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Prophylactic Anticoagulation Reduces the Risk of Kidney Graft Venous Thrombosis in Recipients From Uncontrolled Donation After Circulatory Death Donors With High Renal Resistive Index

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Background. Uncontrolled donation after circulatory death (uDCD) increases organ availability for kidney transplantation (KT) at the expense of a higher risk of primary graft nonfunction (PNF). At least half of the cases of PNF are secondary to graft venous thrombosis. The potential benefit from prophylactic anticoagulation in this scenario remains unclear. **Methods.** In this single-center retrospective study we compared 2 consecutive cohorts of KT from uDCD with increased (≥0.8) renal resistive index (RRI) in the Doppler ultrasound examination performed within the first 24–72 h after transplantation: 36 patients did not receive anticoagulation ("nonanticoagulation group") and 71 patients underwent prophylactic anticoagulation until normalization of RRI in follow-up Doppler examinations ("anticoagulation group"). **Results.** Anticoagulation was initiated at a median of 2 d (interquartile range, 2–3) after transplantation and maintained for a median of 12 d (interquartile range, 7–18). In 4 patients (5.6%), anticoagulation had to be prematurely stopped because of the development of a hemorrhagic complication. In comparison with the nonanticoagulation group, recipients in the anticoagulation group had a lower 2-wk cumulative incidence of graft venous thrombosis (19.4% versus 0.0%; $P < 0.001$) and PNF (19.4% versus 2.8%; $P = 0.006$). The competing risk analysis with nonthrombotic causes of PNF as the competitive event confirmed the higher risk of graft thrombosis in the nonanticoagulation group ($P = 0.0001$). The anticoagulation group had a higher incidence of macroscopic hematuria (21.1% versus 5.6%; $P = 0.049$) and blood transfusion requirements (39.4% versus 19.4%; $P = 0.050$) compared with the nonanticoagulation group. No graft losses or deaths were attributable to complications potentially associated with anticoagulation. **Conclusions.** Early initiation of prophylactic anticoagulation in selected KT recipients from uDCD with an early Doppler ultrasound RRI of ≥0.8 within the first 24–72 h may reduce the incidence of graft venous thrombosis as a cause of PNF.

(*Transplantation Direct* 2024;10: e1649; doi: 10.1097/TXD.0000000000001649.)

Received 14 February 2024. Revision received 13 March 2024.

Accepted 21 March 2024.

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This work was supported by the Instituto de Salud Carlos III (ISCIII), Spanish Ministry of Science and Innovation (grant no. PIE13/00045)—co-financed by the European Union—and AITER (Asociación para la Investigación y Tratamiento de las Enfermedades Renales). M.F.R. has been supported by a research contract "Miguel Servet" (grant no. CP18/00073) from the ISCIII, Spanish Ministry of Science and Innovation. J.C. has been supported by an ISN-Saulo Klahr-funded fellowship.

The authors declare no conflicts of interest.

Kidney transplantation (KT) is the preferred option for renal replacement therapy in patients with end-stage renal disease.[1] Uncontrolled donation after circulatory death (uDCD) increases the organ pool for KT, with short-term and long-term outcomes comparable with those obtained from donation after brain death (DBD) donors.[2] However, the high rate of primary graft nonfunction (PNF)—ranging from 6.8% to 12.3% in recent series—remains a major concern with this strategy.[2-4] More than half of cases of PNF are secondary to intragraft thrombosis or renal vein thrombosis (RVT) unrelated to technical problems and usually result in early transplantectomy.[2-4] Grafts from uDCD have been considered at increased risk of delayed graft function and RVT compared with those obtained from DBD donors because of the prolonged warm ischemia time during the donation process and resulting ischemic injury.[5] This rationale would support the use of prophylactic anticoagulation in KT recipients from uDCD with the specific aim of reducing the risk of RVT.

