



**HAL**  
open science

## Long-term changes in cardiac remodelling in prevalent kidney graft recipients

Valentin Panisset, Nicolas Girerd, Erwan Bozec, Zohra Lamiral, Quentin d'Hervé, Luc Frimat, Olivier Huttin, Sophie Girerd

► **To cite this version:**

Valentin Panisset, Nicolas Girerd, Erwan Bozec, Zohra Lamiral, Quentin d'Hervé, et al.. Long-term changes in cardiac remodelling in prevalent kidney graft recipients. *International Journal of Cardiology*, 2024, 403, pp.131852. 10.1016/j.ijcard.2024.131852 . hal-04501582

**HAL Id: hal-04501582**

<https://hal.univ-lorraine.fr/hal-04501582v1>

Submitted on 12 Mar 2024

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

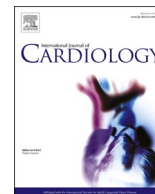


Distributed under a Creative Commons Attribution - NonCommercial - NoDerivatives 4.0 International License



Contents lists available at ScienceDirect

## International Journal of Cardiology

journal homepage: [www.elsevier.com/locate/ijcard](http://www.elsevier.com/locate/ijcard)

## Long-term changes in cardiac remodelling in prevalent kidney graft recipients

Valentin Panisset<sup>a</sup>, Nicolas Girerd<sup>b</sup>, Erwan Bozec<sup>b</sup>, Zohra Lamiral<sup>b</sup>, Quentin d'Hervé<sup>a</sup>,  
Luc Frimat<sup>a</sup>, Olivier Huttin<sup>c</sup>, Sophie Girerd<sup>a,b,\*</sup>

<sup>a</sup> Nephrology Department, University Hospital of Nancy, Vandoeuvre-lès-Nancy, France

<sup>b</sup> Université de Lorraine, Inserm, Centre d'Investigations Cliniques-1433, and Inserm U1116; CHRU Nancy; F-CRIN INI-CRCT, Vandoeuvre-lès-Nancy, France

<sup>c</sup> Cardiology Department, University Hospital of Nancy, Vandoeuvre-lès-Nancy, France

## ARTICLE INFO

## Keywords:

Kidney transplantation  
Kidney graft recipients  
Echocardiography  
Cardiac remodelling  
Heart failure

## ABSTRACT

**Background:** Approximately 15% of kidney transplant (KT) recipients develop *de novo* heart failure after KT. There are scarce data reporting the long-term changes in cardiac structure and function among KT recipients. Despite the improvement in renal function, transplant-related complications as well as immunosuppressive therapy could have an impact on cardiac remodelling during follow-up. We aimed to describe the long-term changes in echocardiographic parameters in prevalent KT recipients and identify the clinical and laboratory factors associated with these changes.

**Methods:** A centralised blinded review of two echocardiographic examinations after KT (on average after 17 and 39 months post-KT respectively) was performed among 80 patients (age  $50.4 \pm 16.2$ , diabetes 13.8% pre-KT), followed by linear regression to identify clinico-biological factors related to echocardiographic changes.

**Results:** Left atrial volume index (LAVI) increased significantly ( $34.2 \pm 10.8$  mL/m<sup>2</sup> vs.  $37.6 \pm 15.0$  mL/m<sup>2</sup>, annualised delta  $3.1 \pm 11.4$  mL/m<sup>2</sup>/year;  $p = 0.034$ ) while left ventricular ejection fraction (LVEF) decreased ( $62.1 \pm 9.0\%$  vs.  $59.7 \pm 9.9\%$ , annualised delta  $-2.7 \pm 13.6\%$ /year;  $p = 0.04$ ). Male sex ( $\beta = 8.112 \pm 2.747$ ;  $p < 0.01$ ), pre-KT hypertension ( $\beta = 9.725 \pm 4.156$ ;  $p < 0.05$ ), graft from expanded criteria donor ( $\beta = 3.791 \pm 3.587$ ;  $p < 0.05$ ), and induction by anti-thymocyte globulin ( $\beta = 7.920 \pm 2.974$ ;  $p = 0.01$ ) were associated with an increase in LAVI during follow-up. Higher haemoglobin ( $>12.9$  g/dL) at the time of the first echocardiography ( $\beta = 6.029 \pm 2.967$ ;  $p < 0.05$ ) and ACEi/ARB therapy ( $\beta = 8.306 \pm 3.161$ ;  $p < 0.05$ ) were associated with an increase in LVEF during follow-up.

**Conclusion:** This study confirms the existence of long-term cardiac remodelling after KT despite dialysis cessation, characterised by an increase in LAVI and a decrease in LVEF. A better management of anaemia and using ACEi/ARB therapy may prevent such remodelling.

### 1. Introduction

*De novo* heart failure (HF) is a frequent complication in kidney transplant recipients and is associated with decreased patient survival

after kidney transplantation (KT) [1,2]. In chronic kidney disease (CKD) including end-stage renal disease patients (ESRD), uraemic cardiomyopathy is frequently observed [3]. Uraemic cardiomyopathy is defined as changes in myocardial structure and function, with left ventricular

**Abbreviations:** ACEi, ACE inhibitors; AF, atrial fibrillation; ARB, angiotensin II antagonist; ATG, anti-thymocyte globulin; AVF, arteriovenous fistula; BMI, body mass index; CKD, chronic kidney disease; CMV, cytomegalovirus; CNI, calcineurin inhibitors; CV, cardiovascular; DSA, donor specific antibodies; ECD, expanded criteria donors; eGFR, estimated glomerular filtration rate; EPO, erythropoietin; ESAs, erythropoietin stimulating agents; ESRD, end-stage renal disease patients; HD, haemodialysis; HF, heart failure; KT, kidney transplantation; LAVI, left atrial volume index; LD, living donors; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; MACE, major adverse cardiovascular events; MMF, mycophenolate mofetil; mTOR, mTOR inhibitors; NODAT, new-onset diabetes mellitus after transplantation; OADs, oral antidiabetic agents; PD, peritoneal dialysis; PTH, parathyroid hormone; SCD, standard criteria donors; TTE, trans-thoracic echocardiographic evaluations.

\* Corresponding author at: Centre d'Investigations Cliniques-1433, INSERM U1116, CHRU de Nancy, Institut lorrain du coeur et des vaisseaux Louis Mathieu, Nancy, France, 4, rue du Morvan. 54500 Vandoeuvre-lès-Nancy.

