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Editorial

Risk stratification in acute heart failure: We need a new agenda for clinical research

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Acute heart failure (AHF) is a complex multifactorial syndrome associated with decreased survival and high costs of care; furthermore, many patients remain clinically vulnerable after discharge, and one-third are rehospitalized within 90 days [1].

Risk stratification in patients hospitalized for AHF is crucial to evaluate the best care setting for the patient at admission and the intensity of care and monitoring, and to plan for further management after discharge.

In the emergency department, the dosage of cardiac biomarkers (CBs) to patients is essential for diagnosis of AHF and coronary syndromes.

CBs reflect different relevant pathophysiological aspects of AHF: natriuretic peptides are used as a measure of the extent of myocyte stretching, and troponins (cTns) are used a measure of myocyte ischemia and injury [2]. CBs have been associated with the prognosis of AHF in previous studies; however, there is a gap in knowledge regarding the best way to integrate information derived from different biomarkers.

Aimo and Coll [3], in a multicenter-cohort study, have examined the prognostic value of hs-TnT dosage relative to natriuretic peptide to identify patients at high risk of both short-term (in-hospital) and long-term (after discharge) mortality and to determine reliable and clinically useful cut-offs for both CBs. The authors analyzed individual patient data from three cohorts, including 1449 patients hospitalized for AHF, all of whom had hs-TNT and NT-proBNP measured at admission. Both biomarkers were treated as continuous variables and subjected to dichotomization according to the median value and then according to the best cut-off, then chosen with an appropriate statistical test.

Patients who died during hospitalization had significantly higher NT-proBNP and hs-TnT, but only hs-TnT was independently associated with outcome when included in a multivariable model; interestingly, no variable was an independent predictor of outcome after dichotomization according to the median value. Patients with both markers greater than or equal to the median had a 2.7-fold higher risk of in-hospital death, whereas patients with both markers greater than or equal to the best cut-off had a 12-fold higher risk of in hospital mortality.

Does this study provide new information about the clinical utility of biomarkers in the management of AHF?

Many studies have shown the associations between natriuretic peptide and troponin and the prognosis of AHF: a clear relationship between admission BNP quartiles and in-hospital mortality has been found in the ADHERE study [4].

Similarly, numerous papers have confirmed the strong association between cTn and clinical outcome in AHF. Among patients enrolled in ADHERE, the in-hospital mortality for troponin-positive patients was 8.0%, compared with 2.7% for troponin-negative patients [5].

Certainly, Aimo's work confirms the hidden pitfalls of prognostic studies, because it indicated that the performance of biomarkers in predicting outcome is largely dependent on the method used to treat the numeric value in the statistical analysis.

Clinicians generally favor dichotomization that summarizes the information on prognosis with the definition of risk group. However, from a methodological perspective, there is no reason to presume an underlying dichotomy. Results obtained by dichotomization demand a validation process, because they are likely to lack predictive value for future patients.

Many multivariable prognostic risk scores for AHF, derived in populations from community registries, statewide databases, clinical trials and observational studies, have been found to have adequate discriminatory accuracy in both derivation and validation populations, and to be sufficient to separate high-risk from low-risk patients.

Owing to an impressive amount of scientific evidence, reliable tools are now available to identify high-risk patients. We know that patients with low blood pressure, a high heart rate, damaged renal function, the highest values of natriuretic peptide, positive troponin and relevant

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comorbidities at admission are in the high-risk group associated with the worst outcome.

Nevertheless, what we really need to know is how to use prognostic information to improve patient outcome. In other words, we need to translate the risk stratification research to bedside use.

European guidelines for heart failure underscore this knowledge gap, stating: "*Numerous clinical and laboratory variables are independent predictors of in-hospital complications and longer-term outcomes in AHF syndromes, but their impact on management has not been adequately established*" [6].

Current treatment for AHF syndrome is largely empirical and driven by signs and symptoms: when congestion is present, diuretics are used, whereas if low output signs are prevalent, inotropes and vasoconstrictors are used.

This approach has no evidence-based demonstration beyond the practical experience gained by physicians over many years, because, to date, no therapy has been demonstrated to provide benefits in a clinical trial.

We need to end this empirical phase and to find stronger evidence to support AHF treatment.

Prognostic models, once derived and validated, should aid in evaluating whether allocation of patients driven by risk group inclusion could improve clinical outcomes, thus allowing the right treatment to be provided to the right patient at the right time. Biomarker dosage could improve the phenotyping of patients with AHF.

In the field of chronic heart failure (CHF), some positive examples support this approach.

In chronic AHF, the Heart Failure Survival Score can be used to select high-risk patients who benefit from heart transplantation in comparison with low-risk patients, in whom heart transplantation is not associated with a survival benefit [7].

In the Paradigm trial, which has shown the advantage of sacubitril/valsartan over enalapril in reducing a composite clinical endpoint in CHF, a natriuretic peptide value exceeding a predetermined cut-off was requested for patient inclusion [8].

More recently, the TIM-HF2 has shown that the combined use of MR-proADM and NT-proBNP may allow for safe, precise, effective and cost-saving allocation of patients with heart failure to remote patient management [9].

Tromp et al., using cluster analysis based on biomarker profiles, have identified six distinct endotypes of CHF patients with marked differences in characteristics, clinical outcomes, and, most importantly, responses to up-titration of guideline directed medical therapy [10].

In conclusion, the agenda for clinical research in the fields of biomarkers and risk stratification of AHF, with the aim of addressing the unmet needs in AHF management, should include use of risk stratification tools to allocate patients to treatments, through endotyping and phenotyping patients to the best extent possible. This approach could overcome the difficulties due to heterogeneity of AHF syndrome, by searching for a targeted treatment and pursuing the aim of implementing precision medicine.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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