Clinical Kidney Journal, 2023, vol. 16, no. 7, 1092–1101

https:/doi.org/10.1093/ckj/sfad020
Advance Access Publication Date: 30 January 2023
Original Article

ORIGINAL ARTICLE

Left-sided valvular heart disease in dialysis recipients: a single-centre observational study

Mohamed Elewa [1], Sandip Mitra [2] and Anuradha Jayanti [3]

[1]Consultant Nephrologist, Manchester University NHS Foundation Trust, Manchester, UK, [2]Consultant Nephrologist, Manchester University NHS Foundation Trust, Honorary Professor of Medicine, University of Manchester, Manchester, UK and [3]Consultant Nephrologist, Manchester University NHS Foundation Trust, Honorary Lecturer of Nephrology, Manchester University NHS Foundation Trust, Manchester, UK

Correspondence to: Mohamed Elewa; E-mail: mohamed.elewa@mft.nhs.uk

ABSTRACT

Background. With the increasing prevalence of chronic kidney disease, the number of people receiving renal replacement is expected to increase by 50% by 2030. Cardiovascular mortality remains significantly higher in this population. The presence of valvular heart disease (VHD) in patients with end-stage renal disease is associated with poor survival. In a dialysis cohort, we assessed the prevalence and characteristics of patients with significant VHD, the association with clinical parameters and the impact on survival.

Methods. Echocardiographic parameters for dialysis recipients from a single centre in the UK were collected. Significant left-sided heart disease (LSHD) was defined as moderate or severe left valvular lesions or left ventricular systolic dysfunction (LVSD) (ejection fraction <45%) or both. Baseline demographic and clinical characteristics were ascertained.

Results. In 521 dialysis recipients {median age 61 years [interquartile range (IQR) 50–72], 59% male}, 88% were on haemodialysis and the median dialysis vintage was 2.8 years (IQR 1.6–4.6). A total of 238 (46%) had evidence of LSHD: 102 had VHD, 63 had LVSD and 73 had both. Overall, 34% had evidence of left-sided VHD. In multivariable regression analysis, age and use of cinacalcet were associated with higher odds of VHD {odds ratio [OR] 1.03 [95% confidence interval (CI) 1.02–1.05] and OR 1.85 [95% CI 1.06–3.23], respectively}, while the use of phosphate binders was associated with increased odds of aortic stenosis [AS; OR 2.64 (95% CI 1.26–5.79)]. The 1-year survival was lower in VHD [78% versus 86% (95% CI 0.72–0.84 and 0.83–0.90), respectively] and in LSHD [78% versus 88% (95% CI 0.73–0.83 and 0.85–0.92), respectively]. In AS, the 1-year survival was 64% (95% CI 0.49–0.82). Using propensity score matching to adjust for age, diabetes and low serum albumin, AS was significantly associated with lower survival ($P = .01$). LSHD was significantly associated with worse survival ($P = .008$) compared with survival in LVSD ($P = .054$).

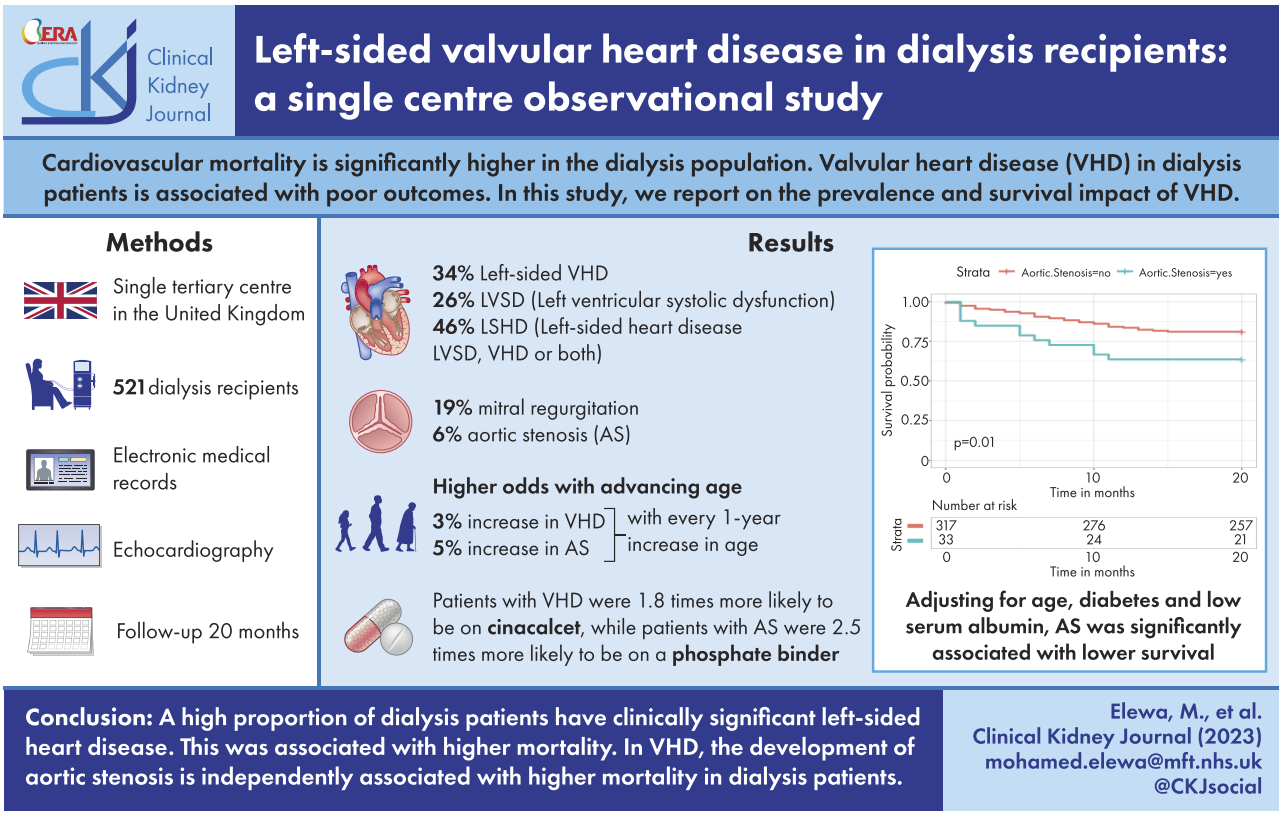
Conclusion. A high proportion of dialysis patients have clinically significant LSHD. This was associated with higher mortality. In valvular heart disease, the development of AS is independently associated with higher mortality in dialysis patients.

LAY SUMMARY

This is an observational study to assess the prevalence and characteristics of patients with significant left-sided valvular heart disease, associations with clinical parameters and its impact on valvular heart disease development and survival.