Nevertheless, because anticoagulation is not free from adverse events, it is necessary to develop an operational approach to select the subgroup of KT recipients from uDCD who are more likely to benefit from this therapy because of their highest baseline risk of RVT.[6] Doppler ultrasound (US) has been validated as a reliable noninvasive examination during the immediate postoperative period and provides an accurate measurement of the renal resistive index (RRI), which may be elevated (≥0.8) in grafts with parenchymal or vascular abnormalities such as RVT, acute tubular necrosis, acute rejection, pyelonephritis, Page phenomenon, or drug-induced nephrotoxicity.[7-9] In the case of RVT, an elevated RRI with absent or diminished venous flow in the main renal vein typically precedes the classical Doppler US finding of complete reversal of diastolic flow in the main renal artery and intrarenal branches.[9]

An active uDCD program was initiated at our center >18 y ago.[2] Following the first period in which we observed a disproportionately high incidence of PNF attributable to RVT, we performed by mid-2009 an interim analysis to identify clinical factors that could be potentially predictive of this complication. We observed that all the cases of RVT during that period exhibited an increased (≥0.8) RRI in the Doppler US examination performed within the first 24–72 h after transplantation, in the absence of other apparent risk factors. Based on this finding, we modified our institutional protocol (effective from November 2009) to include the early initiation (first 72 h) of prophylactic anticoagulation in KT recipients from uDCD donors who met this criterion. In the present retrospective study, the effectiveness—in terms of RVT and PNF—and safety of this strategy are analyzed.

MATERIALS AND METHODS

Study Population and Intervention

We performed a retrospective single-center cohort study that included all consecutive adult (older than 18 y) patients with end-stage renal disease undergoing KT from uDCD donors (Maastricht category II) at the University Hospital "12 de Octubre" (Madrid, Spain) between June 2005 and July 2017. Our uDCD program has been described in detail.[2,10-12] As per institutional protocol, a renal Doppler US was performed beyond 12 h after transplantation and within the first 24–72 h, while the patient was admitted to a semicritical care unit managed by a team of dedicated nephrologists. This examination was repeated weekly until recovery of renal graft function. All the examinations were conducted by a stable team of senior vascular radiologists with extensive experience in the evaluation of KT recipients.

For the present study, we selected those KT recipients with an early (ie, first 24–72 posttransplant hours) RRI of ≥0.8 in the renal graft. Because the upper limit for the normal range of the Doppler RRI is usually set at 0.8, this threshold or above should be considered suggestive of some type of complication.[9] We established such a cutoff value on the basis of this criterion and the observation from an interim analysis performed in mid-2009 that no KT recipient exhibited an RRI of <0.8 in the posttransplant Doppler US-developed RVT. Therefore, we did not perform a formal assessment of the diagnostic accuracy (eg, Youden's index or similar), but rather, we preferred to apply a very sensitive threshold able to provide a high negative predictive value, to not miss any at-risk patient who would have potentially benefit from prophylactic anticoagulation.

Effective from November 2009, the institutional protocol was modified to systematically recommend the early initiation of prophylactic anticoagulation in KT recipients from uDCD in which the criteria of an RRI of ≥0.8 in the Doppler US performed within the first 24–72 h was met. All the patients were initiated on subcutaneous low-molecular-weight heparin (LMWH) on the same day of the US examination according to the following dosing schedule: 20 mg daily if body weight was <70 kg; 40 mg daily if body weight was 70–100 kg; and 60 mg daily if body weight was ≥100 kg. In those recipients with significant bleeding during the transplant surgery, LMWH was replaced with intravenous unfractionated heparin to a target-activated partial thromboplastin time of 1.5–2 times the normal range for 3–4 d. In case of no further bleeding, LMWH therapy could be subsequently initiated thereafter. Patients who were already receiving long-acting anticoagulation (typically acenocoumarol) before transplantation were maintained on the same therapy during the transplant hospitalization (with the standard perioperative adjustment). Previous antiplatelet therapy was temporarily discontinued and restarted at the time of hospital discharge.

Prophylactic anticoagulation was discontinued in case of a decrease of the RRI (<0.8) in the follow-up Doppler US examinations or hemorrhagic event (active bleeding at the surgical

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M.M., M.F.-R.,. and A.A. designed the research. M.M., E.G., J.C., M.P., A.R., A.T-S., J.M, A.M., C.R.-C., A.S., A.P., and A.A. performed clinical evaluation and patient recruitment. M.M., M.F.-R., E.G., and J.C. performed data review. M.M. and M.F.-R. carried out the statistical analysis and wrote the article. E.G., J.C., M.P., A.R., A.T.-S., J.M.-P., A.M., C.R.-C., A.S., A.P., and A.A. critically reviewed and completed the final draft.

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ISSN: 2373-8731

DOI: 10.1097/TXD.0000000000001649

site or significant hematoma [largest diameter >5 cm] in the US examination or computed tomography imaging) or thrombocytopenia ($<50.0 \times 10^9$ platelets/L).

