REVIEW ARTICLE

Accelerated Diagnostic Protocols Based on High-Sensitivity Troponin in the Diagnosis of Thoracic Pain: A Systematic Review

Protocolos de diagnóstico acelerado basados en troponina de alta sensibilidad en el diagnóstico del dolor torácico: una revisión sistemática

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ABSTRACT

Background: The progress of high-sensitivity troponin for accelerated diagnostic protocols to assess chest pain, allows the identification of patients admitted to the emergency room with low-risk chest pain for a major adverse cardiovascular event, that could be early and safely discharged, saving time and resources.
Objective: The aim of this study was to assess clinical trials using accelerated diagnostic protocols based on high-sensitivity troponin.
Methods: A search of randomized clinical trials evaluating accelerated diagnostic protocols based on high-sensitivity troponin in emergency services was carried out in MEDLINE/Ovid, Cochrane and EMBASE database, using the assessment criteria of the Cochrane manual and the PRISMA strategy.
Results: After screening 3509 studies, 5 clinical trials, including 1513 patients, were analyzed. Early discharges were identified in 409 (27%) of patients, in 91% of cases for ESC 0/3-h protocols, 72% for 0/1-h, 48% for EDACS, 40% for HEART, 19% and 32% for ADPT and 8% and 18% for standard care protocols. The negative predictive value was high, in the 99.1-100% range. Mean length of hospital stay was lower for the 0/1-h and ESC 0/3-h protocols, with 4.6 and 5.6 hours, respectively.
Conclusions: Accelerated diagnostic protocols in chest pain using high-sensitivity troponin allow a higher proportion of early discharges with a low rate of major cardiovascular events, with reduction in length of hospital stay and resources used.

Key words: Thoracic pain - Accelerated diagnostic protocols - High-sensitivity troponin - Acute coronary syndrome - Acute myocardial infarction - Coronary disease

RESUMEN

Introducción: Los protocolos de diagnóstico acelerado de dolor torácico, con el avance de la troponina de alta sensibilidad, permiten identificar a los pacientes que ingresan al servicio de urgencias con dolor torácico de bajo riesgo para un evento cardiovascular adverso mayor, que podrían ser dados de alta de forma temprana y segura, con ahorro de tiempo y recursos.
Objetivo: Evaluar ensayos clínicos que utilicen protocolos de diagnóstico acelerado basados en troponina de alta sensibilidad.
Material y métodos: se realizó una búsqueda de ensayos clínicos aleatorizados que evaluaran protocolos de diagnóstico acelerado basados en troponina de alta sensibilidad en los servicios de urgencias, en las bases de datos MEDLINE/Ovid, Cochrane y EMBASE utilizando los criterios de evaluación del manual Cochrane y la estrategia PRISMA
Resultados: Tras una tamización de 3509 estudios se incluyeron 5 ensayos clínicos que incluyeron 1513 pacientes; se identificaron 409 (27%) altas tempranas, el 91% para el protocolo 0/3 h ESC, 72% para el 0/1 h, 48% para el EDACS, 40% para el HEART, 19 y 32% para ADAPT y 8 y 18% para el cuidado usual. El valor predictivo negativo fue alto, en un rango de 99,1 al 100% La duración media de la estancia hospitalaria fue más baja para los protocolos 0/1 h y 0/3 h ESC, con 4,6 y 5,6 horas respectivamente.
Conclusiones: Los protocolos de diagnóstico acelerado en dolor torácico que implementan el uso de troponina de alta sensibilidad permiten lograr alta proporción de altas tempranas con baja tasa de eventos cardiovasculares mayores, con disminución del tiempo de estancia y recursos consumidos.