Received: 13.8.2022; Editorial decision: 2.1.2023

GRAPHICAL ABSTRACT



Keywords: aortic valve disease, dialysis, echocardiography, ESRD, mitral valve disease, valvular heart disease

BACKGROUND

The aging population and the increasing prevalence of diabetes mellitus (DM) and hypertension are contributing to the increase in the prevalence of chronic kidney disease (CKD) worldwide. Globally, it is estimated that 3 million people are currently receiving renal replacement therapy (RRT), and the numbers are expected to increase by 50–100% by 2030 [1]. A total of 50% of all patients with CKD stages 4–5 have cardiovascular disease (CVD) [2], and mortality is significantly higher in patients with CKD compared with the general population, accounting for half of all deaths in patients with advanced CKD [1]. Sudden cardiac death remains an important cause of mortality among those with end-stage renal disease (ESRD) on dialysis [3]. In addition to the high risk of fatal arrythmias and atherosclerotic vascular disease–related complications, valvular heart disease (VHD) poses a significant mortality and morbidity risk in those with advanced CKD [4].

The United States Renal Data System (USRDS) annual report cites the prevalence of VHD at 14% among patients on haemodialysis (HD), 12% in those on peritoneal dialysis (PD) and 7.4% in renal transplant recipients [5]. In patients with ESRD, the presence of VHD is associated with significantly worse survival compared with those without VHD [6]. Valvular calcification occurs 10–20 years earlier in CKD patients and progression is estimated to be 10 times faster in those with ESRD [7]. Patients with CKD are at increased risk of developing VHD due to associated specific risk factors [1, 7, 8]. The pathophysiological hallmark of valvular stenosis or regurgitation in ESRD is calcification of the interstitial cells of the valvular structures [9]. Among the CKD population, mitral annular calcification (MAC) and aortic valve calcification (AVC) have been found to be highly prevalent and commonly lead to valvular stenoses and regurgitation. These are also associated with structural cardiovascular complications, including conduction system abnormalities and endocarditis [10].

The Kidney Disease: Improving Global Outcomes (KDIGO) conference in 2019 identified systematic study of VHD and understanding the incidence, prevalence and outcomes among patients with ESRD important research areas of unmet need [6]. This report is a retrospective observational study from a tertiary renal centre in the UK assessing the prevalence and characteristics of patients with significant left-sided VHD, its association with clinical parameters and its impact on patient survival.

MATERIALS AND METHODS

This is a retrospective cross-sectional analysis of clinical characteristics and outcomes in 521 ESRD patients on dialysis cohorted based on their echocardiogram findings. Study cohorts were grouped based on the presence or absence of significant left-sided VHD. These patients were followed up for 20 months from the time of the original observations.

Study cohort

A total of 672 patients on dialysis [PD or haemodiafiltration (HDF) as the standard of care] from a single tertiary centre in the UK were screened for the study. All patients were ≥18 years of age and had at least one echocardiographic examination available in the electronic patient records. If more than one image was available, the latest one was considered.

Patients on dialysis due to acute kidney injury (AKI), those <18 years of age or those who did not have a reference echocardiogram were excluded from the study. Baseline demographic and clinical characteristics were ascertained from the electronic medical records, including dialysis and renal transplant vintage, vascular access history, Charlson comorbidity index (CCI) [11], laboratory data and the use of calcium supplements, phosphate binders, vitamin D analogues and calcimimetics at the time of data collection.

Echocardiographic parameters

Within the scope of the study, the presence of VHD was considered in patients with moderate or severe aortic stenosis (AS), mitral valve stenosis (MVS), mitral valve regurgitation (MVR) and any degree of aortic regurgitation (mild, moderate or severe). AS diagnosis and severity were based on the peak velocity, the mean pressure gradient (MPG) and the aortic valve area (AVA) according to European Society of Cardiology (ESC) guidelines [12]. MVS was classified as moderate or severe according to valve surface area (valve area <1.5 cm^2 and <1.0 cm^2, respectively). MVR was classified based on qualitative parameters, including mitral valve morphology and colour flow MVR jet, as was aortic regurgitation (AR) (aortic valve morphology and colour flow AR jet width). Left ventricular systolic dysfunction (LVSD) was considered present if the reported ejection fraction (EF) was <45% using the modified Simpson's biplane method [two-dimensional (2D) echocardiography]. The definition of left-sided heart disease (LSHD) is presence of either LVSD, VHD or both.

Statistical analysis

Continuous variables were tested for normality using the Shapiro–Wilk test. Means [± standard deviation (SD)] or medians [interquartile range (IQR)] were used according to normality. Categorical variables were expressed in frequencies and percentages. The relationship between continuous non-normally distributed variables was explored using the Mann–Whitney U test and Fisher's exact test for categorical variables.

Univariable and multivariable analyses of probability of VHD were performed using a binomial logistic regression model to calculate the odds ratio (OR). We used covariates deemed risk factors for development of VHD in dialysis patients in the model.

We used propensity score matching to estimate the survival difference between patients with and without VHD adjusted for age, DM and serum albumin. These variables correlated with mortality in the multivariable model. The propensity score was estimated using a probit regression of VHD on the covariates. After matching, all standardized mean differences for the covariates were <0.1, indicating adequate balance. Patient survival rates were estimated using the Kaplan–Meier method and compared using two-sided logrank tests. Survival curves were plotted with the Kaplan–Meier method in the weighted population. All tests were two-sided, with a level of significance set at $P < .05$.

Using sample size calculations, we calculated that a sample size of 184 would be sufficient to reach a 95% confidence level, with a ±5% margin of error for estimating prevalence. The calculations were based on a total number of dialysis patients in the UK of 30 000 (https://ukkidney.org/audit-research/annual-report) and a prevalence of VHD of 14% [5].

Statistical analyses were performed using R version 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria) and RStudio version 1.4.1106 (Posit Software, Boston, MA, USA).

Our retrospective audit complied with the UK National Health Service Health Research Authority guidelines for clinical audit and service development (https://www.hra.nhs.uk). This was registered with the Audit Department and approved by the institutional lead for research and development. All patient data were anonymized in keeping with the Helsinki Declaration.

RESULTS

Baseline characteristics

Patients in the study cohort were divided into two groups based on the presence or absence of VHD. Compared with patients without VHD, those with VHD were older (median 63 versus 59 years, $P < .001$) and had lower median body mass index (BMI; 25.8 versus 27.5 kg/m^2, $P = .002$). Patients with VHD had a higher prevalence of AF (18.9% versus 7.2%, $P < .001$), CAD (38.9% versus 25.1%, $P = .002$) and congestive heart failure (CHF; 21.1% versus 9.8%, $P = .001$). DM and hypertension were seen in a smaller proportion of patients with VHD (37.7% versus 44.8%, $P = .147$ and 82.3% versus 84.4%, $P = .625$, respectively).

Patients with VHD had overall longer dialysis and RRT vintage. The median dialysis vintage (cumulative years on PD and/or HD) was 3.1 versus 2.6 years ($P = .003$), HD vintage was 3 versus 2.2 years ($P = .009$) and RRT vintage (cumulative years with a functioning transplant and dialysis) was 3.5 versus 2.6 years ($P = .007$) (Table 1).

