

Editorial

Quo Vadis, Troponin?

¿Quo vadis, troponina?

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Cardiac troponin (cTn) is the recommended biomarker for diagnosing acute myocardial infarction (AMI). When a patient has signs and symptoms indicating myocardial ischemia, the existence of AMI can be verified by a cTn increase exceeding the 99th percentile of the reference population plus significant cTn increases or decreases in serial samples.¹ Cardiac troponin has shown excellent diagnostic sensitivity in this condition, but its diagnostic specificity is lower: elevated concentrations indicate myocardial injury, but not the mechanism causing the injury.¹

Apart from AMI, there are other clinical situations in which cTn concentration may be chronically or acutely elevated, thus making AMI diagnosis more difficult. In the absence of AMI, increased cTn concentrations are detected more often with a type of assay called *high-sensitivity assays* than with the methods still in use, referred to as *contemporary assays*.² Concentrations of cTn can be chronically increased in persons of advanced age, patients with diabetes or other cardiovascular risk factors, and individuals with chronic ischemic heart disease, heart failure, pulmonary hypertension, or renal disease. These concentrations can acutely exceed the 99th percentile and can even show dynamic changes in situations such as pulmonary embolism, acute heart failure, atrial fibrillation, postoperative noncardiac surgery, sepsis, or stroke. In all these circumstances, the cTn increase is associated with a poor prognosis, defined as a greater risk of death or cardiovascular complications during follow-up.^{3,4} However, in some situations, such as myopericarditis, acute cTn increases are not related to a worse prognosis.^{3,4}

Bardají et al⁵ analyzed the prognostic value of cTn measurement in patients with a suspected acute coronary syndrome (ACS) evaluated in the emergency department (ED) of a university hospital. The authors retrospectively analyzed 1032 patients who had undergone at least 1 cTn determination in a hospital ED. The final diagnosis in each patient was established by consensus between at least 2 cardiologists, based on clinical data and findings from complementary tests, including cardiac troponin I (cTn-I) concentration, measured with a contemporary method. Acute coronary syndrome was diagnosed in 139 patients (13.5%;

122 AMI, 17 unstable angina) and was excluded in the remaining 893 patients. Among the latter, cTn concentration was greater than the 99th percentile value in 212 (20.5%) patients (classified as cTn-positive) and was below the 99th percentile in 681 (66%) patients (classified as cTn-negative). These data show that 1 of every 5 patients attending a hospital ED have cTn values higher than the 99th percentile, even though they are not experiencing an AMI.

Some of the findings from this study merit discussion. Ascribing a diagnosis by consensus is a common method used in this type of research. In one recent study investigating adjudication of AMI diagnoses between 2 groups of evaluators (1 local and 1 central), 34% of patients were reassigned to a different diagnostic category in the central evaluation from that of the local one, even when agreement between the 2 groups of evaluators was acceptable: $\kappa=0.79$, 95% CI 0.73–0.85.⁶ A lack of complete concordance in assigning the diagnosis is intrinsic to this method and, therefore, it is important to know the degree of consensus between the evaluators for proper interpretation of the results.

The contemporary method used in the Bardají study did not detect cTn in as many healthy individuals as would have been the case with a high-sensitivity method, but it did measure cTn at the 99th percentile with the desired analytical imprecision of < 10%. Only 1 cTn-I value was obtained in 519 (50.2%) patients. In the hospital where the study was conducted, the protocol for assessing nontraumatic chest pain included 1 cTn determination at admittance and another at 6 to 8 hours; however, when the clinical symptoms were of lengthy duration (> 6–8 h) and cTn concentration at admittance was negative, the diagnosis of AMI was excluded without further determinations. This “fast” strategy, also used in other centers, is at least partially attributable to the high daily workload in hospital EDs.⁷ However, this approach does not follow the recommendations of serial cTn determinations for the diagnosis of AMI¹ and calls into question the efficacy of the procedure. Collinson et al⁸ evaluated the reliability of this type of strategy in a prospective study of 773 patients attending a hospital ED. Using a contemporary method to measure cTn such as the one in the Bardají study, the authors evaluated the diagnostic and prognostic value of cTn measured in a sample obtained at 6 hours after symptom onset. The diagnosis of AMI was based on clinical data, ECG findings, and concentrations of creatine kinase MB or cTn-T. A diagnosis of AMI was established in 6.5% of patients. At 6 months’ follow-up, 3.2% of patients experienced a severe cardiovascular complication. Patients identified as *no-AMI* had

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only 2.1% of complications compared with 13.6% of those identified as AMI. These data, obtained in a low-risk population, show that it is safe to exclude the diagnosis of AMI based on a single negative cTn result with a contemporary assay in patients with a low probability of having AMI and symptom onset ≥ 6 hours previously. However, in a Spanish hospital ED population, patients with chest pain testing negative for cTn had up to 4.8% of severe cardiovascular complications at 6 months of follow-up.⁹ Application of a clinical score composed of 4 factors (characteristics of the pain, ongoing diabetes mellitus, history of coronary surgery, and ST segment depression) enabled identification of patient subgroups having very different complication rates—2.5%, 2.9%, 10.2%, and 29.2%—according to whether the number of factors observed was 0, 1, 2, or ≥ 3 . These data indicate that the combination of clinical data and a single negative cTn determination is reasonably safe for diagnosing AMI in patients at low risk and with symptom onset ≥ 6 hours previously.

