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Does an imaging stress-test adds information to prognostic scores in patients with chest pain in the emergency department?

Francesca Innocenti[1] · Margherita Luzzi[1] · Chiara Donnini[1] · Maurizio Zanobetti[1] · Irene Tassinari[1] · Francesca Caldi[1] · Riccardo Pini[1]

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Abstract

We evaluated the ability of a stress-test (Str-T) to improve the risk stratification based on prognostic scores in patients presenting to the ED with chest pain. Between 2008, June and 2013, December, 1082 patients with chest pain were evaluated with an imaging Str-T. With a retrospective analysis, patients were stratified according to: (1) Florence Prediction Rule as low (0–1, LR-FPR), intermediate (2–4, IR-FPR), high risk (5–6, HR-FPR), respectively, 26, 50 and 24% of patients; (2) HEART score as LR-HEART, (0–3) and HR-HEART (≥4), respectively, 36 and 64%; (3) likelihood of CAD according to NICE guidelines, 10–29% LR-NICE, 30–60% IR-NICE and > 60% HR-NICE, respectively, 12, 18 and 70%. Scores' diagnostic performance was calculated with Str-T as reference. One-month follow-up by a phone call was performed, to investigate the occurrence of new cardiovascular events. In LR and HR patients, FPR and NICE score showed sensitivity 66 vs 93%, specificity 59 vs 19% (both $p < 0.001$), Positive Predictive Value (PPV) 36 vs 31%, Negative Predictive Value (NPV) 83 vs 87%. Among LR-HEART patients, Str-T was positive for inducible ischemia in 53 (14%) patients and 12 (4%) of them underwent a percutaneous coronary revascularization. The Str-T was negative for inducible ischemia in 760 (70%) patients, positive in 272 (25%), inconclusive in 50 (5%); among patients in the LR and IR subgroups, incidence of CAD (1.3 and 1.6%) and the cumulative incidence of significant events at 1-month follow-up (both 1%) was very low Str-T improved prognostic scores' diagnostic performance in LR- and HR-subgroups.

Keywords Chest pain · Imaging stress test · Prognostic scores

Introduction

Chest pain is one of the most common presenting complaints in the Emergency Department (ED), accounting for 9–10% of annual visits [1]. While the majority of these cases do not result in a diagnosis of acute coronary syndrome (ACS), incorrect diagnosis can potentially result in severe complications and mortality [2]. A number of prognostic scores have been proposed, but many of them were derived from heterogeneous groups of patients, pooling ST-segment elevation acute myocardial infarction together with unstable angina with troponin below the upper reference limit. Therefore, it is uncertain whether these scores are useful in non-selected, lower risk populations [3–5].

In patients with a negative initial diagnostic assessment, NICE guidelines [6] suggest estimation of the likelihood of coronary artery disease (CAD) with a score that takes into account symptom characteristics, age, gender and risk factors. The guidelines indicate the necessity for a coronary angiography procedure as a first-line investigation if the estimated likelihood of CAD is 61–90%. If the estimated likelihood of CAD is 30–60%, functional imaging as the first-line diagnostic investigation is recommended, while if the estimated likelihood of CAD is 10–29%, CT calcium scoring can be performed. The same parameters adopted by NICE guidelines to estimate risk are included in the Florence Prediction Rule (FPR), which was specifically validated in a population of patients who presented in the ED with a chief complaint of chest pain, without acute ischemic ECG changes or an increase in the troponin dosage. FPR has the great advantage of including variables

✉ Francesca Innocenti
innocenti.fra66@gmail.com

[1] High-Dependency Unit, Department of Clinical and Experimental Medicine, Azienda Ospedaliero-Universitaria Careggi, Lg. Brambilla 3, 50134 Florence, Italy

immediately available at the ED entrance: chest pain characteristics, evaluated through the Chest Pain Score [7], age, gender and a known history of diabetes or metabolic syndrome. On the basis of the sum of the score, patients are assigned a low (score 0–1), intermediate (score 2–4) or high (score 5–6) risk of new events [7].

In the validation paper [8], an ECG exercise test did not substantially modify prognostic stratification ability of the score. Patients in the high-risk subgroup with a negative ECG exercise test retain a high cardiovascular risk, and the authors emphasize that further evaluation should be considered, to rule out the presence of coronary artery disease.

Finally, we tested the HEART score [9, 10], which is a recently developed decision aid designed to identify ED chest pain patients, who can safely forgo objective cardiac testing.

