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Original Contribution

Short- and long-term cardiac events in patients with chest pain with or without known existing coronary disease presenting normal electrocardiogram

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Abstract

Aim: The aim of this study is to evaluate incidence of adverse cardiac events in patients with chest pain with or without known existing coronary disease presenting normal electrocardiogram (ECG) and initial troponin.

Methods: Prospective, nonrandomized study enrolled low-risk patients with normal ECG and troponin on admission who underwent observation and/or stress testing by unstandardized clinical judgment. Patients who experienced recurrent angina or positive ECGs or positive troponins during observation or patients with positive stress testing were admitted; otherwise, they were discharged.

End Point: The end points are cardiac events at short- and long-term follow-up including cardiovascular death, myocardial infarction, unstable angina, and revascularization.

Results: Of 5656 patients considered, 1732 with ischemic ECG were initially admitted and, therefore, excluded from the analysis; 2860 with pleuritic chest pain and normal ECG were discharged; 1064 with visceral chest pain and normal ECG were enrolled. Patients with known coronary disease (45%) were older and likely presented known vascular disease. Patients with known vascular disease, older age, female sex, diabetes mellitus, and lower chest pain score were likely managed with observation. In patients with known coronary disease as compared with patients without, overall cardiac events account for 35% vs 14%, respectively ($P < .001$), as follows: in-hospital, 23% vs 10%, ($P < .001$); 1 month, 4% vs 2% ($P = .133$); and 9.9 ± 4.9 months, 8% vs 2%, respectively ($P < .001$).

Conclusions: One-third of patients with chest pain with known coronary disease, negative ECG, and biomarkers were subsequently found to have adverse cardiac events. The value of this research for an emergency medicine audience could be extended to all clinicians and general practitioners beyond cardiologists.

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1. Introduction

Chest pain is one of the most frequent complaints of patients presenting to the emergency department (ED); they represent approximately 10% of the population in second-level EDs or reference centers [1,2]. Among these patients, approximately one-third presented electrocardiographic (ECG) changes suggestive of acute myocardial ischemia; however, approximately one-half of patients with acute myocardial infarction do not show any diagnostic ECG changes at presentation [1-3]. Of note, up to 5% of patients without diagnostic ECG changes sent home turn out to be affected by acute myocardial infarction; mortality rate among this population resulted 2 times higher than patients identified and treated, with legal consequences [3]. Thus, immediate evaluation on presentation to the ED is unreliable to rule out myocardial ischemia, so an updated risk assessment by a 6-hour workup with serial ECGs and serial troponins is needed eventually in patients presenting visceral chest pain to separate patients at high risk for cardiac event who need admission from those at low risk who could be directly discharged. In addition, only patients presenting hard clinical risk profile suspected of myocardial ischemia, beyond first-level workup, could be subjected to further instrumental evaluation [1,2,4-7]. Thus, diagnosis of acute coronary syndromes in patients presenting to the ED with chest pain and nondiagnostic ECG, considered at low risk for coronary events, is still a challenge for physicians despite careful observation and diagnostic tools. Large part of articles exists that have discussed this issue in low-risk patients with no history of ischemic heart disease. In those articles, patients have been recognized as having a substantial percentage of coronary disease [1,8-11]. Conversely, the incidence of actual risk in patients presenting chest pain and nondiagnostic ECG associated with known existing ischemic heart disease is still unclear. Thus, aim of present study was to evaluate in the real world how high could be the presence of myocardial ischemia in patients with chest pain with or without known existing coronary disease presenting normal ECG and nondiagnostic first-line workup. The value of this research for an emergency medicine audience could be extended to all clinicians and general practitioners beyond cardiologists.

2. Methods

The study enrolled patients with chest pain presenting to the ED of the tertiary care teaching hospital in Florence, Italy, with a catchment area serving a population of half million. Facilities for triage of patients with suspected acute coronary syndrome included an observation unit with monitor equipped beds and dedicated personnel (resident, faculty, and cardiologist on call). The observation unit is located inside the ED in the same building of catheterization laboratory, coronary care unit, cardio surgery ward, and radiology and includes a 6-bed intensive unit plus a 22-bed unit. Coded diagnoses are entered into a electronic medical chart, allowing easy selection of all patients with a diagnosis of interest. Data were collected from August 1, 2008, to December 31, 2009. All patients gave their consent for study participation. The study was conducted according to good clinical practice and the Helsinki Principles. The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the *International Journal of Cardiology*.