In the study cohort, 33.6% had evidence of significant left-sided VHD, 19.2% had MVR, 6.4% had AS, LVSD was detected in 136 (26.1%) patients and 25 (4.8%) patients had a previous valvular intervention (Table 2). LSHD was present in 238 patients (45.7%): 102 patients had VHD, 63 patients had LVSD and 73 patients had both.

Univariable analysis

Logistic regression was applied to study associations of clinical parameters with the presence of VHD. Older age and longer dialysis vintage were associated with increased odds of VHD [OR 1.03 (95% CI 1.01–1.04), $p < .001$; OR 1.09 (95% CI 1.03–1.14), $P = .001$; and OR 1.09 (95% CI 1.04–1.15), $P = .001$, respectively]. Patients with VHD were more likely to be on cinacalcet [OR 1.87 (95% CI 1.11–3.12), $P = .017$]. In contrast, higher BMI and the use of calcium supplements was associated with reduced odds of VHD [OR 0.95 (95% CI 0.92–0.98), $P = .002$ and OR 0.64 (95% CI 0.43–0.95), $P = .029$, respectively] (Table 3).

Multivariable regression model

In the multivariable logistic regression model, using the covariates that were found to be statistically significantly associated with VHD in the univariate analysis (age, BMI, use of cinacalcet and/or calcium supplements, dialysis vintage, HD vintage and RRT vintage), a 1-year increase in age was associated with 3% higher odds of VHD [adjusted OR 1.03 (95% CI 1.02–1.05), $P < .001$], while an increase in BMI of 1 kg/m^2 was associated with 6% lower odds of VHD [adjusted OR 0.94 (95% CI 0.91–0.98),

Table 1: Baseline demographic characteristics of the study population according to the presence of VHD.

Characteristics	Overall	No VHD	VHD	P-value
Patients, *n*	521	346	175	
Age (years), median (IQR)	61 (50–72)	59 (49–69)	63 (55–74)	<.001
Gender, *n* (%)				
Female	214 (41.1)	136 (39.3)	78 (44.6)	.289
Male	307 (58.9)	210 (60.7)	97 (55.4)	
Smoker, *n* (%)				
Ex-smoker	11 (2.1)	7 (2.0)	4 (2.3)	.98
Smoker	87 (16.7)	58 (16.8)	29 (16.6)	
BMI (kg/m^2), median (IQR)	26.8 (23.6–31)	27.48 (24.1–31.48)	25.8 (23.–29.69)	.002
Comorbidities, *n* (%)				
Hypertension	436 (83.7)	292 (84.4)	144 (82.3)	.625
Atrial fibrillation	58 (11.1)	25 (7.2)	33 (18.9)	<.001
Coronary artery disease	155 (29.8)	87 (25.1)	68 (38.9)	.002
Congestive heart failure	71 (13.6)	34 (9.8)	37 (21.1)	.001
DM	221 (42.4)	155 (44.8)	66 (37.7)	.147
CCI, median (IQR)	4 (3–5)	4.00 (2–5)	4 (3–6)	.051
Laboratory data, median (IQR)				
Adjusted calcium (mmol/L; reference 2.20–2.60)	2.38 (2.29–2.50)	2.36 (2.27–2.49)	2.41 (2.30–2.52)	.072
Phosphate (mmol/L; reference 0.8–1.5)	1.62 (1.27–1.99)	1.62 (1.27–1.99)	1.62 (1.29–2.04)	.997
PTH (pmol/L; reference 1.6–6.9)	30 (13.90–53.7)	29.8 (14–50.77)	30.7 (13.55–57.6)	.605
Albumin (g/L; reference 34–48)	32 (28–35)	32 (29–35)	32 (27–35)	.301
Medications, *n* (%)				
Alfacalcidol	376 (72.2)	249 (72.0)	127 (72.6)	.966
Cinacalcet	69 (13.2)	37 (10.7)	32 (18.3)	.023
Calcium supplements	173 (33.2)	126 (36.4)	47 (26.9)	.037
Phosphate binders	223 (42.8)	138 (39.9)	85 (48.6)	.072
RRT-related parameters, *n* (%)				
Prior transplant	90 (17.3)	57 (16.5)	33 (18.9)	.578
Dialysis modality				
HD	458 (87.9)	303 (87.6)	155 (88.6)	.851
PD	63 (12.1)	43 (12.4)	20 (11.4)	
HD				
Incident (<3 months)	30 (5.8)	20 (5.8)	10 (5.7)	.945
Prevalent	428 (82.1)	283 (81.8)	145 (82.9)	
Modality setting, *n* (%)				
Home	131 (25.1)	88 (25.4)	43 (24.6)	.915
In-centre	390 (74.9)	258 (74.6)	132 (75.4)	
Dialysis vintage, median (IQR)	2.80 (1.60–4.60)	2.60 (1.60–4.20)	3.10 (1.70–5.90)	.003
HD vintage, median (IQR)	2.40 (1.10–4.30)	2.20 (1.00–3.88)	3.00 (1.25–5.70)	.009
RRT vintage (years), median (IQR)	2.90 (1.60–5.40)	2.60 (1.60–4.60)	3.50 (1.75–6.65)	.007
Access type, *n* (%)				
Arteriovenous fistula	317 (60.8)	219 (63.3)	98 (56.0)	.068
Arteriovenous graft	18 (3.5)	14 (4.0)	4 (2.3)	
Tunnelled venous catheter	123 (23.6)	70 (20.2)	53 (30.3)	
Access blood flow rate (ml/min), median (IQR)	976.5 (720–1500)	970.5 (728.5–1400)	1000 (682.5–1600)	.731
Low (<600)	52 (10.0)	36 (10.4)	16 (9.1)	.164
Moderate (600–1500)	189 (36.3)	136 (39.3)	53 (30.3)	
High (>1500)	73 (14.0)	46 (13.3)	27 (15.4)	
Deceased, *n* (%)	97 (18.6)	55 (15.9)	42 (24.0)	.034

$P = .002$]. Patients with VHD were 1.8 times more likely to be on cinacalcet treatment [OR 1.85 (95% CI 1.06–3.23), $P = .03$) (Fig. 1).

Subgroup analysis of patients with AS

In this cohort of 521 patients, 33 patients (6.4%) had AS, with 5 (1.0%) in the severe category. Patients with AS were older (median 71 versus 60 years, $P < .001$), had a higher prevalence of coexisting coronary artery disease (CAD; 54.5% versus 28.1%, $P = .003$) and were receiving phosphate binders (63.6% versus 41.4%, $P = .02$). Those patients had longer dialysis vintage compared with those without AS (4.6 versus 2.7 years, $P = .021$).

