

# High-sensitivity troponin T as a prognostic marker in patients undergoing aortic valve replacement

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**Introduction** Given the change of the paradigm in invasive therapy of aortic stenosis and a shift towards the use of percutaneous aortic valve replacement (AVR) in lower-risk patients, there is a need to consider also other tools when determining the risk in patients eligible for surgical AVR. Recently, troponin T (TnT) has been recognized as a biomarker of myocardial injury.<sup>1,2</sup> Numerous reports have demonstrated that the measurement of high-sensitivity TnT (hs-TnT) levels may have prognostic value in various cardiovascular disorders, such as coronary artery disease (CAD),<sup>3</sup> heart failure,<sup>4</sup> and pulmonary embolism.<sup>5</sup> The ability of baseline hs-TnT levels to predict the postoperative outcome in cardiac surgical patients has been recently demonstrated in patients undergoing coronary artery bypass grafting and other cardiac surgeries.<sup>6</sup> However, the predictive value of preoperative hs-TnT levels in addition to the EuroSCORE II model has not been specifically evaluated in a sufficiently large group of patients with significant aortic stenosis undergoing AVR to define the role of these levels in risk stratification.

**Methods** This was a prospective study involving 224 consecutive patients with hemodynamically significant aortic valve stenosis who underwent elective replacement of the valve at the Institute of Cardiology in Warsaw, Poland. The exclusion criteria were as follows: refusal to participate in the study, age below 18 years, acute coronary syndrome, unstable CAD, and acute kidney disease. The following data were collected from patients who provided their consent to participate in the study: age, sex, body mass index, comorbidities, echocardiographic findings, and the results of coronary artery assessment. For each patient, the risk of surgery was calculated

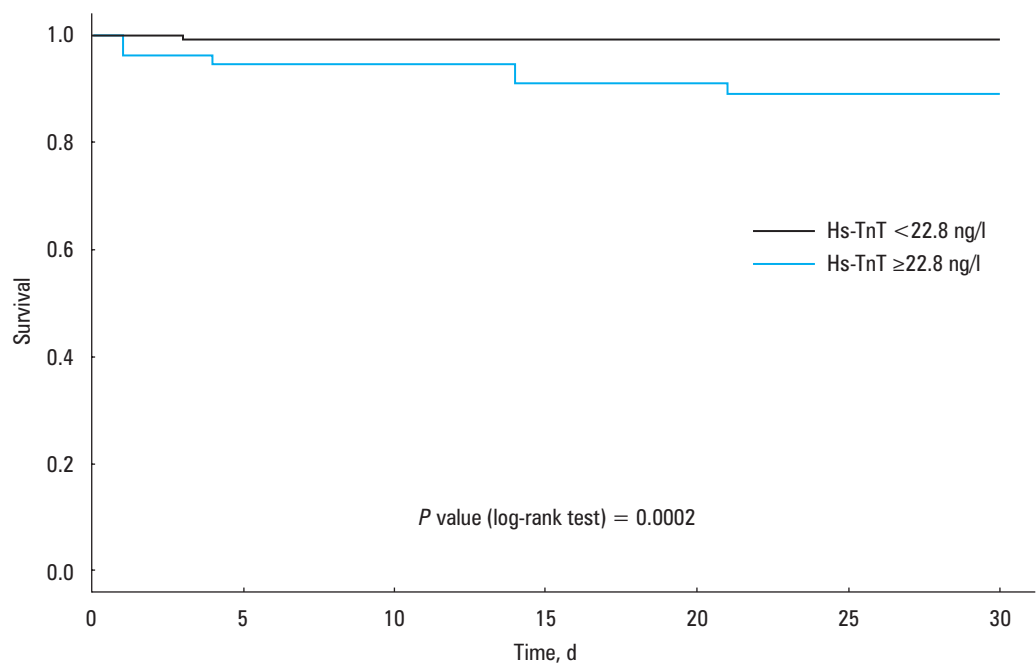
using EuroSCORE II. On the day before surgery, blood samples for the measurement of biomarker levels were collected from each patient. Complete blood count was performed with K<sub>2</sub>-EDTA samples, using a Cobas 6000 electronic counter (Roche, Mannheim, Germany). The plasma levels of cardiac TnT (cTnT) concentrations were measured by the Troponin T hs-STAT (Roche). The endpoint was all-cause death. Patients were followed by direct observation during hospitalization, telephone interviews, or clinic visits for 30 days after the surgery or until death. The study protocol was approved by an institutional review board.

