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Aortic stenosis in patients with kidney failure: Is there an advantage for a *PD-first policy*?

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Abstract

Aortic stenosis (AS) is the most common valvular disease. It is twice as prevalent in patients with kidney failure as compared to the general population. In addition, AS progresses at a faster rate and is associated with a higher risk of death and poorer quality of life in patients on dialysis. Chronic kidney disease–mineral and bone disorder (CKD-MBD), inflammation, and hemodynamic disturbances contribute to the pathophysiology and progression of AS. Whether the type of dialysis modality, that is, hemodialysis (HD) versus peritoneal dialysis (PD), has a differential impact on the development and progression of AS in patients with kidney failure remains debated. Recent data indicate that the prevalence of valvular calcifications might be lower and the development of AS delayed in PD patients, as compared to those treated with HD. This could be accounted for by several mechanisms including reduced valvular shear stress, better preservation of residual kidney function (with better removal of protein-bound uremic toxins and CKD-MBD profile), and lower levels of systemic inflammation. Given the high morbidity and mortality rates related to interventional procedures in the population with kidney failure, surgical and transcatheter aortic valve replacement should be considered in selected patients with severe AS. Strategies slowing down the progression of aortic valve remodeling should remain the cornerstone in the management of individuals with kidney failure and mild to moderate AS. This review explores the potential benefits of PD in patients with kidney failure and AS and provides some clues to help clinicians in the decision-making process when options for kidney replacement therapy are considered in patients with AS.

Keywords

Aortic stenosis, peritoneal dialysis, residual kidney function, valvular calcification

Introduction

Aortic stenosis (AS) results from fibro-calcific remodeling of valvular leaflets, resulting in progressive narrowing of the aortic valve opening. AS is the most common form of severe valvular disease and its prevalence is substantially higher in dialysis patients compared to the general population (7.8% vs. 3.5%).[1] Pathophysiological remodeling of aortic valve also occurs approximately 10 years earlier in life, progresses more rapidly, and is associated with poorer outcomes in patients on dialysis.[2–4] In addition, dialysis vintage is an independent predictor of aortic valve calcification.[5]

The reason why AS progresses faster in patients with kidney failure remains ill-defined. Interestingly, the prevalence of aortic valvular calcification is lower in peritoneal dialysis (PD) than in hemodialysis (HD) patients and its development is delayed,[6–8] suggesting a major role for the dialysis modality in the evolution of the disease. PD is an effective kidney replacement therapy that sustains life of patients with kidney failure and is associated with a survival similar to HD.[9] However, PD has many advantages over in-center HD, including patients' empowerment, lack of

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transportation to the hospital, preservation of residual kidney function (RKF), and reduced costs, contributing to make it the first home-based dialysis modality worldwide. Recent data suggesting that PD associates with lower prevalence and delayed progression of AS warrant an in-depth and critical review of the topic.

This review provides clinicians first with a general overview on AS in dialysis patients to help in the decision-making process when kidney replacement therapy options are considered, and second with a discussion of the potential benefits of PD over HD in patients with kidney failure and AS.

Epidemiology of AS in dialysis

Compared to the general population, the prevalence of AS is twice as high in dialysis patients,[1] independently from age, sex, and comorbidities (odds ratio 2.51, 95% confidence interval (CI) 1.90–3.32; $p < 0.01$).[10] In patients with kidney failure, AS is much more frequently from degenerative (91%) than bicuspid origin,[10] whereas bicuspid AS is found in 20% of subjects without chronic kidney disease (CKD). AS also progresses faster in patients on dialysis versus those without kidney disease. In a retrospective case-control study, after a mean follow-up of 1.6 years, the reduction in valvular area was -0.19 versus -0.07 cm^2/year ($p < 0.001$) and the valvular gradient increased by 4.9 versus 2.5 mmHg/year ($p = 0.04$) among patients on dialysis versus controls, respectively.[4] Similarly, a faster decrease in valvular area was reported in a small cohort of dialysis (13 HD and 3 PD) compared to non-dialysis patients after a mean follow-up of 2.7 years.[11] In a study comparing 74 dialysis (69 HD and 5 PD) patients with 79 age- and gender-matched controls with normal kidney function, accelerated AS progression, defined as a valve area loss >0.128 cm^2/year, was found in 35% of the dialysis versus 18% in the control subjects during a 48-month follow-up.[10] Finally, it has been suggested that severe AS symptoms appear faster in patients with kidney failure than in non-uremic people, resulting in earlier death or surgical referral.[3]