The aim of this study is to evaluate the ability of a stress-test (Str-T) associated with imaging to improve the risk stratification based on prognostic scores.

Methods

Study population

In our hospital, all patients who arrive at the ED with chest pain of suspect cardiac origin and initial negative assessment (non-diagnostic ECG and troponin below the upper reference limit) are taken care of by the Emergency Physicians in the Observation Unit (OU). Careggi University-Hospital (Florence, Italy) is an urban, 1300-bed tertiary care center, with 130,000 ED visits per year. Until 2013, patients admitted into the OU, have been undergoing troponin evaluations, after 6 and 12 h from ED admission. Since 2012, with the introduction of High Sensitivity Troponin, the troponin evaluations have been reduced to one sample after 3 h from ED admission. In this retrospective study, we identified all consecutive patients who were evaluated in the OU with Str-T associated with an imaging modality between June 2008 and December 2013; exclusion criteria were not applied. The initial provocative test was the exercise stress-echo (ESE). If a patient had an exercise deconditioning, a coexisting disease which made it difficult to perform at a maximum level, or a permanent left bundle branch block on the ECG, we employed dobutamine as the stressor (DSE). In the presence of a bad acoustic window, we employed myocardial perfusion imaging (SPECT-MPI).

Chest pain characteristics were encoded according to the Chest Pain Score (CPS) [7].

Patients were then stratified according to the following scores:

1. FPR [7], that takes into account CPS value (CPS $\geq$ 7=3, < 7=0), male gender = 1, age > 50 years = 1 and metabolic syndrome = 1: according to this score, patients are classified as low risk (0–1, LR-FPR), intermediate risk (2–4, IR-FPR) and high risk (5–6, HR-FPR). The FPR score was available for all patients.
2. The risk score proposed by the NICE guidelines [6]: 10–29% is considered low risk (LR-NICE), 30–60% intermediate risk (IR-NICE) and > 60% high risk (HR-NICE). The score was available in 1069 patients (99%).
3. HEART score, which takes into account the age, the medical history, ECG modifications, Troponin level and presence of risk factors: in the original paper by Backus and coll. [11], HEART score 0–3 indicates low risk, 4–6 intermediate risk and > 6 high risk. However, no patients in this study population had a HEART score > 6, as they all had troponin below the upper reference limit and non-diagnostic ECG, which represent the criteria to undergo early evaluation with stress-test. Therefore, as proposed by Mahler and coll. [10, 12], patients were classified as Low risk (LR-HEART, 0–3) and High risk (HR-HEART, $\geq$ 4). The score was available in 1077 patients (99.5%). We collected basic demographic data and previous medical conditions from medical records of all patients, using a standardized collection template.

Informed patients gave their consent to perform Str-T (rate of refusal 5%). The study is consistent with the principles of the Helsinki Declaration for clinical research involving human patients.

Stress test protocol

The ESE was performed according to the standard Bruce protocol, aiming at reaching at least 85% of the age-adjusted maximum predicted heart rate (%MPHR: (220-age in years) × 0.85); the test was considered positive if $\geq$ 1 mm ST-segment depression measured at 80 ms after the J point developed at peak stress or during recovery. Before and immediately after exercise completion, echocardiographic images (iE33; Philips Medical System, Andover, MA) in the parasternal long and short axis and apical 4 and 2 chambers views, were acquired to allow quad-screen visualization.

Patients underwent DSE according to standard protocol [13]. Test end-points were: achievement of %MPHR, positive ischemic response indicated by new wall motion worsening in two or more myocardial segments, systolic blood pressure (SBP) > 240 mmHg or reduced SBP (drop > 40 mmHg from precedent phase, or SBP < 90 mmHg), repetitive ventricular or supraventricular ectopic beats, or ischemic ECG changes. With the evidence of new or worsening wall motion abnormalities in two or more segments at post-stress

examination, the test was considered positive, regardless of the presence of symptoms or ECG changes.

Nuclear stress testing

All SPECT-MPI examinations were performed with pharmacological (adenosine, 140 γ/kg/min for 6′ or dipyridamole 56 mg/kg for 4′) stress, according to standard protocol. The echocardiographic 16-segment model was used for perfusion analysis. Using visual inspection, each segment was classified as "normal", "hypoperfused", or "equivocal" [14].

