Results of the First Patients with Suspected Acute Coronary Syndrome Evaluated with the 1-hour Algorithm Proposed by the European Society of Cardiology

Resultados de los primeros pacientes con sospecha de síndrome coronario agudo evaluados con el algoritmo de 1 hora propuesto por la Sociedad Europea de Cardiología

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ABSTRACT

Background: The European Society of Cardiology (ESC) recommends an algorithm for the evaluation of chest pain with serial measurement of two high sensitivity troponins separated by one hour. However, the high efficacy and safety of the algorithm has only been estimated according to assumptions based on theoretical models. We tested for the first time its performance in the real world by incorporating it into the daily routine of our center.
Methods: This is a prospective, single center study using the ESC 0/1h algorithm with high sensitivity troponin T on unselected patients who presented at the emergency department with suspected non-ST-segment elevation acute myocardial infarction. Efficacy and safety were assessed in terms of the 30-day incidence of acute myocardial infarction, cardiovascular death and the composite of acute myocardial infarction, death or coronary revascularization.
Results: A total of 1,351 patients were included in the study. Mean age was 61±14 years, 12.4% were diabetics and 35.8% had previous history of coronary events. The rate of acute myocardial infarction was 11% and the rate of mortality 0.29%. According to the application of the algorithm, 917 patients were catalogued as "rule out" (67%), 270 as "observe" (20%) and 164 as "rule in" (13%). The rate of acute myocardial infarction was 0.3% in "rule out", 7% in "observe" and 77.4% in "rule in" (p <0.001). Moreover, death or coronary revascularization was 7.7% in "rule out", 17.7% in "observe" and 80.4% in "rule in" (p <0.001).
Conclusions: The 1-hour algorithm showed a good capacity to stratify patients presenting with suspicion of acute myocardial infarction and a high negative predictive value to exclude infarction at 30 days, although this capacity decreases when the event considered is the need for coronary revascularization.

Key words: Chest Pain – Acute Coronary Syndrome – Biomarker

RESUMEN

Introducción: La Sociedad Europea de Cardiología recomienda para la evaluación del dolor torácico un algoritmo con medición seriada de dos troponinas de alta sensibilidad separadas por una hora. Sin embargo, la alta eficacia y seguridad solo se han estimado según supuestos basados en modelos teóricos. Probamos por primera vez su desempeño en nuestro medio cuando se integra en la rutina diaria.
Métodos: Estudio prospectivo unicéntrico que incluyó a pacientes no seleccionados que presentaban sospecha de infarto sin elevación del ST en el servicio de emergencias, a los que se les practicó el algoritmo SEC 0/1h utilizando troponina T de alta sensibilidad. Se evaluó el comportamiento en términos de incidencia a 30 días de los eventos de infarto agudo de miocardio, muerte cardiovascular y el combinado de infarto agudo de miocardio, muerte o revascularización coronaria.
Resultados: Se incluyeron 1351 pacientes con una edad media de 61±14 años, 12,4% de diabéticos y 35,8% de evento coronario previo. La tasa de infarto agudo de miocardio fue del 11% con una mortalidad del 0,29%. De acuerdo con la aplicación del algoritmo, 917 pacientes fueron catalogados como "externar" (67%); 270, como "observar" (20%); y 164, como "internar" (13%). La tasa del evento infarto agudo de miocardio resultó del 0,3% en "externar"; del 7%, en "observar"; y del 77,4%, en "internar" (p < 0,001). Por su lado, la muerte o revascularización coronaria resultó de 7,7% en "externar"; del 17,7%, en "observar"; y del 80,4%, en "internar" (p < 0,001).
Conclusiones: El algoritmo de 1 hora presentó una buena capacidad para estratificar a pacientes que consultan con sospecha de infarto agudo de miocardio con un gran valor predictivo negativo para excluir el evento de infarto a los 30 días, aunque dicho valor disminuye cuando el evento considerado es la necesidad de revascularización coronaria.

Palabras claves: Dolor torácico - Síndrome coronario agudo – Biomarcadores

Abbreviations

AMI	Acute myocardial infarction		**ESC**	European Society of Cardiology
MACE	Major adverse cardiovascular events (death or coronary revascularization)		**hsTnT**	High sensitivity troponin T

INTRODUCTION

Chest pain represents 5% to 20% of the annual emergency department consultations and almost 25% of hospital admissions. Its diagnosis is often difficult, added to the question of patients discharged with acute coronary disease or unnecessary hospitalizations in the coronary care unit (30% to 70% of cases) (1-3).

