

ORIGINAL ARTICLE

High-sensitivity versus conventional troponin for management and prognosis assessment of patients with acute chest pain

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ABSTRACT

Objectives High-sensitivity troponin (hs-cTn) is substituting conventional cTn for evaluation of chest pain. Our aim was to assess the impact on patient management and outcome.

Methods A total of 1372 consecutive patients presenting at the emergency department with non-ST-elevation acute chest pain were divided into two periods according to the cTn assay used, conventional (n=699, March 2008 to July 2010) or hs-cTn (n=673, November 2010 to March 2013). Management policies were similar and according to guidelines. The primary endpoint was major adverse cardiac events (MACE) at 6 months (death, myocardial infarction, readmission by unstable angina or postdischarge revascularisation).

Results There were minor differences in baseline characteristics. In the hs-cTn period, more patients elevated cTn (73% vs 37%, p=0.0001) leading to more coronary angiograms (77% vs 55%, p=0.0001) and revascularisations (45% vs 31%, p=0.0001); conversely, fewer patients were initially assigned to exercise testing (14% vs 36%, p=0.0001) and, therefore, discharged early after a negative result (7% vs 22%, p=0.0001). At 6 months, 135 patients suffered MACE, including 54 deaths. After adjusting for a Propensity Score, hs-cTn use was not significantly associated with MACE (HR=0.99; 95% CI 0.70 to 1.41; p=0.98) or mortality (HR=1.02; 95% CI 0.59 to 1.77; p=0.95), though the risk of longer hospitalisation stay increased at the index episode (OR=1.35, 95% CI 1.07 to 1.71, p=0.02).

Conclusions hs-cTn simplified chest pain triage on avoiding a more complex evaluation with non-invasive tests in the chest pain unit, but prompted longer hospitalisations and more invasive procedures without impacting on the 6-month outcomes.

INTRODUCTION

Troponin (cTn) plays a central role in the management of acute chest pain. The conventional cTn assays lack precision for measuring cTn at low concentrations corresponding to the 99th percentile value of a normal reference population; this is the cut-off for the diagnosis of acute myocardial infarction (AMI).^{1 2} In contrast, the high-sensitivity cTn (hs-cTn) assays show precision at the 99th percentile cut-off.^{3 4}

Due to this better accuracy, hs-cTn allows the identification of some high risk patients from

within the vast population of acute chest pain who would otherwise go undetected using conventional cTn.⁵⁻⁷ In addition, cTn release can be detected as early as 2 h from AMI onset.⁸⁻¹⁰ However, ruling in AMI when hs-cTn is mildly elevated or ruling out unstable angina when hs-cTn is normal remains matters of debate.

Currently, hs-cTn is substituting conventional cTn in many hospitals, but there is scarce information regarding how this change is modifying patient management and outcome. Some data suggest that hs-cTn use might improve patient prognosis, but more information is needed to confirm these findings.¹¹ In this study, two consecutive series of patients with acute chest pain managed with conventional or hs-cTn assay were compared. The main purpose was to investigate the impact of hs-cTn on postdischarge outcome as well as on the in-hospital diagnostic work-up and management.

METHODS

Study design

This prospective cohort study included 1372 patients who presented at the emergency department with acute chest pain. The study group comprised two cohorts corresponding to different periods according to the cTn assay used: (1) the conventional cTn period (from 1 March 2008 to 1 July 2010, n=699) and (2) the hs-cTn period (from 1 November 2010 to 1 March 2013, n=673). In the time interval between the two periods, a different provisional cTn assay was used until the new high-sensitivity assay was implemented, and these interim patients were not considered. The study was reviewed and approved by the ethics board of the University Clinic Hospital of Valencia.

