

# Serum copeptin might improve risk stratification and management of aortic valve stenosis: a review of pathophysiological insights and practical implications

Kenan Yalta,  Orkide Palabiyik, Muhammet Gurdogan and Yekta Gurlertop

**Abstract:** Over recent decades, the prevalence of aortic valve stenosis (AVS) has been constantly increasing possibly owing to the aging of general population. Severe AVS as determined by an aortic valve area (AVA) of  $<1\text{ cm}^2$  has been regarded as a serious clinical condition potentially associated with a variety of adverse outcomes, including sudden cardiac death (SCD). However, patients with severe AVS (in the absence of overt high-risk features) are usually evaluated and managed exclusively based on symptomatology or imperfect prognostic tools including exercise testing and biomarkers, with a potential risk of mismanagement, suggesting the need for further objective risk stratifiers in this setting.

Within this context, copeptin (C-terminal pro-vasopressin), a novel neurohormone widely considered as the surrogate marker of the arginine-vasopressin (AVP) system, may potentially serve as a reliable prognostic and therapeutic guide (e.g. timing of aortic valvular intervention) in patients with severe AVS largely based on its hemodynamic, fibrogenic as well as autonomic implications in these patients. Accordingly, the present paper aims to discuss clinical and pathophysiological implications of copeptin in the setting of AVS along with a summary of biomarkers and other prognostic tools used in this setting.

**Keywords:** aortic valve stenosis, copeptin, prognostic implication, prognostic tool, therapeutic implication

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## Introduction

In recent decades, the prevalence of aortic valve stenosis (AVS) appears to be on the rise, probably due to the aging of general population.<sup>1,2</sup> Severe AVS as determined by an aortic valve area (AVA) of  $<1\text{ cm}^2$  has been one of the most devastating cardiovascular conditions, largely owing to its inherent risk for adverse cardiac events including sudden cardiac death (SCD) and progressive heart failure.<sup>1,2</sup> In the setting of severe AVS, the risk for adverse events is well known to be much higher in the presence of clinically evident high-risk features such as low left ventricular ejection

fraction (LVEF) values, very high or rapidly progressive transaortic gradients, hypotensive response to exercise testing and heavily calcified valves, suggesting urgent or earlier valvular intervention in these patients.<sup>2,3</sup> However, in clinical practice, a large portion of patients with severe AVS do not harbor these objective high-risk features, and hence are generally evaluated and managed solely on the basis of their subjective findings including symptomatology (e.g. dyspnea, angina) or imperfect prognostic tools with a potential risk of misguidance in some instances:<sup>1,2</sup> for instance; an asymptomatic patient with a

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severe AVS might tragically and unexpectedly suffer SCD on follow up, or conversely a similar patient with a vague symptomatology (e.g. atypical angina) may unnecessarily undergo an aortic valve surgery (with potential life-time complications)<sup>1</sup> who, if left untreated, may remain event-free with a normal life expectancy. Therefore, there exists an obvious need for absolute predictors for risk stratification and hence, proper management of these patients.<sup>4</sup>

In the setting of asymptomatic severe AVS, a variety of prognostic tools, including exercise testing [fall or failure to rise in blood pressure (BP) values], echocardiogram (e.g. degree of calcification, rapid progression in transaortic jet velocity) and certain arrhythmogenic indices have been suggested with variable positive and negative predictive values for adverse events and survival.<sup>3</sup> On the other hand, plasma biomarkers have drawn a substantial interest largely due to their cost-effective, replicable and widely available features in cardiovascular practice.<sup>4</sup> Among these, a variety of biomarkers including N-terminal pro B-type (NT-proBNP) and B-type natriuretic peptides (BNPs) that are generally known as conventional markers of heart failure have been tested in the setting of AVS.<sup>3-6</sup> However, their use in this setting has not gained widespread approval. Conversely, novel biomarkers of the arginine-vasopressin (AVP) axis including copeptin (C-terminal pro-vasopressin) may potentially serve as potential risk stratifiers, and hence may help guide the management algorithm in patients with severe AVS (despite the absence of clinical trials in this setting). Accordingly, the present hypotheses-generating review primarily aims to focus on the pathophysiological and clinical relevance of copeptin in the setting of AVS and its management, along with a brief summary of biomarkers and other prognostic tools in this setting.

