The rapid emergence of transcatheter heart valve therapies for a wide range of valvular heart disease (VHD) substrates has cast renewed spotlight on the VHD landscape. The global burden of VHD is heterogeneous, with rheumatic heart disease being the dominant form of VHD and VHD-related deaths in Asia, Africa, and Oceania, whereas degenerative calcific aortic valve disease and mitral valve disease are predominant in aging, affluent societies in which these populations demonstrate increasing life expectancy. Although access to valve treatment technologies has helped an increasing proportion of patients in Western societies, there remains a considerable lag in the diagnosis and treatment availability in minority populations, including those in whom rheumatic heart disease is prevalent.

Clinical examination is a poor indicator of the presence of an underlying VHD substrate, and cardiac imaging remains the cornerstone for diagnosing the presence and severity of disease, although it has poor penetrance in many regions where it is needed the most at a grass roots level for early diagnosis. Valvular heart disease exists on a disease spectrum and evolves from a normal functioning valve toward mild, moderate, and ultimately severe disease. Thus far, most research has focused on the association between moderate to severe VHD and clinical events, with treatment algorithms directed toward the severe end of the disease spectrum when overt structural heart disease becomes manifest. Whether the presence of mild VHD has prognostic significance remains controversial, and much less is understood of the factors associated with VHD progression.

With this background in mind, Matsushita and colleagues sought to better understand the association, if any, between mild VHD lesions (aortic sclerosis, trace or mild aortic regurgitation, and trace or mild mitral regurgitation) and important clinical end points over a 25-year follow-up period in the Atherosclerosis Risk in Communities (ARIC) study, a community-based prospective cohort study of 15,792 adults from 4 communities in Maryland, Minnesota, Mississippi, and North Carolina. For their study, Matsushita and colleagues analyzed a cohort of 2,106 individuals from the Mississippi site, which enrolled only Black patients. These patients, who had a mean age of 59 years and included 64.3% women, underwent echocardiography during follow-up or surveillance visits from 1993 to 1995. The outcomes of interest were cardiovascular mortality, coronary heart disease, stroke, heart failure, and atrial fibrillation. The prevalence of aortic sclerosis was 7.7%, of trace or mild aortic regurgitation was 15.1%, and of trace or mild mitral regurgitation was 43.0%. Through almost 25 years of follow-up, 42.3% of the participants developed at least 1 of the cardiovascular outcomes, the most frequent of which was heart failure (27.3%), followed by atrial fibrillation (14.5%), stroke (13.1%), and cardiovascular mortality (10.5%). Each valvular lesion was independently associated with at least 1 outcome, even after adjusting for potential confounders. Matsushita and colleagues found a dose-response association for the total number of valvular lesions: patients with 2 or more valvular lesions had a higher hazard ratio for cardiovascular mortality compared with those with 1 lesion.

The study had several strengths, including (1) segregation of trace or mild aortic regurgitation and trace or mild mitral regurgitation for reporting outcomes; (2) a 25-year follow-up period; (3) rigorous adjustment for confounding factors, including adiposity, blood pressure, and kidney function; and (4) demonstration of a dose-response association for the total number of valvular lesions. One of the major limitations of the study was the magnitude of association between VHD and the defined outcomes. For aortic sclerosis, the hazard ratio for cardiovascular mortality was 1.54 (95% CI, 1.06-2.22), with an E value of 1.31 for the lower CI. This result means that a cofounder as low
as 1.3 on a risk ratio scale would be sufficient to fully explain the increased hazard of cardiovascular mortality in patients with aortic sclerosis. This interpretation was true for most of the other significant outcomes reported in the study for all 3 subsets of VHD, except cardiovascular mortality in patients with mild aortic regurgitation, which had the highest E value of 1.9 for the lower CI. A second limitation was that, although the authors adjusted for systolic dysfunction in the regression analysis, they ignored the diastolic dysfunction in these patients. In acknowledging type II error, the possibility of the competing risk of mortality with other end points (coronary heart disease, stroke, heart failure, and atrial fibrillation) cannot be excluded, and the study did not account for these concomitant clinical events. Other limitations were the lack of generalizability of the results to other racial and ethnic groups, lack of adjudication for all reported outcomes, and residual confounding. Given these limitations, the findings of this observational study need to be interpreted with caution. Nevertheless, it is a unique study in that, to our knowledge, it is one of the first to cast a spotlight on the importance of mild VHD for patient outcomes; this has not been the focus of previous VHD cohort studies.

Although Matsushita and colleagues highlighted the association between early VHD and adverse cardiovascular outcomes in the Black population, there are a number of other important implications for the way VHD should be addressed in the broader population. The widespread availability of diagnostic cardiac imaging within at-risk communities or geographic areas wherein VHD or rheumatic heart disease is underdiagnosed and/or prevalent should be prioritized to enhance early screening and surveillance. Further research should seek to unravel mechanistic pathways and biomarkers that promote VHD progression from trace or mild to the moderate to severe end of the disease spectrum. Although contemporary pharmacotherapies have thus far failed to alter the natural progression of calcific degenerative aortic sclerosis, identifying patients earlier in the disease spectrum may help clinicians implement valve repair or valve replacement strategies in a more timely manner, before the onset of overt structural heart disease and cardiac damage.

The emergence of machine learning and artificial intelligence algorithms should be coupled with broader access to cardiac imaging (to automate image interpretation), referral pathways, and surveillance programs. This approach may enable true lifetime management of patients, beginning at the point when their VHD has been diagnosed as mild.

ARTICLE INFORMATION
Published: May 12, 2022. doi:10.1001/jamanetworkopen.2022.11955
Open Access: This is an open access article distributed under the terms of the CC-BY License. © 2022 Puri R et al. JAMA Network Open.
Corresponding Author: Rishi Puri, MBBS, PhD, Department of Cardiovascular Medicine, Heart, Vascular & Thoracic Institute, Cleveland Clinic, 9500 Euclid Ave, Mail Code J2-3, Cleveland, OH 44195 (purir@ccf.org).
Author Affiliations: Department of Cardiovascular Medicine, Heart, Vascular & Thoracic Institute, Cleveland Clinic, Cleveland, Ohio (Puri); West German Heart and Vascular Center, Department of Cardiology and Vascular Medicine, University of Duisburg-Essen, Essen, Germany (Dykun); Krannert Cardiovascular Research Center, Division of Cardiovascular Medicine, Indiana University School of Medicine, Indianapolis (Kalra).
Conflict of Interest Disclosures: None reported.
REFERENCES