Follow-up data

Data of coronary angiographies performed by patients with positive Str-TE were collected from medical records to verify the presence of significant coronary lesions. Significant coronary disease was defined as > 50% luminal diameter stenoses in any of the major coronary branches. One month after the test, we attempted to contact all patients to verify the occurrence of new cardiac events (cardiac death, non-fatal acute coronary syndrome, ACS, revascularization procedures) by means of a physician-directed telephone interview using a standardized questionnaire. Non-responders were contacted at least two-times, in different time slots. All hospital medical records of patients who reported new cardiac events were reviewed, to confirm data reported by patients during the phone call.

Statistical analysis

Data of prognostic scores and Str-T results were available for all patients. Data were analyzed with the SPSS statistical package version 24 (SPSS Inc., Chicago, IL, USA). Parametric data were reported as mean ± standard deviation. The Student's test for non-coupled parametric data was used to compare two groups and Analysis of Variance (ANOVA) to compare more than two groups, while Fisher exact test was used to analyze non-parametric data.

Str-T sensitivity, specificity and positive and negative predictive values (PPV and NPV) were calculated according to standard formulas. A p value < 0.05 was considered significant.

Results

Study population

Between June, 2008 and December, 2013, 1202 patients underwent Str-T with imaging modality for CAD screening. The 1082 patients (90%) who answered our phone call at 1-month follow-up represent our study population: out of these patients, 614 (57%) underwent ESE, 340 (31%) DSE and 128 (12%) SPECT-MPI. To ascertain if the study participants were representative of the whole population, we compared them with the patients ($n = 120$, 10%), who did not answer the phone call. Participants were slightly older (66 ± 13 vs 64 ± 14 years, $p = 0.038$) than non-participants; LV EF was comparable between the two groups (59±14% vs 60±12%, p = NS), while the Str-T showed inducible ischemia in a higher proportion of participants compared with non-participants (25% vs 11%, $p = 0.001$).

Clinical and rest echocardiographic characteristics, in the whole study population and according to prognostic scores stratification, are shown in Table 1; NICE score was not available in 13 patients (0.1%) and HEART score in 6 (0.05%). Risk stratification according to different prognostic scores was as follows: 26% LR group, 50% IR group and 24% HR group according to FPR and 12, 18 and 70% according to NICE score ($p < 0.001$ between the two assessment). HEART score identified 36% LR and 64% HR patients ($p < 0.001$ with both the other scores).

The Str-T showed inducible ischemia in 272 patients (25%), while it was negative in 760 (70%) and inconclusive in 50 (5%): as this was a retrospective study, the need for further diagnostic testing after the Str-T was decided in accordance with the physician's judgment.

Current Guidelines recommend a stress test, possibly associated with an imaging modality, in IR patients according to FPR and NICE risk stratification. Conversely, HR patients should undergo a coronary angiography without further tests, while for LR patients according to NICE score, a coronary CT scan is recommended; indications for LR FPR patients are less clear, but the Authors suggest forgoing further tests. In Figs. 1 and 2 we report risk stratification according to FPR and NICE scores and how the Str-T modifies it. In Fig. 3, we report the scores' diagnostic performance in LR and HR subgroups, using Str-T results as reference: NICE score shows a better sensitivity than FPR, but specificity, as well as positive predictive value, are unacceptably low for both scores. If the indication had been given according to the scores, it would have implied sending a large number of HR patients to coronary angiography, which was positive for critical coronary lesions in 30% of HR patients. In patients with a negative Str-T, new cardiac events' rate was very low in all risk classes according to both scores (FPR: 0.05, 0.08 and 0.2%; NICE score: 0, 0.06 and 0.1%, respectively, among LR, IR and HR patients).

According to the classification proposed by Mahler and coll [12], HEART score identifies only LR and HR patients (Fig. 4) and patients in the LR group, according to the validation papers, can be safely discharged without further testing. In this subgroup, Str-T was positive for inducible ischemia in 53 (14%) patients, and 12 (4%) of them

Table 1 Clinical and echocardiographic characteristics in the whole study population and according to prognostic scores' risk stratification

