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Editorial Comment

EDITORIAL COMMENT

Valvular heart disease in patients on kidney replacement therapy: "opening Pandora's box"

Rafael de la Espriella [1], Gregorio Romero-González [2,3] and Julio Núñez [1,4,5]

[1]Department of Cardiology, Hospital Clínico Universitario de Valencia (INCLIVA), Valencia, Spain, [2]Department of Nephrology, Hospital Universitario Germans Trias I Pujol, Badalona, Spain, [3]International Renal Research Institute of Vicenza (IRRIV), Vicenza, Italy, [4]Centro de Investigación Biomédica en Red en Enfermedades Cardiovasculares (CIBERCV), Madrid, Spain and [5]Department of Medicine, Universitat de Valencia, Valencia, Spain

Correspondence to: Julio Núñez; E-mail: yulnunez@gmail.com or juenuvi@uv.es

ABSTRACT

Valvular heart disease (VHD) is highly prevalent among dialysis patients, affecting up to 30%–40% of the population. Aortic and mitral valves are the most frequently affected and commonly lead to valvular stenosis and regurgitation. Although it is well established that VHD is associated with a high morbimortality burden, the optimal management strategy remains unclear, and treatment options are limited due to the high risk of complications and mortality after surgical and transcatheter interventions. In this issue of *Clinical Kidney Journal*, Elewa *et al.* provide new evidence in this field by reporting the prevalence and associated outcomes of VHD in patients with kidney failure on renal replacement therapy.

Keywords: cardiorenal syndrome, cardiovascular, chronic hemodialysis, dialysis, echocardiography

'When it is obvious that the goals cannot be reached, don't adjust the goals; adjust the action steps.' —*Confucius*

The burden of cardiovascular disease in patients with chronic kidney disease (CKD) has been classically attributed to an increased risk of atherosclerosis-related complications; however, much of the excess cardiovascular risk is due to non-atherosclerotic pathologies such as heart failure, arrhythmias, sudden cardiac death, valvular heart disease (VHD) and arterial calcification [1]. Indeed, VHD is highly prevalent in patients with CKD [2], particularly among those on dialysis [2–4], significantly impacting patient outcomes [5, 6]. Unfortunately, CKD patients often have a long asymptomatic period or exhibit nonspecific symptoms, which may be mistakenly attributed to other coexisting and common comorbidities (i.e. anemia or sarcopenia), delaying diagnosis and treatment. Moreover, there are no specific recommendations in current clinical practice guidelines on how to manage patients with combined VHD and kidney failure [7, 8]. Similarly, there is little or no evidence regarding the effect of dialysis modality on valvular disease progression [9].

In this issue of *Clinical Kidney Journal*, Elewa *et al.* [10] . provide new evidence in this field by reporting the prevalence and associated outcomes of VHD in patients with kidney failure on renal replacement therapy. The authors conducted a retrospective cross-sectional clinical characteristics and outcomes analysis, including 521 dialysis patients (peritoneal dialysis or hemodiafiltration) divided into two groups based on the presence or absence of VHD. In the study cohort, 33.6% had evidence

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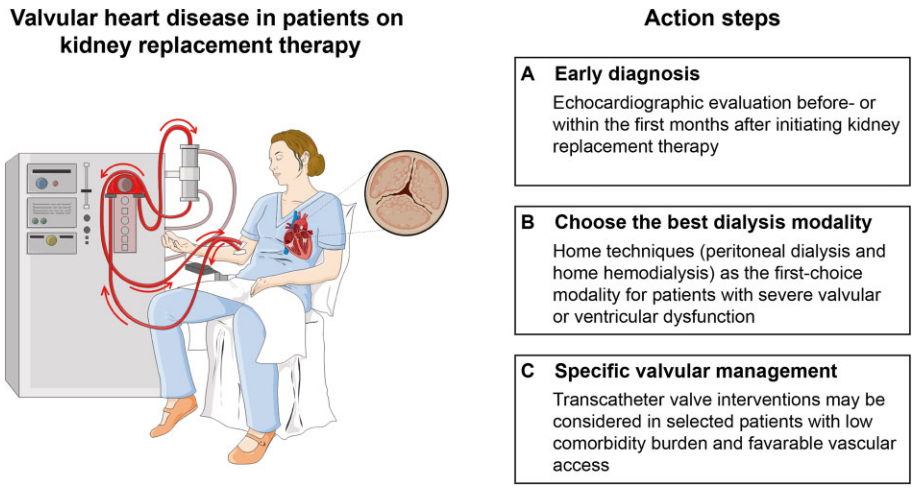