In the univariable analysis, a 1-year increase in age was associated with a 5% increase in the odds of AS [OR 1.05 (95% CI 1.02–1.08), $P = .001$] and each additional year of dialysis was associated with 11% increased odds of developing AS [OR 1.11 (95% CI 1.03–1.19), $P = .003$]. Patients with AS were 2.5 times more likely to be on a phosphate binder [OR 2.48 (95% CI 1.21–5.30), $P = .015$] (Table 4).

In multivariable logistic regression analysis, age and the use of phosphate binders were associated with increased odds of AS

Table 2: Echocardiography results.

Finding		*n* (%)	VHD (*n* = 175), %	*P*-value
Mitral valve disease		108 (20.7)	61.70	
MVS	Moderate	2 (0.4)	1.10	
	Severe	2 (0.4)	1.10	
MVR	Moderate	85 (16.3)	48.60	
	Severe	15 (2.9)	8.60	
Aortic valve disease		94 (18.0)	53.10	
AS	Moderate	28 (5.4)	16	
	Severe	5 (1.0)	2.90	
AR	Mild	37 (7.1)	21.10	
	Moderate	25 (4.8)	13.70	
	Severe	1 (0.2)	0.60	
	Overall	No VHD	VHD	<.001
LVSD, *n* (%)	136 (26.1)	63 (18.2)	73 (41.7)	

[adjusted OR 1.06 (95% CI 1.03–1.09), $P < .001$ and OR 2.64 (95% CI 1.26–5.79), $P = .012$, respectively) (Fig. 2).

VHD in deceased patients

Of the patients in this cohort, 18.6% ($n = 97$) died during the 1.7 years of study follow-up. The 1-year survival in the study cohort was 84% (95% CI 0.80–0.87). More patients with VHD and LSHD died compared with patients without VHD (43.3% versus 31.4%, $P = .034$ and 59.8% versus 42.5%, $P = .003$, respectively) (Table 5). Deceased patients were older (median 69 versus 59 years, $P < .001$), greater proportion had DM (59.8% versus 38.4%, $P \leq .001$) and had lower serum albumin (median 27 versus 33 g/L, $P < .001$). Echocardiographic findings in the group of deceased patients is shown in Table 5.

Survival analysis

The 1-year patient survival was 78% for those with evidence of VHD on echocardiography versus 86% in patients without VHD (95% CI 0.72–0.84 and 0.83–0.90, respectively). This decreased to 64% in those with AS (95% CI 0.49–0.82) and to 81% in those with MVR (95% CI 0.74–0.89). LSHD (i.e. LVSD and VHD) was associated with worse survival [78% versus 88% (95% CI 0.73–0.83 and 0.85–0.92, respectively)]. Kaplan–Meier survival plots for patients with VHD, LVD and LSHD in matched cohorts is provided in Figs. 3 and 4.

DISCUSSION

Published literature on VHD in ESRD patients on dialysis shows a prevalence of ≈12–14% [5]. Various studies report a prevalence of severe AS of 6–13% in HD recipients [13]. In a study by Samad *et al*. [14] in 1326 dialysis recipients, the prevalence of moderate–severe MVR was 12%, AS was 3% and AR was 4%. In a cohort of 521 patients on dialysis, we report a prevalence of significant left-sided VHD of 34%. Moderate and severe MVR was most common (19%), followed by AS (6%) and AR (5%). The coexistence of LVSD was 26%, which is in line with reports from other studies (18–48%) [15, 16]. In our study, the prevalence of LSHD (defined as LVSD and/or moderate–severe left valvular heart disease) was 46%. In a study of 247 dialysis recipients, LSHD was present in 22% of patients and moderate–severe VHD in 11% [17]. Patients in our cohort were younger [median age 61 years (IQR 50–72) versus 66 years (IQR 64–67)], with shorter dialysis vintage [2.80 years (IQR 1.6–4.6) versus 3.8 years (IQR 3.3–4.2)] compared with the above-mentioned study [17].

Multiple risk factors are thought to be implicated in the pathophysiology of VHD in patients with CKD, and many may explain the high prevalence and early development of VHD in patients with ESRD. The calcification of interstitial cells of the valve leaflets remains a unifying pathophysiological feature of VHD in CKD patients [6]. Consequently, various studies have highlighted multiple risk factors that are thought to contribute to the development of VHD, including DM, hypertension, malnutrition, secondary hyperparathyroidism, increased calcium–phosphate product, high vitamin D supplements, mechanical shear stress, volume overload and a potential role of arteriovenous fistulae (AVFs) [6, 8]. Dialysis-related amyloid deposition in calcific valves could be a contributing factor in the development and progression of AS [6, 18].

In this study, serum calcium and phosphate levels were not associated with higher odds of VHD. In multivariable analysis, only the use of cinacalcet was associated with nearly 2-fold higher odds of VHD [OR 1.85 (95% CI 1.06–3.23), $P = .03$]. In accordance with national guidance, cinacalcet is prescribed in patients with significant secondary hyperparathyroidism [>85 pmol/L (normal 1.6–6.9)] [19]. It can therefore be assumed

Table 3: Clinical variables associated with the presence of VHD.

Variable	No VHD	With VHD	OR (95% CI)	*P*-value
Age (years), mean (SD)	58.2 (15.5)	64.0 (14.1)	1.03 (1.01–1.04)	<.001
BMI, mean (SD)	28.4 (6.2)	26.7 (5.2	0.95 (0.92–0.98)	.002
DM (%)	155 (70.1)	66 (29.9)	0.75 (0.51–1.08)	.123
Serum calcium, mean (SD)	2.4 (0.2)	2.4 (0.2)	1.84 (0.64–5.33)	.262
Serum phosphate, mean (SD)	1.7 (0.6)	1.7 (0.6)	0.97 (0.70–1.35)	.872
PTH, mean (SD)	38.3 (34.1)	47.8 (65.7)	1.00 (1.00–1.01)	.040
Cinacalcet, *n* (%)	37 (53.6)	32 (46.4)	1.87 (1.11–3.12)	.017
Calcium supplement, *n* (%)	126 (72.8)	47 (27.2)	0.64 (0.43–0.95)	.029
Phosphate binder, *n* (%)	138 (61.9)	85 (38.1)	1.42 (0.99–2.05)	.059
Dialysis vintage (years), mean (SD)	3.5 (3.2)	4.6 (4.3)	1.09 (1.03–1.14)	.001
HD vintage (years), mean (SD)	2.9 (3.0)	4.0 (4.2)	1.09 (1.04–1.15)	.001
RRT vintage (years), mean (SD)	4.3 (4.9)	5.6 (6.2)	1.04 (1.01–1.08)	.014
Arteriovenous flow rate (ml/min), mean (SD)	1210.0 (812.8)	1277.9 (897.5)	1.00 (1.00–1.00)	.509
High-flow access (>1500 ml/min), *n* (%)	51 (63.0)	30 (37.0)	1.49 (0.87–2.53)	.144