In both periods, consecutive patients presenting at the emergency department with a chief presentation of chest pain considered by the cardiologist on duty to be of possible coronary origin were included. The clinical screening process involved a first evaluation by a member of the emergency staff to determine if the chest pain was of obvious non-cardiac origin (eg, muscular, skeletal or pleuritic pain). The remaining conditions were initially considered as of a possible cardiac origin. At the second evaluation, the cardiologist on duty excluded clinical settings suggestive of cardiac diseases other than coronary heart disease (such as



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pericarditis or acute aortic dissection) and, finally, patients were included in the registry.^{12–14} Other exclusion criteria were: (1) ST-segment elevation in the initial ECG suggesting AMI and (2) prior known heart disease other than coronary artery disease (such as heart valve disease or cardiomyopathy).

Patient management

The management protocol was identical in the two cohorts, consisting of the successive evaluation of the initial ECG, serial cTn tests and early exercise testing for those patients without ECG ischaemia or cTn elevation and who were able to exercise.^{12–14} Ischaemic changes in the initial ECG were considered if ST-segment depression was ≥ 1 mm or T wave inversion was ≥ 1 mm. Serial cTn determination was performed upon arrival and later according to the physician's criterion. The recommendation for the second cTn measurement was at 8 h after patient arrival in the conventional cTn period and at 6 h in the hs-cTn period.

Patients with cTn elevation were hospitalised with a diagnosis of non-ST elevation AMI and were scheduled for a coronary angiogram. Patients with a negative cTn result but with ECG ischaemia were also hospitalised and underwent cardiac magnetic resonance with dipyridamole or a coronary angiogram, as directed by the attending physician. In the absence of ischaemia in the ECG or of cTn elevation, patients were assigned to an early exercise test or were hospitalised for further evaluation in the case of any contraindication to exercise. Those patients with a negative result in the exercise test were directly discharged.

All patients with acute coronary syndrome diagnosis received antithrombotic treatment consisting of dual antiplatelet therapy (aspirin and clopidogrel) and enoxaparin.

cTn measurement

In the conventional cTn period, the cTn-I Siemens Dimension RxL assay (Dade Behring, Newark, Delaware, USA) was used. With this assay, the 99th percentile value of a reference population is at 70 ng/L, while the precision limit with a 10% coefficient of variation is at 140 ng/L. In our institution, following the recommendation of the manufacturer, the cut-off selected for AMI diagnosis was 200 ng/L. In the hs-cTn period, the Elecsys hs-cTn-T assay (Roche Diagnostics, Basel, Switzerland) was used. With this assay, the precision limit is at 14 ng/L. This value also corresponds to the 99th percentile cut-off and was used for AMI diagnosis.

Data collection

Clinical data were collected at admission. The length of hospital stay (LOS, days), number of diagnostic and revascularisation procedures performed and medical treatment at discharge were also recorded.

Outcomes

The main outcome was major adverse cardiac events (MACE) at 6 months, including all-cause death, readmission for AMI, readmission for unstable angina and postdischarge revascularisation. AMI was defined by a new episode of acute chest pain with cTn elevation.² Readmission for unstable angina was considered in case of rehospitalisation by suggestive chest pain with evidence of ischaemia in the imaging ischaemia test or significant stenosis in the coronary angiogram. Postdischarge revascularisation was considered if coronary angioplasty or coronary surgery was performed during follow-up. Secondary outcomes were 6-month mortality and the LOS at the index episode. Periprocedural myocardial infarction was also registered and

defined by an increase of creatine kinase isoenzyme (CK-MB) >3 times after coronary angioplasty or >5 times after coronary surgery at 8 and 24 h after the procedure.

Information on the endpoints was collected in the outpatients' department. In patients who did not return to the outpatients' department, the information was obtained by establishing contact with the patient, his or her general physician or the regional registry on mortality.

A total of 9 (1.3%) patients were lost at the follow-up in the hs-cTn period and 3 (0.4%) were lost in the conventional cTn-period.

Statistical analysis

The baseline characteristics of the patient population were compared between the two study periods, using the χ^2 test for categorical variables and unpaired t test for continuous variables. Likewise, patient management was also compared between these periods.