Clinical presentation of AS in dialysis

AS is a progressive disease for which clinical manifestations appear at a late stage, and interpretation of clinical symptoms is challenging. Shortness of breath, angina, and syncope are alarming signs of severe AS. At physical examination, an ejectional, intense, rough, and rasping murmur at the aortic region or low systolic blood pressure with a narrow pulse pressure may suggest AS. Finally, a low intensity or absence of second heart sound (S2) is typically found in tight AS. In dialysis patients, nonvalvular causes of murmurs, including anemia, fistulae, or hyperdynamic circulation, can make the interpretation of heart sounds difficult. Palpatory throbbing reflects the presence of a hemodynamically significant AS. However, the murmur can be almost inaudible in case of AS with low flow. It is therefore essential to rely on transthoracic echocardiography (TTE) to make an accurate, quantitative AS diagnosis.

Pathophysiology and risk factors of AS in dialysis patients

Whereas AS development has long been considered to result from passive deposition of calcium and phosphate salts on the valve leaflets, it is now recognized as an active process, involving both pro- and anti-calcific factors.

The aortic valve undergoes major biomechanical constraints as it opens and closes approximately 3 billion times during a human lifetime. It is composed of three thin and flexible triangular cusps. As shown in Figure 1, cusps are composed of an outer layer of valvular endothelial cells (VECs) surrounding three layers of extracellular matrix in which valvular interstitial cells (VICs) are found. The innermost part, called "ventricularis," is mainly composed of elastin fibers aligned radially, perpendicularly to the free edge of the valve, and is the major contributor to tissue elasticity. The external part called "fibrosa" essentially comprises collagen fibers parallel to the free edge, to make it resistant to mechanical stress. The layer between these two barriers, called "spongiosa," is rich in glycosaminoglycans and proteoglycans, which dissipate shocks and absorb shear forces.[12] All layers are disorganized during AS development and all types of cells detrimentally participate in the reshaping.[13] Traditional cardiovascular risk factors such as age, diabetes, smoking, dyslipidemia, and obesity are associated with the development of AS[14] but specific risk factors related either to impaired kidney function or to dialysis modalities themselves are also associated with faster AS progression in dialysis patients.

CKD-mineral and bone disorder (CKD-MBD) is well known to be associated with valvular calcification in HD patients.[5] In PD, multivariate regression analysis revealed that elevated serum calcium and phosphorus levels were independent factors positively correlated with the risk of valvular calcification.[15] In vitro, an increase in phosphate concentration is responsible for VICs activation enabling them to differentiate toward an osteoblastic phenotype. This phenomenon called "osteogenic transition" is characterized by an increased expression of osteogenic factors, such as RunX2 (Runt-related transcription factor 2), Osx (Osterix), and differentiation factors such as BMP2 (bone morphogenetic protein 2), usually found in osteoblasts.[16] Activated VICs participate in the synthesis of metalloproteinases and cathepsins which in turn degrade collagen and elastin fibers into pro-inflammatory peptides leading to a pathological remodeling of the extracellular aortic valve matrix. The mechanisms involved in calcium crystal formation in valve leaflets are poorly understood, but apoptotic bodies derived from VICs may act as nucleating

