ORIGINAL ARTICLE

# Cohort study: "Outcomes of kidney transplantation in patients with prosthetic heart valves"

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## SUMMARY

The number of kidney transplant candidates with prosthetic heart valves (PHVs) is increasing. Yet, outcomes of kidney transplantation in these patients are still unclear. This is the first report of post-transplant outcomes in patients with PHVs at time of kidney transplantation. We conducted a matched cohort study among recipients from the multicentric and prospective DIVAT cohort to compare the outcomes in patients with left-sided PHVs at time of transplantation and a group of recipients without PHV matched according to age, dialysis time, initial disease, pretransplant DSA, diabetes, and cardiovascular events. Of 23 018 patients, 92 patients with PHVs were included and compared to 276 patients without PHV. Delayed graft function and postoperative bleeding occurred more frequently in patients with PHVs. Kidney graft survival was similar between groups. 5-year overall survival was 68.5% in patients with PHV vs. 87.9% in patients without PHV [HR, 2.72 (1.57–4.70), $P = 0.0004$]. Deaths from infection, endocarditis, and bleeding were more frequent in patients with PHV. Mechanical valves, but not bioprosthetic valves, were independent risk factors for mortality [HR, 2.89 (1.68–4.97), $P = 0.0001$]. Patients with PHV have high mortality rates after kidney transplantation. These data suggest that mechanical valves, but not biological valves, increase risks of post-transplant mortality.

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## Introduction

The prevalence of valvular heart disease is increasing in patients with end-stage kidney disease (ESKD) [1]. There is a corresponding increase in the number of ESKD patients who require heart valve replacement [2,3]. Mortality is high in these patients, with only about half the patients younger than 65 years surviving beyond 2 years after heart valve surgery [4]. There is currently no recommendation on the type of valve prosthesis to choose in ESKD patients because studies comparing mid-long-term survivals after bioprosthetic or mechanical valve replacement have yielded conflicting results in this population [5–12]. As for renal replacement therapy, kidney transplantation is theoretically the best option [13–15]. If successful, it provides patients with the best possible quality of life and reduces cardiovascular mortality as compared to dialysis [16–18]. However, patients with prosthetic heart valves (PHV) are high-risk kidney transplant recipients. Transplantation should only proceed in these patients if there is an expectation of the graft and patient surviving for a significant period of time. Given the risks of failure, transplantation from a living donor may also be problematic. Although the clinical team requires a realistic prediction of possible success and risks of failure to evaluate eligibility for transplantation and inform patients, there are currently no data on the incidence of complications, graft failures, and deaths after transplantation in patients with PHVs. The aim of the present study was to assess post-transplant outcomes in patients with PHVs at time of transplantation. To this end, we conducted a matched cohort study among kidney transplant recipients from the French multicentric and prospective DIVAT (Données Informatisées et VAlidées en Transplantation) cohort.

## Materials and methods

### Study type and data source

An observational, multicenter, matched cohort study was conducted in kidney transplant recipients of the French DIVAT (Données Informatisées et VAlidées en Transplantation) database, which is a prospectively maintained database including transplant and follow-up data of all adult kidney and/or pancreas transplant recipients from French university hospitals including Lyon, Montpellier, Nancy, Nantes, Necker (Paris), Bordeaux, and Nice.

### Patients

The study included all adult patients (≥18 years old) who underwent left-sided cardiac surgical valve replacement before kidney transplantation and received transplantation between March 9, 2000 and August 21, 2019. One patient was excluded because he had transcatheter aortic valve replacement. Each recipient with PHV was matched individually with three kidney transplant recipients without PHV on (i) four possible confounders known to be at time of transplantation major risk factors for post-transplant mortality: recipient age (±10 years), pretransplant dialysis (no dialysis or dialysis time ≤6 months vs. dialysis time >6 months),

diabetes, cardiovascular events [19–21] and (ii) two possible confounders known to be at time of transplantation risks factors for allograft loss: recurrent nephropathy and preformed donor-specific anti-HLA antibodies (DSA) [22–24]. Matching ensured an equal distribution of these variables among patients with or without PHVs (Table 1).