Propensity Score

Due to its observational nature, there were systematic differences between the two management periods (table 1). This prompted us to use a Propensity Score (PS) technique to minimise the effect of this confounding.¹⁵ In this analysis, the PS was calculated using generalised boosted models using the twang package in R3.02.¹⁶ Once calculated, we opted for using the estimated-PS as inverse probability of treatment weighted (IPTW) in a Cox regression analysis because it is shown to estimate the marginal HRs with minimal bias and greater precision as compared with other methods.¹⁶

The pretreatment variables of the PS included: age (years), male gender, admission heart failure, ≥ 2 pain episodes in 24 h, hypertension, current smokers, hypercholesterolaemia, diabetes, family history of ischaemic heart disease, prior myocardial infarction, prior percutaneous coronary intervention, prior coronary surgery, prior admission for heart failure, peripheral

Table 1 Baseline characteristics in the two study periods

	Conventional cTn N=699	hs-cTn N=673	p Value
Age (years)	65.8 \pm 12.6	67.9 \pm 13.0	0.002
Male	447 (64)	455 (68)	0.2
Admission HF	39 (5.6)	47 (7)	0.3
≥ 2 chest pain episodes in 24 h	300 (43)	308 (46)	0.3
Hypertension	434 (62)	480 (71)	0.0001
Current smokers	172 (25)	138 (21)	0.07
Hypercholesterolaemia	355 (51)	401 (60)	0.001
Diabetes	224 (32)	242 (36)	0.2
Family history	45 (6.4)	29 (4.3)	0.09
Prior myocardial infarction	153 (22)	166 (25)	0.2
Prior PCI	74 (11)	137 (20)	0.0001
Prior CABG	43 (6)	42 (6)	1
Prior admission HF	38 (5.4)	27 (4.0)	0.3
Peripheral artery disease	47 (6.7)	43 (6.4)	0.8
Prior stroke	45 (6.4)	47 (7.0)	0.7
ST-segment depression	145 (21)	119 (18)	0.2
T wave inversion	78 (11)	71 (11)	0.9
Creatine (mg/dl)	1.09 \pm 0.6	1.1 \pm 0.7	0.7

Absolute values with percentages are shown in brackets, with the exception of age and creatine levels presented as mean \pm SD. CABG, coronary artery bypass surgery; cTn, troponin; HF, heart failure; hs-cTn, high-sensitivity troponin; PCI, percutaneous coronary intervention.

artery disease, prior stroke, ST-segment depression, T wave inversion and serum creatine (mg/dL). The variables used for the creation of the PS were selected based on three criteria: (1) clinically they are predictors of the treatment strategy (hs-cTn vs conventional), (2) most of them are also predictors of the outcome (MACE) and (3) they are temporally aligned with the treatment (none of them are consequence of the treatment). The PS discrimination was evaluated by estimating the area under the receiver operating characteristic curve (0.9171). As a calibration measure, the Hosmer–Lemeshow test was estimated ($p=0.21$).

Outcomes

A PS-weighted survival parametric regression analysis was carried out for determining the prognostic effect that the study period had on either all-cause death or MACE.¹⁷ The HR and 95% CI were calculated. In addition, a PS-weighted survival function at each study period was estimated for each clinical endpoint, and depicted in [figures 1 and 2](#).

Length of stay analysis

A PS-weighted multivariable binary logistic analysis was also performed to analyse the relation between the study period and LOS at the index episode. To this effect, the continuous variable LOS was dichotomised taking the median value as cut-off (≥ 5 days). Results for this analysis are expressed as OR and 95% CI.

A two-sided p value of <0.05 was considered to be statistically significant for all analyses. All analyses were performed using STATA V.12.1 (StataCorp. 2011. Stata Statistical Software: Release 12. College Station, Texas, USA: StataCorp LP) and R (R Development Core Team (2013). R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0, URL <http://http://www.R-project.org/>).