All the patients with radiological findings suggestive of RVT during the follow-up period were subjected to early transplantectomy and histological examination of the explanted allograft.

We established 2 mutually exclusive groups in the subgroup of KT recipients from uDCD donors with an early RRI of ≥0.8 measured within the first 24–72 posttransplant hours: patients who underwent transplantation from June 2005 to October 2009 (ie, before the recommendation of prophylactic anticoagulation was implemented) and received no anticoagulation ("nonanticoagulation group"), and those that underwent transplantation from November 2009 to July 2017 and were given prophylactic anticoagulation in the immediate posttransplant period as per the institutional protocol in place ("anticoagulation group"). Demographics, major pretransplant comorbidities, dialysis vintage, perioperative and transplant-related variables, immunosuppression, and graft and patient outcomes were retrospectively collected by means of a standardized case report form. Patients were followed up for at least 5 y after transplantation, graft loss, or death (whichever occurred earlier). The study was performed in accordance with the ethical standards laid down in the Declarations of Helsinki and Istanbul. The local clinical research ethics committee approved the study protocol. The need for specific, informed consent was waived because of the retrospective and noninterventional nature of the research.

Study Outcomes

The effectiveness outcomes were the cumulative incidence of RVT, overall PNF (ie, thrombotic and nonthrombotic causes), and graft loss during the first 2 wk after transplantation, as well as 1-y graft and patient survival. Safety outcomes included the incidence of macroscopic hematuria, blood product transfusion requirement, and major hemorrhagic complications requiring surgical intervention during the initial transplant hospitalization.

Study Definitions

Warm ischemia time was the time that elapsed between cardiac arrest and the initiation of organ preservation by normothermic extracorporeal membrane oxygenation. Macroscopic hematuria was defined as visible hematuria that required continuous bladder irrigation via a 3-way Foley catheter to obtain clear washing fluid without blood clots. Blood product transfusion was restricted to patients with hemorrhagic shock or clinically symptomatic anemia (ie, persistent tachycardia, postural hypotension). Massive transfusion was defined as ≥10 units of packed red blood cells (RBCs) within 24 h. Surgical intervention for hemorrhagic complications was performed in case of persistent hemodynamic instability despite transfusion support.

Immunosuppression Regimen

The immunosuppression protocol was published previously.[2,10-13] There were no changes in the immunosuppression protocol and clinical management during the study period.

Statistical Analysis

Quantitative data were shown as the mean ± SD or the median with interquartile range (IQR). Qualitative variables were expressed as absolute and relative frequencies. Categorical variables were compared using the χ^2 test or Kruskal-Wallis test, whereas continuous variables were compared using the Student *t* test or the Mann-Whitney *U* test, as appropriate. Survival curves were plotted by the Kaplan-Meier method, and differences between groups were compared with the log-rank test. A univariate Cox regression model was performed. The results are expressed as hazard ratios (HRs) with 95% confidence intervals (95% CIs). A competing risk analysis for nonthrombotic causes of PNF was performed to assess the effect of prophylactic anticoagulation on the incidence of graft venous thrombosis. All the significance tests were 2-tailed. Analyses were performed with SPSS version 20.0 (IBM Corp., Armonk, NY) and RStudio version 1.3.1093.

RESULTS

Study Population and Outcomes

Overall, 311 patients underwent KT from uDCD during the study period, 107 of whom (34.4%) had an increased (≥0.8) RRI in the Doppler US examination performed within the first 24–72 h. Thirty-six patients (33.6%) and 71 patients (66.4%) were analyzed in the nonanticoagulation and anticoagulation groups, respectively (Figure 1). The demographics and donor and recipient characteristics of both groups are detailed in Table 1. No patients developed intraoperative events, and the Doppler US examination performed in the first 24–72 h did not reveal stenosis of the main renal artery or vein. Most patients (84.6%) still had an RRI of ≥0.8 in the second Doppler US performed at a median interval of 8 d (IQR, 6–12) from the first examination.