#### *Biomarkers and AVS*

Given the strong relation of AVS with endothelial dysfunction and progressive valvular calcification,<sup>4</sup> a variety of associated biomarkers including inflammation markers [e.g. tumor necrosis factor- $\alpha$ , C-reactive protein (CRP)], oxidative stress markers (e.g. malondialdehyde, glutathione, homocysteine), osteoblastic factors (e.g. fetuin, osteopontin), endothelial markers

[asymmetric dimethylarginine (ADMA)] and neurohormones (NT-proBNP and BNP) have been tested in patients with AVS.<sup>4,7</sup> Among these, leptin,<sup>8</sup> fetuin,<sup>4,9</sup> osteopontin,<sup>4,7,10</sup> ADMA<sup>4,11</sup> and a variety of inflammation markers including neutrophil/lymphocyte ratio,<sup>12</sup> were suggested to have clinical value in determining the presence and severity of AVS. However, the utility of these markers lacks information regarding the progression of valvular disease or prognosis.<sup>4</sup> Similarly, widely available markers, including total or low density lipoprotein (LDL) cholesterol, were previously demonstrated to have no value in monitoring AVS progression in major clinical trials.<sup>4,7,13</sup> In contrast, another widely available inflammation marker, CRP, was previously suggested to confer valuable information regarding severity, progression as well as prognosis of AVS in patients with asymptomatic valvular disease.<sup>4,7,14</sup> However, the nonspecific nature of this marker might theoretically limit its reliability and hence, its widespread use in patients with AVS.<sup>4</sup> Interestingly, malondialdehyde (an oxidative stress marker) and growth differentiation factor (GDF)-15 were found to have a clinical value for the prediction of adverse events following aortic valve intervention.<sup>4,15,16</sup>

On the other hand, certain drugs with pleiotropic actions, including statins, might be associated with a substantial reduction in serum levels of AVS-associated biomarkers, including LDL, bone turnover markers [including osteoprotegerin, soluble RANK (regulators of osteoclast maturation and function), osteopontin], inflammation markers [including CRP and interleukin (IL)-6] and markers of platelet activation [including soluble CD 40 ligand (sCD40L)].<sup>17-19</sup> Within this context, as opposed to the reported neutral influence of statins on AVS progression in large clinical trials,<sup>13,17</sup> statin therapy was previously shown to have a significant favorable impact in this setting particularly when initiated in the earlier stages of the disease course (including aortic valve sclerosis and mild AVS where endothelial dysfunction and ectopic mineralization are still nascent).<sup>17-19</sup> Therefore, it seems reasonable that the favorable impact of targeted medical strategies (including statins) on AVS progression might possibly appear to be inversely correlated with the duration and extent of valvular pathology potentially warranting earlier initiation of these strategies in patients with AVS.<sup>17-19</sup>

*Natriuretic peptides: potential limitations in the setting of AVS?* Even though conventional neurohormones including NT-proBNP and BNP were previously suggested as independent prognosticators in patients with AVS,<sup>3–6</sup> current American Heart Association (AHA)/American College of Cardiology (ACC) guidelines on valvular heart disease do not encourage the routine use of these peptides<sup>2</sup> in the setting of AVS, suggesting important limitations of these markers. Similarly, a recently published prospective study also reported the potential challenges regarding the utility of NT-proBNP as a single prognostic marker with a possible risk of mismanagement, particularly in patients with asymptomatic AVS.<sup>1</sup> In comparison with other physiological systems including the AVP–copeptin axis, the potential inferiority of natriuretic peptides in this setting has a potential mechanistic basis.

Physiologically, the primary determinant of the AVP system appears to be a state of systemic hypoperfusion<sup>20–22</sup> regardless of cardiac morphological determinants, including cavity dimensions, wall thickness or tension. On the other hand, myocardial stretch (wall tension) serves as the major trigger of natriuretic peptide release.<sup>23</sup> However, myocardial wall tension, in addition to pressure or volume load, is also well known to be dependent on cavity dimensions, wall thickness, ejection fraction etc. More interestingly, end diastolic pressure and end diastolic wall stress might serve as stronger triggers of BNP release in comparison with systolic wall stress.<sup>24</sup> This potentially suggests that transaortic gradient (hence, systolic pressure load) might not serve as the only determinant of natriuretic peptide release in the setting of AVS, suggesting a wide overlap in the levels of these peptides across all grades of AVS (mild to severe gradients<sup>1</sup>). Therefore, natriuretic peptides generally have a limited value, even in determining the severity of AVS.<sup>1</sup>