RESULTS

Baseline characteristics

[Table 1](#) shows the baseline characteristics of patients in both periods. Patients belonging to hs-cTn period were slightly older

(67.9 ± 13.0 vs 65.8 ± 12.6 years, $p=0.002$) and exhibited higher rates of hypertension (71% vs 62%, $p=0.0001$), hypercholesterolaemia (60% vs 51%, $p=0.001$) and prior percutaneous coronary intervention (20% vs 11%, $p=0.0001$).

As a whole, it was a medium risk population according to the thrombolysis in myocardial infarction (TIMI) risk score (conventional cTn period= 2.4 ± 1.5 ; hs-cTn period= 3.0 ± 1.5 points). The distribution of patient risk within each period (low=0–1, medium=2–4 and high=5–7 points) was as follows: conventional cTn period=29%, 63% and 8%; hs-cTn period=16%, 69% and 15%. When considering the figures of the TIMI risk score, it must be taken into account that cTn elevation, one of the score's variables, was more frequent using the hs-cTn assay due to the characteristics of this assay, leading to higher scores.

Management

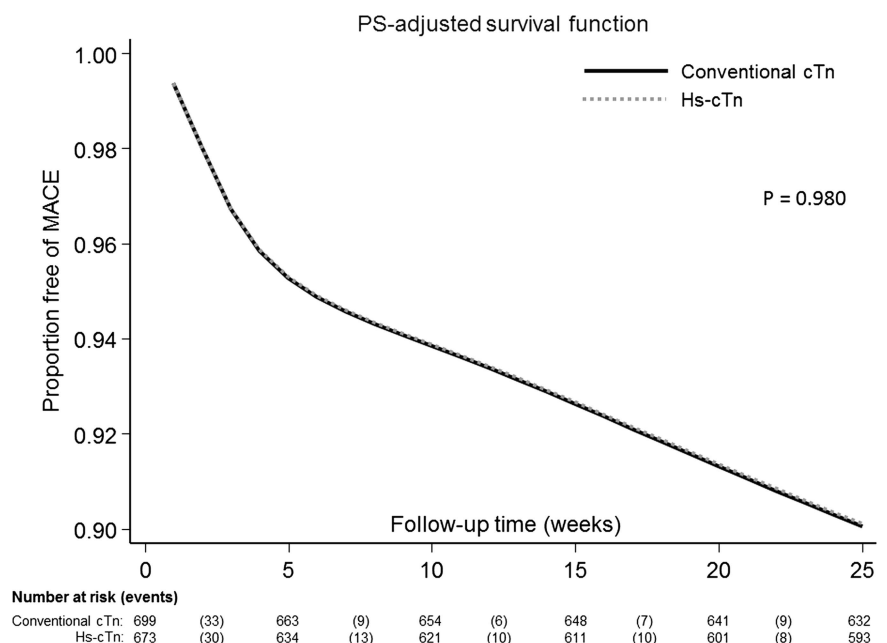
[Table 2](#) illustrates patient management. cTn elevation rate was twofold higher in the hs-cTn period (73% vs 37%, $p=0.0001$); this fact prompted a higher number of coronary angiograms (77% vs 55%, $p=0.0001$) and, consequently, a higher number of revascularisations (45% vs 31%, $p=0.0001$). In contrast in the conventional cTn period, more patients were initially assigned to exercise testing evaluation (36% vs 14%, $p=0.0001$), which facilitated a higher rate of early discharges because of a negative exercise test result (22% vs 7%, $p=0.0001$). Unstable angina was diagnosed in 142 (20%) patients in the conventional cTn period but in 54 (8%) in hs-cTn period ($p=0.0001$).

The use of recommended medications for acute coronary syndromes at discharge was more frequent in the hs-cTn period ([table 2](#)).