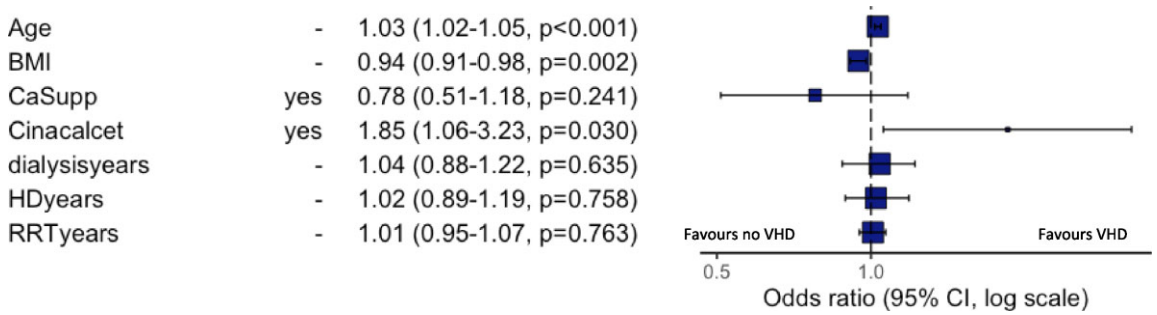


Figure 1: Multivariable logistic regression for VHD. OR (95% CI, *P*-value).

Table 4: Clinical variables associated with AS ($n = 33$).

Variable	No	Yes	OR (95% CI)	*P*-value
Age (years), mean (SD)	59.5 (15.3)	68.8 (13.1)	1.05 (1.02–1.08)	.001
Serum calcium, mmol/L	2.4 (0.2)	2.4 (0.1)	2.45 (0.32–16.93)	.377
Serum phosphate, mmol/L	1.7 (0.6)	1.8 (0.5)	1.28 (0.68–2.34)	.424
Serum PTH, pmol/L	40.6 (43.0)	54.6 (89.7)	1.00 (1.00–1.01)	.116
Calcium supplements, *n* (%)	162 (93.6)	11 (6.4)	1.01 (0.46–2.08)	.987
Phosphate binders, *n* (%)	202 (90.6)	21 (9.4)	2.48 (1.21–5.30)	.015
Cinacalcet, *n* (%)	62 (89.9)	7 (10.1)	1.85 (0.72–4.23)	.169
Dialysis vintage (years), mean (SD)	3.7 (3.5)	5.7 (4.6)	1.11 (1.03–1.19)	.003
HD vintage (years), mean (SD)	3.2 (3.3)	5.2 (4.8)	1.13 (1.04–1.21)	.002
RRT vintage (years), mean (SD)	4.6 (5.2)	7.2 (6.9)	1.06 (1.01–1.11)	.011
Arteriovenous flow rate (ml/min), mean (SD)	1243.9 (823.9)	1048.0 (1030.5)	1.00 (1.00–1.00)	.303
High-flow access (>1500 ml/min), *n* (%)	78 (96.3)	3 (3.7)	0.46 (0.11–1.40)	.222

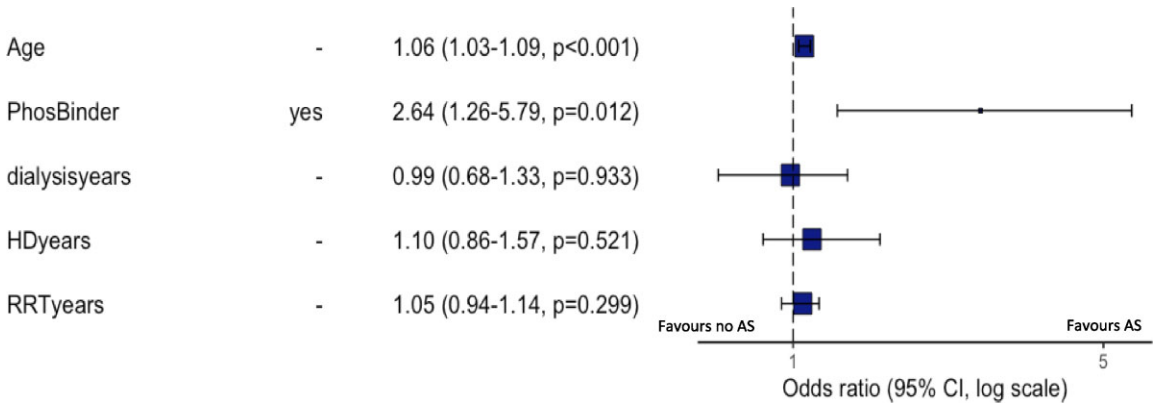


Figure 2: Multivariable logistic regression for AS. OR (95% CI, *P*-value).

that patients from our cohort receiving cinacalcet therapy have historically had very high serum parathyroid hormone (PTH) levels.

In the subgroup analysis of patients with AS ($n = 33$), the use of non-calcium-based phosphate binders was associated with a 2.6-fold increase in the odds of having AS [OR 2.64 (95% CI 1.26–5.79), $P = .012$]. This could be explained by the possibility that these patients have historically had higher serum phosphate levels, and consequently higher calcium–phosphate product, prompting binder prescription or a switch from historic calcium-based binders to non-calcium-based binders.

In patients with ESRD, premature AVC and MAC are associated with abnormal calcium and phosphate metabolism [20]. In one study of 52 dialysis recipients, the authors report that higher phosphate levels and higher serum calcium–phosphate product are significantly associated with valvular calcification [21]. These findings were replicated in other studies [22–24]. In moderate CKD, higher phosphate levels, even if within the normal range, were associated with 25% and 62% increased prevalence of AVC and MAC, respectively [25].

Several previous studies have shown the association between vascular and valvular calcification and longer dialysis vintage [26–29]. This has been replicated in our study. However,

Table 5: Comparison of echocardiographic findings in patients who died during 20 months of follow-up.

Findings		Completed follow-up ($n = 424$)	Died ($n = 97$)	P-value
VHD, n (%)		133 (31.4)	42 (43.3)	.034
Mitral valve disease, n (%)		82 (19.3)	26 (26.8)	.134
MVS, n (%)	Moderate	1 (0.2)	1 (1.0)	.006
	Severe	0 (0.0)	2 (2.1)	
MVR, n (%)	Moderate	66 (15.6)	19 (19.6)	.612
	Severe	12 (2.8)	3 (3.1)	
Aortic valve disease, n (%)		71 (16.7)	23 (23.7)	.143
AS, n (%)	Moderate	19 (4.5)	9 (9.3)	.009
	Severe	2 (0.5)	3 (3.1)	
AR, n (%)	Mild	31 (7.3)	6 (6.2)	.11
	Moderate	18 (4.2)	7 (7.2)	
	Severe	0 (0.0)	1 (1.0)	
LVSD, n (%)	Yes	102 (24.1)	34 (35.1)	.036

