this study, the costs were calculated based on the observed number and type of health care resources used and the type of hospital (academic or general). Data on resource use were collected for each patient in the 5 participating hospitals; no data were missing.

Quality of life was derived from the EQ-5D-3L questionnaire, a quality-of-life questionnaire consisting of 5 questions (dimensions) with 3 answers each, from which quality-of-life scores (utility values) can be directly derived. More information is available at www.euroqol.org. Quality-adjusted life-years were calculated over a period of 3 months, based on the estimated quality-of-life values at 0 weeks, 2 weeks, and 3 months.

For quality-of-life estimates (that is, utilities), some follow-up data were missing, and multiple imputation (with 10 imputed data sets) was therefore performed. The MICE package in R, version 3.3.1 (R Foundation for Statistical Computing), was used for multiple imputation (40). The imputation was based on patient characteristics (such as age and sex), quality-of-life scores (the answers to the EQ-5D questionnaires) recorded at each follow-up, and the included hospital and the period in which usual care was replaced by HEART care. The process of imputation was repeated for each of the 2500 bootstrap samples. The average across the imputed data sets was used to obtain CIs around the differences in costs and quality-of-life estimates for HEART care versus usual care. Differences in outcomes for the complete cases and multiple imputations and their 95% CIs are shown in **Appendix Table 6**.

Appendix Table 7 shows the probabilities that HEART care versus usual care would improve health outcomes, reduce costs, or both. Probabilities were calculated by dividing the number of bootstrap samples resulting in better or worse health outcomes and in lower or higher costs for HEART care compared with usual care by the total number of bootstrap samples (n = 2500).

