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Aortic Stenosis: Predictive Value of Cardiac Biomarkers in Older Patients

Alexander E Berezin*

Internal Medicine Department, State Medical University of Zaporozhye, Zaporozhye, Ukraine

Abstract

Aortic stenosis is one of the most common forms of acquired valvular heart disease in older patient population. Clinical implementation of cardiac biomarker measurement for risk stratification in patients with aortic stenosis has been shown to be promising to predict disease progression and outcomes. The aim of the short communication is summary knowledge regarding clinical perspectives in use of biological markers for risk stratification in the patients with aortic stenosis. The review is confirmed that two-dimensional and Doppler echocardiographies remains to be key tool for the evaluation and monitoring of aortic stenosis in older patients. Although there is no consensus on the prognostic value of biomarkers to stratify older patients with aortic stenosis at risk, BNP / NT-proBNP, galectin-3, sST2 appear to be promising predictors of C death and clinical outcomes in this population. Whether combined biomarker approach might have an impact on clinical decision-making for risk stratification in aortic stenosis patients is still not understood and requires further investigations.

Keywords: Aortic stenosis; Older patients; Biomarkers; Mortality; Prediction

Introduction

Aortic stenosis is one of the most common forms of acquired valvular heart disease in older patient population [1]. It is well known that clinical signs and symptoms of aortic stenosis, i.e. angina, exertional dyspnea, syncope, and chronic heart failure (HF), might strongly predict a high likelihood of mortality in short-term perspective [2,3]. In contrast, asymptomatic patients with severe aortic stenosis have better clinical outcomes, but prognostication among these individuals remains very difficult yet [4,5]. Once a determination is made that cardiac surgery will be considered, the patient should be evaluated for the risk of a cardiovascular (CV) complications. Obviously, cardiac functional status should be determined. To our knowledge, whether integrated ventricular, vascular and valvular components in asymptomatic patients with moderate to severe aortic stenosis could have utility at risk stratification and in enrollment for aortic valve replacement is still not clear [6]. Theoretically, a single symptom-limited exercise stress test could offer more precise risk stratification of these patients and increased a predictive power of echocardiographic parameters [7,8]. In symptomatic patients with aortic stenosis, however, an assessment of hemodynamic obstruction defined by two- and three-dimensional echocardiographic and Doppler indexes might be suboptimal due to technical difficulties and poor correlation with symptoms [9]. Other important diagnostic tools include cardiac catheterization, treadmill stress testing, and dobutamine stress echocardiography, although their use is limited to specific patient populations [10]. Therefore, aortic valve calcification may be an independent risk factor for adverse clinical outcome in persons with asymptomatic and symptomatic aortic stenosis [11,12]. In this context clinical implementation of cardiac biomarker measurement for risk stratification among patients with aortic stenosis depending lower and higher CV risk would appear to be attractive. Nevertheless, it is not clear how could be combined risk prediction by echocardiography / other cardiac functional status diagnostic tool with cardiac biomarkers' measurement. The aim of the short communication is summary knowledge regarding clinical perspectives in use of biological markers for risk stratification of the older patients with aortic stenosis.

Biomarkers and aortic stenosis

As well known a prominent attribute of aortic stenosis is calcification of valve leaflets / aortic rout, accelerated atherothrombosis, endothelial dysfunction, and low-grading inflammation. All these factors might contribute in angina, syncope, HF, and worsening of kidney function. Recent pre-clinical, observation, and clinical studies have shown that several biomarkers might have a powerful predictive utility in patients with asymptomatic and symptomatic aortic stenosis, as well as predictors of clinical outcomes after aortic valve implantation (Table 1). Unfortunately, no any head-to-head studies to compare cardiac biomarkers measurement and echocardiography and yet this is a powerful limitation for scientifically discussion around advantages of cardiac biomarkers in older aortic stenosis individuals, whereas there are perspectives of continuing investigations toward this direction.

Brain natriuretic peptides

Natriuretic peptides (NPs) are recognized as markers of biomechanical cardiac stress that are secreted resulting in stretching cardiac wall / volume overload and they have demonstrated high diagnostic and predictive value for heart failure (HF) [13]. Recent clinical studies have shown that brain natriuretic peptide (BNP) and NT-proBNP levels are elevated in patients with aortic stenosis and decrease acutely after replacement of the stenotic valve including transcatheter aortic valve implantation (TAVI) [14]. Moreover, high pre-intervention serum BNP level independently predicted two-year cardiovascular outcomes after TAVI [14]. Indeed, authors reported that patients with high baseline BNP (higher tertile $\geq$ 591 pg/ml) had increased risk of all-cause mortality (adjusted hazard ratio 3.16, 95% confidence interval 1.84 to 5.42; $p<0.001$) and cardiovascular death at 2 years (adjusted hazard ratio 3.37, 95% confidence interval 1.78 to 6.39; $p<0.001$). Outcomes were most unfavorable in patients with persistently high BNP before and after intervention. Comparing the two biomarkers, NT-pro-BNP levels measured after TAVI showed the highest prognostic discrimination for 2-year mortality (area under the curve 0.75; $p<0.01$). Therefore, BNP and NT-proBNP levels have shown a correlation with outcomes in studies of aortic valve surgery