E-mail address: [s.girerd@chru-nancy.fr](mailto:s.girerd@chru-nancy.fr) (S. Girerd).

<https://doi.org/10.1016/j.ijcard.2024.131852>

Received 21 June 2023; Received in revised form 26 January 2024; Accepted 10 February 2024

Available online 13 February 2024

0167-5273/© 2024 The Author(s). Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

hypertrophy being the most often reported abnormality although ventricular dilatation as well as systolic and diastolic dysfunctions have also been described. After KT, these cardiac abnormalities may reverse, although evidence remains controversial [4].

In KT recipients, the pathogenesis of cardiac diseases is complex and multifactorial, involving pre-existing cardiomyopathy and KT-related factors (immunosuppressive therapy and its adverse events, KT-related complications) [5]. As a result, traditional and non-traditional HF risk factors may coexist despite the restoration of a normal or subnormal glomerular filtration rate and the reversal of the uraemic milieu. Of note, it is well established that patients with coexisting HF and CKD/KT frequently receive much less HF medication than patients without coexisting CKD/KT [6]. The factors most associated with long-term post-KT remodelling have not been sufficiently reported to date.

In the present study, we aimed to identify factors associated with changes in functional and structural cardiac parameters during long-term follow-up of prevalent KT patients.

## 2. Materials and methods

### 2.1. Study population

We conducted a retrospective descriptive study among patients who received a KT between 2007 and 2018 at the Nancy University Hospital. Patients who had undergone at least two trans-thoracic echocardiographic evaluations (TTE) during the post-KT period in the echocardiography laboratory of the Nancy University Hospital were included in the study. Patients were excluded if they had a) a duration <3 months between KT and the first echocardiography (TTE1) b) a duration >6 years between KT and the second echocardiography (TTE2) or c) a duration between TTE1 and TTE2 <3 months. Patients whose TTE had been performed in a critical care setting as well as heart transplant patients were also excluded from the study. Overall, 80 patients were enrolled in the present analysis. Clinical data were retrieved from the French DIVAT database (Computerised and Validated data in Transplantation) ([www.DIVAT.Fr](http://www.DIVAT.Fr)) (French Research Ministry: RC12\_0452, latest agreement number: 13334, cohort CNIL number: 891735). The study was approved by the clinical research committee, and written informed consent was obtained from all participants.

### 2.2. Study design

The echocardiographic parameters of each patient were compared between the first and second echocardiography (TTE1 and TTE2). Every echocardiography was reviewed in a standardised manner by a single operator, blinded from the clinical-biological data. The association of clinical and laboratory parameters with cardiac parameters at baseline (time of TTE1) was evaluated as well as the changes in cardiac parameters between TTE1 and TTE2. The association between the changes in clinical and laboratory parameters with the changes in cardiac parameters were also assessed.

### 2.3. Echocardiography

Echocardiograms were performed at the University Hospital of Nancy by experienced cardiologists according to current recommendations using a commercially available standard ultrasound scanner (Vivid 7, E9 or E95, GE Medical Systems, Milwaukee, WI, USA) with a 2.5-MHz transducer, and were all reviewed offline with dedicated software (Echo PAC® PC, GE Healthcare). Briefly, conventional functional and structural echocardiographic parameters were measured for both ventricles according to recommendations for cardiac chamber quantification [7]. The following diastolic parameters were recorded: maximal early and late mitral inflow velocities with pulsed-wave doppler (PW) (E wave, A wave, A wave duration, E wave deceleration time and E/A ratio), lateral and septal mitral annular e' velocity with TDI, average E/e' ratio, peak

velocity of tricuspid regurgitation jet by continuous-wave Doppler (CW) and LA biplane volume index (or 4 chamber volume only if 2C was not available).

### 2.4. Data collection

The following clinical and laboratory data were collected:

-*Pre-transplant cardiovascular (CV) risk factors*: sex, body mass index (BMI), age, hypertension, diabetes, valvular heart disease, coronary artery disease, heart failure and atrial fibrillation (AF).

-*Renal history and KT data*: causal nephropathy, type of dialysis (haemodialysis (HD)/peritoneal dialysis (PD)/preemptive KT), type of arteriovenous fistula (AVF) (proximal/distal), AVF flow rate, type of donor (standard criteria donors (SCD), expanded criteria donors (ECD), living donors (LD)), delayed graft function defined as the necessity of at least one dialysis session during the first week following KT, induction therapy (anti-thymocyte globulin (ATG), basiliximab), kidney graft artery stenosis during follow-up, AVF closure during follow-up, detection of *de novo* donor specific antibodies (DSA), cytomegalovirus (CMV) infection.

-*Post-transplant CV events*: hypertension, new-onset diabetes mellitus after transplantation (NODAT), pulmonary embolism, acute coronary syndrome, heart failure, atrial fibrillation.

Hypertension and diabetes were defined as the use of antihypertensive drug treatment, oral antidiabetic agents, or insulin. A history of coronary artery disease was established by coronary angiography, myocardial scintigraphy, or in case of a previous acute coronary syndrome. Heart failure was recorded if there was an echocardiographic description (left ventricular ejection fraction (LVEF) < 50%) and/or hospitalisation for acute heart disease. Valvular heart disease was considered only if the grade was described as moderate or above. Hypertension, diabetes, coronary heart disease, valvular heart disease or heart failure were deemed as post-KT events only if they were unknown prior to KT.

-*Laboratory data*: haemoglobin, calcium, parathyroid hormone (PTH), estimated glomerular filtration rate (eGFR) according to the MDRD formula, ferritinaemia, transferrin saturation coefficient.

-*Medications*: number and class of antihypertensive drug treatments (ACE inhibitors or angiotensin II antagonist (ACEi/ARB), beta-blockers, calcium channel blockers, loop diuretics, mineralocorticoid receptor antagonists), oral antidiabetic agents (OADs), insulin, statins and anti-coagulants, and erythropoietin (EPO).

-*KT medications*: immunosuppressive therapy (calcineurin inhibitors (CNI), mTOR inhibitors (mTOR), mycophenolate mofetil (MMF)).

### 2.5. Statistical analysis

All analyses were performed using SAS® R9.4 software (SAS Institute, Cary, NC, USA). The two-sided significance level was set at  $p < 0.05$ .

Continuous variables are described as mean  $\pm$  standard deviation, median, first quartile and 3rd quartile, while categorical variables are presented as numbers with percentages.