Different systems for the evaluation of patients with chest pain and suspicion of acute coronary syndrome have been developed in the last decades, most of which incorporate a few hours of observation and serial measurements of serum markers of myocardial injury. High sensitivity troponin has made an important contribution to the evaluation of this type of patients, mainly due to its high negative predictive value added to its fast positivization in cases of myocardial injury (4-6).

In recent years and in accordance with international guideline recommendations, we have used diagnostic algorithms with two troponin assessments separated by 3 hours in order to evaluate its changes during this interval and to have a greater time window from symptom onset (7). In 2015, we published in this same journal the initial experience with a 3-h algorithm using high sensitivity troponin T (hsTnT) (8). Different subsequent studies showed that the variation that could be found with two measurements separated by one hour was proportional to that of 3 hours; therefore, fast algorithms were developed with two samples of troponin separated by 1 hour, considering as first troponin assessment that of hospital admission (9, 10). Today this algorithm appears as a recommendation of the European Society of Cardiology (ESC) (7). However, as an important limitation, all these findings were based on hypothetical assumptions of purely observational studies, in which the ESC 0/1h algorithm was not applied clinically. It is unknown whether these promising results also apply to a real-world setting with routine use of the ESC 0/1h algorithm in unselected patients. Therefore, the aim of this study was to evaluate for the first time in Latin America the real performance of the ESC 0/1h algorithm using hsTnT incorporated into the clinical routine of a prospective, single center study.

METHODS

A prospective, observational study was conducted including patients presenting at the emergency department with suspected acute coronary syndrome.

Inclusion criteria

- Patients older than 18 years who present at the emergency department with suspected acute coronary syndrome.

Exclusion criteria

- Non-cardiac chest pain.
- Hospital admission indicated by another professional.
- Impossibility of conducting follow-up.
- Presence of ST-segment elevation in the ECG.

Events

The occurrence of events based on laboratory results, echocardiographic studies, functional tests, coronary angiography, or coronary computed tomography were analyzed by a cardiologist unrelated to the initial treatment of patients. This professional was in charge of adjudicating the final events.

Endpoints

- Acute myocardial infarction (AMI) at 30 days.
- Composite of AMI, death or coronary revascularization at 30 days (MACE).

Acute myocardial infarction was defined according to the latest recommendations of the universal definition of infarction (11). In essence, myocardial infarction was diagnosed when there was evidence of myocardial necrosis in association with a clinical condition compatible with myocardial ischemia. Myocardial necrosis was diagnosed by at least one hsTnT value above the 99th percentile along with a significant increase or decrease.

Coronary revascularization was defined as percutaneous coronary intervention or coronary bypass surgery.

Routine evaluation of patients

Patients underwent a clinical evaluation that included clinical history, physical exam, blood tests, comprising serial measurements of hsTnT , 12-lead ECG and chest x-ray, and continuous monitoring of ECG rhythm and pulse oximetry. The ESC 0/1h algorithm was part of the local standard operating procedures for the treatment of patients with suspected non-ST-segment myocardial infarction. Patient management was left completely at the discretion of the attending physician, who had full legitimacy to rule out any triage recommendation of the ESC 0/1h algorithm.

ESC 0/1h algorithm

The ESC 0/1h algorithm should always be used together with all available clinical information, including the ECG. It classifies patients with suspected non-ST-segment elevation myocardial infarction in "rule out, "observe" and "rule in" based on the cut-off values of the assay-specific hsTnT concentrations obtained in the presentation and after one hour.

Follow-up

In all the patients included, follow-up was performed 30 days after the index event in the outpatient clinic or by telephone contact.

Statistical analysis

Discrete variables are expressed in percentages and continuous variables as mean and standard deviation, or median and interquartile range P25-P75, according to their distribution. Data normality was analyzed with the Kolmogorov Smirnov test. Discrete variables were compared using the chi-square test and continuous variables with Student's t-test or the Mann-Whitney test, according to sample distribution. Kaplan Meier survival curves were calculated and compared using the log rank test. A two-tailed p value <0.05 was considered statistically significant.

Ethical considerations

A written informed consent was requested from all participants prior to their inclusion in the study. This consent was submitted for approval by the Ethics Committee of our institution. The study was carried out in compliance with the National Law on the protection of personal data 25.326 and conducted according to national ethical standards (CABA Law 3301, National Law on Clinical Research in Humans, Declaration of Helsinki and others).