Figure 1: Action steps to improve diagnosis and management of VHD in dialysis recipients.

of significant left-sided valvular lesions. Among them, mitral regurgitation was the most common VHD (19.2%), followed by aortic stenosis (6.4%) and aortic regurgitation (5%). Moreover, 136 (26.1%) patients had a left ventricular ejection fraction ≤45%, and 63 (12%) had combined VHD and left ventricular systolic dysfunction [10]. Although the study has the inherent limitations of the retrospective cross-sectional analysis, the results are relevant for clinical practice by showing the burden of left-sided heart disease in a large cohort of patients on kidney replacement therapy.

Calcification of the extracellular matrix of the aortic valve leaflets and the annulus and subvalvular apparatus of the mitral valve is the unifying pathophysiological feature of left-sided valvular degeneration [11, 12]. Although calcification was earlier believed to be a passive and unmodifiable degenerative process, it is now recognized as an active disease process driven by several factors such as chronic inflammation, lipoprotein deposition, active calcification and renin–angiotensin system activation (all common in CKD patients) [11, 12]. However, although multiple CKD-related factors have been proposed as triggers and accelerating mechanisms for valve degeneration/calcification (uremic milieu, hyperphosphatemia, calcium-phosphate product, parathyroid hormone, decreased Klotho levels, β2-microglobulin, calcium supplements, excessive vitamin D supplementation and calcium-based phosphate binders), the exact contribution of each component and their synergy remains to be clarified [2]. Moreover, another important mechanism associated with valve dysfunction in patients on renal replacement therapy is the shear stress related to the hemodynamic milieu of CKD patients and the increased volume load linked to systemic shunting in patients with arteriovenous fistulas (AVF) [3]. Although AVF has been classically considered a risk factor for left-sided heart disease progression and dysfunction, right-sided involvement, particularly tricuspid regurgitation, may be equally common and often unappreciated [3]. This aspect is especially relevant in patients with concomitant right-sided heart failure and pulmonary hypertension, in which an AVF may accelerate disease progression.

Considering the complex, cross-related and multifactorial mechanisms behind the natural history of VHD in CKD patients, it is necessary to modify the action steps to move away from the traditional "one-size-fits-all" approach and provide more individualized or personalized care according to the patient profile:

(i) Diagnosis. The clinical practice guidelines for cardiovascular disease in dialysis recommend an echocardiographic evaluation for all dialysis patients 1–3 months after the start of renal replacement therapy and in intervals of 3 years subsequently, regardless of the symptoms [9]. However, this indication is not included as a criterion for transthoracic echocardiography in current cardiology guidelines [13, 14], and such screening is not widely incorporated into clinical practice. In fact, the most common approach to managing cardiac-related complications in patients on kidney replacement therapy is a reactive disease intervention once symptoms develop. In our opinion, echocardiographic screening in this high-risk population may offer a window of opportunity for early detection of cardiac-related alterations that may influence dialysis management or transplant candidacy, prompt care coordination, closer follow-up and optimization of specific therapies to prevent or delay disease progression.

(ii) Dialysis modality. In the study by Elewa *et al.*, most patients with VHD were on hemodialysis (88.6%), with in-center as the most frequent modality setting (75.4%) and AVF as the most common access type (56%) [10]. While conventional thrice-weekly in-center HD programs may be well tolerated for most patients with mild or moderate VHD, it should not be the first-choice modality for those with severe valvular/ventricular dysfunction because of hemodynamic stability concerns during sessions (which often limits fluid removal) and the possibility of interdialytic volume overload [15]. In this framework, home techniques (peritoneal dialysis and home hemodialysis) provide a more physiological approach to volume removal and solute clearance, which may ultimately translate into improved cardiovascular outcomes [15].

