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Conventional Troponin-I versus high-sensitivity troponin-T: Performance and incremental prognostic value in non-ST-elevation acute myocardial infarction patients with negative CK-MB based on a real-world multicenter cohort

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In the late nineties unstable angina (UA) was classified based on clinical history, presence or absence of EKG changes, and intensity of anti-ischemic therapy [1]. Subsequently UA with an elevation of creatine kinase (CK)-MB was defined as a non-ST elevation acute coronary syndromes (NSTE-ACS) with myocardial necrosis and the further refinement of UA classification and definition is still ongoing. Indeed, the introduction of cardiac-specific troponin (Tn) assays allowed for a more sensitive detection of cardiomyocyte death in NSTE-ACS without CK-MB elevation, thus reclassifying a subgroup of UA patients as non-ST elevation myocardial infarction (NSTEMI). Interestingly, up to one-third of patients previously diagnosed with UA showed Tn elevation [2] accompanied by a 4-fold increase in the risk of death or acute myocardial infarction (AMI) at 6 months [3].

Recent advances in technology have resulted in more sensitive and precise assays, able to detect circulating Tn levels more precisely than conventional ones, particularly in the low range, which strongly impact the definition of NSTE-ACS and its clinical management. High-sensitivity Tn (hsTn) assays were proven to provide earlier detection of AMI [4], to have higher negative predictive value and to improve overall diagnostic accuracy in patients with suspected ACS [5].

In addition to the diagnostic accuracy, several studies showed that hsTn increase prognostic accuracy, identifying higher-risk patients in the conventional Tn (cTn) negative group [6–8], thereby having important implications in driving decision making during initial ACS management. Nevertheless, many aspects related to the prognostic value of hsTn remain, despite encouraging results obtained in previous studies. For instance, previous studies focused primarily on hard endpoints, i.e., cardiovascular death (CVD) and AMI, whereas the relationship between Tn and recurrent UA, a frequent cause of rehospitalization and reduced quality of life, was not or only partially explored. In addition, the majority of the studied populations derived from clinical trials employed strict mostly high-risk inclusion criteria, which do not allow direct translation of these findings to the general UA population.

In this issue of IJC *Heart & Vasculature*, Magnoni et al. [8] investigated the diagnostic and prognostic value of hsTn in relation to hard endpoints (CVD, AMI and recurrent UA) comparing the performances of a hsTn-T assay with cTn-I assay in a prospectively enrolled Italian multicenter real-world population admitted to Coronary Care Unit with a diagnosis of NSTE-ACS (the SPAI study). Of note, only CK-MB negative patients were enrolled. This allowed to precisely investigate this specific range of NSTE-ACS patients, where the diagnostic and prognostic accuracy of a assay with enhanced sensitivity should have the greatest clinical impact.

In this study, hsTn-T and cTn-I were measured in 644 patients, who were then stratified at the 99th percentile reference limit for each assay. Follow-up lasted 180 days. Patients with hsTn-T ≥ 99th percentile were at higher risk of CVD/MI also after adjusting for TIMI Risk Score. However, no significant difference in CVD/MI at 180-day was found between hsTn-T-positive/cTn-I-negative and hsTn-T-negative/cTn-I-negative patients. The occurrence of UA was similarly distributed between hsTn-T groups dichotomized at the 99th percentile. The authors concluded that while demonstrating good prognostic performance in the risk stratification of the hard endpoint, hsTn-T did not demonstrate the hypothesized superior prognostic ability over contemporary cTn-I. Moreover, Tn assay did not predict the recurrence of UA, suggesting that the acute rise of cardiac Tn is a marker of coronary artery disease severity, but does not predict the recurrence of UA. The apparent lack of superiority in stratifying hard endpoints, which appear inconsistent with previous reports, require a careful appraisal of between-studies differences to reach definitive conclusions. The population of the