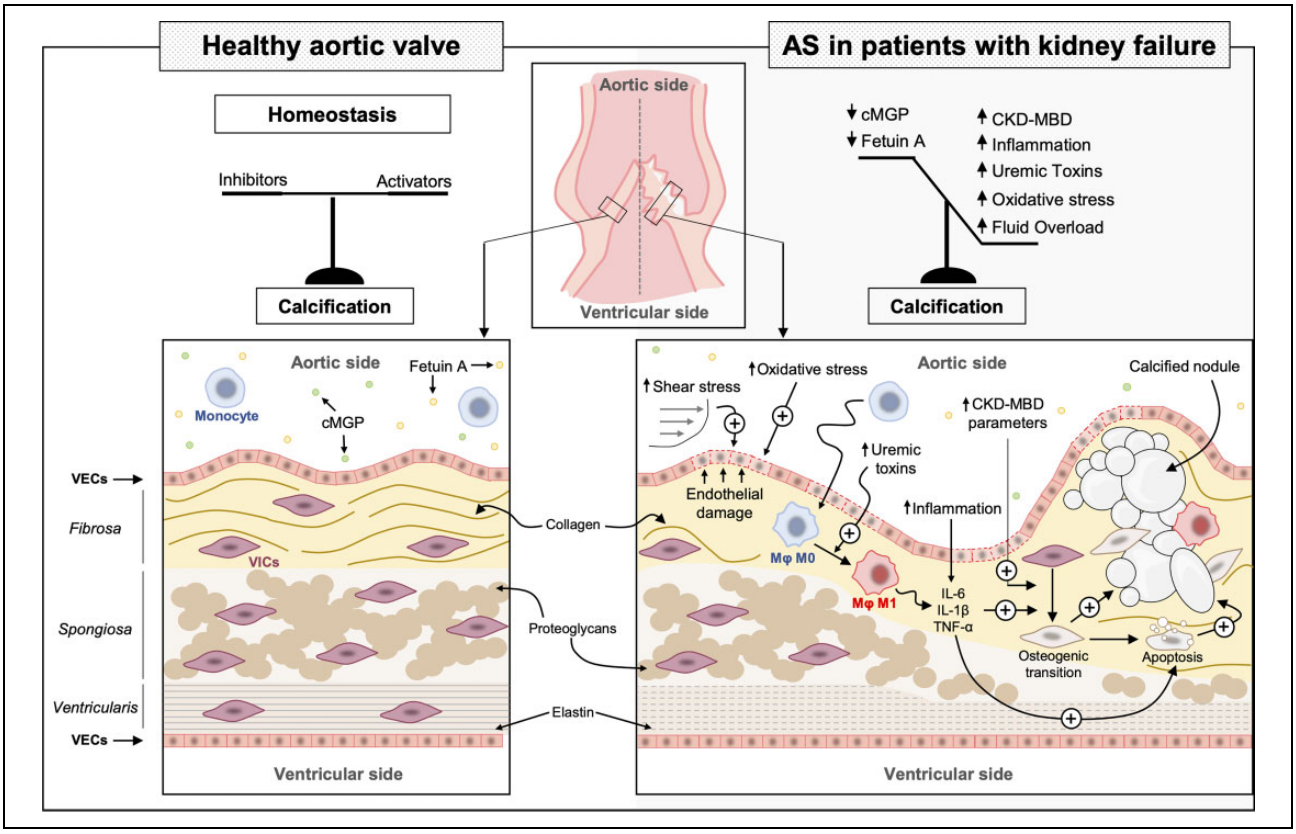

Figure 1. Histological characteristics of healthy valve and molecular, cellular, and biomechanical mechanisms of aortic valve calcification in CKD.

Aortic valve cusps are composed of an outer leaflet of VECs surrounding three layers of extracellular matrix containing VICss. The innermost part (*ventricularis*) is mainly composed of elastin fibers and external part (*fibrosa*) essentially comprises collagen fibers. *Spongiosa* is rich in glycosaminoglycans and proteoglycans, which dissipate shocks and absorb shear forces. In a healthy aortic valve, the balance between pro- and anti-calcific parameters (e.g. cMGP, fetuin A) is maintained. All these layers are disorganized during aortic valve calcification and all types of cells detrimentally participate in the reshaping. In patients with kidney failure, specific pathways are involved in valvular calcification. Exacerbated shear stress experienced by VECs plays an important role in the early development of AS by promoting tissue remodeling after endothelial damage. Exposure of infiltrated monocytes/macrophages to uremic toxins accumulated within the aortic valve promotes macrophages polarization toward a pro-inflammatory phenotype M1 characterized by increased expression of inflammatory cytokines such as IL-6, IL-1β, and TNF-α. The latter cytokines, together with systemic inflammation, promote osteogenic transition and apoptosis of VICs. CKD-MBD induces osteoblast-like formation of VICs. Altogether, these parameters lead to pathological remodeling of the different aortic valve layers. Reduced concentration of fetuin A inhibits the resorption of cardiovascular Ca/P nanocrystals. AS: aortic stenosis; CKD: chronic kidney disease; VIC: valvular interstitial cell; VEC: valvular endothelial cell; cMGP: carboxylated matrix Gla protein; Mφ: macrophage; IL: interleukin; TNF: tumor necrosis factor; CKD-MBD: chronic kidney disease–mineral and bone disorder.

structures for calcium crystal formation. In PD, parathyroid hormone elevation is associated with increased aortic valve calcification.[8,17] Moreover, parathyroid hormone level was significantly higher in patients with rapid progression of AS.[10] In contrast, fibroblast growth factor 23 concentration does not seem to correlate with valvular calcifications.[18] No study has evaluated the association, if any, of 25-hydroxyvitamin D_3 or sclerostin with AS, even though they play a key role in vascular calcification development.[19,20]