		NICE score			FPR score			HEART score	
	All ($n=1082$)	LR ($n=130$)	IR ($n=196$)	HR ($n=743$)	LR ($n=278$)	IR ($n=549$)	HR ($n=255$)	LR ($n=384$)	HR ($n=692$)
Age (years)	66 ± 13	50 ± 12*°	58 ± 8§	71 ± 10	63 ± 16*°	67 ± 13	68 ± 10	59 ± 14°	70 ± 10
Male gender (%)	595 (56%)	107 (82%)	178 (91%)	312 (42%)	66 (24%)*°	339 (62%)§	196 (77%)	235 (61%)°	363 (53%)
Art. hypertension (%)	673 (63%)	46 (35%)	112 (57%)	506 (68%)	151 (54%)*°	352 (64%)	170 (68%)	159 (41%)°	510 (74%)
Diabetes (%)	181 (17%)	0 (0%)	35 (18%)	148 (20%)	0 (0%)*°	105 (19%)§	79 (31%)	22 (06%)°	160 (23%)
Dyslipidemia (%)	410 (39%)	0 (0%)	86 (44%)	321 (44%)	67 (25%)*°	216 (40%)§	126 (49%)	79 (21%)°	330 (48%)
Vascular disease (%)	92 (9%)	4 (3%)	16 (8%)	72 (11%)	9 (4%)*°	50 (10%)	33 (13%)	12 (4%)°	80 (13%)
Known CAD (%)	272 (26%)	14 (11%)	55 (28%)	204 (28%)	25 (9%)*°	162 (30%)	88 (35%)	34 (9%)*°	240 (35%)
Chest Pain Score	5.8 ± 3.0	4.5 ± 2.5*	4.6 ± 2.5§	6.3 ± 3.0	3.9 ± 2.0*°	5.4 ± 3.0§	8.6 ± 1.4	3.9 ± 2.6°	6.8 ± 2.6
LVEDVI (ml/m^2)	50 ± 19	54 ± 31*	53 ± 16	48 ± 15	45 ± 12*°	51 ± 22	52 ± 15	51 ± 23	49 ± 15
LVESVI (ml/m^2)	21 ± 12	20 ± 13	22 ± 11	21 ± 12	18 ± 9*°	22 ± 13	23 ± 13	21 ± 12	21 ± 13
LV EF (%)	59 ± 15	63 ± 9	59 ± 11	59 ± 16	61 ± 11°	60 ± 12	56 ± 22	61 ± 11°	59 ± 17

All comparisons were performed within each risk score stratification

LVEDVI Left ventricular end-diastolic volume index, *LVESVI* Left ventricular end-systolic volume index, *LV EF* Left ventricular ejection fraction

*$p<0.05$ among Low (LR) and Intermediate (IR) risk group

°$p<0.05$ among Low and High risk (HR) group

§$p<0.05$ among Intermediate and High risk group

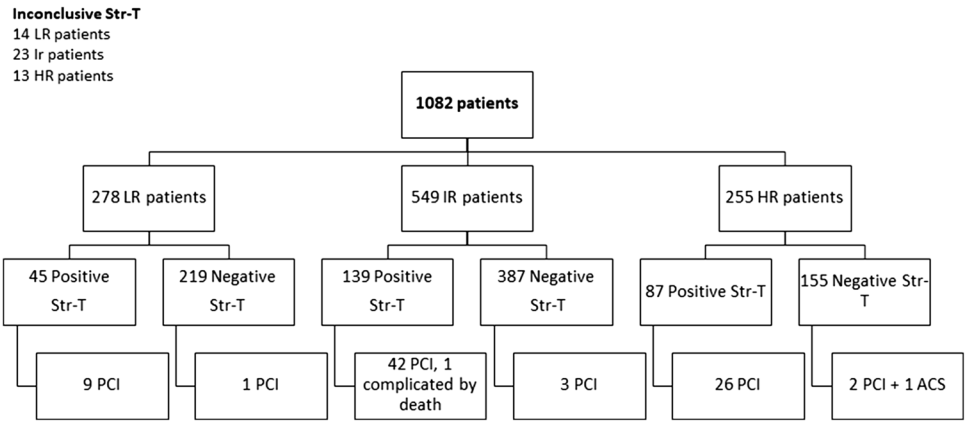

Fig. 1 Risk stratification according to FPR

underwent a percutaneous coronary revascularization: all these patients had a double negative Troponin dosage.

In summary, coronary angiography demonstrates critical coronary lesions in 4% LR patients according to HEART score, 3% according to NICE score, 5% according to FPR (all $p=$ NS) and 1% according to Str-T ($p=0.002$ vs HEART score and <0.001 vs FPR). On the other side, in a comparable proportion of HR patients according to FPR and HEART (respectively, 61 and 63%), Str-T is negative for inducible ischemia; among HR patients according to NICE the proportion is significantly higher (69%, $p<0.05$ vs both scores).