Palabras clave: Dolor torácico - Protocolos de diagnóstico acelerado - Troponina de alta sensibilidad - Síndrome coronario agudo - Infarto agudo del miocardio - Enfermedad coronaria

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INTRODUCTION

People consulting the emergency services for chest pain require a fast assessment to rule out conditions that may put their life at risk. (1) The standard procedure when myocardial ischemia is suspected is to determine its clinical probability according to risk stratification based on clinical history, physical examination, electrocardiographic findings and biochemical markers. (2,3) To optimize this process, accelerated diagnostic protocols (ADP), consisting of the periodic serial assessment of electrocardiograms and markers of myocardial injury to identify very low risk of coronary disease patients, have been established to adopt an early discharge conduct. (4)

The inclusion of high-sensitivity troponins has been an important landmark in the development of these protocols, as they allow the fast and safe detection of apparently healthy patients, (5) denoting a high negative predictive value (NPV) for the diagnosis of acute myocardial infarction, reducing the time of diagnosis and increasing by 4% the sensitivity compared with conventional troponins. This has improved the possibility of rapidly and safely defining patients' condition. (6) Normally, ADP classify patients for study in the following groups: those of very low probability (rule out), those of low or intermediate probability (rule-in) who are hospitalized for stratification, and those of high probability, considered non-ST-segment acute coronary syndromes (NSTE-ACS), who are managed accordingly. (7,8) Generally, the focus has been placed in achieving a greater proportion of cases safely classified as rule out, which implies the successful discharge that is met when the percentage of events in discharged patients is below 1% in the following 30 days. (9,10)

Three recent guidelines highlight the importance of using these protocols: the English National Institute for Health and Care Excellence guideline for the use of high sensitivity tests for the early discharge of NSTE-ACS, (11) several American Societies of Cardiology, Emergency and Imaging guidelines for chest pain assessment and diagnosis, (12) and the European guidelines for NSTE-ACS diagnosis and treatment. (13) In light of this situation, we carried out a systematic review of randomized clinical trials evaluating ADP using high-sensitivity troponins to assess chest pain in patients presenting at the emergency room with suspected NSTE-ACS.

METHODS

Inclusion and exclusion criteria

Randomized clinical trials (RCT) published in English, evaluating ADP to manage patients with chest pain and suspected NSTE-ACS in the emergency services, that used high-sensitivity troponins and reported clinical events as early discharge (within 4 to 6 hours after admission to the emergency room), major cardiovascular events (MACE), and length of hospital stay were included. Studies whose protocols did not have early discharge as endpoint, those considering the concomitant use of other biomarkers, and those evaluating troponin only once after admission were excluded. Also, studies published as poster or abstracts, as well as duplicate reports were excluded from the analysis. Titles and abstracts of studies identified were independently screened by two authors (JCB and JEH); the final decision of eligibility was given by consensus and disagreements were resolved by a third investigator (JJS).

Study search and selection

A search of the literature was carried out in three databases: MEDLINE, Cochrane and EMBASE. The terms used for the search were those grouping the following key words: chest pain, acute coronary syndrome, accelerated diagnostic protocols, 0/1-, 0/2- and 0/3-hour protocols, high-sensitivity troponin, emergency department, risk stratification, rule-out strategies and fast confirmation. Figure 1 shows the search strategy. The search was updated on February 20, 2023.

Data collection

Information was independently collected by two reviewers (GEH and JAG) using a format in which the information collected from the studies was recorded: authors, publication year, center or centers where the studies were performed, study design and methodology, number of randomized patients in each group, as well as effectiveness taking into account 30-day, 6-month or one-year MACE, early discharges, length of hospital stay and data for building a 2 × 2 table to calculate the operative characteristics for the detection of infarction or death at 30 days.

Risk of bias assessment

Two reviewers (GEH and JAG) independently performed risk of bias assessment of the studies using the checklist of the Cochrane collaboration. (14) The points assessed included random sequence generation, concealment, blinding, incomplete output data, selective output report and other biases. They were classified by judgement as low, intermediate or high risk of bias creating graphical descriptions and summaries. The decision was taken by consensus and disagreements were resolved by a third investigator (JPA).

Statistical analysis

Considering the study methodological heterogeneity assessed using the I2 test and the concept resulting from the individual evaluation of studies under a clinical orientation, it was seen that they were not comparable, and therefore, we decided against a statistical combination of results (meta-analysis).

The number of events and the total population of each study were recorded in 2 × 2 tables to calculate the operative characteristics for the presence of 30-day MACE outcomes for the different protocols in the cases in which this information was available in the articles.

The present systematic review is registered as PROSPERO CRD42021255495.