**Statistical analysis** A statistical analysis was performed using SAS version 9.2 (World Headquarters SAS Institute, Cary, North Carolina, United States). Logistic regression was used to assess relationships between variables. The following covariates were investigated for association with the endpoint in a univariate analysis: age, atrial fibrillation, body mass index, chronic obstructive pulmonary disease, CAD, current smoking, EuroSCORE II, hyperlipidemia, hypertension, insulin-dependent diabetes mellitus, left ventricular ejection fraction, New York Heart Association class, peripheral atherosclerosis, previous myocardial infarction, pulmonary blood pressure, history of stroke, tricuspid annulus plane systolic excursion, the levels of bilirubin, creatinine, high-sensitivity C-reactive protein, hs-TnT, hematocrit, hemoglobin, mean corpuscular hemoglobin, and N-terminal pro-B-type natriuretic peptide, glomerular filtration rate, mean corpuscular volume, and platelet and white blood cell counts.

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Received: May 11, 2016.  
Revision accepted: July 24, 2017.  
Published online:  
September 29, 2017.  
Conflict of interest: none declared.  
Pol Arch Intern Med. 2017;  
127 (9): 628-630  
doi:10.20452/pamw.4107  
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Kraków 2017

**FIGURE 1**

Kaplan–Meier event-free survival curves for death following aortic valve replacement according to the cut-off value of high-sensitivity troponin T



A multivariate analysis was not performed because of the relatively small number of patients who died. The receiver operating characteristic (ROC) curves were plotted for the EuroSCORE II model alone and for the model combined of EuroSCORE II and hs-TnT levels for 30-day survival following AVR. The additional predictive value of hs-TnT was assessed by a comparison of the areas under the ROC curves (AUC). On the basis of the Youden index, a cut-off point was determined that met the criterion of the maximum sensitivity and specificity for mortality prediction. For the analysis of survival in all patient groups, the Kaplan–Meier curves were used. The cut-off value and the log-rank test to compare the curves were employed.

**Results** The study included 224 patients who underwent AVR with or without concomitant procedures. The mean (SD) age in the study group was 65.9 (10.8) years, and there were 135 men (60%). All procedures were performed through a midline sternotomy incision under general anesthesia in a mild hypothermia or normothermia (temperature, 32–36°C). The mean (SD) plasma hs-TnT level was 19.8 (16.2) ng/l. Seven patients died during the follow-up as a result of gradually deteriorating multiorgan failure. The actual mortality rate was 3.1%, compared with the mortality rate of 2.9% predicted by the EuroSCORE II model. In the univariate analysis, pulmonary blood pressure (odds ratio [OR], 1.071; 95% confidence interval [CI], 1.030–1.114;  $P = 0.007$ ), red blood cell count (OR, 0.057; 95% CI, 0.00–0.354;  $P = 0.002$ ), hemoglobin (OR, 0.420; 95% CI, 0.234–0.756;  $P = 0.003$ ), hematocrit (OR, 0.776; 95% CI, 0.683–0.942;  $P = 0.01$ ), glomerular filtration rate (OR, 0.950; 95% CI, 0.910–0.992;  $P = 0.02$ ), hs-TnT (OR, 1.110; 95% CI, 1.002–1.218;  $P = 0.03$ ), and EuroSCORE II (OR, 1.281; 95% CI, 1.108–1.480;  $P = 0.0008$ ) were associated with the occurrence of death. Patients with concomitant CAD had significantly higher

preoperative hs-TnT levels ( $P = 0.03$ ) compared with patients without CAD, but in our group, CAD was not a predictor of death ( $P = 0.1$ ). The optimal cut-off point for death was calculated at the hs-TnT level of 22.8 ng/l. The Kaplan–Meier event-free survival curves for death according to the cut-off value of hs-TnT are presented in [FIGURE 1](#). Preoperative hs-TnT levels combined with EuroSCORE II were a better predictor of 30-day mortality in patients with aortic stenosis undergoing AVR (AUC, 0.876; 95% CI, 0.768–0.984) compared with EuroSCORE II alone (AUC, 0.795; 95% CI, 0.651–0.940).