2.1. Study population

Patients presenting chest pain as chief complaint were considered for enrollment and initially evaluated with physical examination including history with coronary risk factors, ECG, and troponin I test [1,2]. Moreover, patients with typical chest pain suspected of myocardial ischemia were subjected to observation with serial ECGs and serial troponin I test. All the patients underwent resting echocardiography [1,2,12,13]. Patients with abnormal ECG and diagnosis of acute myocardial infarction or unstable angina were admitted to the coronary care unit. Patients with moderate to severe comorbidities with other chief complaints and chest pain were admitted to the medical ward or intermediate care unit. Patients with pleuritic chest pain were subjected to a first-line workup lasting up to 6 hours especially those with history of coronary artery disease or multiple coronary risk factors who were subjected to echocardiography [14-16]. Eventually, patients with negative ECGs and negative serum concentrations of troponin I and at least patients with negative echocardiography were considered at very low risk for coronary events and were discharged home [4,5,7,12,17,18]. All the other patients with visceral chest pain and nondiagnostic ECGs were enrolled in the study [1,2]. Chest pain was characterized with a validated chest pain score (Table 1) [19].

Tourists and inhabitants outside the catchment area of Careggi University Hospital serving a population of half

Table 1 Clinical chest pain score

	Score
Location	
Substernal, precordial	+3
Left chest, neck, lower jaw, epigastrium	+1
Apex	−1
Radiation	
Either arm, shoulder, back, neck, lower jaw	+1
Character	
Crushing, pressing, heaviness	+3
Sticking, pleuritic, pinprick	−1
Associated symptoms	
Dyspnea, nausea, diaphoresis	+2

million were not enrolled in the study and were not submitted to follow-up.

2.2. Patients' management

Twelve-lead ECG and troponin I test were performed on the admission and after 6 hours or as required by clinical evolution (ie, recurrent chest pain). Definition of acute coronary syndromes that has been applied was in line with the European and American College of Cardiology/American Heart Association Guidelines for the their management. Patients were considered as having normal, nondiagnostic ECG in the presence of normal ST-segment and T-wave or at least ST-segment elevation or depression less than 0.05 mV (0.5 mm) or asymmetrical T-wave inversion less than 0.2 mV (2 mm) or Q waves less than 0.03 seconds. Such mild changes should be observed in less than 2 contiguous leads. ST elevation or depression between 0.05 and 0.1 mV (0.5-1 mm) or asymmetrical T-wave inversion between 0.2 and 0.25 mV (2-2.5 mm) were considered abnormal nondiagnostic ECG alterations; also, complete bundle-branch block and paced rhythm were considered abnormal nondiagnostic ECG alterations [12,17,19].

The value of troponin was considered positive if above the 99° percentile of a control group in at least 1 set eventually during the first 24 hours after onset of symptoms [1,13]. All the patients received resting echocardiography [1,2,12,13]. Patients showing ischemic ECG changes with or without troponin elevation, with or without cardiac wall motion abnormalities at the echocardiography during observation, were considered at high risk of cardiac events [12,17,19], and they were admitted and considered for coronary angiography. Patients with negative troponins, negative ECGs, normal echocardiography during observation, and pleuritic chest pain were considered at very low risk for coronary artery disease and were discharged with planned office follow-up [1,2]. All the other patients with visceral chest pain were considered for clinical observation or submitted to stress testing without standardized approach. Patients with clinical observation diagnostic of coronary artery disease or positive stress testing were considered at high risk for coronary events, and they were admitted and considered for catheterization laboratory unit. This subset of patients constituted in-hospital cardiac event group [19-22]. Eventually, patients with negative clinical observation or negative stress testing were considered at very low risk and were discharged with office follow-up [1].