An appropriate written informed consent for data collection was obtained from all the participants at time of transplantation. The consent form contained information on the possibility of later anonymous use of the data for research purposes. All the procedures were carried out in accordance with the ethical standards of the institutional review boards, national research committees and the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

## Data collection

### Characteristics of the study population

Variables analyzed included: (i) recipient characteristics at time of transplantation: age, sex, duration of dialysis before transplantation, initial nephropathy, diabetes, malignancies, cardiac events (cardiac arrest, heart failure, coronary events, conduction disorders, rhythm disorders,

**Table 1.** Baseline characteristics of patients with or without prosthetic heart valves (PHVs) at time of transplantation.

| Variable | PHV (n = 92) | No PHV (n = 276) | P value |
|---|---|---|---|
| Recipient characteristics | | | |
|   Age (year)* | 56 ± 13 | 56 ± 13 | 1 |
|   Men | 61 (66.3) | 202 (73.2) | 0.29 |
|   Retransplantation | 27 (29.3) | 56 (20.3) | 0.08 |
|   Preemptive transplantation or dialysis <6 months* | 7 (7.6) | 21 (7.6) | 1 |
|   Time since dialysis (mo) | 62.7 ± 53.2 | 48.1 ± 46.1 | 0.006 |
|   Recurrent nephropathy* | 33 (35.9) | 99 (35.9) | 1 |
|   Cardiovascular events* | 79 (85.9) | 237 (85.9) | 1 |
|   Diabetes | 17 (18.5) | 51 (18.5) | 1 |
|   Neoplasia | 11 (12.0) | 38 (13.8) | 0.73 |
|   Time since valve replacement (year)† | 5.4 ± 5.6 | – | – |
|   Mechanical valve | 59 (64.1) | – | – |
|   Biological valve | 33 (35.9) | – | – |
|   Valve location | | | |
|     Aortic | 72 (78.3) | – | – |
|     Mitral | 13 (14.1) | – | – |
|     Aortic and mitral | 7 (7.6) | – | – |
| Donor characteristics | | | |
|   Age (year) | 56 ± 17 | 57 ± 16 | 0.65 |
|   Deceased | 84 (91.3) | 248 (89.9) | 0.84 |
| Transplant data | | | |
|   Preformed DSA* | 23 (25.0) | 69 (25.0) | 1 |
|   Cold ischemic time (min) | 1059 ± 501 | 1045 ± 541 | 0.62 |
|   Number of mismatches A, B, DR | 3.6 ± 1.3 | 3.2 ± 1.4 | 0.01 |
| Immunosuppression‡ | | | |
|   Anti-ILR2 | 35 (38.0) | 91 (33.0) | 0.31 |
|   Thymoglobulins | 53 (57.6) | 175 (63.4) | 0.32 |
|   Tacrolimus | 78 (84.8) | 209 (75.7) | 0.08 |
|   Ciclosporine | 14 (15.2) | 64 (23.2) | 0.14 |
|   MMF/MPA | 89 (96.7) | 258 (93.5) | 0.31 |
|   Prednisone | 90 (97.8) | 263 (95.3) | 0.37 |
|   Sirolimus/everolimus | 4 (4.3) | 13 (4.7) | 1 |

Anti-ILR2, anti-interleukin receptor 2; DSA, donor-specific antibodies; MMF, Mycophenolate mofetil; MPA, Mycophenolic acid.

Data are no. (%) of patients unless otherwise indicated. Continuous variables are reported as mean ± SD.

*Matching criteria between the PHV and No PHV group.

†Data missing for 4 patients in PHV group.

‡Data missing for 3 patients in No PHV group.

pulmonary arterial hypertension), cerebrovascular events (stroke), peripheral vascular events (peripheral artery disease, venous thromboembolic disease), cardiovascular events (i.e. history of cardiac events, cerebrovascular and/or peripheral vascular events as defined above), type of PHV (biological versus mechanical), and location, time since cardiac valve replacement, (ii) donor characteristics: age and deceased status, iii) transplant characteristics: cold ischemic time, HLA mismatches, induction agent and immunosuppressive treatments at transplantation.

### Outcomes

The onset of the following events was retrieved: delayed graft function (defined as the need for dialysis within the first week after kidney transplantation), hemorrhagic complications, biopsy-proven rejection, *de novo* donor-specific antibodies, graft loss, infections, endocarditis, deaths with and without a functioning graft. Graft survival was calculated from the date of transplantation until the beginning of hemodialysis. Patient survival was calculated from the date of transplantation to death. Causes of death were ascertained from the Centers.

### Statistics

Categorical variables were expressed as percentages and compared with the chi-square test or Fisher exact test whenever appropriate. Continuous variables were expressed as mean $\pm$ SD and compared using the Mann–Whitney $U$ test. Survival curves were constructed with the Kaplan–Meier method and compared with the log-rank test. The Cox proportional hazards regression model was used in both univariate and multivariate models. All significant variables in the univariate analysis with a level set at $P < 0.1$ were incorporated into multivariate cox models considering the number of events. All tests were two sided, and $P$ values <0.05 were considered to represent statistically significant differences. Analyses were performed with GRAPHPAD PRISM 5 and SAS 9.4 Software.