RESULTS

Between March 2016 and March 2017, 1,351 patients were included in the database. Mean age was 61±9 years, and 61.8% were men, 12.4% diabetic and 13.5% current smokers (Table 1). In 35.8% of cases, patients had history of a previous coronary event and 3.3% had an estimated creatinine clearance <30 ml/min.

In 70.2% of patients, the admission ECG did not present acute alterations, 26.4% had nonspecific repolarization abnormalities (T-wave type changes in two or less leads, abnormal repolarization without significant ST-segment depression, branch blocks without clear relation to the ischemic event, typical changes of left ventricular hypertrophy or abnormal repolarization probably secondary to drugs) and finally 3.4% presented significant alterations of the ST-segment or the T wave.

The median time from pain onset to consultation was 4 (2-7) hours, and the term in the emergency department until conduct was defined (hospitalization, discharge or need for more studies) was 143 (120-150) min. The time between the two troponin measurements was 65±5 min. Among the patients evaluated, admission was decided in 26.2% of cases to perform further studies, while the rest was discharged. The distribution of the decisions in relation to the algorithm obtained is shown in Figure 1.

Follow-up was achieved in 99.8% of cases, since only 3 patients were lost to follow-up. The rate of AMI at 30 days was 11%, acute coronary syndrome: 20.6%, cardiovascular mortality: 0.29% and MACE: 13.1%.

Performance of the algorithm for AMI

When analyzing the behavior according to the algorithm, 917 (67%) patients were classified as "rule out", 270 (20%) as "observe" and 164 (13%) as "rule in". In the "rule out" group, 86.9% of cases were managed as outpatients, and the overall infarction rate was 0.3%, only corresponding to inpatients. The sensitivity for this group was 98% and the negative predictive value for AMI was 99.7%. For the "rule in" group, the algorithm had a specificity of 98.3% and a positive predictive value of 77.4%. The remaining "observe" group presented an AMI rate of 7% at 30 days.

Performance of the algorithm for the composite endpoint

In the case of the secondary endpoint of AMI, death and coronary revascularization within 30 days the "rule out" group presented an event rate of 7.7% versus 17.7% in the "observe" group and 65.7% in the "rule in" group, with a statistically significant difference among groups (p <0.001) (Figure 2). Considering that there was no mortality, the difference was obtained at the expense of revascularizations. The analysis of these 71 revascularization events showed that 65 were performed by percutaneous coronary intervention and the rest by coronary artery bypass grafting, 3 due to infarction and 68 due to unstable angina.

Performance according to the admission ECG

The behavior of the algorithm was compared between patients without and with ECG abnormalities. This division was made taking into account the low rate of patients with specific ischemic alterations in the ECG. In the group without abnormalities, the rate of MACE events was 10.6%, 5.6% (0.13% AMI) in the "rule out" group, 13.9% (4.6% AMI) in the "observe" group and 80% (71% AMI) in the "rule in" group (p <0.001). In the group with abnormalities, the rate of MACE was 37.3%, 15.7% in the "rule out" group (1% AMI), 24.7% in the "observe" group (11.3% AMI) and 83.4 % in the "rule in" group (80% AMI) (p <0.001). The ROC curve in the group without and with abnormalities and was 0.77 and 0.80, respectively (p=0.56).

### Performance according to time from pain onset

Taking into account the times of marker positivization, we analyzed the behavior of the algorithm according to the median consultation time of 4 hours. In

**Table 1**. Baseline patient characteristics

Variable	Value (n: 1,464)
Age-years	61± 14
Hypertension - %	51.2
Smoking - %	13.5
Dyslipidemia- %	48.1
Family history- %	9.6
Male gender - %	61.8
Diabetes - %	12.4
Previous coronary event-%	35.8
Previous coronary PCI- %	24.8
Creatinine clearance <30 ml/min - %	3.3