2.3. Stress testing

Early symptoms limited graded exercise ECG was performed after the first 6 hours of observation and no further than 24 hours from presentation. Diagnosis of myocardial ischemia was considered for the development of ST depression of at least 1 mm measured at 60 milliseconds from J point. In patients unable to exercise ECG, pharmacologic stress echocardiography was performed after drug washout. Dobutamine was administered in continuous infusion at initial doses of 5 μg/kg per minute with increases every 3 minutes at 10, 20, and 30 μg/kg per minute reaching the maximum dose of 40 μg/kg per minute [19,23]. If the target heart rate was not reached, atropine was administered in intravenous at doses of 0.25 mg/min up to the maximum dose of 1 mg. Positive stress echocardiography was defined by the new detection or increasing onset of preexisting kinetics alterations or by the onset of angina and/or ECG changes. Eventually, pharmacologic stress myocardial perfusion imaging (single photon emission computed tomography) was performed after drug washout [22,24]. Adenosine was given intravenous at the dose of 140 μg/min per kilogram for a period of 6 minutes, and radioactive tracer (25 MBq of technetium Tc 99m sestamibi myocardial perfusion tracer) was injected at the third minute. After 20 minutes from the injection of radioactive tracer, images were acquired using a double-head gamma chamber with 90° between the 2 heads, equipped with a high-resolution collimator. Gated single photon emission computed tomographic images were acquired at rest and after stress with the patient in supine position (64 angular views at 3° intervals, each one lasting 30 seconds through elliptical orbit of 180° and a matrix of 64 × 64 × 16 bytes, zoom 1.46; at each view the cardiac cycle was split into 8 intervals).

2.4. End point

End point was the evidence of coronary events within short- and long-term follow-up including cardiovascular death, myocardial infarction, unstable angina, and revascularization.

2.5. Follow-up

Follow-up was performed reviewing the ED access archives or by telephone after 1, 6, and 12 months in patients discharged with negative clinical evaluation or negative stress testing. Positive events of suspected coronary events were analyzed and confirmed after clinical charts, ECGs, and laboratory tests review. Tourists and inhabitants outside the catchment area of Careggi University Hospital serving a population of half million were not enrolled in the study and were not submitted to follow-up.

2.6. Statistics analysis

Continuous variables were reported as mean ± SD. Frequencies are shown as percentages and absolute values. Continuous variables were compared through 1-way analysis of variance and t test, whereas percentages were compared with χ^2 or Fisher exact test when expected frequencies were

less than 5%. A 2-tail *P* value less than .05 was considered statistically significant. Statistical analysis were performed using SPSS Package, version 17 (SPSS, Inc, Chicago, IL).

3. Results

A total of 5656 patients presenting to the ED with chest pain as chief complaint were considered; 1732 (31%) were admitted with the evidence of ischemic ECG and acute coronary syndrome or another concomitant disease (813 with moderate to severe comorbidities were submitted to the wards, and 919 with acute coronary syndrome were admitted to the coronary care unit). Of the remaining patients with normal ECGs, 2860 (50%) were discharged home directly from the ED for the relief of pleuritic chest pain associated with negative instrumental and laboratory screening including serial troponins. The remaining 1064 patients (19%) with visceral chest pain were enrolled in the study (Fig. 1).

3.1. Outcomes of patients with known coronary disease and without

Baseline clinical characteristics of the 1064 patients enrolled and submitted to further evaluation are shown in Table 2. Of these, 477 patients (45%) had known existing