The circulating calcification inhibitors, fetuin A and matrix Gla protein (MGP), also play a major protective role in the process of valvular mineralization as potent inhibitors of ectopic soft tissue calcification. Fetuin A forms Ca^{2+} and Pi containing colloidal complexes in serum, termed calciprotein particles. Primary calciprotein particles prevent $Ca^{2+} \times$ Pi precipitation and crystal growth and facilitate the elimination of mineral nanocrystals from the extracellular fluid.[21] Low circulating levels of fetuin A are associated with rapid AS progression both in the general population[22] and dialysis patients.[17] MGP is a protein expressed primarily in the cartilage, heart, and vessels and has an inhibitory action on the development of cardiovascular calcifications. It turns into its active form called "carboxylated MGP" (cMGP) once its glutamate residues are carboxylated by vitamin K. In addition to reducing calcium precipitation, cMGP also reduces the osteogenic transition of VICs involved in calcification.[23] Interestingly, the level of cMGP is lower in CKD than in healthy subjects.[24]

Systemic chronic low-grade inflammation, highly prevalent in patients with kidney failure and chronic dialysis, also has detrimental effects in the calcification process[25,26] and contributes to both mortality and cardiovascular morbidity in dialysis.[27] It doubles the risk of valvular calcification, independently from CKD-MBD.[17] Macrophages derived from circulating monocytes are major contributors of immune and inflammatory responses in vascular and valvular walls. Once they infiltrate the valvular wall, macrophages can adapt their functions to their new environment.[28] In particular, macrophages switch toward a classically highly pro-inflammatory activated phenotype (M1) in response to Th1 cytokines (e.g. interferon-γ, interleukin-6), or toward an alternatively anti-inflammatory phenotype (M2) when facing Th2 cytokines (e.g. interleukin-4 or -10). The production of pro-inflammatory cytokines by M1 macrophages is associated with increased human aortic valve calcification.[29] Finally, chronic inflammation in dialysis patients promotes osteogenic transition of vascular cells, and formation of apoptotic bodies, all able to initiate the mineralization process in cardiac valves.[25,28]

The impact of uremic toxins, and more specifically indoxyl sulfate, in AS development has only recently been studied though their retention appears to exert major deleterious cardiovascular effects.[30,31] Ninety percent of circulating indoxyl sulfate is bound to plasma proteins and its dialysis clearance is a challenge. An increase in its plasma level is associated with its accumulation within the cardiac tissue of uremic mouse.[32] In vitro, macrophages exposure to indoxyl sulfate promotes the expression of macrophage M1 markers and the production of both inflammatory cytokines (such as interleukin-6) and the chemo-attractant factor CCL2.[33] Taken together, these data suggest that inflammation induced by uremic toxins might contribute to the extensive valvular calcification observed in patients with kidney failure. Due to difficulties in removing indoxyl sulfate, one needs to consider ways to limit its production. Indoxyl sulfate is a product of tryptophan degradation by the bacteria of gut microbiota. CKD profoundly alters the composition of the gut microbiome,[34] which in turn contributes to uremic toxicity, inflammation, and various other complications of CKD. In this context, acting on gut microbiota should be promising to reduce both vascular and valvular calcifications in uremic patients.

Finally, fluid overload which is very common in dialysis patients exacerbates the shear stress experienced by VECs. It promotes tissue remodeling in the early phases of AS development, increases inflammation, and thus enhances the calcification process.[35]

Figure 1 illustrates all the mechanisms involved in the development and progression of AS in dialysis patients.

Assessment of AS in dialysis patients

TTE allows to visualize the calcified leaflets, specify the bi- or tricuspid anatomy of the valve, and measure the effective valvular surface area and the consequences of AS such as dilation of the ascending aorta or left ventricular hypertrophy. Finally, it provides left ventricular ejection fraction measurement. Doppler echocardiography contribution is mandatory since it evaluates disease severity from transvalvular pressure gradients, and pulse wave velocity measurements.

The use of stress TTE, when feasible, helps clarifying AS diagnosis, especially in apparently asymptomatic patients, by unmasking an increase in the average transvalvular pressure gradient or alterations in left ventricular function. The presence of left ventricular hypertrophy in the absence of hypertension is a major marker of AS though it has a low positive predictive value in CKD patients because of its high prevalence.[36]

Once AS is diagnosed, TTE is the essential monitoring tool. In patient with normal renal function and asymptomatic severe AS (valve area under 1.0 cm^2 and mean aortic gradient upper 40 mmHg), two TTE are recommended per year[37] supplemented by investigations based on change in patient symptomatology. Evolution toward a fast narrowing valve area is rather frequent in dialysis patients. Nevertheless, as its main clinical manifestations appear at a late stage, aortic valve replacement (AVR) should be considered according to echocardiographic data in asymptomatic patients.[37] Because of that, a close TTE monitoring is required: two or even better three TTE per year should be considered in dialysis patients with severe AS or moderate AS (valve area of 1.0–1.5 cm^2 or mean aortic gradient of 25–40 mmHg) with rapid progression (peak velocity progression >0.3 m/s per year).