Outcomes

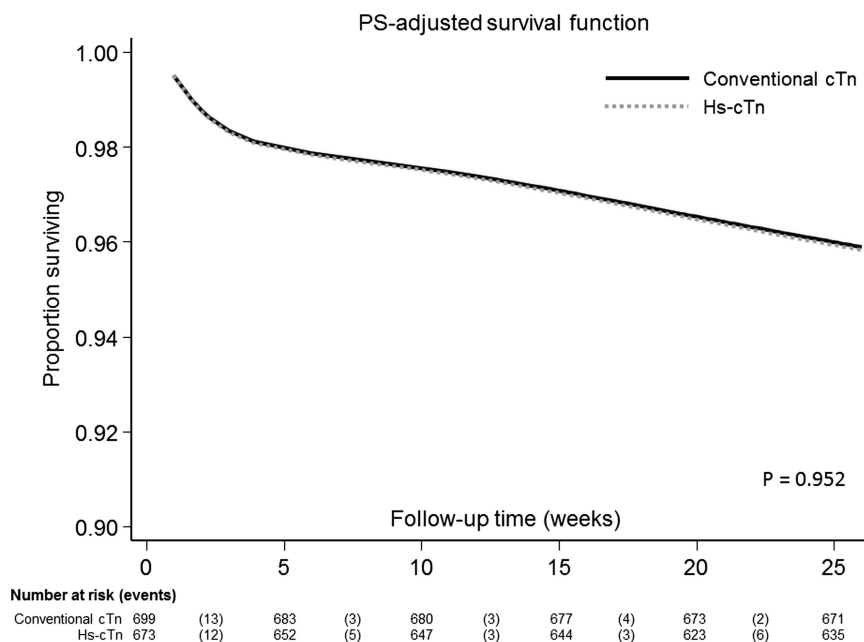
During the 6-month follow-up, 54 patients died and 135 suffered MACE. [Table 3](#) presents the distribution of events in both study periods. The PS-weighted regression analyses revealed no differences between the two study periods with regard to risk of death (HR=1.02; 95% CI 0.59 to 1.77; $p=0.952$) or MACE (HR=0.99; 95% CI 0.70 to 1.41; $p=0.980$) at 6-month follow-up. Moreover, the PS-adjusted survival curves also

Figure 1 Comparison of PS-weighted survival functions for MACE between conventional cTn and hs-cTn periods. Bottom: Number of patients at risk at each time point. Nine patients were lost at the follow-up in the hs-cTn period and three patients in the conventional cTn period. cTn, troponin; hs-cTn, high-sensitivity troponin; PS, Propensity Score. MACE, major adverse cardiac events; P, statistical significance.



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Figure 2 Comparison of PS-weighted survival functions for mortality between conventional cTn and hs-cTn periods. Bottom: Number of patients at risk at each time point. Nine patients were lost at the follow-up in the hs-cTn period and three patients in the conventional cTn period. cTn, troponin; hs-cTn, high-sensitivity troponin; PS, Propensity Score; P, statistical significance.



showed no differences in the proportion of surviving and free of MACE between the two periods (figures 1 and 2).

Regarding complications related to revascularisation procedures, there were no differences between the conventional cTn and hs-cTn periods in periprocedural death (n=1, 0.1% vs n=3, 0.4%; p=0.4) or non-fatal myocardial infarction (n=19, 2.7% vs n=23, 3.4%, p=0.5). The periprocedural non-fatal myocardial infarctions were not considered within the clinical MACE.

Length of hospitalisation

For the analysis of the LOS, patients who underwent coronary surgery at the index hospitalisation were not considered. Therefore, a total population of 1280 patients were analysed,

659 from the conventional cTn period and 621 from the hs-cTn period. The LOS was higher in the hs-cTn period (5.9 ± 3.6 vs 5.4 ± 3.9 days, p=0.02) and the proportion of patients with a LOS longer than the median (5 days) was also superior in the hs-cTn period (63% vs 56%, p=0.005). In the PS-weighted regression analysis, the use of hs-cTn was significantly associated with higher risk of LOS longer than the median (OR=1.35, 95% CI 1.07 to 1.71, p=0.02).