In Spanish hospitals, high-sensitivity assays for cTn determination (hs-cTn) are currently being used or will be implemented in the near future. These techniques enable measurement of very low cTn concentrations with the recommended analytic quality level (imprecision $< 10\%$ at the concentration corresponding to the 99th percentile) for the successive definitions of AMI. This higher analytic sensitivity leads to detection of hs-cTn in a larger number of healthy subjects (more than 50% show detectable values) than detection with contemporary assays. In a study of 524 healthy individuals, the method used in the Bardají study detected cTn in 6% of individuals, whereas the high-sensitivity technique from the same manufacturer detected hs-cTn in 86%.¹⁰ In the case of heart disease other than AMI and in noncardiac disease, values higher than the 99th percentile were found in some patients who had previously had undetectable values with contemporary methods. In patients with suspected AMI, a single hs-cTn measurement had a higher sensitivity and negative predictive value than a single cTn measurement with conventional techniques, although the diagnostic specificity and positive predictive value were lower. Of note, however, although the method used in the Bardají study did not detect cTn in as many healthy individuals as the high-sensitivity method, it did measure the 99th percentile value with adequate imprecision; therefore, it is unlikely that there were many patients with AMI among those testing negative on a single cTn determination.

The Bardají study included a 12-month follow-up in all patients. This of considerable merit considering that there were 1032 patients. Mortality differed between the various study subgroups. In patients with ACS, mortality was 15.1%, whereas in the group without ACS, mortality was 4.7% in patients testing cTn-negative and 30.2% in those testing cTn-positive. Patients without ACS were older, had cardiovascular risk factors, a more frequent history of heart failure and cerebrovascular disease, and, at hospitalization, a larger number of syncope and atrial fibrillation episodes, a lower glomerular filtration rate, and more severe anemia. In summary, this was a population with numerous comorbidities. Positive cTn detection was a risk factor for complications in both the univariate and multivariate statistical analyses, and cardiac, respiratory, or renal failure were all determinants of cTn concentration. The differences in mortality observed between the different subgroups were statistically significant in the 12-month survival analysis (log-rank test, $P < .001$). Relative to cTn-negative cases without ACS, patients with ACS had a hazard ratio (HR) for death of 3.402 (95% confidence interval, 1.832–6.316), a value similar to the 3.536 (95% confidence interval, 2.067–6.048) found in cTn-positive patients without ACS. These data underscore the merit of cTn as a prognostic biomarker beyond the setting of AMI, and corroborate the findings from international studies in a population from Spain. One interesting

aspect that the authors might wish to examine in a substudy is the ability of cTn concentrations do exceeding the 99th percentile, but are detectable by the assays used, for predicting complications. Several studies have shown that a detectable cTn value indicates risk, and that the risk is quantitatively related to the value observed, even when cTn is determined with an assay whose analytic imprecision is higher than the recommended value.¹¹ This situation has been a powerful stimulus for the development of high-sensitivity methods that enable reliable measurement of very low cTn concentrations.

The prognostic value of cTn reported by Bardají et al coincides with the findings from a recent meta-analysis of 8644 patients from 17 studies with AMI rates varying from very low (2.6%) to very high (57.1%) and a follow-up of 1 to 24 months.¹² In that meta-analysis, cTn-positive patients (> 99 th percentile of each analytic method evaluated) had a higher risk of death or non-fatal AMI at 1 year of follow-up than cTn-negative patients. The study assessed the added value of hs-cTn measurement for both the diagnosis and the prognosis of ACS and found hs-cTn was positive in patients testing negative for cTn by contemporary methods. With regard to the AMI diagnosis, the area below the ROC curve for the diagnosis was 0.884 with a single baseline hs-cTn determination vs 0.749 with a single contemporary cTn determination, ($P < .001$). The concentration of hs-cTn also provided greater prognostic information for death and a new AMI compared with contemporary cTn: hs-cTn was found to be elevated in 32.7% more patients who died and in 23% more who experienced an AMI over follow-up.

In summary, the study by Bardají et al alerts to the existence of a significant percentage of patients attended in hospital EDs who do not have AMI, but show cTn concentrations higher than the 99th percentile. These patients have numerous comorbidities and their possibility of experiencing complications is similar to that of ACS patients. What diagnostic and therapeutic approaches should be followed in such cases? Patients should be differentiated into 2 subgroups. Those without comorbidities or other evident factors to justify the elevated cTn values observed should be studied individually to establish the cause of the cTn increase, which, if possible, should be treated. For their part, patients with multiple comorbidities that imply a poor prognosis will not obtain a significant benefit from additional tests or treatment changes. Nonetheless, while waiting for high-quality scientific tests to become available, ED physicians and cardiologists should decide the action to be taken by consensus. A consensus protocol developed by the hospital emergency and cardiology departments such as the one used in the center where the study by Bardají et al was conducted is the best approach to address the clinical challenge presented by these patients.

CONFLICTS OF INTEREST

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