Comparisons of posttransplant TTE1 and TTE2 were performed using Student's *t*-test or Wilcoxon signed ranks test for paired data. The associations between cardiac parameters and exposure variables were performed using univariable and multivariable linear regression models, while adjusting for the first transplant ultrasound parameter (TTE1). In light of the distribution of left atrial volume index (LAVI), LAVI was log-transformed. Exp.(Beta) coefficient was used to express associations with LAVI (rather than its log). Importantly, exp.(Beta) should be interpreted on a multiplicative scale. All exposure variables with a *p*-value of <20% in the univariable models were introduced into the multivariable models, TTE2 echocardiographic variables and changes in echocardiographic variables were adjusted for TTE1 values. A final multivariable model was selected using a stepwise interactive method.

### 3. Results

#### 3.1. Demographics and clinical characteristics

Among the 80 included KT patients, 77.5% were on haemodialysis prior to KT, and 8.8% received a preemptive KT (Table 1). Before KT, 83.8% of patients had a history of hypertension, 13.8% diabetes, and 7.5% heart failure. After KT, we observed the following post-KT complications: 12 patients developed NODAT, 4 experienced coronary disease, 10 exhibited heart failure, and 10 were diagnosed with atrial fibrillation.

Half of the patients received induction therapy with ATG and the other half with basiliximab. Maintenance immunosuppressive therapy predominantly included tacrolimus (78%) and mycophenolate mofetil (80%).

#### 3.2. Evolution of echocardiographic parameters after kidney transplantation

On average, TTE1 was performed at  $16.9 \pm 10.8$  months after KT and TTE2 at  $38.6 \pm 17.0$  months after KT (Table 2).

During follow-up, left atrial volume index (LAVI) increased significantly ( $37.6 \pm 15.0$  mL/m<sup>2</sup> vs.  $34.2 \pm 10.8$  mL/m<sup>2</sup>, delta annualised  $3.1 \pm 11.4$  mL/m<sup>2</sup>/year;  $p = 0.034$ ), while left ventricular ejection fraction (LVEF) decreased ( $59.7 \pm 9.9\%$  vs.  $62.1 \pm 9.0\%$ , delta annualised  $-2.7 \pm 13.6\%$ /year;  $p = 0.04$ ).  $e'$  tended to decrease from  $10.6 \pm 3.6$  cm/s to  $10.1$  cm/s ( $p = 0.098$ ). There was no significant change in the remaining parameters, including left ventricular mass index (LVMI) ( $108.8 \pm 31.0$  g/m<sup>2</sup> vs.  $105.3 \pm 28.8$  g/m<sup>2</sup>, delta annualised  $3.1 \pm 16.5$  g/m<sup>2</sup>/year). We did not observe significant changes in the proportions of eccentric and concentric hypertrophy at TTE1 (26.8% and 70.4%, respectively) and at TTE2 (29.2% and 67.7%, respectively).

#### 3.3. Association of clinical and laboratory factors with baseline LAVI and LVEF (at the time of the first echocardiography)

In multivariable analysis, history of pre-KT hypertension ( $\exp[\beta] = 1.329 \pm 1.121$ ;  $p = 0.018$ ) and valvular heart disease ( $\exp[\beta] = 1.545 \pm 1.127$ ;  $p = 0.001$ ) was associated with significantly higher LAVI at the time of TTE1. Patients who had AVF closing ( $\exp[\beta] = 0.839 \pm 1.081$ ;  $p = 0.031$ ) had significantly lower LAVI at the time of TTE1.

In multivariable analysis, pre-KT diabetes ( $\beta = 6.436 \pm 3.216$ ;  $p = 0.049$ ), higher kidney graft function ( $\beta$  for 1 mL/min eGFR =  $-0.132 \pm 0.053$ ;  $p = 0.016$ ), and ACEi or ARB therapy ( $\beta = 4.455 \pm 2.167$ ;  $p = 0.044$ ) were associated with higher LVEF (Table 3).

#### 3.4. Association of baseline clinical and laboratory factors with the change in LAVI and LVEF during follow-up ( $\Delta TTE = TTE2 - TTE1$ )

Baseline factors associated with an increase in LAVI during follow-up were male sex ( $\beta = 8.112 \pm 2.747$ ;  $p = 0.005$ ), pre-KT hypertension ( $\beta = 9.725 \pm 4.156$ ;  $p = 0.023$ ), graft from an ECD ( $\beta = 3.791 \pm 3.587$ ;  $p$  for the comparison with graft from a SCD =  $0.013$ ), and induction by ATG ( $\beta = 7.920 \pm 2.974$ ;  $p = 0.01$ ).

Haemoglobin  $>12.9$  g/dL at TTE1 ( $\beta = 6.029 \pm 2.967$ ;  $p = 0.047$ ) and ACEi/ARB therapy ( $\beta = -0.826 \pm 0.170$ ;  $p < 0.0001$ ) were associated with an improvement in LVEF during follow-up (Table 4).

#### 3.5. Sensitivity analysis further adjusting on AF status

When adjusting on AF status (i.e. history of AF before KT and de novo AF), the associations retrieved from the models did not change (Supplementary Table 1 and 2). AF status was not significantly associated with LAVI and LVEF as well as LAVI and LVEF changes.

**Table 1**

Patient characteristics.