RESULTS

Initial screening identified 3509 studies, among which 5 met the inclusion criteria. Figure 1 shows the selection process and Table 1 summarizes the methodological characteristic of the studies included. (15-19). These studies used three types of high-sensitivity troponin: two Abbot TnI, (16,17) one Siemens TnI (18) and two Roche TnT (15,19). Three studies compared

ADP versus standard management (15,16,18) and the other two compared different protocols. (17,19) One work was a pilot study with a small number of patients; (15) and only one was a multicenter trial (RAPID-TnT), which included the highest number of patients and was proposed as a non-inferiority study.

Main effectiveness outcomes

The five studies described the outcomes of early discharges, 30-day MACE and length of hospital stay (Table 2). (15,19) In the three trials comparing a protocol versus standard care, the use of ADAPT, HEART and MACS protocols evidenced higher percentages of early discharges versus standard care. In the study comparing two protocols, the EDACS trial showed higher percentages of early discharge compared with the ADAPT trial (41.6% vs. 30.5%, respectively). (17) In the RAPID TnT trial, the 0/1-h and ESC 0/3-h protocols reported effective early discharge rates of 45% and 33%, respectively. (19) Among the studies comparing protocols (ADAPT and HEART) versus standard care and which reported length of hospital stay in hours, the protocols significantly reduced these times: 6 vs. 20 hours and 9.9 vs. 21 hours, respectively. The operative characteristics of the intervention regarding 30-day MACE for each study (Table 3) demonstrate a reduced rate of false negatives, high sensitivity and high negative predictive values in all the protocols evaluated.

Risk of bias assessment

Most studies presented an intermediate risk classification, mainly due to the difficulty of blinding the intervention. Only one study could appropriately blind the intervention (15) (Table 4).

DISCUSSION

This systematic review identified a small number of RCT in which the safety of ADP application was demonstrated with a clear decrease in the length of hospital stay. The results distinctly demonstrate that the different protocols are more effective in identifying patients who are candidates for early discharge compared with standard care, as well as for the reduction of hospital stay. The discussion that we will carry out below will focus on the analysis of each of the protocols used in the various studies.

0/1 hour protocols: The results seen in the RAPID-TnT study showed that 72% expected early discharges and 45% effective discharges were achieved with a