*Corresponding author: Alexander E Berezin, Professor, Consultant of Therapeutic Unit, Internal Medicine Department, State Medical University of Zaporozhye, 26, Mayakovsky avenue, Zaporozhye, Ukraine, Tel: 380612894585; E-mail: dr_berezin@mail.ru

[15]. Overall, in older patients with aortic stenosis beyond clinical presentation elevated plasma BNP is the strongest independent predictor of all-cause and cardiovascular mortality [16,17].

Signature of microRNAs

MicroRNA (miRNA) are short non-coding RNAs that play a pivotal role in posttranscriptional regulation of target cell function. It has been found that miRNA-21-5p has elevated in patients with aortic stenosis without presentation of presence of coexisting coronary artery disease (CAD). In contrast, increased serum concentrations of miR-22-3p, miR-24-3p, miR-382-5p, and miR-451a were not detected. Despite miRNA-21-5p appear to be promised as biomarker of aortic stenosis, there are more evidences regarding clinically significance of miRNA signature refinement in prediction of aortic stenosis evolution [18].

Growth differentiation factor 15

Growth Differentiation Factor-15 (GDF-15) is secreted cytokine belonging to the TGF-β super-family that highly expressed in states of inflammatory stress. GDF-15 may play a critical role in the atherosclerotic process in various vascular beds, starting from endothelial dysfunction and counting all stages of plaque development, as well as in ectopic calcification and aortic stenosis [19]. Elevated GDF-15 was found in older patients with asymptomatic and symptomatic moderate-to-severe aortic stenosis. Recent clinical study revealed that GDF-15 was superior to NT-proBNP for TAVI risk stratification and provided additional prognostic information in aortic stenosis [20].

High-sensitivity soluble toll-like receptor-2

Soluble ST2 (sST2) is receptor for cytokine IL-33 that is up-regulated in response to myocardial stress and exerts cardio-protective actions in the myocardium by reducing fibrosis, hypertrophy and enhancing survival. Recent clinical trials have shown that sST2 concentrations are strongly predictive of death, regardless of the cause and left ventricle (LV) ejection fraction, and contribute relevant information in addition to other prognosticators and biomarkers, as natriuretic peptides or cardiac troponins [21]. Current clinical guidelines have been recommended a measurement of sST2 as useful biomarker for death risk stratification and prognosis prediction in HF patients beyond other CV risk factors, NYHA functional class, LFEF, and renal function [22,23]. Elevated level of sST2 has defined in individuals with aortic stenosis irrespective etiology and coronary artery disease presentation [24]. Although both BNP and sST2 were associated with NYHA class but sST2 (>23 ng/mL, AUC=0.68, p<0.01) was more accurate

to identify asymptomatic patients or those who developed symptoms during follow-up. Furthemore, sST2 was independently related to left atrial index (p<0.0001) and aortic valve area (p=0.004; model R²= 0.32). Using multivariable analysis authors have found that peak aortic jet velocity (HR=2.7, p = 0.007) and sST2 level (HR=1.04, p=0.03) were independent predictors of CV events and that sST2 levels have provided complementary information regarding symptomatic status, new onset HF symptoms and outcome in older aortic stenosis patients [24]. Lindman et al. [25] reported that three biomarkers, i.e. NT-proBNP, GDF15, and sST2, were elevated in older patients with aortic stenosis and closely associated with one-year mortality. Interestingly, the association between a greater number of elevated cardiac biomarkers and increased mortality after valve replacement was similar in the transcatheter and surgical aortic valve replacement populations. Authors concluded that the potential utility of multiple biomarkers to aid in risk stratification of older patients with aortic stenosis. Overall, sST2 is promised biomarker for risk stratification in older individuals with aortic stenosis beyond traditional CV risk factors.