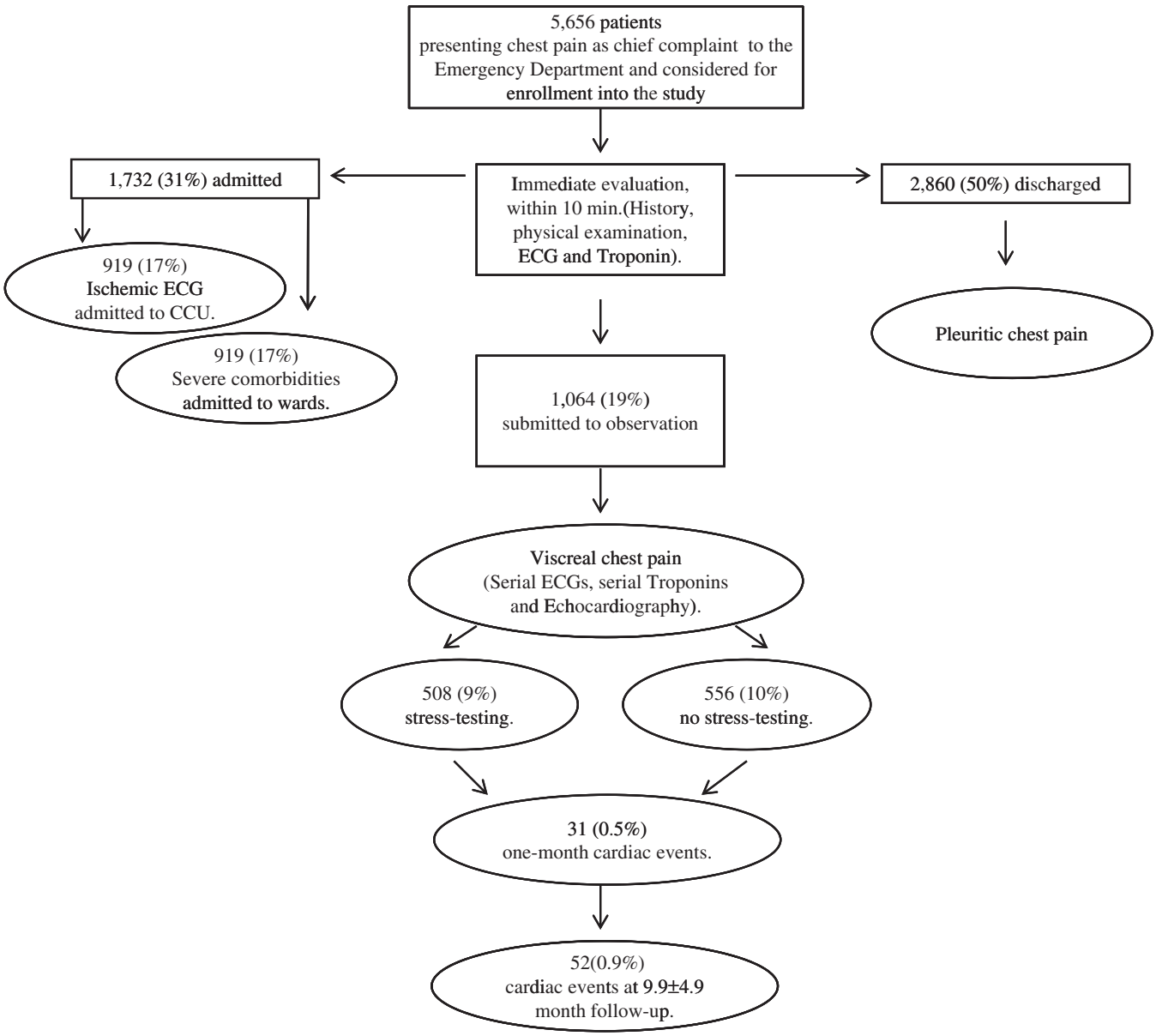

Fig. 1 Flow diagram of management in patients with chest pain presenting to the ED (n = 5656). End point: cardiovascular death, myocardial infarction, unstable angina, and revascularization at short-term (1 month) and long-term (9.9 ± 4.9 months) follow-up.

Table 2 Baseline clinical characteristics of patients enrolled in the study (n = 1064)

	Known coronary disease (n = 477, 45%)	Unknown coronary disease (n = 587, 55%)	*P*
Mean age (y, SD)	72, 12	62, 14	<.001
Male sex	283 (59.3%)	316 (53.8%)	.07
Diabetes mellitus	75 (15.7%)	69 (11.8%)	.06
Hypertension	240 (50.3%)	288 (49.1%)	.68
Hypercholesterolemia	99 (20.8%)	119 (20.3%)	.84
Active smoker	40 (8.4%)	126 (21.5%)	<.001
Obesity	21 (4.4%)	22 (3.7%)	.59
Familiarity	12 (2.5%)	82 (14%)	<.001
Abdominal aneurism of aorta	21 (4.4%)	14 (2.4%)	.07
Peripheral arterial vascular disease	35 (7.3%)	13 (2.2%)	<.001
Stroke	29 (6.1%)	16 (2.7%)	.004
Carotid stenoses	23 (4.8%)	15 (2.6%)	.047
Chest pain score	5.3 1.9	5.5 2.0	.31