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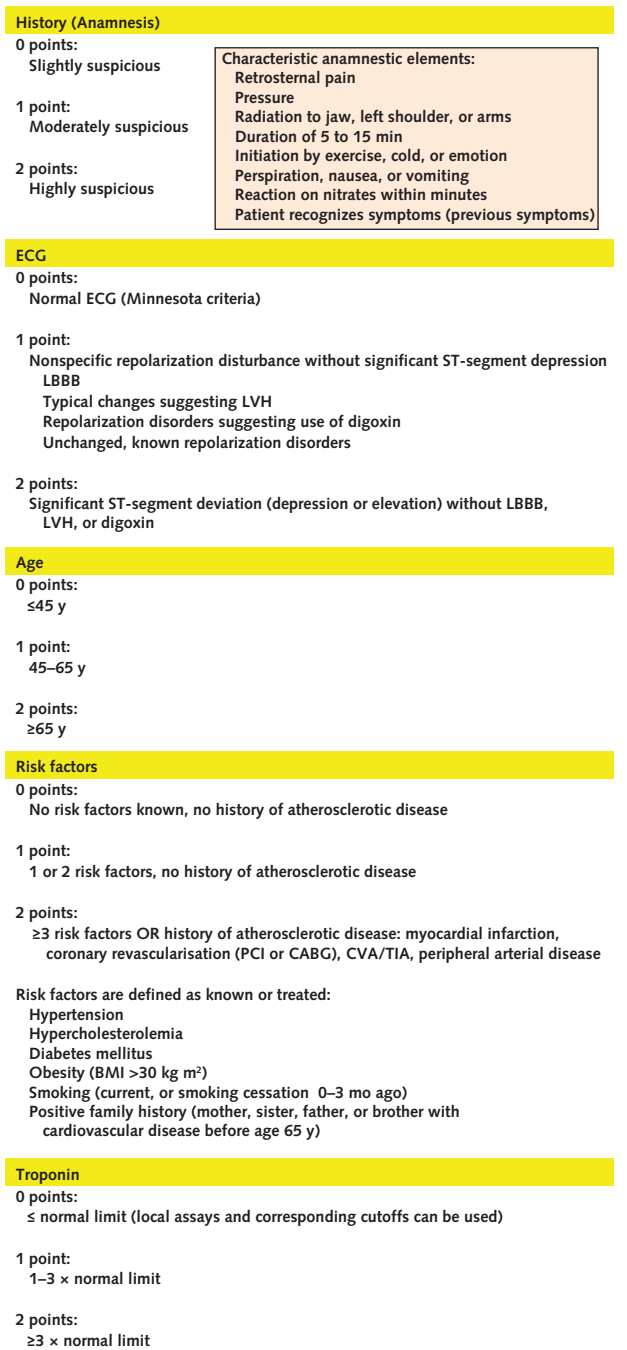
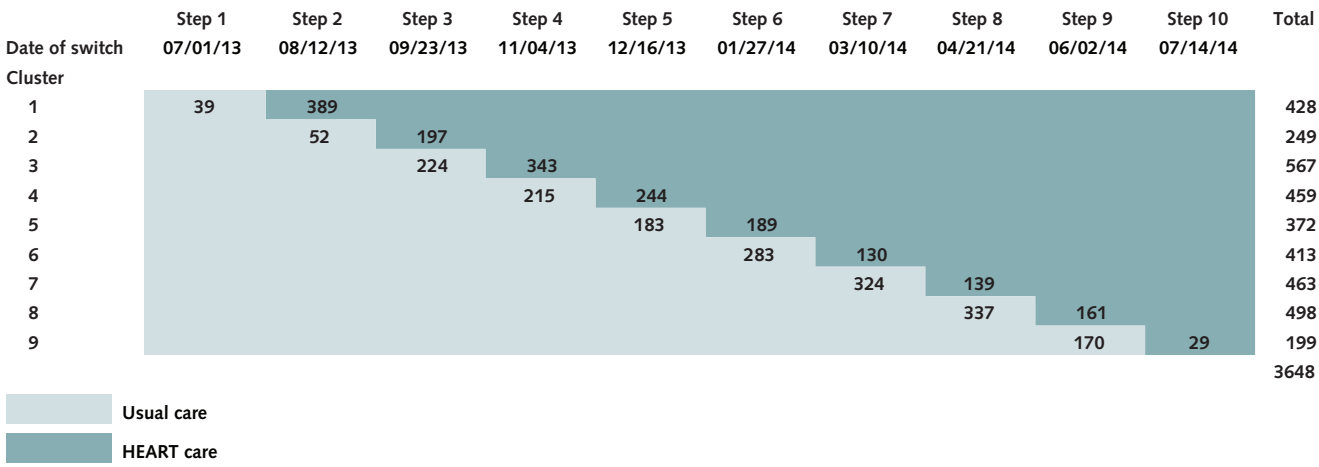
Appendix Figure 1. Instructions for physicians for calculation of the HEART score in the emergency department.



BMI = body mass index; CABG = coronary artery bypass grafting; CVA = cerebrovascular accident; ECG = electrocardiogram; HEART = History, ECG, Age, Risk factors, and initial Troponin; LBBB = left bundle branch block; LVH = left ventricular hypertrophy; PCI = percutaneous coronary intervention; TIA = transient ischemic attack.

Appendix Figure 2. Stepped-wedge design with the number of patients per hospital included in each study period of the HEART-Impact trial.



HEART = History, Electrocardiogram, Age, Risk factors, and initial Troponin.