High sensitive cardiac specific troponins

Cardiac troponins are urgent biomarkers of myocardial injury and they are currently recommended to use for both diagnostic and prognostic purposes in acute coronary syndrome. The patterns of temporal change in highly-sensitivity troponin-T (hs-cTnT) may reflect a subclinical myocardial injury that is suitable for cardiomyopathy, heart failure and stable coronary artery disease. Therefore, mild elevated level of highly-sensitivity circulating cardiac troponins was found in untreated symptomatic aortic stenosis patients independently of traditional CV risk factors unless myocardial infarction. Moreover, high sensitive troponin T can be useful biomarkers to predict the occurrence of heart failure, atrial fibrillation, and death after aortic valve replacement surgery [26]. However, the predictive role of hs-cTnT in older patients with asymptomatic aortic stenosis is not clear yet.

Fibroblast growth factor-23

Fibroblast Growth Factor-23 (FGF-23) is phosphate-regulating 251-amino-acid protein secreted by osteocytes and regulates mineral metabolism and inflammatory response [27]. FGF-23 increases urinary phosphorus excretion by decreasing phosphorus re-absorption in the proximal tubule of nephron and inhibits 1.25-dihydroxyvitamin D synthesis, resulting in decreased dietary phosphorus absorption from the gastrointestinal tract. Therefore, biological role of FGF-23 affects a secretion of parathyroid hormone [28,29]. The exactly mechanisms

Biomarkers	Source of release	Relation to pathophisiology process	Clinical features
BNPs	Cardiac myocites	Biomechanical stress, cardiac wall stretching	Prediction of all-cause and CV mortality, sudden death, re-admission in the hospital due to CV reasons, prediction of CV events after TAVI.
Cardiac specific troponins	Cardiac myocites	Myocardial injury	Prediction of CV events and mortality
miRNAs	Cardiac myocites	Biomechanical stress, fibrosis, inflammation	Progression of aortic stenosis, vascular remodeling
GDF-15	Activated mononuclears, fibroblasts, cardiomyocytes	Inflammation	Prediction of CV mortality, risk of HF and CV events
sST2	Activated mononuclears, cardiomyocytes	Inflammation	Prediction of CV mortality, risk of HF and CV events
Gal-3	Activated mononuclears, cardiomyocytes	Fibrosis, inflammation	Prediction of all-cause and CV mortality, risk of HF and CV events
FGF-23	Activated mononuclears, fibroblasts	stimulating cardiac hypertrophy, promoting cardiomyocyte growth and release of natriuretic peptides	Prediction of all-cause mortality, CV events, and end-stage of CKD
Matricellular proteins	Activated mononuclears	Ectopic calcification	Prediction of CV events and probably CV mortality

Abbreviations: BNP: Brain Natriuretic Peptides; miRNA: microRNA; GDF-15: Growth Differentiation Factor-15; CV: Cardiovascular; Gal-3: Galectin-3; FGF-23, Fibroblast Growth Factor-23; TAVI: Transcatheter Aortic Valve Implantation; CKD: Chronic Kidney Disease; HF: Heart Failure.

Table 1: Perspective cardiac biomarkers for risk stratification in aortic stenosis patients.

leading to increased FGF-23 are not fully investigated. There are evidences that hypoxia and ischemia through unknown mechanisms may induce FGF-23 over production. It is suggested that FGF-23 may effect on target cells directly and through FGF-23-related effects. In animal models FGF-23 directly stimulated left ventricular hypertrophy by activating hypertrophic gene programs, promoting cardiomyocyte growth, and stimulating the release of natriuretic peptides [30,31]. FGF-23 also inhibits 1.25-dihydroxyvitamin D via effects on CYP27B1 and CYP24A1 enzymes, stimulates the renin-angiotensin system via binding with Klotho, which is a key cofactor for FGF-23 [29]. Although elevated intact FGF-23 was found in aotic stenosis patients with heart failure, the role of this biomarker in risk stratification of the patiens is not fully understood. Probably, FGF-23 could help to stratify the older patients with aortic stenosis beyond classical CV risk factors and individualize the medical care.

Galectin-3

Galectin-3 is a soluble beta galactoside-binding lectin produced by activated macrophages which binds and activates the fibroblasts [32]. The main biological role of galectin-3, as reported, is modulation of biological recognition processes, regulation of fibroblast proliferation and matrix synthesis that lead to fibrosis and extracellular remodeling. Results of recent studies have reported that galectin-3 is a biomarker that mediates an important link between inflammation and fibrosis, which play a pivotal role in CV remodeling [33]. The pathogenetic role of galectin-3 in the several setting of pressure overload, neuro-endocrine activation, hypertension, coronary artery disease / myocardial infarction, atrial fibrillation, and HF has strongly established [34-36].