## Results

### Baseline characteristics of the study population

Twenty-three thousand and eighteen patients who received kidney transplantation between 2000 and 2019 were screened. Ninety-two (0.4%) of them had left-sided

prosthetic heart valves at time of transplantation and were compared to 276 patients without PHV. Baseline characteristics of the groups are shown in Table 1. Patients with PHV remained longer on dialysis before transplantation than patients without PHV (14.6 $\pm$ 7.1 months more). Fifty-nine patients had mechanical prosthesis and 33 biological prosthesis. As expected, patients with mechanical prosthesis were younger than patients with biological prosthesis (52 $\pm$ 12 vs. 62 $\pm$ 13 years old, $P = 0.0002$, Table S1), and vascular nephropathies were more frequent in patients with bioprosthetic valves than in patients with mechanical valves (36.4% vs. 13.6%, respectively, $P = 0.02$, Table S1). Glomerulopathies were more frequent in patients with mechanical valves than in those with biological valves (49.2% vs. 27.3%, respectively, $P = 0.048$, Table S1).

### Renal allograft outcomes

Recipients with PHV exhibited a higher percentage of delayed graft function (DGF) (34.8% vs. 14.1%, $P < 0.0001$, Table 2) and postoperative hemorrhagic complications at the surgical site (47.8% vs. 11.6%, $P < 0.0001$, Table 2) than recipients without PHV. Incidences of de novo DSAs (26.1% vs. 29.0% in the PHV and No PHV groups, respectively), cellular rejections (8.7% vs. 11.2% in the PHV and No PHV groups, respectively), and humoral rejections (8.7% vs. 4.7% in the PHV and No PHV groups, respectively) were not significantly different between groups (Table 2). Proteinuria and estimated glomerular filtration rate at 1- and 5-years post-transplant were also similar between groups (Table 2) as was kidney allograft survival (HR, 1.50 [0.82–2.74], $P = 0.19$ by log-rank, Fig. S1).

### Post-transplant overall survival and causes of death

After a mean follow-up of 4.6 $\pm$ 4.3 years in the group of patients with PHVs and 4.2 $\pm$ 1.2 years in the group of patients without PHV ($P = 0.20$), 30 patients with PHVs (32.6%) and 36 patients without PHV (13.0%) died. The 5-year survival was 68.5% in the PHV group and 87.9% in the group of patients without PHV. Overall survival was lower in patients with PHVs than in those without PHV [HR, 2.72 (1.57–4.70), $P = 0.0004$ by log-rank, Fig. 1]. A higher proportion of patients died from infection and endocarditis in the PHV group (14.1% vs. 4.7%, $P = 0.004$ and 3.2% vs. 0.4%, $P = 0.02$, respectively, Table 3). Deaths from bleeding were also more frequent in patients with PHVs (3.3% vs. 0.0%, $P = 0.02$, Table 3) and occurred only in

**Table 2.** Renal outcomes in patients with or without prosthetic heart valves (PHVs).

| Variables | PHV (n = 92) | No PHV (n = 276) | P value |
|---|---|---|---|
| Delayed graft function, yes/no | 32 (34.8) | 39 (14.1) | <0.0001 |
| Hemorrhagic complications* | 44 (47.8) | 32 (11.6) | <0.0001 |
| Immunological outcomes | | | |
| DSA de novo | 24 (26.1) | 80 (29.0) | 0.69 |
| Rejection, yes/no | 16 (17.4) | 51 (18.5) | 0.88 |
| Cellular rejection | 8 (8.7) | 31 (11.2) | 0.56 |
| Humoral rejection | 8 (8.7) | 13 (4.7) | 0.19 |
| Humoral and cellular rejection | 0 (0.0) | 7 (2.5) | 0.20 |
| Kidney graft function at 12 months | | | |
| Proteinuria (g/g) | 0.47 ± 1.10 | 0.36 ± 0.62 | 0.50 |
| eGFR | 53 ± 29 | 48 ± 18 | 0.48 |
| Kidney graft function at 60 months | | | |
| Proteinuria (g/g) | 0.82 ± 2.61 | 0.40 ± 0.68 | 0.89 |
| eGFR | 50 ± 22 | 47 ± 17 | 0.60 |

DGF, delay graft function; eGFR, estimate glomerular filtration rate was calculated with the Modification of Diet Renal Disease formula.