DISCUSSION

Main findings

The results of this study indicate that the replacement of conventional cTn by hs-cTn modified the management of non-ST-segment elevation acute chest pain patients. The number of coronary angiograms and revascularisations performed at the index episode increased, while the number of patients initially evaluated with non-invasive stress tests in the chest pain unit decreased. Pharmacological treatments for acute coronary syndromes also increased. However, all these changes were not associated with changes in clinical outcomes at 6 months.

Patient management

hs-cTn unveils cTn elevation in some patients who otherwise would initially pass undetected using a conventional assay. In our study, the frequency of cTn elevation leading to a diagnosis

Table 2 Diagnosis, patient management and medical treatment at discharge in the two study periods

	Conventional cTn N=699	hs-cTn N=673	p Value
cTn elevation	255 (37)	493 (73)	0.0001
Early exercise testing	249 (36)	97 (14)	0.0001
Early discharge due to negative exercise test	155 (22)	46 (7)	0.0001
Imaging stress test	102 (15)	103 (15)	0.8
Coronary angiogram	386 (55)	519 (77)	0.0001
Unstable angina diagnosis	142 (20)	54 (8)	0.0001
PCI	176 (25)	253 (38)	0.0001
CABG	40 (6)	52 (8)	0.2
Revascularisation	215 (31)	303 (45)	0.0001
	N=691	N=669	
Aspirin	492 (71)	550 (82)	0.0001
Clopidogrel	231 (33)	404 (60)	0.0001
β -Blockers	390 (56)	518 (77)	0.0001
Statins	462 (67)	577 (86)	0.0001

Absolute values are shown with percentages in brackets; medical treatment at the time of discharge in survivors. CABG, coronary artery bypass surgery; cTn, troponin; hs-cTn, high-sensitivity troponin; PCI, percutaneous coronary intervention.

Table 3 Outcomes in each study period

	Conventional cTn N=699	hs-cTn N=673
6-Month MACE	64 (9.2)	71 (10.5)
6-Month all cause-death	25 (3.6)	29 (4.3)
6-Month MI	29 (4.1)	37 (5.5)
6-Month UA readmission	10 (1.4)	11 (1.6)
6-Month postdischarge rev	16 (2.3)	18 (2.7)

Absolute values are shown with percentages in brackets. cTn, Troponin; hs-cTn, high-sensitivity troponin; MACE, major adverse cardiac events; Death, MI, readmission for UA or postdischarge rev; MI, myocardial infarction; rev, revascularisation; UA, unstable angina.

of non-ST elevation AMI was twice higher in the hs-cTn period. Conceivably, using conventional cTn, these patients would have eventually been detected after evaluation in the chest pain unit, though they would have been classified as with unstable angina. Indeed, the frequency of unstable angina diagnosis was higher in the conventional cTn period. The net consequence of this change in management policy is that hs-cTn simplified chest pain triage by avoiding a longer and more complex assessment in the chest pain unit in some patients. Evaluation in the chest pain unit often requires non-invasive tests such as an exercise test, imaging stress test or CT angiography.^{13 18–20} The drawback of using hs-cTn is that fewer patients can be directly discharged because more coronary angiograms are indicated as a consequence of hs-cTn elevation. In fact, our data show that the LOS was longer in the hs-cTn period. In addition, the excess of invasive management can lead to an inappropriate number of revascularisations.

It can be argued that the diagnosis of AMI should have been established by the pattern of cTn rise and fall rather than on cTn elevation alone. Therefore, some patients with cTn elevation not due to an acute coronary syndrome may have been included in the study. However, there are no definitive criteria for what cTn change is significant, because the kinetics of cTn rise and fall depend on many factors.²¹ Indeed, in a recent study, a non-negligible proportion of patients with acute chest pain and cTn elevation but without significant cTn change were finally diagnosed with AMI and had a worse outcome.²²