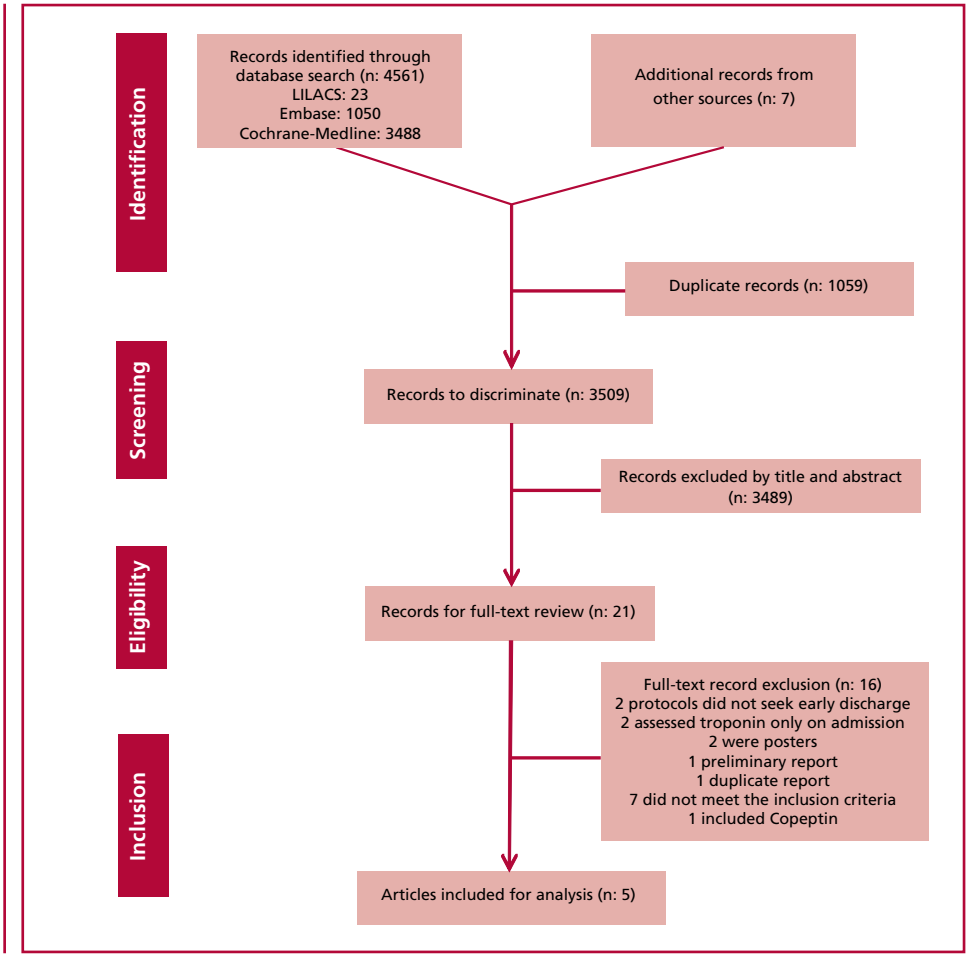

Fig. 1. PRISMA flow diagram of articles included in the study

Table 1. Summary of methodological characteristics of studies included in the systematic review

Study	Protocol	Type of study	Number of patients	Type of troponin	Primary outcome	Other outcomes
Than, 2014 (16)	ADAPT Standard care	Single center	544	Abbott Architect high-sensitivity troponin I (hs-cTnI)	Successful early discharge (6 hours)	MACE on admission and at 30 days
Mahler, 2015 (18)	HEART Standard care	Single center	282	ADVIA Centaur platform TnI-Ultra™ assay (Siemens)	Rate of objective cardiac tests within 30 days of presentation	(1) Successful early discharges (2) length of hospital stay (3) recurrent emergency visits and non-indexed hospitalization at 30 days.
Than, 2016 (17)	EDACS ADAPT	Pragmatic single center	560	Abbott Architect high-sensitivity troponin I (hs-cTnI)	Successful early discharge (6 hours)	Proportion of low-risk patients and 6-month MACE
Body, 2017 (15)	MACS Standard care	Single center	60	hs-cTnT; Roche Diagnostics Elecsys and heart type fatty acid binding protein	Successful early discharge (4 hours)	30-day, 3- and 6-month MACE and length of hospital stay
Chew, 2019 (19)	0/1 hour protocol ESC 0/3 protocol	Non-inferiority multicenter	3288	hs-cTnT; Roche Diagnostics Elecsys 5th generation	30-day MACE	Length of hospital stay; percentage of early discharges.

ADAPT: Accelerated Diagnostic protocol to Assess Chest Pain using Troponins
EDACS: Emergency Department Acute Coronary Syndrome
HEART: History, ECG, Age, Risk factors, Troponin
MACE: Major Adverse Cardiovascular Events
MACS: Manchester Acute Coronary Syndrome

Table 2. Effectiveness results of the different protocols used in the studies

Study	Protocol	Early discharge	30-day MACE	6-month MACE	Average length of hospital stay
Than, 2014 (16)	ADAPT	52 (19.3%)	1	N/R	6 hours
	Standard care	30 (11.0%)	0	N/R	20 hours
Mahler, 2015 (18)	HEART	56 (39.7%)	0	N/R	9.9 hours
	Standard care	26 (18.4%)	0	N/R	21.9 hours
Than, 2016 (17)	EDACS	133 (41.6%)	0	N/R	6 hours
	ADAPT	90 (30.5%)	0	N/R	6 hours
Body, 2017 (15)	MACS	17 (26%)	3	6	1 day
	Standard care	5 (8%)	3	5	1 day
Chew, 2019 (19)	0/1-hour protocol	Effective: 748 (45%) Expected: 1187 (72%)	17 (1%)	N/R	4.6 (3.4–6.4) hours
	ESC 0/3-hour protocol	Effective: 545 (33%) Expected: 1493 (91%)	16 (1%)	N/R	5.6 (4.0–7.1) hours

ADAPT: Accelerated Diagnostic protocol to Assess Chest Pain using Troponins
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MACE: Major Adverse Cardiovascular Events
MACS: Manchester Acute Coronary Syndrome
N/R: not reported