Characteristics	N	
<b>Demographic parameters</b>		
Age (years)	80	50.4 ± 16.2
BMI (kg/m <sup>2</sup> )	80	25.5 ± 5.7
Male sex	80	50 (62.5%)
<b>Comorbidities before KT</b>		
Hypertension	80	67 (83.8%)
Diabetes	80	11 (13.8%)
Valvular heart disease	80	13 (16.3%)
Coronary artery disease	80	8 (10.0%)
Heart failure	80	6 (7.5%)
Atrial fibrillation	80	5 (6.25%)
<b>Initial nephropathy</b>		
IgA nephropathy	64	10 (15.6%)
PKD	64	10 (15.6%)
Malformative uropathy	64	10 (15.6%)
Nephroangiosclerosis	64	7 (10.9%)
Tubulo-interstitial	64	4 (6.3%)
Diabetic nephropathy	64	4 (6.3%)
<b>Type of dialysis</b>		
PD	80	11 (13.8%)
HD	80	62 (77.5%)
Preemptive KT	80	7 (8.8%)
Arteriovenous fistula	80	57 (71.25%)
<b>AVF flow rate (ml/min)</b>		
≥ 2 L/min	51	1163.2 ± 611
< 2 L/min	51	7 (12.5%)
	51	44 (78.5%)
<b>Type of AVF</b>		
Distal	56	34 (60.7%)
Proximal	56	22 (39.3%)
<b>Donor</b>		
LD	80	27 (33.8%)
ECD	80	29 (36.3%)
SCD	80	24 (30.1%)
Delayed graft function	80	19 (23.8%)
<b>Induction treatment</b>		
Basiliximab	73	37 (50.7%)
ATG	73	36 (49.3%)
<b>Post-transplant complications</b>		
Rejection	80	18 (22.5%)
Transplant renal artery stenosis	80	8 (10.0%)
Post-transplant pulmonary embolism	80	5 (6.3%)
AVF ligation	59	16 (27.1%)
De novo DSA	80	7 (8.8%)
CMV Infection	80	17 (21.3%)
Delay Graft/TTE1 (months)	80	16.9 ± 10.8
Delay Graft/TTE2 (months)	80	38.6 ± 17.0
<b>Laboratory parameters at first echocardiography</b>		
Haemoglobin (g/dl)	80	12.8 ± 2.1
Corrected calcaemia (mmol/L)	74	2.4 ± 0.2
PTH (ng/L)	77	56.8 ± 52.0
Ferritin (microg/L)	64	386.2 ± 706.3
Creatinine (micromol/L)	80	142.6 ± 78.0
eGFR MDRD (mL/min/1.73m <sup>2</sup> )	80	49.6 ± 18.4
<b>Medications at first echocardiography</b>		
EPO	80	7 (8.8%)
CNI	80	74 (92.5%)
Ciclosporin	80	11 (13.8%)
Tacrolimus	80	63 (78.8%)
MMF	80	64 (80.0%)

(continued on next page)

Table 1 (continued)

Characteristics	N	
mTOR inhibitors	80	4 (5.0%)
Belatacept	80	2 (2.5%)
Number of antihypertensive treatments		
0	80	25 (31.3%)
1	80	21 (26.3%)
2	80	21 (26.3%)
≥ 3	80	13 (16.3%)
ACEi/ARB	80	28 (35.0%)
Beta-blocker	80	35 (43.8%)
Calcium channel blockers	80	30 (37.5%)
Loop diuretic	80	17 (21.3%)
Antidiabetic therapy	80	15 (18.8%)
Insulin	80	10 (12.5%)
AODs	80	5 (6.3%)
Insulin + AODs	80	0
Other cardiovascular drugs		
Statin therapy	80	22 (27.5%)
Anticoagulants	80	12 (15.0%)

KT: Kidney transplantation; BMI: body mass index; PKD: polycystic kidney disease; PD: peritoneal dialysis; HD: haemodialysis; AVF: arteriovenous fistula; LD: living donor; SCD: standard criteria donor; ECD: expanded criteria donor; ATG: anti-thymocyte globulin; DSA: donor specific antibodies; CMV: cytomegalovirus; PTH: parathyroid hormone; eGFR: estimated glomerular filtration rate according to MDRD formula; EPO: erythropoietin; CNI: calcineurin inhibitors; MMF: mycophenolate mofetil; ACEi: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blockers; AODs: antidiabetic oral drugs. TTE1: first transthoracic echocardiogram; TTE2: second transthoracic echocardiogram.

#### 4. Discussion

In this study reporting changes in echocardiographic parameters in 80 prevalent KT patients performed during the first 5 years after kidney transplantation, a significant deterioration in LVEF and LAVI was observed during follow-up after KT, despite dialysis cessation. Since higher haemoglobin and the use of ACEi/ARB therapy was associated with a better LVEF evolution, an optimised management of patients after KT may in fact prevent cardiac remodelling and ultimately *de novo* heart failure. Another important result of our study is the association of fistula closing and lower LAVI, which may suggest that this procedure improves atrial remodelling following KT.

##### 4.1. Relevance of evaluating long-term changes in CV variables following KT

This study focused on the evolution of cardiac parameters during post-KT follow-up. Most of the studies dedicated to uraemic cardiomyopathy in the setting of KT have focused on the reversibility of this disease after KT [4], with a comparison between pre-KT and generally early post-KT cardiac parameters. Nevertheless, considering the high incidence of *de novo* HF in KT patients [1,2] and the absence of clinical trials dedicated to HF in these patients [6], it is imperative to better understand the evolution of *the cardiac abnormalities* in the long term follow-up and not only during the post-operative period. Factors associated with adverse cardiac remodelling must be identified in order to prevent *de novo* HF. We hypothesised that patients are at risk of developing cardiac abnormalities during long-term follow-up after KT. This may be related to factors associated with KT such as immunosuppressive regimen [8] [9] or graft function [10], as well as pre-existent comorbidities not reversed by KT (such as diabetes or valvular cardiac disease) [9,11]. Dedicated studies are manifestly needed considering the elevated CV morbidity-mortality and the absence of optimal management of HF in these patients [6].

Several studies previously focused on the changes over time in prevalent kidney graft patients [12,13]. Zapolski et al. reported a decrease in LAVI among 42 KT patients at 1, 3, 6, 12 and 36 months after

Table 2

Evolution of echocardiographic parameters between the first (TTE1) and second (TTE2) echocardiography during follow-up.

Characteristics	n	TTE1	TTE2	Annualised Delta	P-value*
		Mean ± SD	Mean ± SD	Mean ± SD	
LV structure and function					
LVM (g)	59	191.7 ± 59.3	197.2 ± 58.5	4.4 ± 28.7	0.24
LVMi (g/m <sup>2</sup> )	59	105.3 ± 28.8	108.8 ± 31.0	3.1 ± 16.5	0.15
4-cavity LVEF (Simpson) (%)	64	62.1 ± 9.0	59.7 ± 9.9	-2.7 ± 13.6	0.04
LVEDVI (mL/m <sup>2</sup> )	63	50.6 ± 13.3	52.0 ± 14.8	0.4 ± 16.9	0.76
Mitral S' wave (cm/s)	44	8.6 ± 2.1	8.2 ± 2.3	-0.3 ± 2.2	0.25
Diastolic function					
LAV (mL)	63	61.6 ± 20.7	68.2 ± 29.7	5.8 ± 20.1	0.027
LAVI (mL/m <sup>2</sup> )	63	34.2 ± 10.8	37.6 ± 15.0	3.1 ± 11.4	0.034
E/A ratio	73	1.1 ± 0.4	1.1 ± 0.4	-0.0 ± 0.4	0.9
E/e' ratio	49	8.8 ± 4.9	9.3 ± 5.2	0.3 ± 2.8	0.25
e'-wave (cm/s)	52	10.6 ± 3.6	10.1 ± 3.7	-0.6 ± 3.7	0.098
DT (ms)	76	210.4 ± 61.0	212.2 ± 60.4	-7.8 ± 81.8	0.89
Right ventricular quantification					
TAPSE (mm)	49	24.2 ± 4.9	23.6 ± 6.1	-0.6 ± 6.4	0.68

LVMi, LAVI and LVEDVI indexed by body surface area (Dubois).