Outcome

In a prior study, Mills *et al* also compared the clinical outcome of patients with suspected acute coronary syndromes between two study periods using different cTn cut-offs (validation and implementation phases) roughly equivalent to our comparison between conventional cTn and hs-cTn.¹¹ The impact upon in-hospital patient management was quite similar to our observations. Remarkably, lowering the cTn cut-off in the implementation phase reduced the rate of death and AMI at 3 and 12 months after discharge. The favourable effect was due to a much better outcome in the subgroup of patients with mild cTn elevation who went undetected in the validation cohort but were identified in the implementation cohort; these patients were therefore managed more aggressively in the implementation phase. However, in contrast to these findings, we found similar outcomes in the two periods. Various approaches to management of chest pain among different countries and centres might explain the different results: (1) One of the most relevant differences might be the management strategy in chest pain with normal cTn, since the routine discharge of these patients entails a non-negligible rate of short-term events.^{12–14} Our chest pain unit routinely performed early exercise tests allowing patients with acute chest pain but normal cTn levels to be thoroughly evaluated. Therefore, in the conventional cTn period, the highest risk patients with normal cTn were detected and properly treated. This policy could explain the lower rate of events in this subgroup in our study. (2) Another influential factor might be the strict fulfilment of current clinical guidelines recommending an invasive management in patients with chest pain and cTn elevation. It is plausible that the use of hs-cTn resulted in some unnecessarily invasive and revascularisation procedures. Indeed, the pitfalls in ruling in AMI using hs-cTn constitute one of its biggest limitations; hs-cTn values are higher in the elderly, men, and those with renal failure, pre-existing stable coronary artery disease and in other conditions with potential myocardial damage.^{23–27} Moreover, in a prior study,

revascularisation of low risk patients with acute chest pain did not show any prognostic benefit.²⁸ (3) AMI events may have been more easily diagnosed in the hs-cTn period by this more sensitive cTn assay. Therefore, some of the events classified as readmission for unstable angina in the conventional cTn period would have been classified as AMI in the hs-cTn period. In fact, there were no differences in recurrent ischaemic events (either readmission for AMI or unstable angina) between both periods. (4) Patients with ST-segment elevation were excluded in our study but included in the study by Mills and colleagues.¹¹

Limitations

This was a sequential two period cohort study from a single centre and some confounding variables cannot be excluded. However, the baseline characteristics were roughly similar in both periods and PS analysis was done to compensate for these differences. The management and evolution of patients with chest pain not considered of possible coronary origin by the cardiologist in charge were not recorded. The follow-up period was 6 months, and so the effect of using the hs-cTn assay over longer follow-up was not assessed. Therefore, the results of this study should not underestimate the potential long-term benefits of diagnosing coronary artery disease thanks to hs-cTn, in particular as regards the introduction of secondary prevention medications such as statins in patients in whom ischaemic heart disease would not have been recognised otherwise.

Conclusions

The introduction of hs-cTn in hospital practice modifies the management policy of acute chest pain towards a more aggressive approach in terms of invasive management and revascularisation procedures. However, no benefits in terms of mid-term prognosis were observed. The results of our study suggest that careful clinical evaluation and diagnosis workup are advisable in some patients with chest pain and hs-cTn elevation before routine invasive management is indicated. Further studies are needed on how to optimise the information provided by hs-cTn for patient management.

Key messages

What is known on this subject?

Currently, high-sensitive troponin (cTn) is substituting conventional cTn in many hospitals, but there is scarce information regarding how this change is modifying patient management and outcome.

What might this study add?

Our results suggest that high-sensitivity cTn use did not improve mid-term prognostic data.

How might this impact on clinical practice?

Further studies are needed on how to optimise the information provided by high-sensitivity cTn for patient management.

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Contributors The contributions of the authors were as follows: (1) Conception and design: JS and JN. (2) Collection and analysis of data: SG-B, LM, AM, LA, SV and CB. (3) Interpretation of data: JS, EN and JN. (4) Drafting of the manuscript or revising it critically: JS, LC, MR, FJCh, EN and JN. (5) Final approval of the manuscript submitted: All authors.

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Competing interests None.

Ethics approval The study was reviewed and approved by the ethics board of the University Clinic Hospital of Valencia.

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