#### *Copeptin: an emerging guide for cardiovascular disease*

Copeptin, the C-terminal part of pro-vasopressin, has recently emerged as a novel neurohormone with distinct structural and clinical features.<sup>23</sup> Structurally, it is a 39 amino acid glycosylated polypeptide, and appears to be co-released with AVP (also known as antidiuretic hormone) from the hypothalamus (neurohypophysis) in response

to certain hemodynamic (systemic hypoperfusion) and osmotic stimuli.<sup>20–22,23</sup> As the initial step, pre-pro-vasopressin, the 164 amino acid polypeptide, serves as the precursor hormone that constitutes AVP, copeptin, neurophysin-2 and signal peptide.<sup>20,23</sup> Stepwise enzymatic processing of this precursor peptide in the supraoptic and paraventricular nucleus of hypothalamus ultimately gives rise to formation of AVP and copeptin that both undergo an axonal transport to the posterior pituitary (neurohypophysis) preceding their systemic co-release.<sup>20,22,23</sup> In contrast with AVP, that primarily mediates its effects through a variety of well-known receptors including V1a (arterial vasoconstriction), V1b (endocrinological effects) and V2 (antidiuretic action in renal collecting duct), the absolute function of copeptin is largely unknown.<sup>20,23</sup> However, copeptin, along with neurophysin 2, was previously suggested to function as a transporter of AVP through the course of its axonal transport.<sup>22,23</sup>

Since copeptin demonstrates a strong correlation with AVP *in vivo* (both released in an equimolar ratio), and harbors a variety of unique structural and methodological advantages, it has universally been considered a surrogate biomarker of the AVP system.<sup>20–23</sup> Its median plasma level was previously reported as 4.2 pmol/l with little or no significant impact of age, sex and obesity on its plasma levels.<sup>20,21,23</sup> Importantly, it is of significant clinical relevance as a diagnostic as well as a prognostic marker in certain cardiovascular conditions such as heart failure, acute coronary syndromes (ACS), takotsubo cardiomyopathy and even metabolic syndrome.<sup>23</sup> Furthermore, copeptin was also suggested to serve as a potential biomarker of nonspecific endogenous stress, and hence; adrenergic activation possibly attributable, in part, to the potential impact of adrenergic substances, including noradrenaline, on AVP release.<sup>23</sup> Importantly, copeptin has a high sensitivity, but relatively low specificity in the setting of associated clinical conditions, potentially labeling it as a rule-out marker with a high negative predictive value in certain conditions, including ACSs<sup>23</sup> and perioperative myocardial injury.<sup>25</sup>

#### *Copeptin elevation in the setting of AVS: pathophysiological implications*

As categorized and described below, elevation of serum copeptin might yield a variety of important

pathophysiological implications with prognostic and therapeutic relevance potentially providing a rationale for the use of copeptin as a clinical guide when evaluating patients with severe AVS.

*Systemic hypoperfusion and failure to augment cardiac output.* It seems reasonable that elevation of serum copeptin levels in the setting of AVS is more likely to be encountered in patients with a far more advanced stage of the disease: severe AVS patients suffering a state of systemic hypoperfusion (with normal or occasionally low BP values at rest) usually with the failure to augment cardiac output under stress, including exercise as well. In other terms, copeptin in the setting of severe AVS might, *per se*, serve as a marker of systemic hypoperfusion relatively independent of the degree of valvular stenosis up to a certain gradient threshold. For instance, among two patients with severe AVS having the same degree of transaortic gradient, one may suffer hypoperfusion, and the other may not. Therefore, this state of hypoperfusion (and hence increased copeptin levels) in patients with severe AVS, might portend a variety of adverse events including coronary ischemic syndromes or even syncope, potentially leading to SCD probably due to the impaired augmentation of systemic perfusion, particularly during physically or emotionally stressful conditions. More subtly, systemic hypoperfusion in these patients initiates or further aggravates heart failure due to progressive ventricular remodeling possibly as a result of neurohormonal activation, including stimulation of AVP<sup>26–29</sup> and adrenergic systems in the chronic setting. Importantly, certain conditions with potential impact on volume status, including fluid loss [diuretic use (though generally avoided in the setting of severe AVS), diarrhea, hemorrhage], fluid overload (iatrogenic, hormonal) as well as changes in venous return (physiological maneuvers) might be associated with serum copeptin changes,<sup>23</sup> and hence, serve as confounding factors when evaluating impact of AVS on systemic perfusion. Therefore, the prognostic power of copeptin might significantly diminish in the setting of severe AVS accompanied by these conditions.