Galectin-3 has emerged a predictive value for the onset of HF in apparently healthy patients and has been found being surrogate marker of a worse prognosis, mortality and re-admission in HF [22,23]. The results of the sub-study of COACH (The Coordinating Study Evaluating Outcomes of Advising and Counselling in Heart Failure) trial have shown that only galectin-3 was significantly associated with the absence of CV events at 180 days in patients with HF at low risk for death or HF re-hospitalization [37]. Therefore, authors indicated that this biomarker demonstrated an incremental value when added to the clinical risk model without NT-proBNP [37]. Overall, galectin-3 is obviously powerful prognosticator of death and re-hospitalization in HF patients at discharge from the hospital and in generally population individuals at higher risk of HF development.

Matricellular proteins

Matricellular proteins belong to family of multifunctional growth factors that are main components of the extracellular matrix which regulate bone developing, vascular remodelling, and tissue regeneration [38]. Although matricellular proteins (osteopontin, osteoprotegrin, osteonectin, thrombospondin) are surrogate biomarkers of vascular calcification and endothelia dysfunction in coronary artery disease, diabetes, obesity, atherosclerosis, dyslipidemia [39-41], the predictive role of these biomarkers in persons with aortic stenosis are still not understood because evidences are limited [42]. It has suggested that over production of matricellular proteins in aortic stenosis and CV diseases may consider as response to prevent vascular calcification [42]. However, the interrelation between CV mortality and circulating level of matricellular proteins in aortic stenosis in older adults is needed to be established.

Limitations of Previous Studies

There are not evidence exists that gait speed is optimal to test in older patients with aortic stenosis, although transthoracic echocardiography is the primary imaging modality that is used in clinical practice to assess the aortic valve morphology, the severity of aortic valve disease, and its repercussions on left ventricular function and aortic circulation [43]. Three-D echocardiography, dobutamine stress echocardiography and, more recently, aortic valve calcium scoring by multidetector computed tomography have been shown to be useful to confirm stenosis severity in the challenging subsets of patients with low-flow, low-gradient of aortic stenosis, despite interpretation of obtained results in older aortic stenosis patients with multipl comorbidities might be limited. Conventional pre- and perioperative surgical risk scores lack accuracy in risk stratification of older patients undergoing TAVI. Moreover, current data support hypothesis regarding use of hemodynamic parameters as sensitive predictors in symptomatic patients. Probably, using of cardiac biomarkers might extend our knowledge about CV risk in asymptomatic persons, whereas asymptomatic older patients are at higher CV risk and require rather cardiac functional status determining to enroll them in the group for further aortic valve replacement procedure. On the other hand, in geriatric population with aortic stenosis adding new biomarkers could increase the discriminative value of contemporary non-invasive hemodynamic characteristics to predict CV complications before non-cardiac surgery and performing of aortic valve replacement within long-term period. Indeed, the rationale for obtaining a preoperative and / or postoperative biomarker levels might have the utility when having a baseline Echo / Doppler parameters and functional cardiac status are abnormal, but there were not enough data to clinical decision making. Here one cannot discuss about pretreatment in this patient population, while the perspective of cardiac biomarkers utility might be determined in future. The next limitation of cardiac biomarker implementation is being low value care for older adults that might reduce the so-called clinical utility. It has suggested that the cardiac biomarkers are to be used in the specific contexts in high-income countries. This assumption requires more investigations using head-to-head comparison biomarkers with echo/Doppler parameters, as well as patient' clinical status. Overall, cardiac biomarker release signifying myocardial injury post-TAVI is common, yet its clinical impact within large TAVI cohort older persons receiving differing types of valve and procedural approaches is unknown.

Directions for further studies

Current clinical recommendations have reported that imaging modalities are essential for the staging and management of aortic valve disease. Because there are a large body of evidence regarding elevated brain natriuretic peptide levels as predictive biomarkers in symptomatic aortic stenosis patients after TAVI, one might resume that serial measurements of BNPs and other markers of biomechanical stress, inflammation, cardiac injury, could be useful for risk stratification of the patients enrolled for TAVI. Moreover, cardiac biomarkers may probably have utility in risk stratification of asymptomatic individuals with aortic stenosis when closely corresponding between two-dimensional and Doppler echocardiographic parameters and clinical outcomes are absent. Other modalities such as biomarkers for the assessment of myocardial fibrosis, cardiac injury or inflammation might be promising to predict aortic stenosis progression and related outcomes in older individuals, but further research is necessary before implementation of these modalities into clinical practice.

In conclusion, two-dimensional and Doppler echocardiographies remain to be key tool for the evaluation and monitoring of aortic stenosis. Although there is no consensus on the prognostic value, sensitivity, and specificity of biomarkers to stratify older patients with aortic stenosis at risk, BNP / NT-proBNP, galectin-3, sST2

appear to be promising predictors of C death and clinical outcomes in this population. Whether combined biomarker approach might have an impact on clinical decision-making for risk stratification in aortic stenosis patients is still not understood and requires further investigations.

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