LVMi: left ventricular mass index; LVEF: left ventricular ejection fraction; LVEDVI: left ventricular end-diastolic volume index; mitral S' wave: mitral valve longitudinal systolic kinetics in Tissue Doppler imaging; LAVI: left atrial volume index; E/A ratio: peak protodiastolic E-wave (m/s) and protosystolic A-wave (m/s) velocities on the mitral profile; E/e' ratio: mitral annulus displacement velocity in protodiastole assessed by Tissue Doppler imaging (e'-wave); DT: E-wave deceleration time; TAPSE: tricuspid annulus plane systolic excursion.

KT, with a significant late decrease between 12 and 36 months [13]. Kensinger et al. reported a significant reverse cardiac remodelling (LVMi, LAVI, LVEF) at 12 months among 85 patients in comparison to 1-month post-KT as well as a significant improvement at 24 months in comparison to 1-month post-KT (in only 33 patients) [12]. Nevertheless, in contrast to our results, they did not report significant changes between 12 and 24 months [12].

Of note, several studies prospectively assessed the effect of CNI reduction/withdrawal with introduction of mTOR inhibitors on cardiac parameters [14–16]. Some authors reported an improvement in left ventricular hypertrophy after one year of CNI reduction [14,15], whereas others did not report any significant changes in LV diastolic function, systolic function, and morphology after three years of CNI withdrawal [16].

The timing of the echocardiograms after KT may potentially have an impact on the observed results. In an informative/insightful study involving two different groups of patients with similar characteristics, Dudziak et al. [17] compared the evolution of LVEF between month 3 and month 33 after KT and the evolution of LVEF between month 34 and month 64 after KT. In the “early” group, LVEF increased from 59.7 ± 9.8% to 62.0 ± 9.1%, whereas it decreased from 68.2 ± 4.5% to 65.7 ± 7.5% in the “late” group. While the authors did not explain these differences, which are factually statistically non-significant, these findings may corroborate/are congruent with the hypothesis of a late adverse cardiac remodelling after KT, possibly related to immunosuppressive

**Table 3**

Association between clinical or laboratory factors with echocardiographic parameters at the time of the first echocardiography (multivariable analysis with echocardiographic parameter as the endpoint).

LAVI determinants		
	exp (Beta)* $\pm$ SD	P
Pre-KT hypertension	1.329 $\pm$ 1.121	0.018
Valvular heart disease	1.545 $\pm$ 1.127	0.001
Causal nephropathy		
Glomerulonephritis	1.398 $\pm$ 1.135	0.043
IgA nephropathy	0.996 $\pm$ 1.156	
Nephroangiosclerosis	1.385 $\pm$ 1.162	
Polycystic disease	1.293 $\pm$ 1.156	
Other	1.447 $\pm$ 1.150	
Malformative uropathy (ref)		
AVF closing	0.839 $\pm$ 1.081	0.031
LVEF determinants		
	Beta $\pm$ SE	P
Pre-KT diabetes	6.436 $\pm$ 3.216	0.049
Post-KT eGFR (ml/min/1.73m <sup>2</sup> )	0.132 $\pm$ 0.053	0.016
Post-KT use of ACEi/ARB	4.455 $\pm$ 2.167	0.044

KT: kidney transplantation; AVF: arteriovenous fistula; LAVI: left atrial volume index (mL/m<sup>2</sup>); LVEF: left ventricular ejection fraction (%); eGFR: estimated glomerular filtration rate (ml/min/1.73m<sup>2</sup>); ACEi: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker.

\* In light of the distribution of LAVI, LAVI was log-transformed. Exp(Beta) coefficient is reported to express associations with LAVI (rather than its log). Importantly, exp(Beta) should be interpreted on a multiplicative scale: e.g., patients with a history of pre-KT hypertension have 33% higher (exp[B] = 1.329) LAVI than patients without.

**Table 4**

Association between clinical or laboratory factors with changes in echocardiographic parameters between the first and second echocardiography during follow-up ( $\Delta = \text{TTE2} - \text{TTE1}$ ).

	Beta $\pm$ SD	P
Determinants of change in LAVI (LAVI2- LAVI1)		
LAVI (mL/m <sup>2</sup> ) at the time of TTE1	-0.321 $\pm$ 0.148	0.034
Male sex	8.112 $\pm$ 2.747	0.005
Pre-KT hypertension	9.725 $\pm$ 4.156	0.023
ECD * (LD as reference)	3.791 $\pm$ 3.587	0.3
SCD * (LD as reference)	-5.924 $\pm$ 3.978	0.14
Induction therapy with ATG (basiliximab as reference)	7.920 $\pm$ 2.974	0.01
Determinants of change in LVEF (LVEF2-LVEF1)		
4-cavity LVEF at the time of TTE1	-0.826 $\pm$ 0.170	<0.0001
Haemoglobin at the time of TTE1 (g/dl) > median (>12.9 g/dL)	6.029 $\pm$ 2.967	0.047
ACEi/ARB	8.306 $\pm$ 3.161	0.011

LAVI: left atrial volume index; ECD: expanded criteria donor; SCD: standard criteria donor; LD: living donor; ATG: anti-thymocyte globulin; LVEF: left ventricular filtration ejection; eGFR: estimated glomerular filtration rate; ACEi: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker.

\* p for the difference between EDC and SCD = 0.013.

drugs, following an early period of reverse remodelling related to dialysis cessation/correction of the uraemic milieu.

#### 4.2. Clinical relevance of LVEF and LAVI in KT patients

Although the mean LVEF of patients of the present study was deemed normal at the first and second evaluation, a mean annual decrease of 2.7% may lead to a grey zone ranging from 50 to 55%, which is associated with an increased risk of mortality in the general population [18] [28].