Transesophageal echocardiography provides additional assessment of concomitant mitral valve abnormalities before and after AVR.[37] Non-gated chest computed tomography provides valuable information on dimensions and geometry of the aortic root, ascending aorta and on calcification extent. The use of aortic valve calcium scoring provided powerful prognostic information in large cohorts of patients without severe CKD.[38] Such a scoring may be helpful when TTE measurements are discordant, particularly in low-flow/low-gradient AS. Coronary angiography is indicated as part of the assessment of AS when open surgery or transcatheter AVR is planned, to determine if coronary revascularization is indicated too.[39] The measurement of the level of natriuretic peptides used in the general population to predict the outcome of severe AS[40] is usually not helpful in dialysis patients,[41] in whom it is very frequently elevated.

AVR or conservative management in dialysis patients?

Despite the poor prognosis of AS, no pharmacological intervention has been demonstrated to prevent or slow down AS progression in dialysis patients. The European Society of Cardiology recommends early management of AS in symptomatic patients with the exception of patients

Table 1. Prevalence of aortic valve calcification in patients with kidney failure.[a]

Study	Year	Dialysis modalities	Number of patients	Age (years)	Time on dialysis (months)	Aortic valve calcification (%)
Braun et al.[48]	1996	HD	92	55 ± 11	77 ± 70	55
Ribeiro et al.[49]	1998	HD	92	59 ± 17	53 ± 46	52
Wang et al.[6]	**2001**	**CAPD**	**137**	**56 (22–77)[b]**	**45 (5–151)[b]**	**24**
Ventura et al.[50]	2002	HD	135	58 ± 17	80 ± 49	78
Wang et al.[7]	**2003**	**CAPD**	**192**	**55 ± 12**	**39 ± 31**	**32**
Holden et al.[51]	2007	HD	108	63 ± 15	47 ± 44	85
Ikee et al.[52]	2010	HD	112	67 ± 10	95 ± 67	75
Raggi et al.[53]	2011	HD	144	55 ± 15	31[c] (IQR 17–68)	44
Ávila-Díaz et al.[8]	**2013**	**APD/CAPD**	**124**	**43 ± 13**	**12 ± 1**	**33**
Wang et al.[15]	**2013**	**APD/CAPD**	**117**	**57 ± 15**	**31 (24–40)**	**32**

APD: automated peritoneal dialysis; CAPD: continuous ambulatory peritoneal dialysis; HD: hemodialysis; PD: peritoneal dialysis; IQR: interquartile range; SD: standard deviation.
[a]Results for age and time on dialysis are expressed as mean ± SD. Studies regarding PD are in bold.
[b]Range.
[c]Median.

with a life expectancy of less than 1 year and patients in whom advanced age or comorbidities could lead to severe interventional complications or death.[37]

At this stage, AS management mainly consists in surgical or percutaneous valve replacement. The recent improvement of surgical and anesthetic techniques has increased the proportion of dialysis patients eligible for valve replacement and decreased in-hospital mortality.[42] However, dialysis remains a preoperative predictor not only of long-term mortality after surgical AVR but also of in-hospital mortality which remains twice as high (11.8% and 6.2%, $p < 0.0001$) in dialysis versus non-dialysis patients, respectively.[43]

With the advent of transcatheter AVR for patients at high surgical risk, valve replacement has become more frequent in the dialysis population[44] with encouraging results and decreased morbidity and mortality compared with surgery.[45] Still, hospital mortality after transcatheter AVR remains twice as high (8.2% vs. 4%, $p < 0.001$) in dialysis patients compared with patients without renal disease.[44,46]

Nevertheless, valve replacement, whether surgical or percutaneous, improves the prognosis of dialysis patients compared to conservative treatment. In a retrospective study comparing 405 HD patients with severe AS, early AVR reduced 5-year mortality and especially the risk of sudden death (60.6% vs. 75.5%, $p < 0.001$) as compared to the conservative management.[47] Recent data suggest that proceeding to AVR before starting dialysis would be beneficial.[44] Altogether, the increased risk of perioperative death should prompt to stratify dialysis patients eligible for transcatheter AVR to avoid their exposure to a futile risk taking into account that (i) the injection of large amounts of contrast agents during the procedure will contribute to loss of RKF and that (ii) improved renal perfusion might improve kidney function if AS is successfully treated.