Data are no. (%) of patients, unless otherwise indicated. Continuous variables are reported as mean ± SD.

*Postoperative hemorrhagic complications at the surgical site.

patients with mechanical valves (not shown). There was no significant difference between groups regarding deaths from cardiovascular events or cancer (4.3% vs. 1.8%, $P = 0.24$ and 4.3% vs. 3.3%, $P = 0.74$, respectively, Table 3).

### Independent risk factors for post-transplant mortality

Exploratory univariate analysis identified seven risk factors for post-transplant mortality in the study population (Table 4): recipient age [HR, 1.06 (1.03–1.09),

$P < 0.0001$], biological prosthesis [HR, 2.90 (1.42–5.94), $P = 0.002$], mechanical prosthesis [HR, 2.35 (1.40–3.96), $P = 0.0009$], pretransplant dialysis time [HR, 1.05 (1.00–1.11), $P = 0.07$], diabetes [HR, 2.59 (1.51–4.44), $P = 0.0003$], cerebrovascular and/or peripheral vascular events [HR, 1.62 (0.99–2.65), $P = 0.05$], and cardiac events [HR, 1.81 (1.02–3.23), $P = 0.04$]. Of note, the type of initial nephropathy, time since valve replacement and localization of the PHV (aortic or mitral) were not identified as risk factors for mortality (not shown). The seven identified variables were integrated in a multivariate analysis (Table 4), which identified five independent predictors for mortality. In contrast with the presence of a bioprosthetic valve, the presence of a mechanical valve was an independent risk factor for mortality [HR, 2.89 (1.68–4.97); $P = 0.0001$]. Other
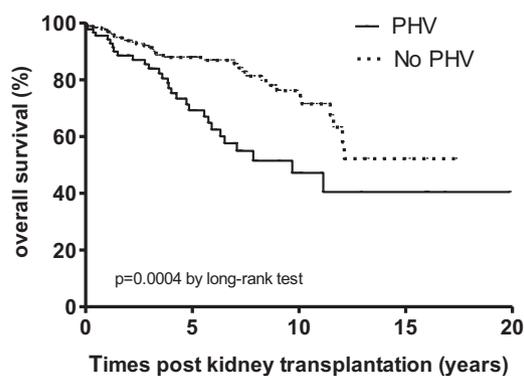


**Figure 1** Prosthetic heart valves are associated with poorer post-transplant overall survival. Kaplan-Meier curves for overall survival are shown for patients with or without PHV.

| | | | | | |
|---|---|---|---|---|---|
| No PHV | 276 | 98 | 34 | 4 | 1 |
| **PHV** | 92 | 34 | 11 | 6 | 1 |

**Table 3.** Causes of death in patients with or without prosthetic heart valves (PHVs).

| Causes of death | PHV (n = 92) | No PHV (n = 276) | P value |
|---|---|---|---|
| Infection | 13 (14.1) | 13 (4.7) | 0.004* |
| Endocarditis | 3 (3.2) | 1 (0.4) | 0.049* |
| Hemorrhage | 3 (3.3) | 0 (0.0) | 0.02* |
| Cardiovascular | 4 (4.3) | 5 (1.8) | 0.24 |
| Cancer | 4 (4.3) | 9 (3.3) | 0.74 |
| Other/unknown | 6 (6.5) | 9 (3.3) | 0.22 |

*$P$-value<0.05 is significant.

**Table 4.** Univariate and multivariate analyses of risk factors for post-transplant death in the study population (*n* = 368).

| Variable | Univariate | | Multivariate | |
|---|---|---|---|---|
| | HR (95% CI) | *P* value | HR (95% CI) | *P* value |
| Recipient age (per 1-year increment) | 1.06 (1.03–1.09) | <0.0001 | 1.06 (1.04–1.09) | <0.0001* |
| Biological prosthesis | 2.90 (1.42–5.94) | 0.002 | – | NS |
| Mechanical prosthesis | 2.35 (1.40–3.96) | 0.0009 | 2.89 (1.68–4.97) | 0.0001* |
| Time since dialysis (per 1-year increment) | 1.05 (1.00–1.11) | 0.07 | 1.07 (1.02–1.13) | 0.01* |
| Diabetes | 2.59 (1.51–4.44) | 0.0003 | 1.99 (1.13–3.53) | 0.02* |
| Cerebrovascular and peripheral events | 1.62 (0.99–2.65) | 0.05 | – | NS |
| Cardiac events | 1.81 (1.02–3.23) | 0.04 | 1.88 (1.04–3.40) | 0.04* |

*$P$-value<0.05 is significant.

independent predictors of mortality were recipient age [HR, 1.06 (1.04–1.09), $P$ < 0.0001], pretransplant dialysis time [HR, 1.07 (1.02–1.13), $P$ = 0.01], diabetes [HR, 1.99 (1.13–3.53), $P$ = 0.02], and cardiac events [HR, 1.88 (1.04–3.40), $P$ = 0.04].