Left atrial dilatation is associated with cardiovascular morbidity-mortality in the general population [19], as well as in patients with chronic kidney disease or end-stage renal disease [20,21]. Among KT patients, LA volume at the time of inscription on the waiting list has reportedly been associated with patient survival after KT [22] and LA volume at the time of transplantation associated with long-term patient survival [23]. Of note, our results are in keeping with the study by Regele et al. [24] conducted in 413 patients with a follow-up of 8 years post-KT in which the authors reported an increase in MRI-assessed LA diameter among 70% of the patients, in comparison to the pre-KT assessment. Of note, the subgroup of patients with a regression of left atrial dilatation during follow-up had a significantly decreased morbidity-mortality after KT [24].

#### 4.3. Factors associated with cardiac remodelling in the present study

In the present study, baseline LVEF was higher in patients receiving ACE inhibitors or ARB. Moreover, the use of ACEi or ARB was associated with an improvement in LVEF during follow-up. ACEi/ARBs are recommended as first-line drugs in the treatment of heart failure with reduced ejection fraction [25]. However, data on the treatment of heart failure in CKD and especially in KT patients are clearly lacking [6]. Several randomised controlled clinical trials conducted among KT patients reported a beneficial impact of ACEi [15,26], as well as calcium channel blockers [26] on left ventricular hypertrophy. In a small RCT of KT patients with left ventricular hypertrophy, lisinopril reduced LV mass index compared with placebo [27]. Intriguingly, in our study, pre-KT diabetes was associated with a higher LVEF, which could lead to hypothesise that the CV treatment of diabetic patients was more optimised than the other KT patients.

The association between haemoglobin level and improved LVEF noted during patient follow-up are consistent with published results on reverse remodelling after KT [28]. Anaemia has been reported as a risk factor of *de novo* HF among KT patients [1]. Moreover, anaemia in KT patients is associated with decreased graft survival [29], as well as decreased patient survival and increased CV morbidity-mortality [30]. As underlined in a recent metaanalysis [31], data on the use of erythropoietin-stimulating agents in KT patients are sparse. Only two RCTs reported the impact of long-term use of ESAs among KT, with a beneficial impact on graft function [32] and quality of life [33]. To date, no RCT has assessed the impact of long-term use of ESAs on CV morbidity-mortality including *de novo* heart failure [31].

In the present study, receiving a graft from an ECD was associated with an increase in atrial volume over time. Grafts from ECD are associated with poorer graft function and survival in comparison to grafts from SCD [34]. Cardiac remodelling after KT among these patients may therefore be related to the persistence of some degree of CKD. Nevertheless, analyses were adjusted for this variable. Moreover, patients receiving grafts from ECD are on average older which may partly explain the worsening of cardiac remodelling after KT. Moreover, grafts for ECD are associated with poorer graft and patient survival in comparison to SCD [34]. It may be of interest to evaluate whether the poor prognosis of these patients is partly related to the absence of reverse cardiac remodelling after KT. In the current study, an induction therapy with ATG was associated with a significant increase in left atrial volume in comparison to basiliximab. The direct association between the type of

induction and adverse cardiac remodelling has not previously been reported. Of note, in contrast with our results, a pre-clinical study reported a T-cell infiltration of the heart in CKD mice and an improvement in cardiac cardiomyopathy with T-cell depletion [35]. Despite multivariate analyses, it is likely that confounding factors not fully taken into consideration by statistical adjustment may explain this observation. Moreover, ATG induction therapy was associated with lower LVEF at baseline. In our centre, this induction therapy is generally administered in patients at higher risk of delayed graft function (including grafts from an ECD) or who are at greater immunological risk, possibly including patients with longer pre-KT dialysis duration and/or a limited access to KT. This may explain the absence of potential beneficial effect of ATG on cardiac parameters.

Finally, patients who experienced AVF closing had significantly lower LAVI at the time of the first echocardiography. Nevertheless, we did not observe a significant association between AVF ligation and changes in cardiac parameters during follow-up. The impact of AVF ligation on the reduction of cardiovascular complications after KT still remains controversial [36]. Several prospective studies reported an improvement in echocardiographic findings after AVF ligation. Nevertheless, some authors reported an increase in diastolic blood pressure after AVF ligation [37], as well as an accelerated decline in graft function [38]. A recent RCT confirmed the beneficial impact of AVF ligation on cardiac remodelling [39] although the long-term impact on patient survival or CV outcomes remains unknown.

#### 4.4. Clinical implications

The two factors identified as counteracting the deterioration in LVEF during follow-up were haemoglobin >12.9 g/dL and ACEi/ARB therapy.

The association between ACEi or ARB treatment and LVEF suggests the need for further prospective studies to assess the prognostic CV impact of these cardio-protective drugs in KT patients. To date, their benefit on morbidity-mortality is not clearly established in KT patients whether for graft or patient survival [40]. Moreover, evidence of optimal treatment of HF among KT patients is clearly lacking [6]. There is no published study evaluating interventions that could potentially prevent *de novo* HF in KT patients. Moreover, there are no trials in KT patients that have included HF as an endpoint. Considering the high incidence of *de novo* HF after KT, this outcome should also be specifically considered as an outcome of interest. Prospective randomised trials should also focus on the impact of erythropoietin stimulating agents (ESAs) on major adverse cardiovascular events (MACE) after KT, including *de novo* heart failure given the scarcity of data in this particular population [31].

#### 4.5. Limitations

The present study has several limitations, notably being a retrospective, single-centre, observational study with a small patient cohort. However, we performed a multiparametric cardiac evaluation not limited to a given parameter, with a centralised, blinded and standardised review of all echocardiograms.

There may be a selection bias considering that the echocardiograms were not performed as part of a protocol with pre-specified post-KT durations between the visits and KT. However, echocardiograms performed in intensive care units were excluded. Moreover, the patients included in this study had a cardiological follow-up at the University hospital, and possibly had more comorbidities than the patients of the entire cohort of KT patients.

In our center, we do not routinely conduct Holter ECG monitoring to screen for atrial fibrillation in asymptomatic patients. Consequently, some patients may have developed undiagnosed paroxysmal AF, which could have influenced the changes in LAVI and LVEF following kidney transplantation.

Biplane LVEF was not attainable in our study due to inconsistent

acquisition of two-chamber views in our cohort or the presence of image quality issues that precluded accurate measurements. Furthermore, several patients exhibited one or more missing echocardiographic variables (besides 2 chamber LVEF). Larger studies should ideally prospectively evaluate echocardiographic changes.