Appendix Table 1. Characteristics of Participating Hospitals

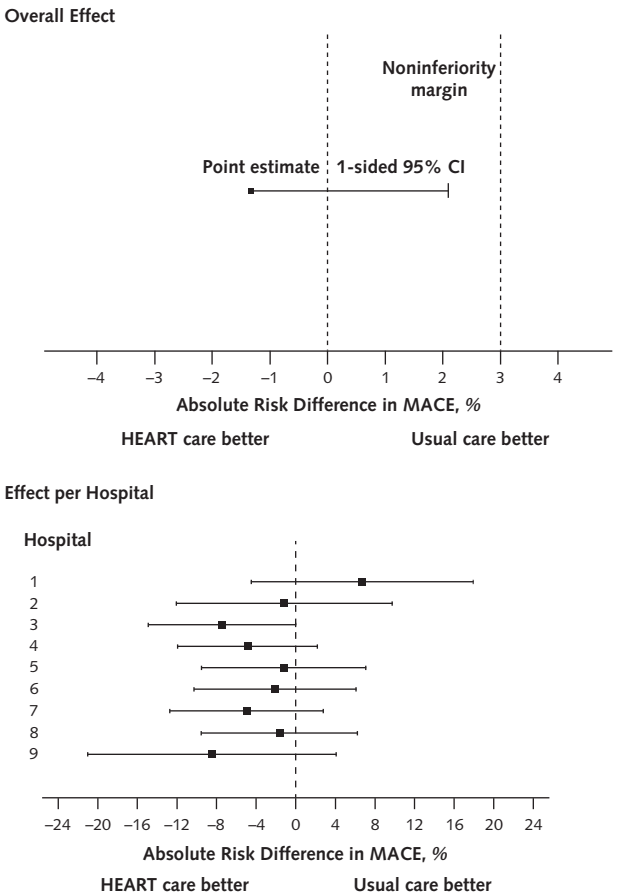
Hospital	Type	Beds, *n*	Revascularization Options in Own Hospital
1	Peripheral	505*	No
2	Peripheral	262*	No
3	Academic	733	PCI and CABG
4	Peripheral	1230†	PCI
5	Academic	1042†	PCI and CABG
6	Peripheral	1102	PCI and CABG
7	Peripheral	550†	PCI and CABG
8	Peripheral	378†	No
9	Peripheral	255	No

CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention.
* In 2012.
† In 2013.

Appendix Table 2. Characteristics of Troponin Kits and Cutoffs Used in Hospitals

Hospital	Type of Assay	Type of Troponin	Analyzer	Cutoff Value, *ng/L*
1	Conventional	I	Siemens Dimension Vista	45
2	Conventional	I	Beckman Coulter DxI	40
3	High-sensitivity	T	Roche modular	14
4	High-sensitivity	T	Roche Cobas	10
5	Conventional	I	Beckman Coulter DxI	60
6	High-sensitivity	T	Roche Cobas	14
7	High-sensitivity	T	Roche Cobas	30 + delta >8
8	High-sensitivity	T	Roche modular	50
9	High-sensitivity	T	Roche Cobas	14

Appendix Figure 3. Absolute differences in risk for MACEs associated with HEART care minus usual care to assess noninferiority for this safety outcome, for the overall effect (*top*) and the effect per hospital (*bottom*).



HEART = History, Electrocardiogram, Age, Risk factors, and initial Troponin; MACE = major adverse cardiac event.

Appendix Table 3. Observed Incidence of MACE Comparing Usual Care With HEART Care, Stratified by Step (Time Period)*

Variable	Usual Care			HEART Care			All Patients		
	MACE, *n*	Total, *n*	Proportion	MACE, *n*	Total, *n*	Proportion	MACE, *n*	Total, *n*	Proportion
Time period									
1	98	403	0.243	–	–	–	98	403	0.243
2	88	392	0.224	18	69	0.261	106	461	0.230
3	75	285	0.263	13	89	0.146	88	374	0.235
4	35	158	0.222	20	110	0.182	55	268	0.205
5	19	145	0.131	19	146	0.130	38	291	0.131
6	44	195	0.226	44	223	0.197	88	418	0.211
7	28	162	0.173	62	291	0.213	90	453	0.199
8	16	74	0.216	46	242	0.190	62	316	0.196
9	4	13	0.308	67	343	0.195	71	356	0.199
10	–	–	–	56	308	0.182	56	308	0.182
All patients	407	1827	0.223	345	1821	0.189	752	3648	0.206

HEART = History, Electrocardiogram, Age, Risk factors, and initial Troponin; MACE = major adverse cardiac event.
* A formal test of homogeneity of the odds ratio across time periods did not indicate heterogeneity (Breslow–Day test $P = 0.34$).