Str-T shows a very good diagnostic performance: among patients in the LR and IR subgroups, incidence of CAD (1.3

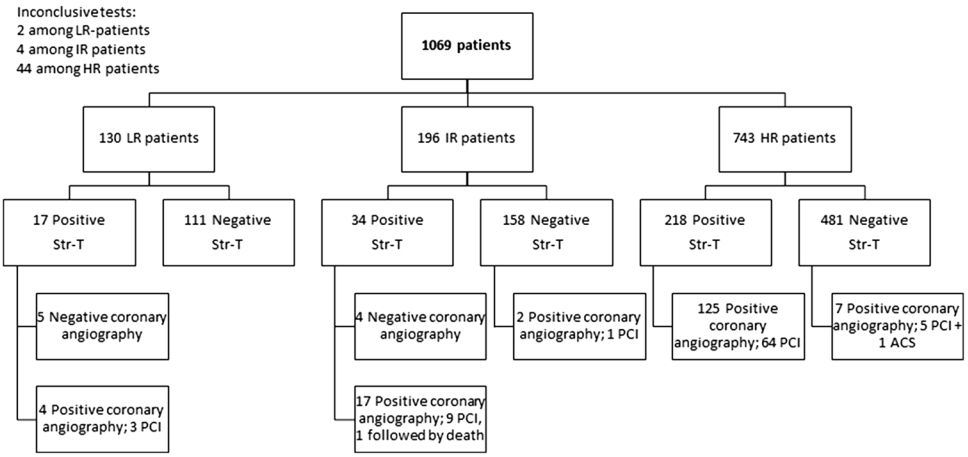

Fig. 2 Risk stratification according to NICE score

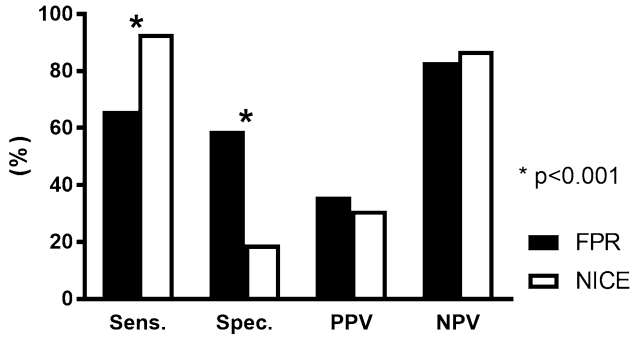

Fig. 3 Comparison of FPR and NICE scores' diagnostic performance

and 1.6%) and the cumulative incidence of significant events at 1-month follow-up (both 1%) is very low.

Discussion

In a population of patients who came to the ED with spontaneous chest pain and negative initial diagnostic assessment, prognostic scores allow assignment of patients to classes of increasing cardiovascular risk, as confirmed by the increasing prevalence of significant coronary artery disease. However, an imaging Str-T improves the scores' diagnostic performance in the HR and LR subgroups. Occurrence of new cardiac events among patients with a negative test is minimal, and an inappropriate radiation exposure was avoided in a significant proportion of patients.

Among LR patients, NICE guidelines recommend CT calcium scoring; according to FPR and HEART score, these patients can safely forgo further assessment. In the