PCI: Percutaneous coronary intervention

Fig. 1. Flow diagram of patient classification. The recommendations of the algorithm are represented in the upper panel, while the final medical decisions (discharged versus hospitalized patients) are represented in the lower panel.
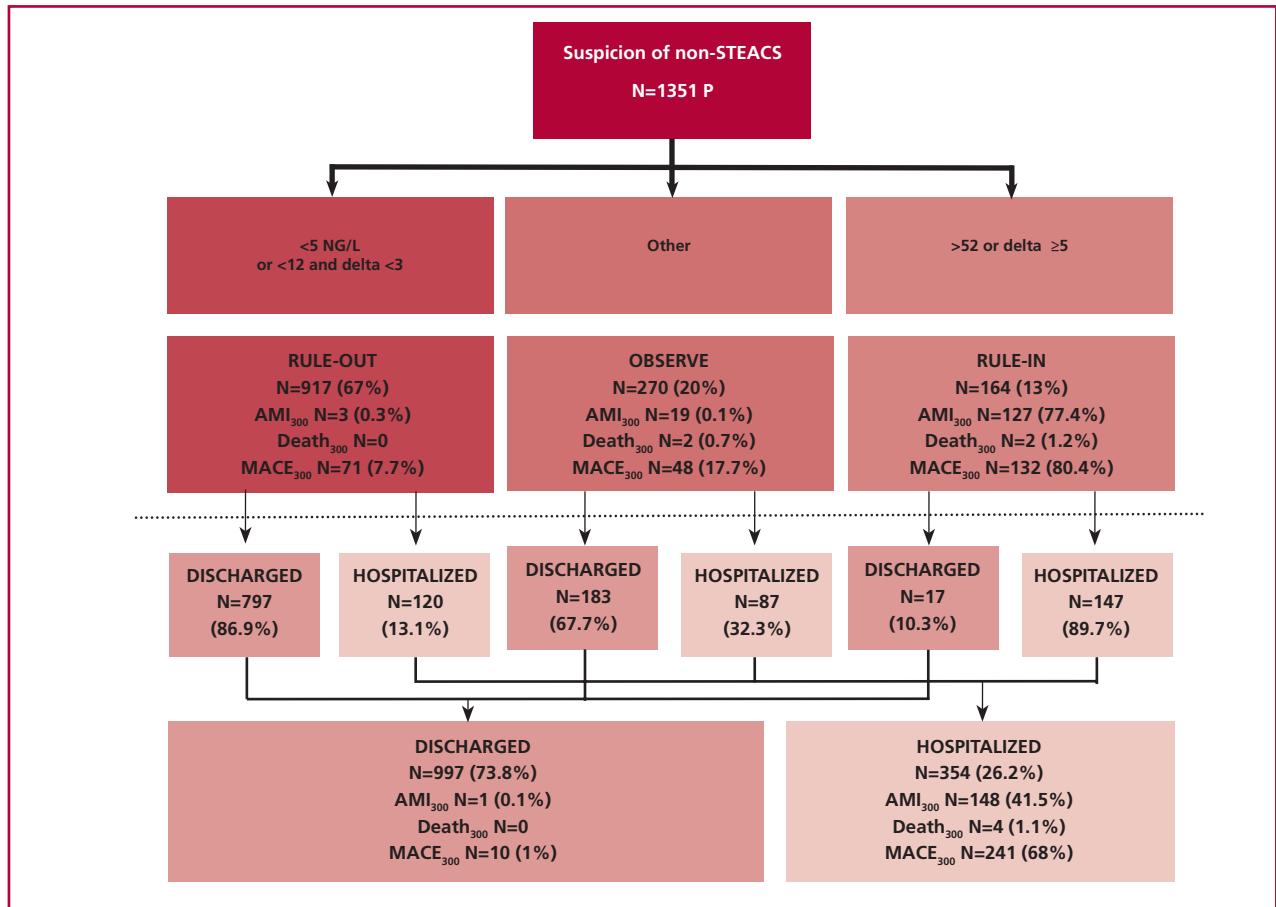
Non-STEACS: Non-ST-segment elevation acute coronary syndrome.
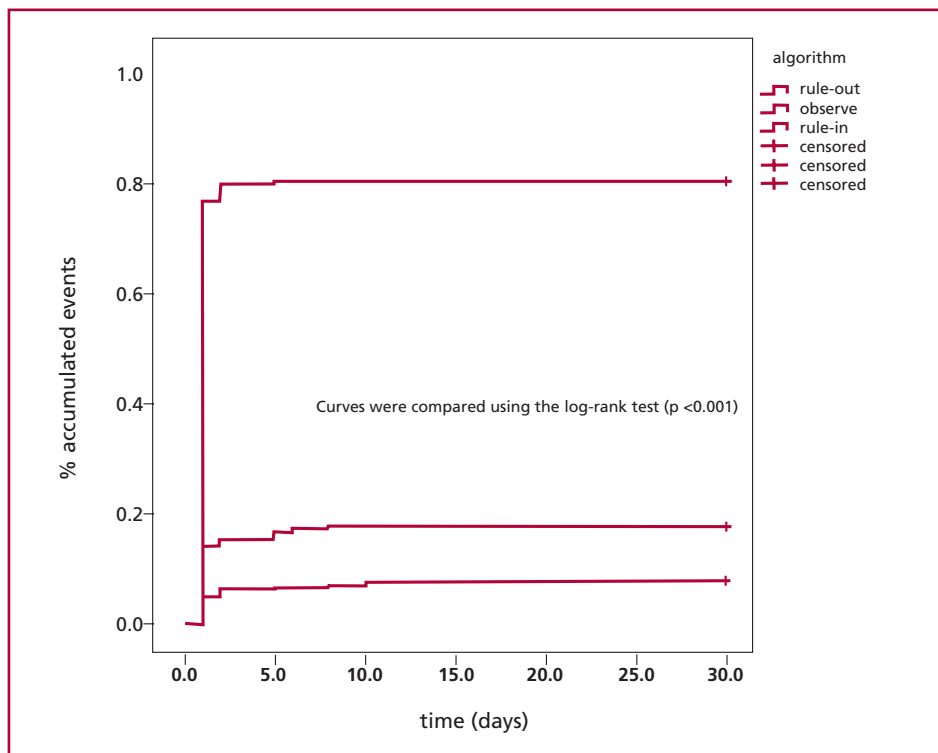
Fig. 2. MACE rate at 30 days according to the algorithm classification