Appendix Table 4. Detailed Characteristics of Low-Risk Patients With MACE Within 6 Weeks

Patient	Age, *y*	Sex	HEART Score						Troponin 1*	Troponin 2*	MACE†	Emergency Department Date	MACE Date	Adherence to HEART Policy
			History	ECG	Age	Risk Factors	Initial Troponin	Total						
1	58	Male	1	0	1	0	0	2	Under	Under	UA; CABG	7/09/13	7/09/13; 16/10/13	No
2	42	Male	1	0	0	1	0	2	Under	Under	**NSTEMI‡; PCI**	4/06/14	4/06/14; 5/06/14	No
3	46	Male	1	0	1	0	0	2	Under	Under	PCI	15/11/13	9/12/13	No
4	46	Male	1	0	1	0	1	3	Above	Above	**NSTEMI**	7/04/14	7/04/14	No
5	61	Female	1	0	1	1	0	3	Under	Above	**NSTEMI**	30/06/14	30/06/14	No
6	67	Female	0	0	2	1	0	3	Under	Under	**Death–unknown cause**	15/07/14	13/08/14	No
7	65	Male	1	0	1	1	0	3	Under	Above	UA; CABG	18/04/14	18/04/14; 29/04/14	No
8	56	Male	1	0	1	1	0	3	Under	Not performed	UA (no CA performed)	24/02/14	24/02/14	Yes
9	49	Male	0	0	1	2	0	3	Under	Not performed	UA; PCI	8/07/14	8/07/14; 10/07/14	No
10	56	Male	1	0	1	1	0	3	Under	Not performed	UA; PCI	2/06/14	2/06/14; 14/07/14	Yes
11	49	Male	0	0	1	2	0	3	Under	Under	PCI	3/07/14	23/07/14	No
12	60	Male	0	0	1	2	0	3	Under	Under	CABG–conservative	1/07/14	29/07/14	No
13	41	Female	1	0	0	1	1	3	Above	Above	**NSTEMI**	20/02/14	20/02/14	No
14	62	Male	1	0	1	1	0	3	Under	Not performed	UA; PCI	19/03/14	19/03/14; 2/04/14	Yes

CA = coronary angiography; CABG = coronary artery bypass grafting; ECG = electrocardiogram; HEART = History, ECG, Age, Risk factors, and initial Troponin; MACE = major adverse cardiac event; NSTEMI = non–ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction; UA = unstable angina.

* Troponin measurements are classified as under or above the 99th percentile.

† Boldface indicates only NSTEMI, STEMI, emergency revascularization, and death.

‡ Troponin 3 level of 77 ng/L.

Appendix Table 5. Use of Diagnostic Procedures Within 3 Months of Presentation at the Emergency Department*

Variable	Usual Care (*n* = 1176)	HEART Care (*n* = 804)	HEART Score 0–3 (*n* = 346)	HEART Score 4–6 (*n* = 361)	HEART Score 7–10 (*n* = 65)	HEART Score Missing (*n* = 32)
Patients with ≥1 of the tests mentioned in this table	765 (65)	461 (57)	137 (40)	250 (69)	56 (86)	18 (56)
Total diagnostic tests	1565	940	228	541	136	35
Tests within the first 2 d	582 (37)	347 (37)	49 (21)	216 (40)	65 (48)	17 (49)
Stress bicycle electrocardiography testing†	465 (40)	300 (37)	96 (28)	175 (48)	18 (28)	11 (34)
Echocardiography (transthoracic)	410 (35)	243 (30)	50 (15)	142 (39)	43 (66)	8 (25)
Nuclear imaging	198 (17)	89 (11)	24 (7)	56 (16)	8 (12)	1 (0)
CT scan or CT angiography (excluding pulmonary embolism)	87 (7)	47 (6)	16 (5)	27 (7)	3 (5)	1 (0)
Coronary CT angiography	40 (3)	26 (3)	14 (4)	10 (3)	0 (0)	2 (1)
Cardiac magnetic resonance imaging	19 (2)	16 (2)	6 (2)	10 (3)	0 (0)	0 (0)
Coronary angiography	346 (29)	219 (27)	22 (6)	121 (34)	64 (98)	12 (38)
Normal coronary arteries	41	19	4	13	2	0
Nonsignificant stenosis	101	69	13	39	14	3
Significant stenosis conservatively treated	28	15	0	12	3	0
Significant stenosis invasively treated	176	116	5	57	45	9