NPV of 99.6%. This result is consistent with a systematic review that included 11 014 patients from 10 cohorts, documenting an early discharge rate of 55% with Roche's high-sensitivity troponin, and greater than 50% for those of Abbott and Siemens with a NPV of 99. 9% for 30-day MACE. (20) In the TRAP-ID-AMI study, 63% early discharges were obtained among 1282 patients, with a NPV of 99.1%, (21) while in the HIGH-US Study of 2113 patients, 50.4% were discharged with a NPV of 99.7%. (22) Another meta-analysis that included 14 cohorts and 13 899 patients reported an aggregate result of early discharge of 54% and a NPV of 99.8%. (23) The application of this protocol has certain practical limitations since it is necessary to have fifth-generation high-sensitivity troponins that have been validated and whose cut-off values vary depending on each test. (24) According to the English NICE guidelines, 9 high-sensitivity troponin tests are currently validated for application in 0/1-hour protocols. (11)

ESC 0/3-hour protocol: The same RAPID-TnT study documented an expected early discharge rate of 92% with a NPV of 99.4% for the 0/3-hour protocol, the highest documented outcome for any protocol. It exceeds the aggregate result of early discharge of 66% and NPV of 98.7% reported by the previously mentioned meta-analysis on 9 works that included 10 237 patients, (23) and the highest report obtained for an individual cohort, 78.9% (961 of 1,218 patients) with a NPV of 97.9%. (25) However, if the results of effective early discharges of the RAPID-TnT trial are considered, the interpretation is different, taking into account the 33% obtained, lower than for the 0/1-hour protocol. This is also consistent with the results of the cohort presented by the Badertscher group, which compared the 0/1- and ESC 0/3-hour protocols among 2547 patients, with early discharges of 60% for 0/1-hour and 44% for 0/3-hour protocols. ($p<0.001$) with a NPV of 99.8% and 99.7%, respectively. (26) A third study on 1920 patients found that early discharges for the 0/3-hour protocol could reach 65%, although their NPV was lower than that of the 0/1-hour protocol

Table 3. Operative characteristic results for the diagnosis of the different protocols used in the clinical trials

Study	Protocol	Sensitivity	Specificity	Precision	PPV	NPV	LR+	LR-
Than, 2014	ADAPT	97.9	22.9	35.9	21.1	98.1	1.270	0.090
(16)	Standard care	100.0	12.6	23.9	14.4	100.0	1.145	0.000
Mahler, 2015	HEART	100.0	49.3	51.8	9.3	100.0	1.971	0.000
(18)	Standard care	100.0	23.5	28.4	8.2	100.0	1.307	0.000
Than, 2016	EDACS	97.3	47.5	54.1	22.1	99.1	1.854	0.057
(17)	ADAPT	100.0	34.0	40.9	14.9	100.0	1.515	0.000
Body, 2017	MACS	100.0	27.0	30.3	6.1	100.0	1.370	0.000
(15)	Standard care	100.0	8.1	12.3	5.0	100.0	1.088	0.000
Chew, 2019	0/1-hour protocol	88.1*	94.7*	N/A	38.2*	99.6&	16.5*	N/A
(19)	ESC 0/3-protocol	N/A	N/A	N/A	N/A	99.4&	N/A	N/A

* for rule in
& for rule out
PPV: Positive predictive value, NPV: negative predictive value, LR: Likelihood ratio, N/A: not applicable
ADAPT: Accelerated Diagnostic protocol to Assess Chest Pain using Troponins
EDACS: Emergency Department Acute Coronary Syndrome
HEART: History, ECG, Age, Risk factors, Troponin
MACE: Major Adverse Cardiovascular Events
MACS: Manchester Acute Coronary Syndrome

Table 4. Risk of bias assessment

	Than, 2014	Mahler, 2015	Than, 2016	Body, 2017	Chew, 2019
Random sequences	•	•	•	•	•
Allocation concealment	•	•	•	•	•
Intervention blinding	•	•	•	•	•
Blinding of outcome	•	•	•	•	•
Incomplete outcome data	•	•	•	•	•
Selective reporting	•	•	•	•	•
Other biases	•	•	•	•	•

Black mark: Low risk of bias
Grey mark: Intermediate risk of bias

(98% vs 99%). (27)

Undoubtedly, the issue is under discussion and the definitions of expected and effective early discharges influence the interpretation of results.