Despite KDIGO guidelines recommending the use of statins in KT patients, treatment in our population was administered to <30% of individuals. This could potentially have contributed, to some extent, to the development of clinical or subclinical coronary disease and subsequent structural cardiac changes.

## 5. Conclusion

This study suggests the development of cardiomyopathy in post-kidney transplantation patients, reflected by an increase in left atrial volume and a reduction in left ventricular systolic ejection fraction. Modifiable factors such as the correction of anaemia or ACEi/ARB administration could limit this cardiac remodelling. The present results furthermore suggest that a sub-group of patients receiving a graft from an expanded criteria donor may particularly benefit from these interventions. Prospective and interventional studies are needed to confirm these findings.

## CRedit authorship contribution statement

**Valentin Panisset:** Data curation, Writing – original draft. **Nicolas Girerd:** Conceptualization, Methodology, Validation, Writing – review & editing. **Erwan Bozec:** Data curation, Investigation. **Zohra Lamiral:** Formal analysis. **Quentin d'Hervé:** Data curation. **Luc Frimat:** Writing – review & editing. **Sophie Girerd:** Conceptualization, Methodology, Supervision, Writing – original draft, Writing – review & editing.

## Declaration of competing interest

NG reports honoraria from AstraZeneca, Bayer, Boehringer, Lilly, Novartis, NovoNordisk, Roche Diagnostics, Np medical, Echosens.

VP, EB, ZL, QD, LF, and SG declare no conflict of interest.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijcard.2024.131852>.

## References

- [1] K.L. Lentine, M.A. Schnitzler, K.C. Abbott, L. Li, T.E. Burroughs, W. Irish, et al., *De novo congestive heart failure after kidney transplantation: a common condition with poor prognostic implications*, *Am. J. Kidney Dis.* 46 (4) (2005) 720–733.
- [2] C.R. Lenihan, S. Liu, A. Deswal, M.E. Montez-Rath, W.C. Winkelmayer, *De novo heart failure after kidney transplantation: trends in incidence and outcomes*, *Am. J. Kidney Dis.* 72 (2) (2018) 223–233.
- [3] N. Patel, M.M. Yaqoob, D. Aksentijevic, *Cardiac metabolic remodelling in chronic kidney disease*, *Nat. Rev. Nephrol.* 18 (8) (2022) 524–537.
- [4] L.C. Pickup, J.P. Law, A. Radhakrishnan, A.M. Price, C. Loutradis, Smith TO, et al., *Changes in left ventricular structure and function associated with renal transplantation: a systematic review and meta-analysis*, *ESC Heart Fail.* 8 (3) (2021) 2045–2057.
- [5] S. Van Laecke, D. Abramowicz, *Cardiovascular disease in kidney transplant recipients: leave no stone unturned*, *Nephrol. Dial. Transplant.* 34 (5) (2019) 727–730.
- [6] A.A. House, C. Wanner, M.J. Sarnak, I.L. Pina, C.W. McIntyre, P. Komenda, et al., *Heart failure in chronic kidney disease: conclusions from a kidney disease: improving global outcomes (KDIGO) controversies conference*, *Kidney Int.* 95 (6) (2019) 1304–1317.
- [7] R.M. Lang, L.P. Badano, V. Mor-Avi, J. Filalo, A. Armstrong, L. Ernande, et al., *Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging*, *J. Am. Soc. Echocardiogr.* 28 (1) (2015) 1–39 e14.
- [8] A. Elezaby, R. Dexheimer, K. Sallam, *Cardiovascular effects of immunosuppression agents*, *Front Cardiovasc Med.* 9 (2022) 981838.