Studies regarding the clinical value of copeptin in the setting of AVS have been extremely rare in the literature, and generally lack the specific design to investigate the prognostic and therapeutic implications of copeptin in this setting. Accordingly, a recently published study reported an overall increase

of copeptin levels in a mixed population of patients with moderate and severe AVS (AVAs:  $1.40 \pm 0.20 \text{ cm}^2$  and  $0.67 \pm 0.18 \text{ cm}^2$ , respectively) in comparison with the control group, along with an inverse correlation between effective orifice area and copeptin levels ( $r = -0.556$ ,  $p < 0.0001$ ).<sup>26</sup> The mean levels of copeptin in severe AVS, moderate AVS and control groups measured as 405, 351 and 302 pg/ml respectively in this study (severe and moderate AVS groups *versus* control group,  $p < 0.05$ , severe *versus* moderate AVS group,  $p < 0.05$ ).<sup>26</sup> Analogously, there was also a significant variation among the groups with regard to mean levels of NT-proBNP ( $p < 0.05$  for all comparisons).<sup>26</sup> Importantly, receiver operating characteristic curve analysis suggested copeptin was a marker of moderate to severe AVS with an optimal cutoff value of 354 pg/ml (specificity 87%, sensitivity 71%).<sup>26</sup> On the other hand, there was no correlation between NT-proBNP and copeptin in this study, potentially suggesting different mechanisms of release kinetics of these two biomarkers.<sup>26</sup> However, due to its design, this study suggested copeptin only as a gross diagnostic marker of moderate to severe AVS, and did not specifically focus on its prognostic relevance in patients with moderate to severe AVS, and did not directly compare patients with and without substantial copeptin levels with regard to adverse events on follow up.<sup>26</sup>

*Excessive baroreflex hyperreactivity and adrenergic hyperactivation.* Copeptin is also known as a potential marker of endogenous stress (due to a variety of stressors including ACS, infections, surgery) and hence; adrenergic activation regardless of an existing systemic hypoperfusion state.<sup>23,25,30,31</sup> Adrenergic hyperactivation in correlation with serum copeptin levels might predispose to a variety of supraventricular and ventricular arrhythmias particularly in the setting of excessive myocardial hypertrophy associated with AVS. In particular, SCD in the setting of severe AVS, to some extent, appears to be attributable to malign ventricular arrhythmias, failure to augment systemic perfusion under stress (as mentioned previously), and to a large extent, to enhanced myocardial baroreceptor reactivity, namely the Bezold–Jarish reflex, (due to ventricular overstretch, particularly during exercise).<sup>32,33</sup> Among these mechanisms, the Bezold–Jarish reflex is of particular importance, and might potentially trigger peripheral vasodilatation and brady arrhythmias leading to syncopal attacks and, if excessive,

**Table 1.** Pathophysiological implications of copeptin elevation in the setting of severe AVS.**Copeptin elevation in the setting of severe AVS potentially signifies:**<sup>23,26–31,34,35</sup>

-Systemic hypoperfusion with the failure to augment CO: mostly manifests with normal BP values, and is potentially associated with coronary ischemic syndromes and SCD predominantly under stressful conditions as well as occurrence of clinical heart failure due to progressive myocardial remodeling in the long term.

-Adrenergic hyperactivation: may be associated with arrhythmogenesis particularly in the setting of excessive myocardial hypertrophy, and may, to some extent, contribute to excessive baroreflex hyper-reactivity.

-Excessive baroreflex hyperreactivity: may present with SCD and is potentially associated with excessive myocardial baroreceptor stimulation possibly due to the direct impact of enhanced AVP activity and, to a lesser extent, adrenergic hyperactivation that all correlate with copeptin levels.

-Rapid progression of valvular stenosis: largely due to profibrotic effects of accompanying enhanced AVP actions on valvular tissue and may potentially denote an imminent risk for adverse events requiring earlier valvular intervention.