(iii) VHD management. As is too often the case with patients on dialysis, evidence remains elusive about whether, when or how to manage individuals with severe VHD and concomitant kidney failure. In patients with severe aortic stenosis on dialysis, available evidence suggests that mortality rates after transcatheter aortic valve replacement are significantly

higher than comparable high-risk nondialysis patients [16, 17]. However, it is important to highlight that the comorbidity burden and the need for alternative access to the femoral approach strongly influenced the prognosis [16, 18]. Similar findings have been observed in high–surgical risk CKD patients with severe mitral regurgitation treated with edge-to-edge mitral valve repair [19, 20]. Therefore, efforts should concentrate on identifying the factors associated with survival after transcatheter valve intervention in patients on dialysis to identify the subgroup that would benefit the most (fewer comorbidities, single-valve dysfunction, suitable vascular access). On the contrary, it would be reasonable to recommend against the procedure for highly comorbid patients, shifting the discussion to optimizing dialysis modality (peritoneal dialysis) and enhancing symptoms and quality of life through a multidisciplinary strategy that includes collaborative decision-making, palliative care planning, and psychological and social support [21]. Further dedicated randomized clinical trials evaluating the feasibility, safety and efficacy of different approaches for the management of VHD in patients with advanced CKD are necessary to reduce the uncertainty.

In summary, patients with kidney failure on dialysis have a high risk of developing cardiac morphological and functional alterations that significantly impact individual patient management and outcomes. Therefore, we strongly believe that a proactive-based approach focusing on identifying these alterations in a prompt manner combined with a multidisciplinary team strategy aiming to provide coordinated and specialized care would be a positive shift towards improving patient outcomes and optimizing healthcare resources. Although some may argue that this strategy is like opening Pandora's box, when it is obvious that the goals cannot be reached, don't adjust the goals; adjust the action steps (Fig. 1).

CONFLICT OF INTEREST STATEMENT

J.N. is a member of the *CKJ* editorial board. The other authors have no conflict of interest to declare.

AUTHORS' CONTRIBUTIONS

All authors meet each of the following characteristics defined by the International Committee of Medical Journal Editors in the criteria for authorship of scientific articles: substantial contributions to the conception or design of the manuscript; drafting the work or revising it critically for important intellectual content; final approval of the version to be published; and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the manuscript are appropriately investigated and resolved.

ETHICAL APPROVAL

This article does not contain any studies with human participants or animals performed by any of the authors.

(See related article by Elewa et al. Left-sided valvular heart disease in dialysis recipients: a single-centre observational study. *Clin Kidney J* (2023) 16: 1092–1101.)

REFERENCES

1. Romero-González G, Ravassa S, González O *et al*. Burden and challenges of heart failure in patients with chronic kidney disease. A call to action. *Nefrologia* 2020;**40**:223–36. https://doi.org/10.1016/j.nefro.2019.10.005.
2. Ureña-Torres P, D'Marco L, Raggi P *et al*. Valvular heart disease and calcification in CKD: more common than appreciated. *Nephrol Dial Transplant* 2020;**35**:2046–53. https://doi.org/10.1093/ndt/gfz133.
3. Marwick TH, Amann K, Bangalore S *et al*. Chronic kidney disease and valvular heart disease: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Kidney Int* 2019;**96**:836–49. https://doi.org/10.1016/j.kint.2019.06.025.
4. Saran R, Robinson B, Abbott KC *et al*. US Renal Data System 2017 annual data report: epidemiology of kidney disease in the United States. *Am J Kidney Dis* 2018;**71**:A7. https://doi.org/10.1053/j.ajkd.2018.01.002.
5. Varma R, Aronow WS, McClung JA *et al*. Prevalence of valve calcium and association of valve calcium with coronary artery disease, atherosclerotic vascular disease, and all-cause mortality in 137 patients undergoing hemodialysis for chronic renal failure. *Am J Cardiol* 2005;**95**:742–3. https://doi.org/10.1016/j.amjcard.2004.11.025.
6. Raggi P, Bellasi A, Gamboa C *et al*. All-cause mortality in hemodialysis patients with heart valve calcification. *Clin J Am Soc Nephrol* 2011;**6**:1990–5. https://doi.org/10.2215/CJN.01140211.
7. Vahanian A, Beyersdorf F, Praz F *et al*. 2021 ESC/EACTS guidelines for the management of valvular heart disease: developed by the Task Force for the management of valvular heart disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2022;**43**:561–632. https://doi.org/10.1093/eurheartj/ehab395.
8. Otto CM, Nishimura RA, Bonow RO *et al*. 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation* 2021;**143**:E72–227. https://doi.org/10.1161/CIR.0000000000000923.
9. K/DOQI Workgroup. K/DOQI clinical practice guidelines for cardiovascular disease in dialysis patients. *Am J Kidney Dis* 2005;**45**:S1–153.
10. Elewa M, Mitra S, Jayanti A. Left sided valvular heart disease in dialysis recipients: a single centre observational study. *Clin Kidney J;* published online 30 January 2023; https://doi.org/10.1093/ckj/sfad020.
11. O'Brien KD. Pathogenesis of calcific aortic valve disease: a disease process comes of age (and a good deal more). *Arterioscler Thromb Vasc Biol* 2006;**26**:1721–8. https://doi.org/10.1161/01.ATV.0000227513.13697.ac.
12. Rutkovskiy A, Malashicheva A, Sullivan G *et al*. Valve interstitial cells: the key to understanding the pathophysiology of heart valve calcification. *J Am Heart Assoc* 2017;**6**:e006339. https://doi.org/10.1161/JAHA.117.006339.
13. Steeds RP, Garbi M, Cardim N *et al*. 2014–2016 EACVI Scientific Documents Committee; 2014–2016 EACVI Scientific Documents Committee. EACVI appropriateness criteria for the use of transthoracic echocardiography in adults: a report of literature and current practice review. *Eur Heart J Cardiovasc Imaging* 2017;**18**:1191–204. https://doi.org/10.1093/ehjci/jew333.

