



Serum uric acid and valvular heart disease: a new window into cardiometabolic risk stratification

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See Article on Page 748-762

Valvular heart disease (VHD) is an increasingly important contributor to cardiovascular morbidity and mortality in aging populations. Traditionally, VHD has been considered a structural consequence of aging, rheumatic injury, congenital abnormalities, or degenerative calcification. However, accumulating evidence suggests that VHD, particularly calcific aortic valve disease and mitral annular calcification, is not merely a passive degenerative process but rather an active disease involving inflammation, endothelial dysfunction, lipid deposition, oxidative stress, and metabolic dysregulation [1]. In this context, Jung et al. provided timely and clinically relevant evidence linking serum uric acid (SUA) levels to incident VHD in a large population-based cohort.

Using data from 462,705 UK Biobank participants without baseline VHD or congenital heart disease, the authors categorized individuals according to SUA levels: normal (< 6.0 mg/dL), high (6.0–8.9 mg/dL), and very high ($\geq$ 9.0 mg/dL). During a mean follow-up of 12.3 years, 14,573 participants developed VHD. The study demonstrated a dose-response association between SUA levels and incident VHD. Compared with individuals with SUA < 6.0 mg/dL, those with SUA 6.0–8.9 mg/dL and $\geq$ 9.0 mg/dL had progressively higher risks of VHD. Importantly, this association persisted after adjustment for demographic factors, lifestyle behaviors, metabolic parameters, renal function, and relevant medications. The association was observed not only for aortic VHD and aortic stenosis but also for mitral VHD, broadening the potential relevance of hyperuricemia beyond calcific aortic valve disease.

The study has several strengths. First, the large sample size

and long follow-up duration allowed for robust estimation of incident VHD risk. Second, the authors used clinically interpretable SUA categories rather than purely data-driven quartiles or quintiles. The threshold of 6.0 mg/dL corresponds to the widely accepted therapeutic target in gout management, whereas SUA $\geq$ 9.0 mg/dL identifies individuals with marked hyperuricemia and a substantially increased risk of gout. Third, the authors conducted multiple sensitivity and subgroup analyses according to age, sex, obesity, diabetes, hypertension, dyslipidemia, metabolic syndrome, and cardiovascular disease. These analyses showed that the association between SUA and VHD was generally consistent across clinically relevant subgroups.

A particularly noteworthy aspect of the study is its analysis of obesity and abdominal obesity as potential modifiers of VHD risk. In the overall cohort, both higher body mass index and abdominal obesity were associated with increased VHD risk. However, when the analysis was stratified by SUA categories, the effect of obesity appeared more prominent among individuals with SUA < 9.0 mg/dL and less evident among those with SUA $\geq$ 9.0 mg/dL. This finding suggests that very high SUA levels may represent a risk state in which mechanisms other than obesity-related pathways become more dominant. In other words, although weight management remains important for cardiometabolic health and VHD prevention, individuals with severe hyperuricemia may require broader risk evaluation beyond conventional obesity-focused strategies.

The biological plausibility of the association between SUA and VHD warrants careful consideration. Hyperuricemia is associated with hypertension, chronic kidney disease, metabolic syndrome, coronary artery disease, heart failure, and

cardiovascular mortality. Several mechanisms may explain these associations, including oxidative stress, endothelial dysfunction, activation of the renin–angiotensin–aldosterone system, vascular smooth muscle proliferation, and chronic low-grade inflammation [2]. These processes are increasingly recognized as contributors to valvular calcification and degeneration. Previous studies have demonstrated associations between SUA and calcific aortic stenosis, while experimental evidence suggests that uric acid may promote osteogenic differentiation of valvular interstitial cells and endothelial dysfunction [3]. The current study extends this framework by showing that SUA is associated with incident VHD at the population level.

The association with mitral VHD is particularly intriguing. Degenerative mitral valve disease and mitral annular calcification have historically been considered distinct from atherosclerotic disease. However, mitral annular calcification is now understood to be an active process linked to aging, chronic kidney disease, inflammation, oxidative stress, and metabolic abnormalities [4]. The observation that SUA was significantly associated with mitral VHD suggests that hyperuricemia may influence broader valvular pathology, rather than only aortic valve calcification. This finding may stimulate future research into valve-specific mechanisms through which urate metabolism contributes to structural heart disease.

From a clinical perspective, the study raises an important but unresolved question: should SUA be considered a marker for VHD risk stratification? Currently, there is insufficient evidence to recommend urate-lowering therapy for preventing VHD in asymptomatic hyperuricemic individuals. Randomized trials of urate-lowering therapy have not established a clear benefit for major cardiovascular prevention [5], and no trial has specifically evaluated VHD incidence or progression as an endpoint. However, the current findings suggest that SUA may be a useful marker of cardiometabolic risk, particularly in middle-aged and older adults. In patients with marked hyperuricemia, clinicians may consider a more careful assessment of overall cardiovascular risk, renal function, metabolic syndrome, and symptoms suggestive of structural heart disease. Whether echocardiographic screening should be considered in selected high-risk individuals remains an open question requiring further investigation.

Additionally, the study has implications for gout and rheumatology practice. Patients with gout frequently have a cluster of cardiometabolic comorbidities, including hyper-

tension, chronic kidney disease, obesity, diabetes, and cardiovascular disease. The present findings add VHD to the broader landscape of potential cardiovascular conditions associated with hyperuricemia. However, it is important to avoid overinterpreting association as causation. For patients with gout, treat-to-target urate-lowering therapy remains essential for preventing flares, tophi, and joint damage. Whether achieving and maintaining SUA < 6.0 mg/dL also reduces long-term VHD risk remains unknown. Future studies using longitudinal SUA trajectories, echocardiographic endpoints, and interventional designs are required to clarify this issue.

Several directions for future research are warranted. First, replication in ethnically diverse cohorts, particularly in Asian populations, is needed. Second, studies incorporating serial echocardiography could determine whether SUA is associated with the onset, severity, or progression of specific valvular lesions. Third, mechanistic studies should investigate whether urate directly contributes to valvular inflammation, calcification, and extracellular matrix remodeling. Finally, clinical studies should evaluate whether weight reduction, improved metabolic control, or urate-lowering therapy modifies VHD risk among individuals with hyperuricemia.

In conclusion, Jung et al. [6] provide compelling population-based evidence that elevated SUA is associated with an increased risk of incident VHD, including both aortic and mitral valve disease. Their findings support the concept that VHD is closely linked to systemic cardiometabolic health and that SUA may serve as a clinically accessible marker of risk. Although the results do not yet justify urate-lowering therapy for VHD prevention, they open an important avenue for research into the intersection of urate metabolism, obesity, inflammation, and VHD. As populations age and the burden of degenerative VHD increases, identifying modifiable or measurable risk factors will become increasingly important. SUA may be one such marker that deserves closer attention.

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