AVP, arginine vasopressin; AVS, aortic valve stenosis; BP, blood pressure; CO, cardiac output; SCD, sudden cardiac death.

to a variety of catastrophic consequences, including severe coronary ischemia, ventricular arrhythmias (including torsades de pointes) or asystole in patients with AVS.<sup>32–34</sup>

Interestingly, it was previously suggested that AVP, *per se*, might have a direct impact on baroreflex reactivity suggesting its pivotal role in the genesis of vasovagal syncope.<sup>34,35</sup> This might also apply to the genesis of syncopal attacks and SCD among patients with AVS. Accordingly, myocardial baroreceptor stimulation (only leading to syncopal attacks normally) may even be more pronounced in the setting of severe AVS with excessive copeptin levels possibly due to direct impact of enhanced AVP activity,<sup>35</sup> and to a lesser extent, to myocardial hypercontractility primarily induced by adrenergic stimulation that all correlate with copeptin levels. In other terms, copeptin elevation in the setting of severe AVS might be associated with excessive Bezold–Jarish reflex (far more pronounced than in the setting of syncopal attacks) potentially leading to the occurrence of adverse clinical outcomes, including SCD.

*Rapid progression of AVS: a direct effect of enhanced AVP activity?* Increased copeptin levels were also suggested to accelerate progression of AVS possibly through profibrotic and mitogenic impact of enhanced AVP actions.<sup>23,26–29</sup> Therefore, AVP antagonism within the valvular tissue may hypothetically slow down the progression of AVS.

However, AVP receptor antagonists (such as tolvaptan, previously studied in patients with heart failure<sup>36</sup>) primarily mediate their effects through systemic blockade of AVP receptors [V1 (vasoconstriction), V2 (renal water reabsorption)] leading to a state of peripheral vasodilatation and water diuresis that should be strictly avoided in the setting of severe AVS. Therefore, future studies should not only focus on the potential impact of AVP antagonists on AVS progression, but also on potential routes and feasibility of local delivery of these agents into the diseased aortic valvular tissue without systemic adverse effects. In summary, increased copeptin levels in patients with AVS denote a rapidly progressive stage with an imminent risk for adverse events that warrants earlier valvular intervention. This may represent another aspect of copeptin elevation in these patients potentially suggesting a causative role of enhanced AVP activity in aortic valve disease. Taken together, elevation of serum copeptin levels in patients with severe AVS might potentially signify important pathophysiological implications (Table 1).

*Prognostic and therapeutic implications: can we harness serum copeptin as a potential guide when evaluating patients with AVS?*

In the clinical setting, the above-mentioned pathophysiological implications might potentially translate into important practical implications. As expected, serum copeptin may not confer further

clinical information about high-risk patients [with low LVEF (<50%), very high gradients (max velocity  $\geq 5$  m/sec) on echocardiogram, hypotension at rest or exercise] who already have poor prognosis, if left untreated, and hence; need urgent valvular intervention.<sup>2,3</sup> However, the majority of patients with severe AVS do not harbor these overt high-risk features, and are evaluated solely based on their subjective findings, including symptomatology.<sup>1</sup> Copeptin may potentially work well in this group of patients.

It should be borne in mind that symptoms including angina, dyspnea or syncope (generally defined as major symptoms of severe AVS)<sup>3</sup> might be due to a variety of alternative causes (including coronary artery disease, vasovagal syncope) in patients with AVS as well. More importantly, patients with severe AVS may be prone to downplay<sup>3</sup> or overrate their symptoms. On the other hand, a significant portion of these patients may be actually asymptomatic. However, solely relying on symptomatology (in the absence of overt high-risk features) might potentially lead to mismanagement of these patients: for ins; a truly asymptomatic (or reportedly asymptomatic) patient with severe AVS may unexpectedly suffer SCD on follow up.<sup>1</sup> On the other hand, patients with severe AVS may undergo an unnecessary aortic valvular intervention<sup>1</sup> even in the presence of vague symptomatology or symptoms due to an alternative etiology.