**Discussion** The present study demonstrated the prognostic value of preoperative hs-TnT levels in predicting all-cause death in patients with severe symptomatic aortic stenosis undergoing AVR in the postoperative follow-up. TnT is a protein forming part of the contractile apparatus of the striated muscle. The function of TnT in all types of striated muscles is the same, but cTnT is different from TnT found in skeletal muscles. Therefore, cTnT detected in plasma is a highly specific marker of myocardial damage (necrosis).<sup>7</sup> High-sensitivity troponin tests, available for the past several years, detect troponin levels with a high degree of credibility. In severe valvular heart defects, pressure or volume overload typically occurs and myocardial hypertrophy develops in response to an increasing overload. This mechanism initially restores and maintains the tension of the left ventricular walls. However, an additional long-lasting burden on the heart muscle causes progressive degeneration of cardiomyocytes, as well as the slow development of necrosis and fibrosis. This is due to the decrease of myocardial perfusion mainly in the endocardial layer of the heart.<sup>8</sup>

Patients with severe valvular disease have significantly increased hs-TnT levels when compared with healthy individuals. Moreover, patients with

valvular heart disease have elevated troponin levels accompanied by fibrosis in the heart muscle, which can be demonstrated by magnetic resonance imaging or endomyocardial biopsy.<sup>9</sup> Patients with stable CAD were shown to have higher plasma troponin levels compared with patients without CAD.<sup>10</sup> Additionally, our patients with significant valvular defects with CAD had elevated troponin levels compared with patients without CAD ( $P = 0.03$ ). However, CAD was not a predictor of mortality in our group ( $P = 0.1$ ), which may suggest that its presence in patients with severe aortic stenosis may enhance cardiac damage.

Studies have demonstrated a relationship between higher values of troponin and worse prognosis in patients with acute myocardial infarction<sup>1,2</sup> and heart failure.<sup>3,4</sup> There have been a few papers reporting the use of TnT as a biomarker of predictive value in patients undergoing AVR, limited to those with aortic stenosis. In a small study, Piekarska et al<sup>11</sup> proved that postoperative troponin levels had no significance in patients undergoing AVR. The relationship between preoperative serum troponin levels and prognosis has not been reported. In another study, in a group of 60 patients with severe aortic stenosis, Saito et al<sup>12</sup> demonstrated that preoperative troponin levels were a significant biomarker of complications, including death, in a long-term follow-up after AVR. However, its prognostic value when used with other surgical risk calculators, either the EuroSCORE II or the STS score, was not examined. More recently, Petaja et al,<sup>6</sup> in a larger group of patients, demonstrated that the measurement of hs-TnT levels added information to the EuroSCORE II model regarding major adverse events in all cardiac surgical patients and 180-day mortality in patients not undergoing coronary artery bypass grafting. The subgroup analysis included 200 patients with "other cardiac surgery." However, again patients with aortic stenosis were not specifically evaluated.<sup>6</sup> A rise in troponin levels was reported to be a significant predictor of death in patients with severe aortic stenosis undergoing transcatheter aortic valve implantation.<sup>6</sup> However, the relationship between baseline troponin levels and prognosis, independent of the STS or EuroSCORE, was not evaluated.

In summary, the results of our study demonstrate that the addition of the preoperative hs-TnT measurement to EuroSCORE II may improve the ability of predicting mortality in patients with aortic stenosis who were treated surgically. The results of such measurements may be used to further assess risk in patients with aortic stenosis, which has practical importance in clinical practice when percutaneous AVR is considered in lower-risk patients.

This was a single-center study with a relatively small number of patients, which limits the generalizability of these findings. The inclusion of baseline troponin levels in a large multinational surgical registry would enable us to define the role of hs-TnT in the risk assessment of aortic valve

surgery and possibly lead to the inclusion of this parameter in surgical risk calculators in these patients. The predictive value of hs-TnT levels in addition to specific risk calculators should also be examined in patients undergoing percutaneous AVR. Hence, further research on the usefulness of TnT as a predictor of complications in patients with valvular defects is necessary. Consequently, the results of our research can be helpful in deciding whether patients with aortic stenosis should undergo AVR surgery.

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