14. American College of Cardiology Foundation Appropriate Use Criteria Task Force; American Society of Echocardiography *et al*. ACCF/ASE/AHA/ASNC/HFSA/HRS/SCAI/SCCM/SCCT/SCMR 2011 Appropriate Use Criteria for Echocardiography. A report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, American Society of Echocardiography, American Heart Association, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, Society of Critical Care Medicine, Society of Cardiovascular Computed Tomography, Society for Cardiovascular Magnetic Resonance American College of Chest Physicians. *J Am Soc Echocardiogr* 2011;**24**:229–67. doi: 10.1016/j.echo.2010.12.008.
15. Sarnak MJ, Auguste BL, Brown E *et al*. American Heart Association Council on the Kidney in Cardiovascular Disease; Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Cardiovascular Radiology and Intervention; Council on Clinical Cardiology; Council on Hypertension; and Council on Lifestyle and Cardiometabolic Health. Cardiovascular Effects of Home Dialysis Therapies: a scientific statement from the American Heart Association. *Circulation* 2022;**146**:e146–64. doi: 10.1161/CIR.0000000000001088.
16. Szerlip M, Zajarias A, Vemalapalli S *et al*. Transcatheter aortic valve replacement in patients with end-stage renal disease. *J Am Coll Cardiol* 2019;**73**:2806–15. https://doi.org/10.1016/j.jacc.2019.03.496.
17. Ogami T, Kurlansky P, Takayama H *et al*. Long-term outcomes of transcatheter aortic valve replacement in patients with end-stage renal disease. *J Am Heart Assoc* 2021;**10**:e019930. https://doi.org/10.1161/JAHA.120.019930.
18. Hahn J, Virk HUH, Al-Azzam F *et al*. Outcomes of transcatheter aortic valve implantation in patients with chronic and end-stage kidney disease. *Am J Cardiol* 2022;**164**:100–2. https://doi.org/10.1016/j.amjcard.2021.10.039.
19. Panchal HB, Stone GW, Saxena A *et al*. In-hospital outcomes after transcatheter edge-to-edge mitral valve repair in patients with chronic kidney disease: an analysis from the 2010-2016 National inpatient sample. *Catheter Cardiovasc Interv* 2021;**98**:1177–84. https://doi.org/10.1002/ccd.29712.
20. Khan MZ, Zahid S, Khan MU *et al*. In-hospital outcomes of transcatheter mitral valve repair in patients with and without end stage renal disease: a national propensity match study. *Catheter Cardiovasc Interv* 2021;**98**:343–51. https://doi.org/10.1002/ccd.29517.
21. De la Espriella R, Cobo M, Ronco C *et al*. Practical approaches to building up a cardiorenal clinic. *Clin Kidney J* 2022;sfac258. https://doi.org/10.1093/ckj/sfac258.