There are currently no comparative data on the outcome after surgical or transcatheter AVR in HD versus PD patients.

Are there any data to support an advantage of PD over HD in patients with AS?

Epidemiological observations

To date, data available concerning the potential benefit of PD over HD on AS development are scarce. Nevertheless, in a prospective cohort of 124 incident PD patients, aortic valve calcification was detected by M-mode bidimensional echocardiogram in less than one-third of the patients after a mean follow-up of 12.3 months.[8] Surprisingly, in multivariable analysis, age and diabetes were not independent risk factors for aortic valve calcification, but patients were younger than in other studies. In 2003, Wang et al. reported a 32% prevalence of aortic valvular calcification in a prospective cohort of 192 patients after 39 months of continuous ambulatory peritoneal dialysis (CAPD).[7] These results were consistent with the 32% prevalence reported in 117 prevalent automated peritoneal dialysis (APD) and CAPD patients with a follow-up of 31 months.[15] As a matter of comparison, a prevalence of aortic valvular calcification ranging between 44% and 85% has been reported in various studies on HD patients.[48–53] Though it is always difficult to make comparisons between different populations, mean age, causes of primary kidney diseases, and preexisting comorbid conditions were similar in patients from these HD and PD studies (Table 1); this might suggest some advantage of PD over HD in AS progression. A recent study including 30 stable PD and 34 HD patients showed significantly higher prevalence of valve calcification in HD compared to PD patients (70.6% vs. 29.4%) and strengthened data concerning the benefit of PD.[54] In this study, diabetic nephropathy was the underlying cause of kidney failure in 14.1% of patients (2 HD and 7 PD patients), and although PD cohort was older than HD group (57 vs. 51 years), their higher RKF could potentially

overcome the negative age impact.[54] Finally, it is also interesting to note in this context that cardiac (valvular and coronary) calcifications are more prevalent in children receiving HD as compared to those on PD.[55]

How PD might limit the development and progression of AS?

Though a strong causative association between valvular calcification prevalence and dialysis modality has not been demonstrated so far, some theoretical and pathophysiological mechanisms discussed below point to some advantages of PD over HD regarding AS development and progression.

Better CKD-MBD control. CKD-MBD parameters are associated with the increased incidence and progression of AS. The Netherlands Cooperative Study on Adequacy of Dialysis has shown that hyperphosphatemia is associated with similar cardiovascular complications in PD and HD.[56] Nevertheless, epidemiological studies showed lower phosphorus concentrations in PD as compared with HD patients,[54,56,57] further keeping in mind that mid-day phosphorus (in PD patients) were compared in these studies to pre-dialysis concentrations (in HD patients). In the recent study by Evenepoel et al., including 79 HD and 61 PD patients, total mass removal of phosphorus was significantly higher in PD as compared to HD (2799 $\pm$ 1592 mg/week in PD vs. 2178 $\pm$ 746 in HD, $p = 0.007$) patients.[58]

As mentioned above, an imbalance between pro- and anti-calcific factors in patients with kidney failure increases the calcification process. Specifically, dialysis subjects with accelerated valvular calcification had lower serum fetuin A levels.[59] In this respect, higher circulating levels of fetuin A in PD than in HD patients (0.73 $\pm$ 0.16 vs. 0.59 $\pm$ 0.15, $p < 0.0001$, respectively) have been documented in a large cohort study.[60] MGP levels in HD and PD patients have not been well documented though higher concentrations of the inactive form have been found in HD patients as compared to PD patients.[61] Reduction of the MGP active form (by the inhibition of its enzymatic gamma-carboxylation) is also observed in patients given vitamin K antagonists, a prescription more likely to occur in HD than in PD patients, because of a higher prevalence of atrial fibrillation[62] in the HD population.

Lower inflammatory status. Microinflammation in HD is ascribed to the contact of blood with non-biocompatible dialyzers and various pyrogens in dialysate. Although this has improved significantly over the last two decades, HD patients still show significantly higher levels of C-reactive protein and other inflammation markers compared to the PD population. In a recent prospective cohort study on 228 HD and 80 PD prevalent patients with similar baseline clinical characteristics (except for dialysis duration), circulating concentrations of inflammatory markers were higher in the HD population.[63] C-reactive protein significantly increases at initiation of HD but not of PD, despite similar baseline inflammatory cytokine status.[64] Finally, lower accumulation of oxidative products and lower losses of antioxidants are observed in PD as compared to HD.[65] For those reasons, PD could be considered as a more biocompatible, less inflammatory, and thus less pro-calcifying form of dialysis compared to HD.