CT = computed tomography; HEART = History, Electrocardiogram, Age, Risk factors, and initial Troponin.
* Data based on patients from the 5 hospitals participating in the cost-effectiveness analysis. Values are numbers (percentages).
† Divided by the total number of patients in the study period (465/1176).

Appendix Table 6. Results of Cost-Effectiveness Analysis in 5 Hospitals: Differences in Cost and Quality-of-Life Estimates Between HEART and Usual Care

Variable	Usual Care: Complete Cases	HEART Care: Complete Cases	Difference: Complete Cases*	Usual Care After Multiple Imputation	HEART Care After Multiple Imputation	Difference After Multiple Imputation
Mean baseline quality of life (95% CI)	0.71 (0.00 to 1.00)	0.71 (0.10 to 1.00)	0.01	0.70 (0.69 to 0.72)	0.71 (0.69 to 0.73)	0.01 (−0.02 to 0.03)
Missing values, *n* (%)	64 (6.1)	49 (6.9)	-	-	-	-
Mean quality of life at 2 wk (95% CI)	0.71 (0.03 to 1.00)	0.74 (0.06 to 1.00)	0.02	0.71 (0.69 to 0.73)	0.73 (0.71 to 0.75)	0.02 (−0.01 to 0.05)
Missing values, *n* (%)	324 (30.7)	233 (32.6)	-	-	-	-
Mean quality of life at 3 mo (95% CI)	0.73 (0.03 to 1.00)	0.77 (0.16 to 1.00)	0.04	0.73 (0.71 to 0.75)	0.77 (0.75 to 0.79)	0.04 (0.01 to 0.07)
Missing values, *n* (%)	391 (37.1)	249 (34.9)	-	-	-	-
Mean quality-adjusted life-years (95% CI)	0.17 (0.03 to 0.23)	0.17 (0.04 to 0.23)	0.01	0.16 (0.16 to 0.17)	0.17 (0.17 to 0.18)	0.01 (0.00 to 0.01)
Missing values, *n* (%)	487 (46.2)	339 (47.5)	-	-	-	-
Mean total costs (after 3 mo) (95% CI), €†	3256 (8 to 20 405)	3070 (8 to 23 718)	−186	3258 (2827 to 3762)	3061 (2623 to 3527)	−197 (−876 to 450)

HEART = History, Electrocardiogram, Age, Risk factors, and initial Troponin.
* Calculated by subtracting the values for usual care from those for HEART care.
† Costs of diagnostic testing, laboratory tests, inpatient hospital days (normal, intensive care unit, and cardiac care unit), and visits to the general practitioner.

Appendix Table 7. Four Main Categories of Cost-Effectiveness Results for HEART Care and Their Associated Probabilities

HEART Care Compared With Usual Care	Probability
Better health outcomes and cheaper	0.710
Better health outcomes and more expensive	0.284
Worse health outcomes and cheaper	0.003
Worse health outcomes and more expensive	0.004

HEART = History, Electrocardiogram, Age, Risk factors, and initial Troponin.