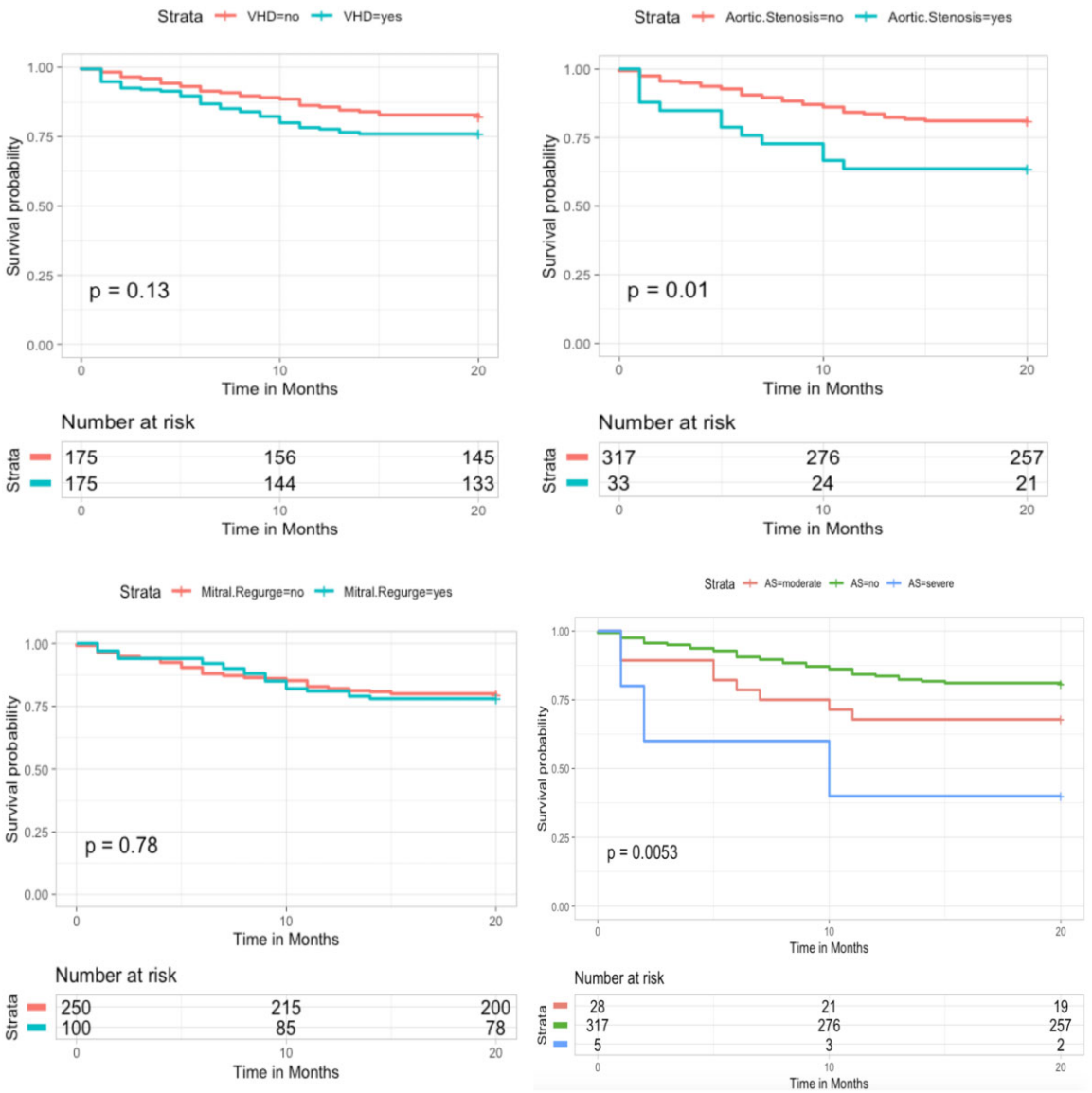


Figure 3: Multivariable logistic regression identified age, presence of DM and lower serum albumin to be associated with increased odds of mortality [OR 1.03 (95% CI 1.01–1.05), $P = .001$); OR 2.22 (95% CI 1.21–4.16), $P = .011$); and OR 0.84 (95% CI 0.80–0.88), $P < .001$), respectively]. Using propensity score matching to adjust data for age, DM and serum albumin levels, the sample size after matching was 350 patients, with 175 in each group (VHD versus no VHD). Using matched data, there was no significant difference in survival in patients with VHD compared with those without VHD, but survival remained significantly lower in patients with AS ($P = .01$). Clockwise from the top: Kaplan–Meier plots for VHD, AS, AS severity and MVR. P-values for two-sided logrank test provided.

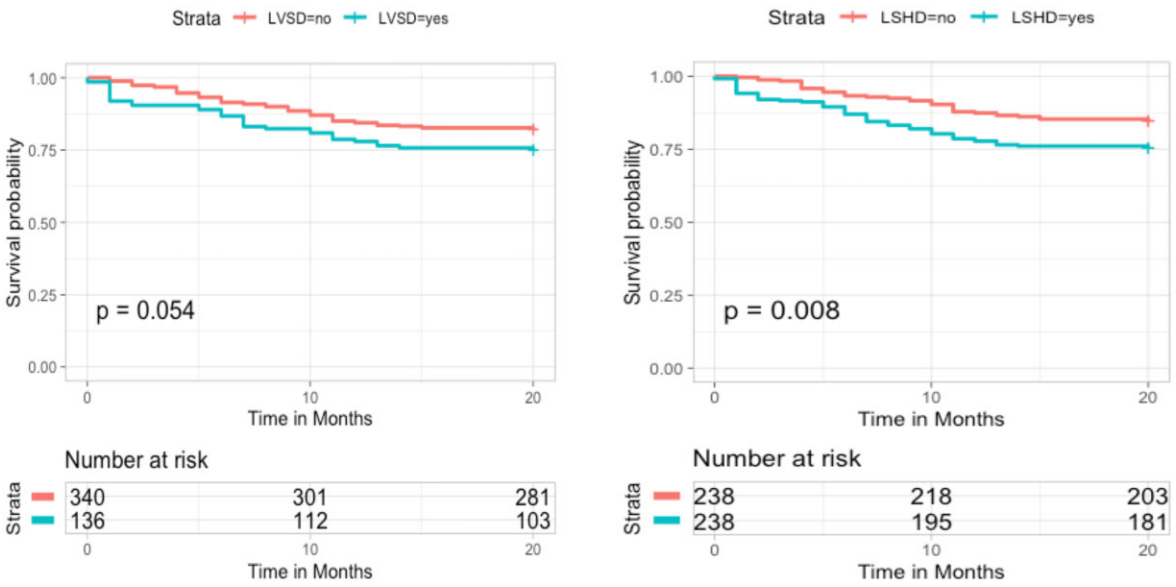


Figure 4: Using propensity score matching, patients were matched for age, DM and serum albumin. The process yielded a new sample of 476 patients, 238 with and 238 without LSHD. There was no significant survival difference in LVSD alone, but survival was significantly worse in patients with LSHD ($P = .008$). Kaplan–Meier survival plots in patients with LVSD (left) and LSHD (right).

in the multivariable analysis, compared with other risk factors, dialysis vintage did not emerge as a significant risk factor. This could be attributed to the fact that HDF is the standard of care in our centre. HDF has better middle molecule clearance compared with standard HD, with some evidence pointing to better cardiovascular outcomes and overall survival [30–33]. Several studies have shown the potential benefits of HDF versus conventional HD in reducing cardiovascular calcification via inhibition of inflammation-related endothelial dysfunction [34], improved fibroblast growth factor 23 removal [35] and amelioration of bone biomarkers [36]. Another possible explanation for our finding is the fact that most previous studies correlated any valvular calcification with dialysis vintage, while we only considered clinically significant VHD [28].

