



## EDITORIAL COMMENT

## How to predict futility: The holy grail of transcatheter aortic valve implantation

### Como prever a futilidade? O santo graal da implantação percutânea de válvulas aórticas

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Transcatheter aortic valve implantation (TAVI) is currently the gold standard for the treatment of severe aortic stenosis in patients with high risk or contraindication for open heart surgery. However, a considerable proportion of patients do not benefit from TAVI, either dying or failing to improve. Markers of prognosis and futility have been extensively investigated, and frailty and clinical risk scores are the cornerstone of prognosis assessment.<sup>1</sup> Nonetheless, substantial research remains to be done in order to arrive at an accurate and meaningful prognosis with a limited number of parameters that can be easily collected during clinical practice.<sup>1</sup> Biomarkers are generally not included in these scores, even though their potential independent predictive value has been documented.<sup>2</sup> Various biomarkers have been explored in the particular setting of aortic stenosis treated by TAVI. A recent systematic review elegantly presented the most important evidence regarding the predictive value of B-type natriuretic peptide (BNP), troponin, cancer antigen 125, red cell distribution width, growth differentiation factor,

malonaldehyde, galectin-3, soluble ST2 and von Willebrand factor.<sup>2</sup>

BNP and its prohormone N-terminal proBNP (NT-proBNP) have considerable prognostic value in patients with heart failure and valvular heart disease.<sup>3,4</sup> Natriuretic peptides correlate with aortic stenosis severity and area, peak velocity and gradient, other echocardiographic markers of high risk, and prognosis.<sup>4,5</sup> In some studies, the confounding effect of reduced left ventricular function and concomitant valvulopathies has been effectively excluded.<sup>6,7</sup> According to the most recent guidelines by the joint task force of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS), serum BNP levels are related to New York Heart Association (NYHA) functional class and prognosis in aortic stenosis and may be of value for risk stratification and timing of intervention, particularly in asymptomatic patients.<sup>8</sup> The prognostic value of BNP in the specific setting of TAVI has also been addressed by several authors. There are disparities regarding the recommended timing for assessing BNP levels, with some authors reporting that baseline BNP is independently associated with mortality, while others state that variation, particularly an increase, from baseline is the most informative and predictive parameter. Abramowitz et al. reported a series of 780 patients in which baseline BNP levels were associated with increased short- and medium-term

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mortality after TAVI.<sup>9</sup> A recent meta-analysis by Giordana et al., including 25 studies and almost 9000 patients, concluded that high preprocedural BNP levels were a strong independent predictor of both 30-day and one-year mortality.<sup>10</sup> These findings imply that elevated baseline BNP may reflect irreversible loss of ventricular reserve and could play a role as a marker of futility. On the other hand, Koshinas et al., in a study of 219 patients with serial measurements of BNP and NT-proBNP before and after intervention, found that outcomes were most unfavorable in patients with persistently high BNP both before and after the intervention. Comparing the two biomarkers, NT-proBNP levels measured after TAVI showed the highest prognostic discrimination for two-year mortality. Baseline-to-discharge reduction, but not baseline BNP levels, were related to functional improvement (NYHA class).<sup>11</sup> In the PARTNER trial,<sup>12</sup> baseline and 30-day BNP levels were assessed in 933 patients who underwent TAVI via transfemoral access. An increase in BNP at 30 days from baseline was independently associated with one-year mortality.<sup>12</sup> The OCEAN-TAVI multicenter prospective registry, with 1094 patients, also suggests that an elevation of BNP (>202 pg/ml) at discharge is associated with two-year mortality and hospitalization after TAVI.<sup>13</sup> A time-dependent net reclassification improvement and integrated discrimination improvement analysis revealed that incorporation of BNP stratification with other clinical variables significantly improved predictive accuracy for two-year mortality.<sup>13</sup> However, the authors did not explore the value of baseline BNP levels or the value of the difference or ratio between pre- and post-intervention levels.

In the current issue of the *Journal*, Vale et al.<sup>14</sup> present an interesting single-center retrospective analysis of 151 patients undergoing TAVI in whom both baseline and one-month post-procedure NT-proBNP were measured. Receiver operating characteristic curve analysis was used to identify the best discriminative values for one-year mortality. Independent predictors of one-year mortality were assessed by Cox regression. Only post-procedural NT-proBNP (>2500 pg/ml, area under the curve 0.72) was independently and negatively associated with one-year survival (hazard ratio 5.9, 95% confidence interval 1.6-21.7,  $p=0.008$ ). Baseline NT-proBNP and the difference and the ratio between NT-proBNP pre- and post-procedure did not predict one-year mortality. A major limitation derives from the fact that collection of post-procedural NT-proBNP was not possible for patients who died in the first month, who were therefore not included in the protocol. Nevertheless, this paper also suggests that pre-procedural natriuretic peptide levels may have a limited role in assessing prognosis and futility. Post-procedural myocardial response, and the subsequent reset of natriuretic peptide levels, appear to be more useful for determining prognosis and identifying high-risk patients who will require closer and optimized follow-up. However, this high-value information is only available after making the commitment to perform TAVI.

A famous Portuguese soccer player, João Domingos da Silva Pinto, was once asked to predict the result of an important match. His answer became part of our national

heritage: "Prognostics only after the game." This is exactly what natriuretic peptides seem to be able to offer for TAVI. Unfortunately, biomarkers are still unable to help us to avoid futility.

## Conflicts of interest

The authors have no conflicts of interest to declare.

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