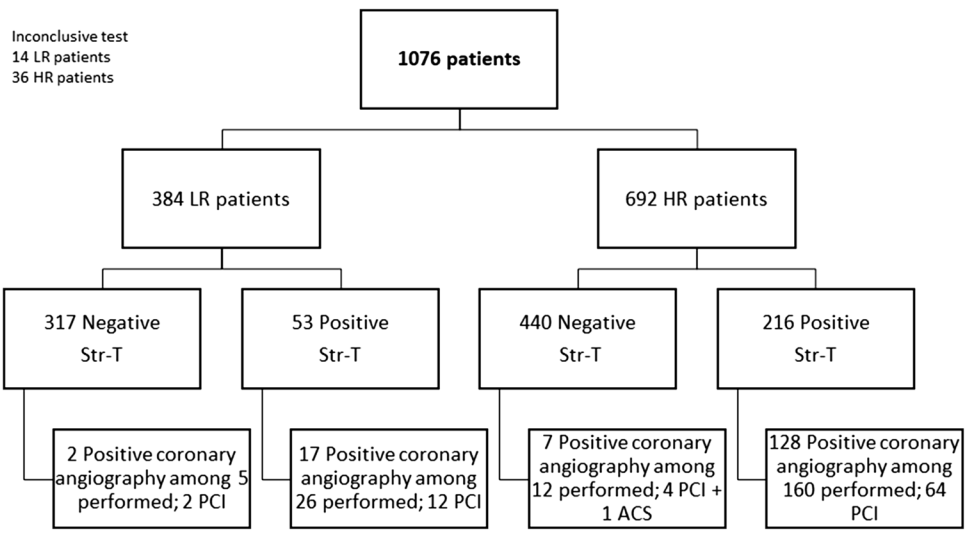

Fig. 4 Risk stratification according to HEART score

validation paper [10], HEART score reduces cardiac stress testing among LR chest pain patients, with a minimal incidence of new cardiac events in this subgroup (0.5%). In a limited population of patients, Mahler and coll [12] show that the application of HEART Pathway (calculation of HEART score plus two Troponine measures at 0 and 3 h) reduces objective cardiac testing during 30 days, shortens length of stay, and increases early discharges, without any patients identified for early discharge suffering a new cardiac event at 30 days. We adopted the HEART score risk stratification proposed by Mahler because our aim is to verify if, in LR-HEART patients, Str-T improves the risk stratification; in all the other patients, a further evaluation is recommended anyway. Our study is limited by the retrospective design, but in a large study population, we demonstrate that 14% of these patients have a positive Str-T and 4% of them underwent coronary angiography. HEART score sensitivity is significantly lower compared with other scores: the need to use appropriately healthcare resources has to be balanced against the risk of discharging a patient with a significant CAD. In the absence of an evaluation by means of a Str-T, it could have occurred in several patients.

According to NICE risk stratification, 70% of our patients would have undergone coronary angiography and 12% CT calcium scoring. Coronary angiography, which would have been positive in only 30% of patients, carries a greater risk than CT calcium scoring. Nevertheless, it is important to underline the risks of these procedures, such as the risks of an invasive procedure, significant radiation and contrast medium exposure of many young patients. Rogers et al. [15] demonstrate that the diagnostic pathway, proposed by NICE GL in 2010, nearly doubles the total cost of investigation per patient compared with standard management. The increase in cost is primarily due to the excess of invasive coronary angiography in the subgroup with a risk score of 61–90%, which represents nearly 40% of the entire population.

NICE guidelines discourage employing the ECG-stress test to establish the presence of CAD in patients without a history of CAD: the original paper [7] on FPR validation confirms the idea that exercise ECG does not substantially increase the ability to rule out future coronary events, as compared to the score itself. In our study population, a functional evaluation with Str-T demonstrates a very good diagnostic performance to establish a CAD diagnosis [16–19]. No adjunctive test was performed, except for coronary angiography in patients with a positive test for inducible ischemia: incidence of new cardiac events at the 1-month follow-up was extremely low. A 25% proportion of false-positive tests has to be weighed against the risks linked to invasive procedures and relevant radiation exposure of a significant number of patients with a long life expectancy; in fact, subjects in the LR class according to all scores are usually in their fifties.

Limitations

The retrospective design of this study and the single center design represent significant limitations. The proportion of patients lost to follow-up was significant, and included 25% percent of foreign citizens; moreover, study participants were older and were diagnosed with inducible ischemia more frequently than non-participants were. Patients lost to follow-up appear to be at a lower risk compared to study participants, but we cannot exclude that their inclusion in the study would have altered our results.

As in previous works, we assume that the absence of cardiac events in the first month after the Str-T is a confirmation of a true-negative exam: although we cannot exclude the presence of non-critical lesions undetected by the Str-t, the very low incidence of new cardiac events at the follow-up confirms that our assumption is correct for most patients.

Conclusions

In a population of ED patients with chest pain and negative initial diagnostic assessment, prognostic scores allowed patients to be grouped in classes of increasing cardiovascular risk: the following diagnostic investigations confirm an increase of significant CAD incidence in different subgroups. However, a considerable proportion of LR patients were diagnosed with significant CAD, while an even more remarkable proportion of HR patients did not show inducible ischemia during the Str-t. The ESE demonstrated an excellent ability and feasibility to establish a CAD diagnosis in most patients, and it significantly improves the scores' diagnostic performance. These results confirm that a diagnostic assessment using the Str-t is accurate, radiation-free and does not require additional non-invasive tests to confirm or exclude a CAD diagnosis.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Statement of human and animal rights This article does not contain any studies with human or animal subjects performed by any of the authors.

Informed consent For this type of study formal consent is not required.

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