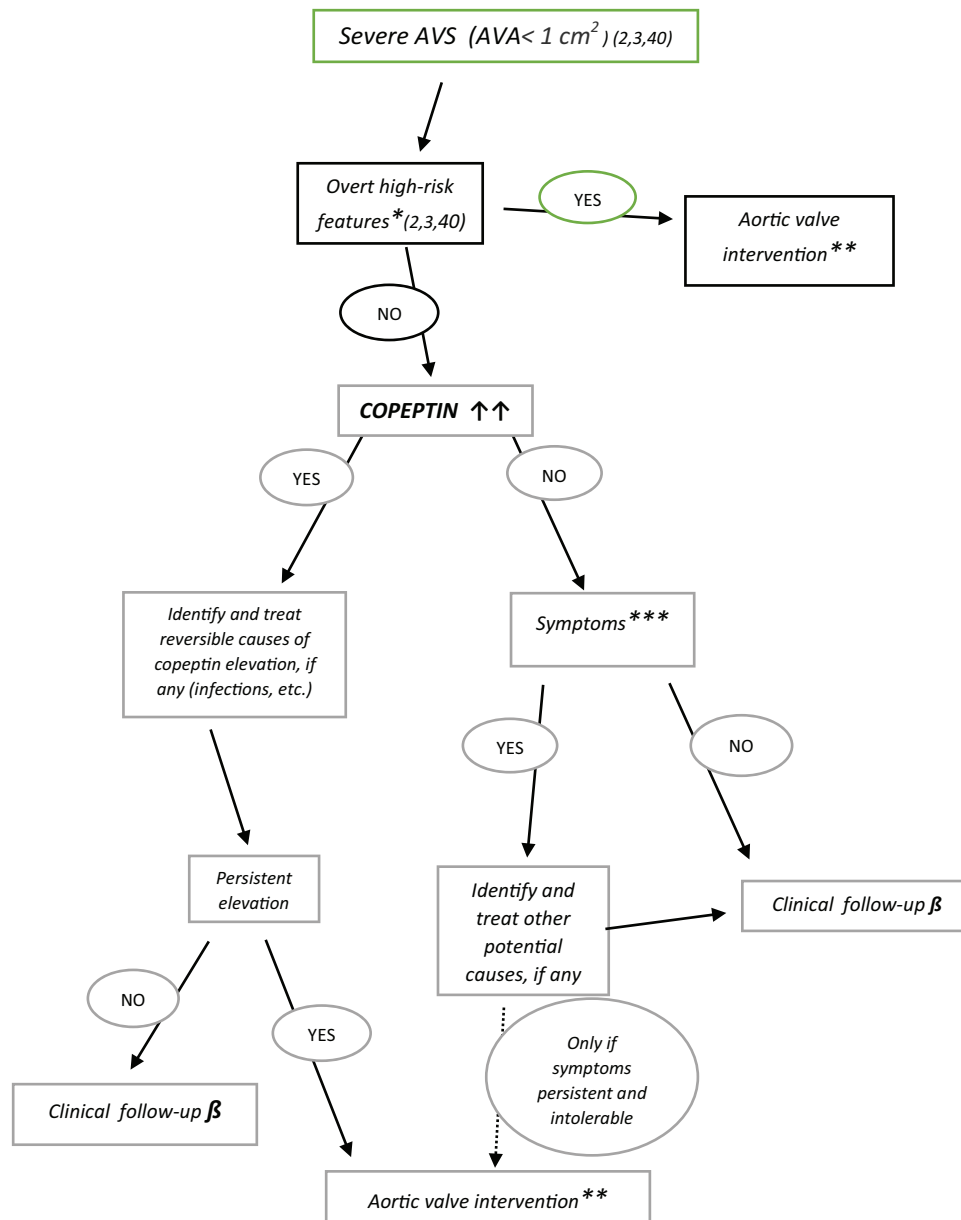
In clinical practice, asymptomatic patients with severe AVS are watchfully monitored till they become symptomatic.<sup>3</sup> This attitude is largely based on a variety of studies demonstrating low rates of SCD on follow up in these patients (around 3% at most).<sup>3,37</sup> In contrast, a large scale study investigating the long-term prognosis of asymptomatic severe AVS clearly demonstrated a significantly higher rates of mortality and heart failure admissions in conservatively managed patients in comparison with those managed with aortic valve replacement (AVR) at 5 years (mortality rates: 26.4% and 15.4%, respectively,  $p = 0.009$ )<sup>3,38</sup> potentially suggesting the need for further prognosticators in the setting of asymptomatic severe AVS.