those patients who presented with less than 4 hours from symptom onset, the rate of MACE events in the "rule out" group was 4.8% (0% AMI), 18.3% (8% AMI) in the "observe" group, and 80.7% (78.2% AMI) in the "rule in" group.

DISCUSSION

This prospective study, carried out with the purpose of assessing the behavior of the algorithm proposed by the ESC, presents, in our opinion, some findings that we would like to share.

First, we wish to emphasize that the this protocol could be applied in a sufficiently large population of consecutive patients, with an average time between measurements of 65 min, very close to the proposed 60 min. In an indirect analysis, this seems to impact on the length of stay in the emergency room until decision making, that is shorter than the one previously published in this journal with the 3-hour algorithm (143 [120-150] min vs. 270 ± 150 min., p <0.001).

Second, the distribution of patients in the different groups, "rule out", "observe" and "rule in" (67%, 20%, 13%) was similar to that found by Reichlin et al. in their validation article (59.5%, 24.1% and 16.4%, respectively) or in the article that gave rise to the protocol of the same author (60%, 17%, 23%, respectively) (10). This meant that in our case, 80% of the patients were defined as "rule out", or "rule in" according to the algorithm and that only 20% of cases required further observation, which shows a protocol with great defining capacity.

Third, the "rule out" group showed a 30-day AMI rate of 0.3%, as low as in the rest of the publications, making the negative predictive value of the protocol extremely high for a hard event such as a heart attack. This fact occurred in a population that consulted at the emergency department with relatively short time from the onset of symptoms, a situation that theoretically could reduce the capacity of the algorithm due to the short time for the elevation of markers. In our work, the ability to discriminate was very good, even when patients with less than 4 hours of symptom onset were analyzed. Regarding the latter, we still consider the need to maintain prudent behavior towards patients with a consultation interval very close to pain onset.

Fourth, when analyzing the behavior of the algorithm for the composite event, we see that the rate of events in the "rule out" group was significantly higher than for AMI alone, at the expense of a greater number of revascularizations. In most of the series published this data does not appear, based on the fact that in many cases the condition that leads to revascularization depends on the subjectivity of the attending doctor. In a review article recently published in JACC, Twerenbold et al. highlight the fact that the value of the marker should not be the only factor that guides the behavior in the emergency department, since there is a group of patients with coronary events

and negative markers (12). In our case, the revascularization rate corresponded to 7.7% of the patients in the "rule out" group, with 7.4% defined as unstable angina. This number is not negligible, but due to the methodology of our work we cannot define what would have been these patients' outcome at 30 days if they were not hospitalized. Nevertheless, it makes us think that the sole application of the algorithm is not enough to rule out a coronary event in our patient, especially in the case of unstable angina.

Limitations

Our work was carried out in an institution where all patients were evaluated by cardiologists, a situation that is not repeated in all centers.

CONCLUSIONS

The 1-hour algorithm could be applied in all the assessed patients, presenting a good capacity to stratify patients who consult with suspected acute myocardial infarction and with a high negative predictive value to exclude infarction at 30 days. This capacity decreases when the event considered is the need for coronary revascularization.

Conflicts of interest

None declared. (See authors' conflicts of interest forms on the website/Supplementary material).

Acknowledgements

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