Better removal of uremic toxins. Experimental and clinical studies suggest a major impact of uremic toxins in the development of cardiovascular calcifications. A Chinese retrospective study documented lower serum indoxyl sulfate level in CAPD than in low-flux HD patients (28.05 $\pm$ 13.98 vs. 39.64 $\pm$ 18.25 μg/mL, $p < 0.001$).[66] In this study, the concentration of indoxyl sulfate was 40% lower in patients with RKF, a finding more common in PD patients than in HD.[66] In PD modalities, CAPD might improve the clearance of uremic toxins compared to APD, despite lower dialysate volumes, probably due to longer dwell times.[67,68]

In the context of uremic toxicity, the influence of different primary kidney diseases, diet, antibiotics, but also dialysis modalities, on microbiota alterations is of interest. The composition of the intestinal microbiota, mainly *Lactobacillus* and *Bifidobacterium* species, differs between PD and HD patients, and healthy controls.[69,70] A concomitant increased proliferation of potentially pathogenic species and decreased proliferation of beneficial species have been observed in HD, but to a lesser extent in PD patients. Interestingly, these trends have been associated with elevated systemic inflammation in HD patients.[70]

Better RKF. There is a growing body of evidence that maintenance of RKF must be a major goal in dialysis. Interestingly, the preservation of RKF is strongly linked to cardiovascular mortality. In the CANUSA study, a 250 mL increment of daily urine volume decreased the relative risk of all-cause mortality by 36%.[71] Comparing 30 PD with 34 HD patients, Rroji et al. found a close inverse correlation between the presence of valvular calcifications and the mean of creatinine and urea clearance ($r = -0.304$, $p = 0.004$).[54] Similar findings were reported in another cohort where each increase of 1 mL/min in residual glomerular filtration rate decreased the risk of valvular calcification by 28%.[72] Many studies have highlighted the beneficial effect of PD on RKF maintenance.[73,74] In patients starting dialysis, HD is associated with a 24–80% higher rate of RKF loss as compared with PD.[74] The maintenance of RKF is also strongly associated with phosphate balance control.[75] It is therefore likely that, in the non-anuric population, the lower prevalence of valvular calcifications observed in PD patients might be accounted for by a better phosphate control linked to better RKF preservation.