AVFs have been associated with significant effects on cardiac structure and function [37]. Whether there is a direct role of AVF creation on valve leaflet damage remains unclear [6]. Increased fistula flow is associated with volume load that could lead to cardiac chamber enlargement and worsening MVR and may cause cardiac decompensation in patients with AS [38]. In our study we did not find an association between AVF blood flow rate (treated as a continuous or categorical variable) with the odds of VHD, including AS.

The logistic regression model applied to our study cohort identified age, low serum albumin and DM as factors associated with mortality. We did a propensity score matching to adjust for these factors and we found that AS is independently associated with high mortality in ESRD.

In the matched groups, AS and LSHD were significantly associated with lower survival ($P = .01$ and $P = .008$, respectively). In patients with AS, 1-year survival was 64% [versus 85% (95% CI 0.73–0.83)] and 78% in LSHD [versus 88% (95% CI 0.85–0.92)]. The survival of ESRD patients with VHD was reportedly 30% lower compared with persons without VHD [6, 39]. Despite lower survival in persons with LSHD, the survival difference was not statistically significant for MVR.

We acknowledge the study has limitations. As a cross-sectional study, it is difficult to make causal inferences, and the associations identified should be interpreted with this in mind. Despite being a single-centre study, we believe our study cohort is representative of a general dialysis population in the UK, as it includes a diverse population of a multi-ethnic background, a broad range of demographic characteristics and a relatively even comorbidity burden. The echocardiograms used in this study were undertaken at different time points of the dialysis journey of the study cohort, while the laboratory data were from a single time point and cumulative medication information was not available. The limitations of 2D echocardiography in cardiac evaluation, particularly in dialysis populations, were previously reported [40, 41]. Although a number of cardiac imaging tools are available, echocardiography remains the most widely available, non-invasive, inexpensive and usually the first investigation used to assess cardiac function and structure. The numerical values of the echocardiographic variables were not included in our analysis and the timing of the echocardiogram in relation to the dialysis session among HD patients was not reported. We assume that most of the studies were performed on non-dialysis days during the week, with most participants receiving thrice-weekly dialysis. It has been previously reported that echocardiographic assessment may be influenced by the timing of the dialysis session [42]. This may have resulted in the high reported prevalence of MVR, likely influenced by the presence of an element of volume overload. It is worth noting that in the context of MVR, estimated left ventricular EF would not accurately reflect the degree of left ventricular systolic impairment [43] and that the true proportion of patients with left systolic dysfunction could be higher. In terms of our findings that higher BMI was associated with lower odds of VHD in the study cohort, we suspect this to be an incidental finding. Various reports have concluded that echocardiograms in patients with higher BMI are associated with poor image quality and an increased incidence of non-diagnostic studies [44], which could explain these findings and suggests that VHD may be underdiagnosed in these individuals. However, obesity may exacerbate pressure gradients in patients with left ventricular tract outflow obstruction; thus for the same aortic valve area, the transvalvular gradients may be

higher in obese patients, causing overestimation of the degree of AS [45, 46].

CONCLUSION

A high proportion (46%) of dialysis patients have clinically significant LSHD. Development of AS is independently associated with higher mortality. Further research is needed into early management of metabolic bone disease in CKD and beyond. The role of early identification, monitoring and potential intervention in left-sided valve disease may improve outcomes and this warrants further studies.

FUNDING

None declared.

AUTHORS' CONTRIBUTIONS

M.E.: methodology, investigation, formal analysis, data curation and writing - original draft. S.M.: writing - review and editing. A.J.: conceptualisation, methodology, writing - review and editing, supervision.

DATA AVAILABILITY STATEMENT

The data underlying this article are available in the article.

CONFLICT OF INTEREST STATEMENT

S.M. is member of the *CKJ* editorial board, Vice Chair EUDIAL, European Renal Association and Chair, Dialysis Society, UK.

(See related article by de la Espriella et al. Valvular heart disease in patients on kidney replacement therapy: "opening Pandora's box". *Clin Kidney J* (2023) 16: 1045-1048.)