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current study was enrolled in cardiology centers with heterogeneous treatment capabilities, where patients were managed according to local protocols. This reflects real-world management including use of disease-modifying treatment options not necessarily being used in controlled clinical trials, where patients were managed according to precise treatment protocols in highly specialized healthcare structures, ultimately affecting the prognostic significance of biomarkers measured at the admission. In addition, a non-significant trend of improved prognostic ability of hsTn-T over cTn-I was noted, which likely missed statistical significance potentially due to the relatively small sample size of this study population. Most importantly, all previous comparison but one, used a cTn-T assay as a benchmark, while the study Magnoni et al. [8] compared the hsTn-T with a cTn-I assay. Interestingly the authors detected a very low proportion of hsTn-T-positive patients in the cTn-I-negative group (2.9%), which is consistent with a previous study using cTn-I as comparator (4.2%) [7], but contrasts the high proportion of hsTn-T-positive patients in the cTn negative group reported in the studies, in which cTn-T was used as benchmark (77.1% [9]). A potential explanation is the relatively poor precision of the specific fourth-generation cTn-T assays used at the low end of concentration rather than a class effect of hsTn over fourth-generation assays (i.e. both cTn-T and cTn-I). The authors concluded that the poor precision of the fourth-generation cTn-T assay at the low range of concentration may have led to an overestimation of the overall hsTn incremental value in respect to conventional assays, having important clinical implications for the management of this clinical condition. Overall, the wide variability in analytical features of available assays clearly prevents generalization of their diagnostic and prognostic and although a prognostic stratification advantage of new over conventional assays may exist, its magnitude was very likely overestimated in previous studies.

In conclusions, although this study showed that the performance of cTn-I is quite similar to hsTn-T, the implementation of hsTn-T assays has provided clear advantages in ACS management. It improved patient care by speeding up the rule-in and rule-out of AMI and allowed rapid and safe discharge. Recently another nationwide cohort study including 87,879 patients with first AMI demonstrated that the use of hsTn-T was associated with a reduced risk of reinfarction [9]. On the other side it must be noted that although hsTn-T has a high sensitivity for ACS, its specificity is modest, with several non-coronary causes also producing elevated hs-Tn-T levels, leading to overdiagnosis and potentially to overtreatment of patients based on hsTn-T findings. Thus, the translation in an improvement of outcome based on hsTn requires further studies.

Disclosure statement

All authors have no conflicts of interest to disclose.

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References

[1] E. Braunwald, Unstable angina. A classification, Circulation 80 (1989) 410–414. Available at: https://doi.org/10.1161/01.CIR.80.2.410.
[2] M. Galvani, F. Ottani, D. Ferrini, et al., Prognostic influence of elevated values of cardiac troponin I in patients with unstable angina, Circulation 95 (1997) 2053–2059.
[3] E.M. Antman, M.J. Tanasijevic, B. Thompson, et al., Cardiac-specific troponin I levels to predict the risk of mortality in patients with acute coronary syndromes, N. Engl. J. Med. 335 (1996) 1342–1349 , Available at: http://www.ncbi.nlm.nih.gov/pubmed/8857017.
[4] E. Giannitsis, M. Becker, K. Kurz, G. Hess, D. Zdunek, H.A. Katus, High-sensitivity cardiac troponin T for early prediction of evolving non-ST-segment elevation myocardial infarction in patients with suspected acute coronary syndrome and negative troponin results on admission, Clin. Chem. 56 (2010) 642–650.
[5] N.L. Mills, Implementation of a sensitive troponin I assay and risk of recurrent myocardial infarction and death in patients with suspected acute coronary syndrome, JAMA 305 (2011) 1210 , Available at: https://doi.org/10.1001/jama.2011.338.
[6] E.A.B. May, M.P. Bonaca, P. Jarolim, et al., Prognostic performance of a high-sensitivity cardiac troponin i assay in patients with non-ST-elevation acute coronary syndrome, Clin. Chem. 60 (2014) 158–164.
[7] M.P. Bonaca, R.G. O'Malley, S.A. Murphy, et al., Prognostic performance of a high-sensitivity assay for cardiac troponin I after non-ST elevation acute coronary syndrome: Analysis from MERLIN-TIMI 36, Eur. Heart J. Acute Cardiovasc. Care 4 (2015) 431–440 , Available at: https://doi.org/10.1177/2048872614564081.
[8] M. Magnoni, G. Gallone, F. Ceriotti, et al., Prognostic implications of high-sensitivity cardiac troponin T assay in a real-world population with non-ST-elevation acute coronary syndrome, Int. J. Cardiol. Heart Vasc. (2018).
[9] M. Odqvist, P.O. Andersson, H. Tygesen, K.M. Eggers, M.J. Holzmann, High-sensitivity troponins and outcomes after myocardial infarction, J. Am. Coll. Cardiol. 71 (2018) 2616–2624.