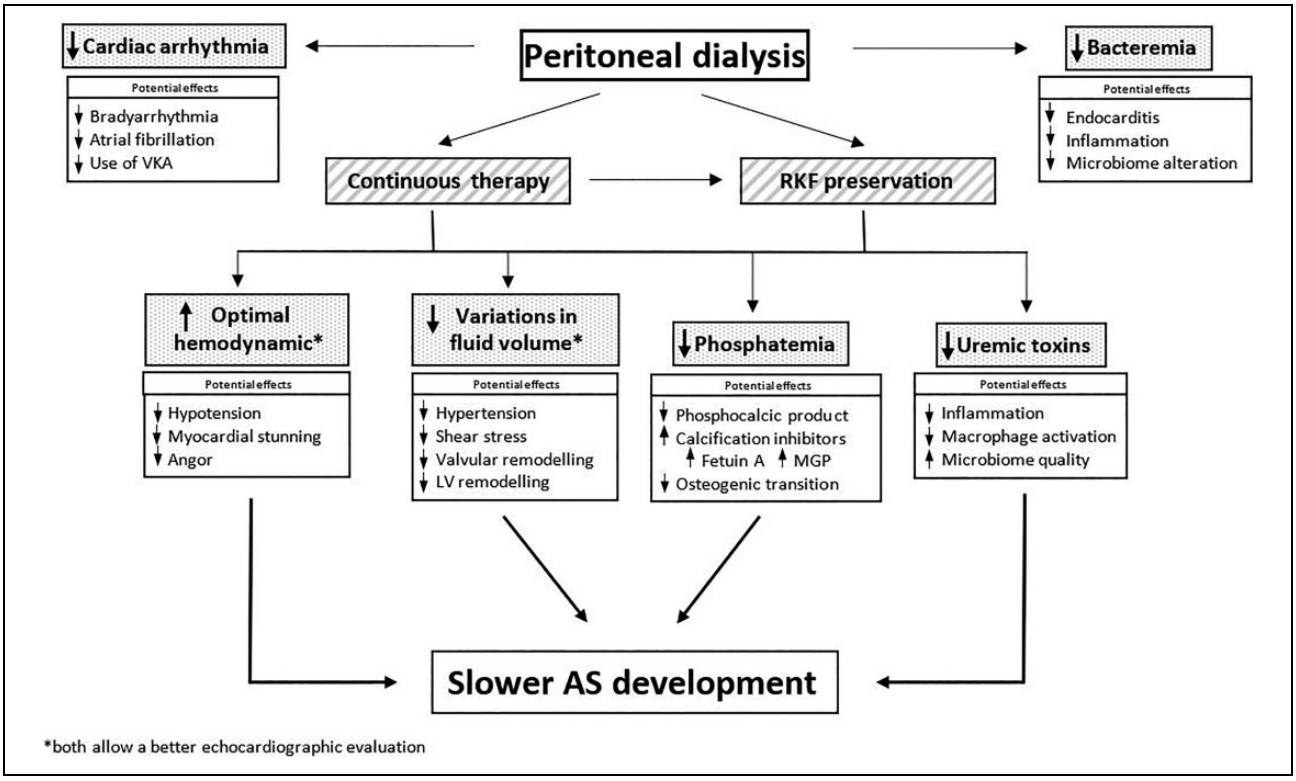

Figure 2. A schematic view of the potential benefits of PD, as compared to HD, on AS onset and progression.
AS: aortic stenosis; MGP: matrix Gla protein; RKF: residual kidney function; VKA: vitamin K antagonist; HD: hemodialysis; PD: peritoneal dialysis.

Figure 2 summarizes mechanisms supporting a potential benefit of PD over HD in the development and progression of AS among dialysis patients.

Clinical advantages of PD in patients with AS

Better hemodynamic control. The discontinuous nature of HD causes fluid accumulation in the interdialytic period followed by rapid correction during dialysis. Excessive interdialytic fluid gain is associated with worse outcomes[76] and exacerbates AS-related symptoms. In comparing 74 dialysis patients with AS with 79 age- and gender-matched controls with normal kidney function, Kim et al. reported an increased incidence of hospitalization for heart failure (HR 37.4, 95% CI 8.5–64.2; $p < 0.001$) in dialysis patients versus controls.[10] No distinction was made, however, between patients on HD and PD. Patients with AS are particularly vulnerable to hypotensive episodes. Blood pressure is frequently low in AS and the HD-related hemodynamic variations contribute to worsen per-dialytic angina[77] and subclinical myocardial ischemia.[78] In contrast, the slow ultrafiltration carried out in PD is less harmful. In the single study that has examined myocardial stunning in response to PD, no change was observed.[79] Atrial fibrillation, also more frequent in HD than in PD patients, is particularly deleterious in cases of AS, as it results in a loss of active ventricular filling leading to a decrease in cardiac output and hypotension. HD aggravates the diastolic dysfunction induced by AS and fluid overload contributes to an increased left atrial volume index. In addition, excessive development of the arteriovenous fistulae in some HD patients leads to an increased cardiac output that worsens the process.[80] A high-flow fistula also complicates the assessment of the severity of valvular disease[81] based on transvalvular flow rates.

Infectious diseases. Aortic valve disease increases the risk of endocarditis. According to the Danish Dialysis Registry, the risk of endocarditis is 2.65 (1.68–4.18) times higher in patients with preexisting degenerative aortic valve.[82] The risk of infective endocarditis is five times higher in patients on HD compared to PD (HR 5.46, 95% CI 3.28–9.10).[82] Indeed, bacteremia is less common in PD and this can be explained by the absence of central venous catheters (and of any vascular access in general). A lower prevalence of *Staphylococcus aureus* bacteremia,[83] which has a pronounced tropism for heart valves, can explain this discrepancy between HD and PD patients.

Conclusion

Despite recent advances in pathophysiology and extensive research, the mechanisms underlining AS development in patients with kidney failure remain complex. Current

literature suggests that PD might reduce the onset and progression of aortic valve calcification and improve AS symptomatology, as compared to HD. Such a beneficial impact may be linked to the slow continuous dialysis effect of PD and the better maintenance of fluid balance, better control of serum phosphate, reduced inflammatory cytokine profile and oxidative stress, and a potential impact on uremic toxins, such as indoxyl sulfate. However, this still relies on scarce data and additional studies are deserved in particular larger prospective TTE studies of PD and HD appropriately matched patients.

All therapeutics options, including AVR, should be considered when AS-related symptoms appear in a dialysis patient despite the increased risk of complications. Studies on AVR outcomes, specifically in PD patients, are urgently needed.

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Author contributions

AC, EG, and LH researched literature and conceived the study. AC wrote the first draft of the manuscript. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

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