REFERENCES

1. Jankowski J, Floege J, Fliser D *et al*. Cardiovascular disease in chronic kidney disease: pathophysiological insights and therapeutic options. *Circulation* 2021;**143**:1157–72.
2. Stevens PE, O'Donoghue DJ, De Lusignan S *et al*. Chronic kidney disease management in the United Kingdom: NEOERICA project results. *Kidney Int* 2007;**72**:92–9.
3. Collins AJ, Foley RN, Herzog C *et al*. United States Renal Data System 2008 Annual Data Report. *Am J Kidney Dis* 2009;**53**(1 Suppl):S1–374.
4. Thompson S, James M, Wiebe N *et al*. Cause of death in patients with reduced kidney function. *J Am Soc Nephrol* 2015;**26**:2504–11.
5. 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.
6. 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.
7. 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.
8. Hoevelmann J, Mahfoud F, Lauder L *et al*. Valvular heart disease in patients with chronic kidney disease. *Herz* 2021;**46**:228–33.
9. Yutzey KE, Demer LL, Body SC *et al*. Calcific aortic valve disease: a consensus summary from the Alliance of Investigators on Calcific Aortic Valve Disease. *Arterioscler Thromb Vasc Biol* 2014;**34**:2387–93.
10. Umana E, Ahmed W, Alpert MA. Valvular and perivalvular abnormalities in end-stage renal disease. *Am J Med Sci* 2003;**325**:237–42.
11. Radovanovic D, Seifert B, Urban P *et al*. Validity of Charlson comorbidity index in patients hospitalised with acute coronary syndrome. Insights from the nationwide AMIS Plus registry 2002–2012. *Heart* 2014;**100**:288–94.
12. Baumgartner H, Falk V, Bax JJ *et al*. 2017 ESC/EACTS guidelines for the management of valvular heart disease. *Eur Heart J* 2017;**38**:2739–91.
13. Rattazzi M, Bertacco E, Del Vecchio A *et al*. Aortic valve calcification in chronic kidney disease. *Nephrol Dial Transplant* 2013;**28**:2968–76.
14. Samad Z, Sivak JA, Phelan M *et al*. Prevalence and outcomes of left-sided valvular heart disease associated with chronic kidney disease. *J Am Heart Assoc* 2017;**6**:1–14.
15. Derthoo D, Belmans A, Claes K *et al*. Survival and heart failure therapy in chronic dialysis patients with heart failure and reduced left ventricular ejection fraction: an observational retrospective study. *Acta Cardiol* 2013;**68**:51–7.
16. Bansal N, Keane M, Delafontaine P *et al*. A longitudinal study of left ventricular function and structure from CKD to ESRD: the CRIC study. *Clin J Am Soc Nephrol* 2013;**8**:355–62.
17. Axelsson RA, Warming PE, Nielsen TL *et al*. Left-sided heart disease and risk of death in patients with end-stage kidney disease receiving haemodialysis: an observational study. *BMC Nephrol* 2020;**21**:413.
18. Kurita N, Fujii A, Kotera N *et al*. Dialysis amyloid deposition in the aortic valve and its association with aortic stenosis. *Blood Purif* 2015;**40**:146–54.
19. National Institute for Health and Care Excellence. Cinacalcet for the treatment of secondary hyperparathyroidism in patients with end-stage renal disease on maintenance dialysis therapy (quick reference). London: National Institute for Health and Care Excellence, 2009.
20. Maher ER, Young G, Smyth-Walsh B *et al*. Aortic and mitral valve calcification in patients with end-stage renal disease. *Lancet* 1987;**330**:875–7.
21. Rufino M, García S, Jiménez A *et al*. Heart valve calcification and calcium x phosphorus product in hemodialysis patients: analysis of optimum values for its prevention. *Kidney Int* 2003;**85**:S115–8.
22. Abd Alamir M, Radulescu V, Goyfman M *et al*. Prevalence and correlates of mitral annular calcification in adults with chronic kidney disease: results from CRIC study. *Atherosclerosis* 2015;**242**:117–22.
23. Wang AYM. Vascular and valvular calcification in chronic peritoneal dialysis patients. *Int J Nephrol* 2011;**2011**:198045.
24. Torun D, Sezer S, Baltali M *et al*. Association of cardiac valve calcification and inflammation in patients on hemodialysis. *Ren Fail* 2005;**27**:221–6.
25. Adeney KL, Siscovick DS, Ix JH *et al*. Association of serum phosphate with vascular and valvular calcification in moderate CKD. *J Am Soc Nephrol* 2009;**20**:381.
26. Goodman WG, Goldin J, Kuizon BD *et al*. Coronary-artery calcification in young adults with end-stage renal disease who are undergoing dialysis. *N Engl J Med* 2000;**342**:1478–83.
27. Guérin AP, London GM, Marchais SJ *et al*. Arterial stiffening and vascular calcifications in end-stage renal disease. *Nephrol Dial Transplant* 2000;**15**:1014–21.

28. Raggi P, Boulay A, Chasan-Taber S *et al*. Cardiac calcification in adult hemodialysis patients: a link between end-stage renal disease and cardiovascular disease? *J Am Coll Cardiol* 2002;**39**:695–701.
29. London GM, Guérin AP, Marchais SJ *et al*. Arterial media calcification in end-stage renal disease: impact on all-cause and cardiovascular mortality. *Nephrol Dial Transplant* 2003;**18**:1731–40.
30. Davenport A. Moving beyond small solute clearance: what evidence is there for more permeable dialyzers and haemodiafiltration? *Hemodial Int* 2018;**22**(Suppl 2): S24–8.
31. Peters SAE, Bots ML, Canaud B *et al*. Haemodiafiltration and mortality in end-stage kidney disease patients: a pooled individual participant data analysis from four randomized controlled trials. *Nephrol Dial Transplant* 2016;**31**: 978–84.
32. Daugirdas JT. Lower cardiovascular mortality with high-volume hemodiafiltration: a cool effect? *Nephrol Dial Transplant* 2016;**31**:853–6.
33. Blankestijn PJ, Fischer KI, Barth C *et al*. Benefits and harms of high-dose haemodiafiltration versus high-flux haemodialysis: the comparison of high-dose haemodiafiltration with high-flux haemodialysis (CONVINCE) trial protocol. *BMJ Open* 2020;**10**:e033228.
34. Cavallari C, Dellepiane S, Fonsato V *et al*. Online hemodiafiltration inhibits inflammation-related endothelial dysfunction and vascular calcification of uremic patients modulating miR-223 expression in plasma extracellular vesicles. *J Immunol* 2019;**202**:2372–83.
35. Patrier L, Dupuy AM, Granger Vallée A *et al*. FGF-23 removal is improved by on-line high-efficiency hemodiafiltration compared to conventional high flux hemodialysis. *J Nephrol* 2013;**26**:342–9.
36. Małyszko J, Małyszko JS, Koźminski P *et al*. Markers of bone metabolism in hemodialyses and hemodiafiltration. *Ren Fail* 2007;**29**:595–601.
37. Agarwal AK. Systemic effects of hemodialysis access. *Adv Chronic Kidney Dis* 2015;**22**:459–65.
38. Alkhouli M, Sandhu P, Boobes K *et al*. Cardiac complications of arteriovenous fistulas in patients with end-stage renal disease. *Nefrologia* 2015;**35**:234–45.
39. Patel KK, Shah SY, Arrigain S *et al*. Characteristics and outcomes of patients with aortic stenosis and chronic kidney disease. *J Am Heart Assoc* 2019;**8**:e009980.
40. Chiu DYY, Green D, Abidin N *et al*. Echocardiography in hemodialysis patients: uses and challenges. *Am J Kidney Dis* 2014;**64**:804–16.
41. Chiu DYY, Green D, Abidin N *et al*. Cardiac imaging in patients with chronic kidney disease. *Nat Rev Nephrol* 2015;**11**:207–20.
42. Ersbøll M, Raja AA, Warming PE *et al*. Changes in left ventricular filling parameters before and after dialysis in patients with end stage renal disease. *Int J Cardiovasc Imaging* 2019;**35**:1673–81.
43. Kamperidis V, Marsan NA, Delgado V *et al*. Left ventricular systolic function assessment in secondary mitral regurgitation: left ventricular ejection fraction vs. speckle tracking global longitudinal strain. *Eur Heart J* 2016;**37**:811–6.
44. Ellenberger K, Jeyaprakash P, Sivapathan S *et al*. The effect of obesity on echocardiographic image quality. *Heart Lung Circ* 2022;**31**:207–15.
45. el Hajj MC, Litwin SE. Echocardiography in the era of obesity. *J Am Soc Echocardiogr* 2020;**33**:779–87.
46. Goyal A, Crabtree CD, Harfi TT *et al*. Cardiac magnetic resonance imaging and echocardiography in morbidly obese patients: an assessment of image quality. *J Am Coll Cardiol* 2022;**79**:1347.