Within this context, persistent and substantial elevation of copeptin levels, regardless of symptomatology, may warrant urgent aortic valvular intervention in patients with severe AVS (largely based on its pathophysiological implications.<sup>23,26–31,34,35</sup>). Conversely, normal or

near-normal copeptin levels may be considered as a predictor of favorable prognosis in the setting of severe AVS, and may initially prompt the clinician to search and treat alternative causes of symptoms (if any). Moreover, even if the clinical scenario is a truly symptomatic AVS with a normal serum copeptin level, the associated symptoms in this setting may be attributable to a variety of relatively benign (including myocardial hypertrophy leading to exercise angina that might potentially be managed with anti-ischemics) rather than life-threatening mechanisms (e.g. systemic hypoperfusion, baroreflex hyperactivation). In this setting, clinician, after excluding alternative causes of symptomatology, may consider aortic valvular intervention only in the presence of severe and limiting symptoms, refractory to medical therapy. More importantly, potential impact of particular conditions or co-medications on serum copeptin levels including surgery,<sup>25</sup> infections, alterations in volume status<sup>23</sup> as well as certain drugs (including fentanyl)<sup>39</sup> should be taken into consideration and eliminated accordingly before evaluating these patients. Figure 1 summarizes the potential therapeutic algorithm in the setting of severe AVS based on copeptin guidance. If the initial decision of the clinician is a clinical follow up (largely based on absence of high-risk features and initially normal copeptin levels), this algorithm may be repeated at future visits to detect a possible copeptin rise and other clinical changes at a relatively early stage, and then; to refer the patient to valvular intervention without further delay. On the other hand, randomized trials are still needed to test clinical relevance of copeptin, and also to define a cutoff copeptin value, above which adverse events are more frequently and seriously encountered in this setting.

#### *Current prognostic tools: a theoretic comparison with copeptin*

As mentioned previously, a variety of biomarkers including natriuretic peptides have been tested in the setting of AVS.<sup>1,4,7–16</sup> However, these markers, in general, may provide information about the presence and severity of AVS, but fail to yield any significant prognostic benefit in the pre-intervention setting.<sup>4</sup> However, as opposed to AHA/ACC guidelines,<sup>2</sup> the recent European Society of Cardiology guideline has recommended the potential use of natriuretic peptides for the prediction of adverse outcomes in asymptomatic



**Figure 1.** Potential therapeutic algorithm for the management of severe AVS based on copeptin guidance (a proposed scheme that is largely based on pathophysiological implications and the authors' perspective, and hence, warrants clinical studies to be used as a routine management algorithm).

AVA, aortic valve area; AVS, aortic valve stenosis; LVEF, low left ventricular ejection; TAVI, transcatheter aortic valve implantation.

\*LVEF < 50%, hypotension at rest or exercise, very high transaortic gradient (max jet velocity  $\geq$  5 m/sec), severe valvular calcification, rapid progression in jet velocity (0.3 m/s/y).<sup>2,3,40</sup>

\*\*Surgical or percutaneous TAVI.

\*\*\*Dyspnea, orthopnea, angina, syncope, dizziness.

β Should include clinical visits at regular intervals. The whole algorithm (with copeptin measurement) should be repeated at each visit to timely detect copeptin rise and other clinical changes, and to make the clinical decision accordingly.

patients with severe AVS (though the absolute cutoff value has not been defined).<sup>40</sup> Therefore, further studies on natriuretic peptides are still needed in this setting.

On the other hand, current guidelines encourage the utility of exercise (stress) testing in symptom-free patients with severe AVS to identify high-risk patients particularly with a hypotensive response

during exercise (and; hence those with the failure to augment cardiac output under stress).<sup>2</sup> A variety of positivity criteria including fall or failure to rise BP by 20 mmHg, ventricular arrhythmias or ST segment depression were previously suggested with relatively high positive and negative predictive values for future adverse events among these patients (81% and 85%, respectively).<sup>3,37</sup> However, in clinical practice, only a portion of these patients reach a sufficient exercise threshold to induce such changes largely due to their age-related chronotropic incompetence. Accordingly, exercise testing over the age of 70 has limited clinical value.<sup>3</sup> Moreover, clinicians generally consider it risky, and hence; feel reluctant to perform exercise testing in such patients even if they are totally symptom-free. More importantly, exercise testing fails to confer further information regarding other pathophysiological aspects of poor prognosis including baroreflex hyperreactivity and rapid progression of AVS.