- [9] J.C. de la Fuente-Mancera, I. Forado-Benatar, M. Farrero, Management of long-term cardiovascular risk factors post organ transplant, *Curr. Opin. Organ Transplant.* 27 (1) (2022) 29–35.
- [10] T.Y. Koo, C. Ahn, J. Yang, Renal allograft function is a risk factor of left ventricular remodeling after kidney transplantation, *Transplant. Proc.* 49 (5) (2017) 1043–1047.
- [11] M. Kobayashi, O. Huttin, J. Schikowski, E. Bozec, L. Zohra, L. Frimat, et al., Cardiovascular comorbidities are the Main predictors of cardiac reverse remodeling following kidney transplantation, *Cardiology.* 145 (2) (2020) 71–76.
- [12] C. Kensing, A. Hernandez, A. Bian, M. Fairchild, G. Chen, L. Lipworth, et al., Longitudinal assessment of cardiac morphology and function following kidney transplantation, *Clin. Transpl.* 31 (1) (2017).
- [13] T. Zapolski, J. Furmaga, A.P. Wysokinski, A. Wysocka, S. Rudzki, A. Jaroszynski, The atrial uremic cardiomyopathy regression in patients after kidney transplantation - the prospective echocardiographic study, *BMC Nephrol.* 20 (1) (2019) 152.
- [14] E. Paoletti, L. Marsano, D. Bellino, P. Cassottana, G. Cannella, Effect of everolimus on left ventricular hypertrophy of de novo kidney transplant recipients: a 1 year, randomized, controlled trial, *Transplantation.* 93 (5) (2012) 503–508.
- [15] D. Hernandez, P. Ruiz-Esteban, D. Gaitan, D. Burgos, A. Mazuecos, R. Collantes, et al., Regression of cardiac growth in kidney transplant recipients using anti-m-TOR drugs plus RAS blockers: a controlled longitudinal study, *BMC Nephrol.* 15 (2014) 65.
- [16] K. Murbraech, R. Massey, L.H. Undset, K. Midtvedt, H. Holdaas, S. Aakhus, Cardiac response to early conversion from calcineurin inhibitor to everolimus in renal transplant recipients—a three-yr serial echocardiographic substudy of the randomized controlled CENTRAL trial, *Clin. Transpl.* 29 (8) (2015) 678–684.
- [17] M. Dudziak, A. Debska-Slizien, B. Rutkowski, Cardiovascular effects of successful renal transplantation: a 30-month study on left ventricular morphology, systolic and diastolic functions, *Transplant. Proc.* 37 (2) (2005) 1039–1043.
- [18] C.W. Tsao, A. Lyass, M.G. Larson, S. Cheng, C.S. Lam, J.R. Aragam, et al., Prognosis of adults with borderline left ventricular ejection fraction, *JACC Heart Fail.* 4 (6) (2016) 502–510.
- [19] J.R. Kizer, J.N. Bella, V. Palmieri, J.E. Liu, L.G. Best, E.T. Lee, et al., Left atrial diameter as an independent predictor of first clinical cardiovascular events in middle-aged and elderly adults: the strong heart study (SHS), *Am. Heart J.* 151 (2) (2006) 412–418.
- [20] K.K. Kadappu, K. Abhayaratna, A. Boyd, J.K. French, W. Xuan, W. Abhayaratna, et al., Independent echocardiographic markers of cardiovascular involvement in chronic kidney disease: the value of left atrial function and volume, *J. Am. Soc. Echocardiogr.* 29 (4) (2016) 359–367.
- [21] A. Tanasa, L. Tapoi, C. Ureche, R. Sascu, C. Statescu, A. Covic, Left atrial strain: a novel “biomarker” for chronic kidney disease patients? *Echocardiography.* 38 (12) (2021) 2077–2082.
- [22] R.K. Patel, C. Pennington, K.K. Stevens, A. Taylor, K. Gillis, E. Rutherford, et al., Effect of left atrial and ventricular abnormalities on renal transplant recipient outcome—a single-center study, *Transp. Res.* 3 (1) (2014) 20.
- [23] A. Kainz, G. Goliash, F. Wiesbauer, T. Binder, G. Maurer, H.J. Nesser, et al., Left atrial diameter and survival among renal allograft recipients, *Clin. J. Am. Soc. Nephrol.* 8 (12) (2013) 2100–2105.
- [24] F. Regele, A. Kainz, M. Kammer, A. Beer, R. Steringer-Mascherbauer, T. Binder, et al., Regression of left atrial diameter after kidney transplantation is associated with prolonged survival: an observational study, *Transpl. Int.* 31, (2018) 999–1007.
- [25] T.A. McDonagh, M. Metra, M. Adamo, R.S. Gardner, A. Baumbach, M. Bohm, et al., 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure, *Eur. Heart J.* 42 (36) (2021) 3599–3726.
- [26] K. Midtvedt, H. Ihlen, A. Hartmann, P. Bryde, B.L. Bjerkely, A. Foss, et al., Reduction of left ventricular mass by lisinopril and nifedipine in hypertensive renal transplant recipients: a prospective randomized double-blind study, *Transplantation.* 72 (1) (2001) 107–111.
- [27] E. Paoletti, P. Cassottana, M. Amidone, M. Gherzi, D. Rolla, G. Cannella, ACE inhibitors and persistent left ventricular hypertrophy after renal transplantation: a randomized clinical trial, *Am. J. Kidney Dis.* 50 (1) (2007) 133–142.
- [28] N. Hawwa, K. Shrestha, M. Hammadah, P.S.D. Yeo, R. Fatica, W.H.W. Tang, Reverse remodeling and prognosis following kidney transplantation in contemporary patients with cardiac dysfunction, *J. Am. Coll. Cardiol.* 66 (16) (2015) 1779–1787.
- [29] N. Kamar, L. Rostaing, S. Ignace, E. Villar, Impact of post-transplant anemia on patient and graft survival rates after kidney transplantation: a meta-analysis, *Clin. Transpl.* 26 (3) (2012) 461–469.
- [30] P. Mekraksakit, N. Leelawiwat, J. Benjanuwattra, S. Duangkham, G. Del Rio-Pertuz, C. Thongprayoon, et al., A systematic review and Meta-analysis of Posttransplant Anemia with overall mortality and cardiovascular outcomes among kidney transplant recipients, *Prog. Transplant.* 33 (1) (2023) 78–89.
- [31] E.Y. Chung, S.C. Palmer, V.M. Saglimbene, J.C. Craig, M. Tonelli, G.F. Strippoli, Erythropoiesis-stimulating agents for anaemia in adults with chronic kidney disease: a network meta-analysis, *Cochrane Database Syst. Rev.* 2 (2) (2023) CD010590.
- [32] G. Choukroun, N. Kamar, B. Dussol, I. Etienne, E. Cassuto-Viguier, O. Toupance, et al., Correction of postkidney transplant anemia reduces progression of allograft nephropathy, *J. Am. Soc. Nephrol.* 23 (2) (2012) 360–368.
- [33] T. Pile, M. Raftery, R. Thuraisingham, C.J. Kirwan, S. Harwood, M.M. Yaqoob, Treating Posttransplant Anemia with erythropoietin improves quality of life but does not affect progression of chronic kidney disease, *Exp. Clin. Transplant.* 18 (1) (2020) 27–33.
- [34] A.H. Querard, Y. Foucher, C. Combescure, E. Dantan, D. Larmet, M. Lorent, et al., Comparison of survival outcomes between expanded criteria donor and standard criteria donor kidney transplant recipients: a systematic review and meta-analysis, *Transpl. Int.* 29 (4) (2016) 403–415.
- [35] P.D. Winterberg, J.M. Robertson, M.S. Kelleman, R.P. George, M.L. Ford, T cells play a causal role in diastolic dysfunction during uremic cardiomyopathy, *J. Am. Soc. Nephrol.* 30 (3) (2019) 407–420.
- [36] P. Vanderweckene, L. Weekers, P. Lancellotti, F. Jouret, Controversies in the management of the haemodialysis-related arteriovenous fistula following kidney transplantation, *Clin. Kidney J.* 11 (3) (2018) 406–412.
- [37] P. Unger, O. Xhaet, K.M. Wissing, B. Najem, P. Dehon, P. van de Borne, Arteriovenous fistula closure after renal transplantation: a prospective study with 24-hour ambulatory blood pressure monitoring, *Transplantation.* 85 (3) (2008) 482–485.
- [38] L. Weekers, P. Vanderweckene, H. Pottel, D. Castanares-Zapatero, C. Bonvoisin, E. Hamoir, et al., The closure of arteriovenous fistula in kidney transplant recipients is associated with an acceleration of kidney function decline, *Nephrol. Dial. Transplant.* 32 (1) (2017) 196–200.
- [39] N.N. Rao, M.B. Stokes, A. Rajwani, S. Ullah, K. Williams, D. King, et al., Effects of arteriovenous fistula ligation on cardiac structure and function in kidney transplant recipients, *Circulation.* 139 (25) (2019) 2809–2818.
- [40] S. Hiremath, D.A. Fergusson, N. Fergusson, A. Bennett, G.A. Knoll, Renin-angiotensin system blockade and long-term clinical outcomes in kidney transplant recipients: a Meta-analysis of randomized controlled trials, *Am. J. Kidney Dis.* 69 (1) (2017) 78–86.