Appendix Table 8. Adherence to the HEART Score Recommendation for Further Patient Management*

Variable	Usual Care (*n* = 1827)	HEART Care (*n* = 1766)†		HEART Low-Risk (*n* = 715)‡		HEART High-Risk (*n* = 190)	
		Adhered to HEART Policy (*n* = 1453 [82.3%])	Did Not Adhere to HEART Policy (*n* = 313 [17.7%])	Adhered to HEART Policy (*n* = 424 [59.3%])	Did Not Adhere to HEART Policy (*n* = 291 [40.7%])	Adhered to HEART Policy (*n* = 168 [88%])	Did Not Adhere to HEART Policy (*n* = 22 [12%])
MACE within 6 wk	405 (22.2)	315 (21.7)	14 (4.5)	3 (0.7)	11 (3.8)	137 (82)	3 (14)
MACE (only acute myocardial infarction, emergency revascularization, and death)	243 (13.3)	203 (14.0)	5 (1.6)	0 (0)	5 (1.7)	113 (67)	0 (0)
Discharge ≤4 h after presentation	564 (47)	549 (37.8)	66 (21.1)	359 (84.7)	57 (19.6)	0 (0)	9 (40)
Prolonged observation at ED	635 (53)	438 (30.1)	180 (57.5)	65 (15.3)	167 (57.4)	7 (4)	13 (59)
Initial admission to hospital	628 (34)	466 (32.1)	67 (21.4)	0 (0)	67 (23.7)	161 (100)	0 (0)
Recurrent ED visits within 3 mo	266 (15)	233 (16.0)	36 (11.5)	41 (9.7)	31 (10.7)	41 (24)	5 (23)
Nonelective readmissions within 3 mo	221 (12)	164 (11.3)	26 (8.3)	26 (6.1)	24 (8.2)	35 (21)	2 (9)
Outpatient clinic visits within 3 mo	1093 (60)	1025 (70.5)	207 (66.1)	187 (44.1)	189 (64.9)	144 (86)	18 (82)

ED = emergency department; HEART = History, Electrocardiogram, Age, Risk factors, and initial Troponin; MACE = major adverse cardiac event.
* Adherence to HEART policy was defined as admission and additional testing in low-risk patients (overtesting) or no objective testing in high-risk patients (undertesting). Nonadherence was not defined for patients in the intermediate-risk group, and all patients in this risk category were counted as adherent. Values are numbers (percentages).
† 1821 patients in HEART care period minus 55 patients without a HEART score.
‡ See **Appendix Table 4**.

Appendix Table 9. Observed Incidence of MACE by the 2 Study Periods (Usual Care and HEART Care), Stratified by Hospital and Overall

Variable	Usual Care			HEART Care			All Patients		
	MACE, *n*	Total, *n*	Proportion	MACE, *n*	Total, *n*	Proportion	MACE, *n*	Total, *n*	Proportion
Hospital									
1	5	39	0.128	76	389	0.195	81	428	0.189
2	8	52	0.154	28	197	0.142	36	249	0.145
3	67	224	0.299	77	343	0.224	144	567	0.254
4	44	215	0.205	38	244	0.156	82	459	0.179
5	40	183	0.219	39	189	0.206	79	372	0.212
6	58	283	0.205	24	130	0.185	82	413	0.199
7	72	324	0.222	24	139	0.173	96	463	0.207
8	81	337	0.240	36	161	0.224	117	498	0.235
9	32	170	0.188	3	29	0.103	35	199	0.176
All patients	407	1827	0.223	345	1821	0.189	752	3648	0.206

HEART = History, Electrocardiogram, Age, Risk factors, and initial Troponin; MACE = major adverse cardiac event.

Correction: Effect of Using the HEART Score in Patients With Chest Pain in the Emergency Department

The following sentence in a recent article (1) contains an error: The proportion of patients with early discharge from the emergency department (≤4 hours) was slightly higher during HEART care (34.4% vs. 30.6%, leading to a difference after adjustment for clustering and time steps of 0.7% [CI,–5.6% to 7.0%]). The "34.4% vs 30.6%" should be "34.8% vs 30.9%".

This has been corrected in the online version.

Reference

1. Poldervaart JM, Reitsma JB, Backus BE, Koffijberg H, Veldkamp RF, ten Haaf ME, et al. Effect of using the HEART score in patients with chest pain in the emergency department. A stepped-wedge, cluster randomized trial. Ann Intern Med. Ann Intern Med. 2017;166:689-97. [PMID: 28437795] doi:10.7326/M16-1600