## Discussion

Due to the aging of the population, an increasing number of patients with end-stage kidney disease require cardiac valve replacement and may be candidates for kidney transplantation. While cardiac valve replacement has been associated with poor outcomes in kidney transplant patients [25], outcomes of kidney transplantation in ESKD patients with PHVs at time of transplantation remain unknown. This study is the first to evaluate the results of kidney transplantation in recipients with left-sided prosthetic heart valves. We found that mechanical valves were associated with a 3-fold increased risk of post-transplant mortality. In contrast, biological valves were not identified as a risk factor for post-transplant mortality. This observation suggests that the presence of a biological valve in a kidney transplant candidate should not, or only marginally, influence the medical decision to allow or not registration on the transplant waiting list. Since the presence of a mechanical valve is an additional risk factor of post-transplant mortality, a clear information should be given to patients about their specific risk. Eligible patients should be referred for transplantation as soon as possible to anticipate and limit dialysis time that was identified as an additional independent risk factor for mortality. In our study population, patients with PHVs remained for a longer period of time on dialysis before transplantation than patients without PHVs, which may reflect some hesitation in referring these high-risk patients to transplantation centers.

It is likely that anticoagulant therapy is a key explanation for the poor outcomes of recipients with mechanical valves. Indeed, postoperative hemorrhage at the surgical sites occurred in almost half of these patients who also had a higher risk of death from bleeding. This may be due to their high target INRs since the use of warfarin at lower dose for atrial fibrillation in kidney transplant patients was not associated with an increased risk of mortality [26]. Perioperative management of anticoagulation in these patients varies according to the transplant teams. A limit of this study is the lack of information on the perioperative management of anticoagulation by the different centers. Standardized protocols for anticoagulation management in kidney transplant recipients with mechanical valves are still required. Direct oral anticoagulants, which show a better tolerance than vitamin K antagonists, could be an alternative. However, they have not proved their noninferiority in the prevention of thromboembolic events in patients with mechanical valves and a trial has been discontinued because of high numbers of thromboembolic and bleeding events in patients with mechanical valves receiving Dabigatran [27]. Another alternative could be the use of new generation mechanical valves with lower anticoagulation requirements [28], but no analysis of these valves has been performed in ESKD patients [2].

The choice of prosthetic heart valve in patients with ESKD on dialysis remains debated. Mid-long-term survival was similar after bioprosthetic or mechanical valve replacement and [8,10,12], despite a lower rate of bleeding and thromboembolic events in the bioprosthetic groups [5,11], there is currently no guideline on the type of valve prosthesis to choose in ESKD patients [29]. The choice is based on an individual risk assessment. To our knowledge, none of the above-mentioned studies have analyzed long-term outcomes of valve replacement in ESKD patients separately in those who did or did not

receive subsequent kidney transplantation. The correction of abnormal calcium and phosphate metabolism, chronic inflammation or malnutrition after transplantation may decrease the risk of accelerated calcification and degeneration of bioprosthetic valves observed in dialysis patients [30]. We believe that the potential eligibility of patients to kidney transplantation has to be taken into account, with the standard criteria, when choosing the type of prosthetic heart valves in ESKD patients.

In conclusion, this is the first report of kidney transplantation outcomes in patients with a prosthetic heart valve at time of transplantation. We here show that the post-transplant mortality is high in these patients and that mechanical valves, but not biological valves, are independent risk factors of post-transplant mortality. These data will help clinical teams in (i) assessing eligibility of PHV patients for transplantation and (ii) choosing the type of valve in ESKD patients eligible for subsequent kidney transplantation.

## Authorship

All authors certify that they have participated sufficiently in the work to take public responsability for the content, including participation in the concept, design, analysis, writing, and/or revision of the manuscript.

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## Conflict of interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Table S1.** Baseline characteristics of patients with mechanical and biological prosthesis at time of transplantation.

**Figure S1.** Graft survival is similar between PHV and No PHV groups.

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## APPENDIX