Echocardiogram, besides its excellent diagnostic value, may also confer prognostic implications in patients with AVS; accordingly, valve morphology including presence of heavy calcification, severity of baseline transaortic gradient, rapid progression of transaortic jet velocity (0.3 m/s/y), left atrial functions, LV (left ventricular) mass and certain tissue Doppler parameters (longitudinal strain), have all been suggested to predict adverse events in these patients, to some extent.<sup>3,41,42</sup> An interesting index, namely valvulo-arterial impedance, that is equal to systolic LV pressure (mean transvalvular gradient + arterial systolic pressure / stroke volume index), takes into account the impact of BP as well potentially assessing the severity of global hemodynamic burden on LV in the setting of AVS.<sup>3,43</sup> A numerical value of  $>3.5$  mmHg/ml/m<sup>2</sup> might predict a poor outcome in this setting.<sup>43</sup> However, this index was also criticized for lacking the discrimination between relative contributions of BP and the valvular stenosis itself on prognosis.<sup>44</sup> On the other hand, exercise Doppler echocardiogram suggests that an increment of  $\geq 18$  mmHg in mean transaortic gradient during exercise might have an incremental predictive value for cardiac events on top of rest echocardiogram and exercise testing.<sup>45</sup> Certain sophisticated diagnostic methods (magnetic resonance imaging, electron beam tomography) might also be informative about valvular calcification and

ventricular fibrosis, and might theoretically guide risk stratification of these patients.<sup>3</sup> However, they are not widely available and cost-effective, and further studies are still needed to confirm their efficacy in this setting. Taken together, measures obtained on imaging tools, including echocardiogram, potentially demonstrate an inter and even intra-observer variation, and may only mirror certain aspects of valvular disease (e.g. morphology, progression, load on LV) mostly in a static manner without identifying its impact on peripheral hemodynamics, autonomic and humoral systems.

Lastly, certain arrhythmogenic markers including fragmented QRS and the ratio of Tp-e (interval between peak and terminal points of T wave) / QTc (corrected QT interval) were recently reported to be the independent predictors of severe AVS (potentially associated with myocardial fibrosis leading to arrhythmias).<sup>3,46,47</sup> However, prognostic and therapeutic implications in this setting have yet remained to be established. On the other hand, copeptin might also serve as a marker of arrhythmogenesis largely due to the myocardial effects of AVP (including induction of cardiac hypertrophy and fibrosis) and associated adrenergic hyperactivation<sup>30</sup> potentially rendering copeptin an arrhythmogenic risk stratifier in the setting of AVS as well. Taken together, future studies focusing on head-to-head comparison between copeptin and above-mentioned prognostic tools are still needed to approve the superiority of copeptin in this setting.

#### *Copeptin after aortic valve intervention: still valuable?*

Copeptin may possibly guide prognostication and therapeutic strategy even after successful aortic valve intervention particularly in the setting of persistent LV hypertrophy that does not regress in time. Accordingly, persistently high copeptin levels on post-intervention follow up may potentially portend an increased risk for arrhythmic events as well as adverse myocardial remodeling in the long term,<sup>23</sup> and hence; may help tailor patient specific therapeutic strategies: for instance, persistent elevations of copeptin levels may warrant intensive regimens of sympatholytic agents and prophylactic use of anti-arrhythmic drugs or even implantable cardioverter defibrillator therapy in certain settings for



arrhythmia prevention.<sup>23</sup> As in the setting of heart failure,<sup>48</sup> copeptin, may also help identify patients who would most likely benefit from anti-remodeling therapy, including AVP antagonists and RAAS blockers for the prevention of clinical heart failure in the short and long term.<sup>23</sup>

### Conclusion

In the setting of AVS, copeptin, the surrogate marker of the AVP system, may serve as a relatively objective risk stratifier, largely due to its strong fibrogenic (profibrotic impact on aortic valves and myocardium), hemodynamic as well as autonomic implications. This may help guide clinical decision-making both in symptomatic and asymptomatic cases with severe AVS. Moreover, it may also have certain implications in the post-intervention setting, particularly in the presence of persistent LV hypertrophy. However, a certain cutoff value for the prediction of life-threatening adverse events, including SCD, should also be defined in future studies. Notably, reversible causes of copeptin elevation including endogenous stress (e.g. infections, surgery) and changes in volume status (e.g. diuretic use) should be corrected before evaluation of patients with severe AVS based on copeptin guidance. Taken together, clinical utility of copeptin instead or, at least, on top of current prognostic tools might help better risk stratification and proper guidance of therapeutic strategy in these patients. In particular, implementing the management strategy primarily based on serum copeptin levels (without evident high-risk features) might potentially prevent excess mortality and morbidity in asymptomatic cases as well as unnecessary aortic valvular intervention in cases with a vague or ambiguous symptomatology. However, there exists an obvious necessity for randomized clinical studies to substantiate clinical use of copeptin (including a head-to-head comparison with current prognostic tools) in the setting of severe AVS.

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### Conflict of interest statement

The authors declare that there is no conflict of interest.

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