EDACS protocol: It reported 42% early discharges, with 99.1% NPV, (17) a slightly lower result than that seen in the cohort study of the same research group, which reported 51% early discharges and 99.6% NPV (28). Other validation cohort studies documented possible early discharges of 66.7% (29), 41.6% (30), 35.2% (31), and 58.1% (32), all with NPV higher than 99%. These findings confirm good performance for this protocol along with a high degree of safety.

HEART protocol: the RCT in which it was evaluated obtained 39.7% early discharges with a NPV of 100%; (18) it also had a one-year follow-up in which MACE was documented in 9.9% in the HEART arm vs. 11.3% in the standard care group (p=0.85). (33) A validation cohort found early discharge rates of 38.4% with a NPV of 99.6 %. (32) Another publication questions the safety of this protocol by documenting a NPV of 98.1% with a possible early discharge rate of 33.2% (264/794). (34)

ADAPT protocol: it was evaluated in two clinical trials with an early discharge rate of 19.3% and 30.5% and a NPV of 98.1% and 100%. One of the validations for this protocol by the Than group (2012), prior to the use of high-sensitivity troponins, found a possible early discharge rate of 20% with a NPV of 99.7%. (35) A subsequent validation , with high-sensitivity troponin, reached a possible early discharge rate of 19.6%, with a NPV of 99.7%.(36) These results are consistent with what is documented in this systematic review and questions its clinical usefulness, especially taking into account that in one of these studies better results were obtained with the comparator protocol, EDACS.

The decision to exclude two recently published randomized clinical trials should be especially mentioned. Both trials evaluated the rule out strategy based on undetectable levels in patients presenting within the first 6 hours of symptoms. The reason for exclusion was that it was not considered it could be applied to all emergency patients, and it is therefore a study of troponin rather than an ADP, although its results are worth presenting as they are part of the initial strategy of the 0/1-hour protocols: the first was a study that included eight centers in England and Wales, which obtained a 4-hour early discharge rate of 141/309 (46%) patients compared with 114/311 (37%) for standard care. (37) The second was the HiSTORIC (High-Sensitivity Cardiac Troponin on Presentation to Rule Out Myocardial Infarction) study, which included 31 492 patients from 7 hospitals, reduced the length of hospital stay by 3.3 hours and hospital admissions by 59%; non-inferiority was not demonstrated, but the observed differences in myocardial infarction or cardiac death at 30 days and 1 year favored the early rule-out pathway over standard care. (38)

The proliferation of ADP makes us carry out a careful exercise to select the one that adapts to the daily environment of work in the emergency room. Although guideline recommendations seem to favor protocols that focus on fixed high-sensitivity troponin values and their variations at 1, 2, or 3 hours of admission, and do not include clinical prediction rules, we must make the caveat that it is necessary to have a troponin that has been evaluated for the selection of cut-off values and the training of staff so that they become familiar with its implementation. We should note that the 2020 European NSTE-ACS guidelines (13) removed the ESC 0/3-h protocol from their recommendations based on the results of three previously discussed large cohorts (25-27) under the assumption of lower efficacy and safety. What is stated in this review shows that the results are still contradictory and that it is necessary to continue exploring the safety of the ESC 0/3-h protocol.

The high complexity of the problem in question becomes a limitation of this work. Although we guided the discussion towards the safe discharge of patients, the issue of cost-effectiveness, which is tangentially addressed in the studies presented, is beyond discussion. We must note that the approach to chest pain does not end at this point and the evaluation of intermediate probability cases that must be hospitalized implies a series of additional steps not covered by this study.

CONCLUSIONS

The use of ADP in chest pain provides consistent evidence on the possibility of achieving early discharge with a very low rate of major cardiovascular events, as well as a benefit in significantly reducing the length of hospital stay, which decreases overcrowding emergency services, and allows more efficient use of health resources. The results seem to favor the 0/1-h and ESC 0/3 h protocols in accordance with current recommendations.

Conflicts of interest

None declared.

(See authors' conflict of interests forms on the web).

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