coronary disease, and the remaining 587 patients (55%) had not (Figs. 2 and 3). Patients with known coronary disease were older and presented more known vascular disease. Moreover, because of the nonrandomized criteria of enrollment, patients with older age, female sex, diabetes mellitus, known vascular disease, and lower chest pain score were likely managed with observation (Table 3). Overall, 556 patients (52%) were managed with observation, and 508 patients (48%) were managed with stress testing, of whom 440 with exercise ECG and 68, unable to perform exercise, underwent stress echocardiography (n = 65) or myocardial perfusion imaging (n = 3). In patients with known coronary disease as compared with patients without, overall cardiac events account for 35% vs 14%, respectively ($P < .001$) as follows: in-hospital, 23% vs 10%, respectively ($P < .001$); 1 month 4% vs 2%, respectively ($P = .133$); and 9.9 ± 4.9 months 8% vs 2%, respectively ($P < .001$) (Table 4). In the group with known coronary disease, at 1-month follow-up, of 18 patients with coronary events, 10 patients were recognized as having unstable angina subjected to mechanical revascularization, and 8 patients angina subjected to conservative treatment. At 9.9 ± 4.9 months of follow-up, of 39 patients with coronary events, 2 patients were recognized as having unstable angina or myocardial infarction subjected to mechanical revascularization; the remaining 11 patients with myocardial infarction and 36 patients with angina were subjected to conservative treatment. Conversely, in the group without known coronary disease, at 1-month follow-up, of 13 patients with coronary events, 7 patients were recognized as having unstable angina or myocardial infarction subjected to mechanical revascularization; the remaining 1 patient with myocardial infarction and 5 patients with angina were subjected to conservative treatment. At 9.9 ± 4.9 months of follow-up, of 13 patients with coronary events, 1 patient was recognized as having unstable angina subjected to mechanical revascularization; 12 patients with angina were subjected to conservative treatment. Twenty-two patients were lost at follow-up (2% of enrolled patients), 10 patients with known existing coronary disease and 12 patients without.

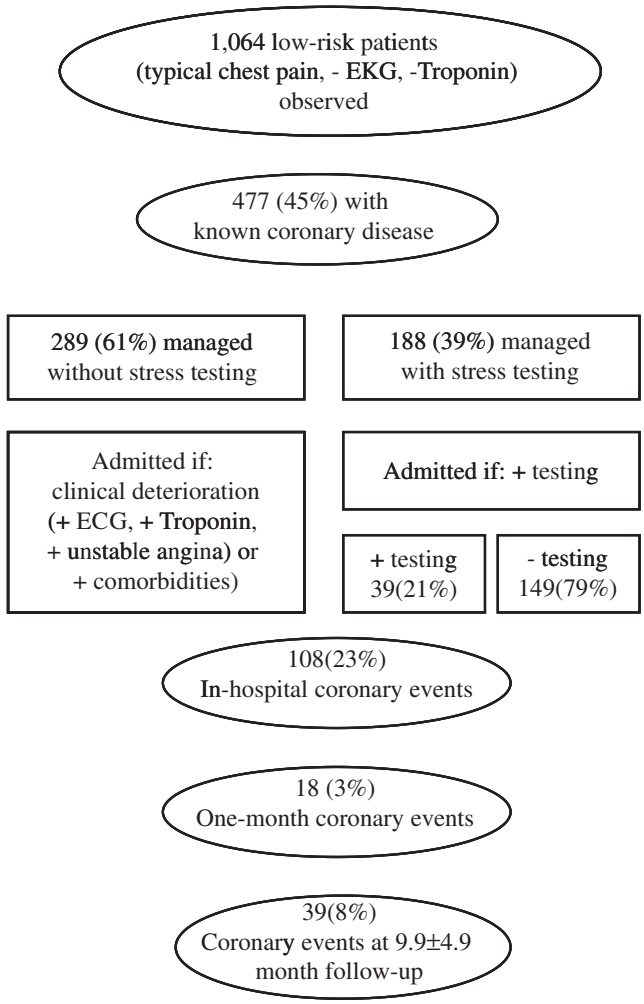

Fig. 2 Flow diagram of patients with known coronary disease enrolled in the study (n = 477). End point: cardiovascular death, myocardial infarction, unstable angina, and revascularization during in-hospital stay, at short-term (1 month) and long-term (9.9 ± 4.9 months) follow-up.

4. Discussion

Diagnosis of myocardial ischemia in patients presenting chest pain and normal ECG, considered at low risk for cardiac events, represented a challenge for physicians in last decades, despite well-planned strategies including diagnostic algorithm, careful observation, and diagnostic tools [1,2,10,11]. Efforts have been planned in improving

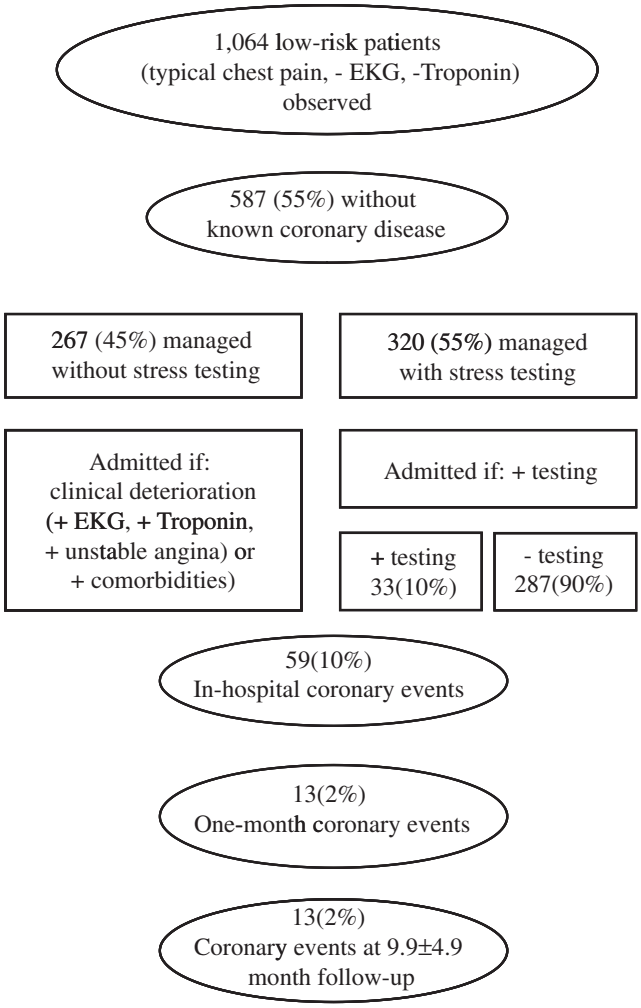

Fig. 3 Flow diagram of patients without known coronary disease enrolled in the study (n = 587). End point: cardiovascular death, myocardial infarction, unstable angina, and revascularization during in-hospital stay, at short-term (1 month) and long-term (9.9 ± 4.9 months) follow-up.

recognition of coronary disease and ruling out myocardial ischemia. Indeed, in recent years, low-risk patients without known existing coronary disease have been recognized as having a substantial percentage of coronary disease up to 15% to 20% [1,2,8-11]. As a consequence of efforts, patients inadvertently discharged home reduced to less than 2% [3,20]. This issue have been discussed in a large part of articles concerning low-risk patients with any history of ischemic heart disease [2,8-10]. However, incidence of myocardial ischemia in patients with chest pain with known existing coronary disease is still unclear. In these patients, present study shows that overall cardiac events were significantly higher in patients with known coronary disease as compared with patients without (35% vs 14%, respectively; $P < .001$) and at long term (8% vs 2%, respectively; $P < .001$; Table 4). Interestingly, patients with known coronary disease showed overall cardiac events 2-fold higher than patients without, and surprisingly, cardiac events were up to 4-fold higher at long term. As a consequence, noninvasive management of patients with known coronary disease could be unreliable in the real world, and physicians in the ED are likely to miss acute myocardial ischemia, particularly when patients had history of coronary disease. The value of this research for an emergency medicine audience could be extended to all clinicians and general practitioners beyond cardiologists.

Previous studies of patients with acute chest pain and absence of ECG signs of myocardial ischemia reported only 4% of patients with a history of coronary artery disease, and 2% of patients without such a history will develop an acute myocardial infarction [1,2]. Observation beyond first-line evaluation associated with serial ECGs and serial troponins demonstrated high sensitivity in recognition non–ST-elevation myocardial infarction in this subset of patients [1,2,4,5]. Moreover, exercise ECG and stress imaging have

Table 3 Baseline clinical characteristics of patients enrolled in the study and subjected to stress testing or tailored observation strategy (n = 1064)

	Stress testing (n = 508)	Observation (n = 556)	*P*
Mean age (y, SD)	64.3, 12.2	68.1, 15.4	<.0001
Sex (male)	310 (61.0%)	289 (52.0%)	.003
Diabetes mellitus	50 (9.8%)	94 (16.9%)	.0008
Hypertension	250 (49.2%)	278 (50.0%)	.80
Hypercholesterolemia	112 (22.0%)	106 (19.1%)	.23
Smoker	86 (16.9%)	80 (14.4%)	.25
Obesity	25 (4.9%)	18 (3.2%)	.16
Familiarity	52 (10.2%)	42 (7.6%)	.12
Known coronary artery disease	188 (37.0%)	289 (52.0%)	<.0001
Abdominal aneurism of aorta	18 (3.5%)	17 (3.1%)	.66
Peripheral arterial vascular disease	15 (3.0%)	33 (5.9%)	.02
Stroke	19 (3.7%)	26 (4.7%)	.45
Carotid stenoses	14 (2.8%)	24 (4.3%)	.17
Chest pain score	6.5 2.6	4.9 1.6	<.0001

Table 4 End point in patients with known or unknown coronary artery disease

	Known CAD	*P*	Unknown CAD
In-hospital cardiac events	108 (22.4%)	<.0001	59 (10.0%)
Short-term cardiac events	18 (3.8%)	.133	13 (2.2%)
Long-term cardiac events	39 (8.2%)	<.0001	13 (2.2%)

End point: cardiovascular death, myocardial infarction, unstable angina, and revascularization during in-hospital stay, at short-term (1 month) and long-term (9.9 ± 4.9 months) follow-up. CAD indicates coronary artery disease.

been highlighted by several authors as first screening tool in diagnosing myocardial ischemia [2,17,21]. This global management allows the physicians to give the patient safe and effective evaluation that can rule out acute myocardial infarction or identify myocardial ischemia. Eventually, dedicated scoring systems including characterization of chest pain and associated risk factors for arteriosclerosis can guide the choice of appropriate diagnostic tool optimizing risk stratification [8,9,19,25,26], but none of them considered differences between patients with or without history of coronary disease. Awareness of positive history of coronary disease as strong risk factor of recurrent acute coronary syndrome in patients with chest pain nonetheless presenting normal ECG could lead to incorporate it into a novel diagnostic strategy and eventually could update prognostic stratification.

4.1. Strength and limitations of the study

Present study analyzed a large consecutive population in the real world of a third-level ED and could represent a pilot study in the emergency setting. In-hospital screening succeed in separating a very large part of patients at high risk for cardiac event who needed admission from those at relatively low risk who could be discharged or submitted to further evaluation. The study attempts to answer a question, which is important for clinicians and academicians alike. Overall results suggest one-third patients with known coronary disease presenting nondiagnostic ECG eventually developed cardiac events. The reported incidences of adverse outcomes are relatively high compared with the literature, but data could be due to the fact that no patient was admitted directly to cardiology ward or coronary care unit. However, chest pain evaluation methodology could explain this discrepancy. Indeed, data could have clinician bias in the nonstructured, nonrandomized methodologies used to manage patients. It does not pose a necessarily novel question, nor does it represent cutting edge decision making.

We are aware with data of literature showing that up to 5% to 15% of patients with acute coronary syndrome could have pleuritic pain, but in our series, patients with pleuritic pain discharged received 6-hour observation with negative serial ECGs and serial troponins. The evaluation of outcome based on dichotomy (normal/abnormal tests) may be a limitation of any screening workup in patients with chest pain. Results of present study could not be extended to general population because patients with moderate to severe comorbidities and chest pain were admitted to the medical ward or intermediate care unit and were excluded from the study. However, further studies are needed to establish standardized criteria to guide the use of invasive or noninvasive diagnostic strategy in these patients. Moreover, our results need validation in other centers or need to be confirmed in a properly designed study.

4.2. Conclusions

Risk stratification with observation and stress testing is safe and effective in patients without existing coronary disease presenting chest pain and nondiagnostic first-line workup. Conversely, one third of patients with chest pain with known existing coronary disease and nondiagnostic ECG and biomarkers eventually were recognized as having coronary events. The value of this research for an emergency medicine audience could be extended to all clinicians and general practitioners beyond cardiologists.

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