The cumulative incidence of PNF in the overall study cohort was 8.4% (9/107), including 7 cases of RVT, 1 case of acute tubular necrosis, and 1 case of urinary tract fistula. All the patients with radiological findings suggestive of RVT underwent early graft removal, and the pathological examination of the transplantectomy specimen showed a clot in the renal venous, marked hemorrhagic infiltration of the renal parenchyma, and tubular necrosis with negative C4d staining, in the absence of other signs of acute rejection. As detailed in Table 2, there were no significant differences in donor or recipient characteristics between patients who developed or

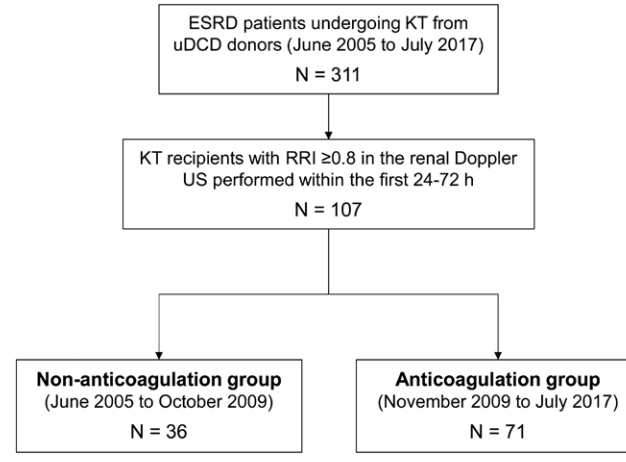

FIGURE 1. Patient flowchart. ESRD, end-stage renal disease; KT, kidney transplantation; RRI, renal resistive index; uDCD, uncontrolled donation after circulatory death; US, ultrasound.

TABLE 1.

Comparison of demographics and donor and recipient characteristics in both study groups

	Overall cohort (N = 107)	Nonanticoagulation group (N = 36)	Anticoagulation group (N = 71)	*P*
Donor age, y, mean ± SD	43.3 ± 10.2	38.6 ± 11.7	45.9 ± 8.5	0.002
Male donor sex, n (%)	93 (86.9)	35 (97.2)	58 (81.7)	0.032
Donor serum creatinine, mg/dL, mean ± SD	1.3 ± 0.3	1.2 ± 0.4	1.3 ± 0.3	0.324
Donor BMI,[a] kg/m^2, mean ± SD	26.6 ± 2.8	28.3 ± 3.0	26.2 ± 2.7	0.015
Warm ischemia time, min, mean ± SD	131.6 ± 20.3	130.9 ± 13.3	132.3 ± 24.8	0.762
Cold ischemia time, h, median (IQR)	13.3 ± 4.8	14.4 ± 5.2	12.8 ± 4.9	0.117
Recipient age, y, mean ± SD	49.7 ± 0.9	46.9 ± 12.5	51.1 ± 10.0	0.091
Male recipient sex, n (%)	70 (65.4)	18 (50.0)	52 (73.2)	0.020
Recipient weight, kg mean ± SD	73.9 ± 16.3	67.3 ± 14.8	77.3 ± 16.1	0.002
Recipient BMI,[b] kg/m^2, mean ± SD	27.1 ± 5.5	24.6 ± 6.1	27.9 ± 5.1	0.045
Cause of ESRD, n (%)				
Glomerulonephritis	21 (19.6)	9 (25.0)	12 (16.9)	0.318
Diabetic nephropathy	27 (25.2)	6 (16.7)	21 (29.6)	0.166
Polycystic kidney disease	16 (15)	3 (8.3)	13 (18.3)	0.253
Nephroangiosclerosis	10 (9.3)	5 (13.9)	5 (7.0)	0.299
Chronic interstitial nephropathy	14 (13.1)	7 (19.4)	7 (9.9)	0.225
Vasculitis or autoimmune disease	4 (3.7)	2 (5.6)	2 (2.8)	0.601
Pretransplant dialysis, n (%)	107 (100.0)	36 (100.0)	71 (100.0)	1.000
Time on dialysis, mo, median (IQR)	19 (10–37)	19 (10–35)	19 (10–39)	0.700
Modality of dialysis, n (%)				0.295
Hemodialysis	87 (81.3)	27 (75)	60 (84.5)	
Peritoneal dialysis	20 (18.7)	9 (25)	11 (15.5)	
Previous transplantation, n (%)	8 (7.5)	3 (8.3)	5 (7)	1.000
Highest PRA value, %, median (range)	0 (0–50)	0 (0–47)	0 (0–50)	0.214
Current PRA value, %, median (range)	0 (0–50)	0 (0–6)	0 (0–50)	0.538
Peak PRA ≥15%, n (%)	2 (1.9)	0 (0)	2 (2.8)	0.549
Pretransplant conditions, n (%)				
Current or previous smoking habit	38 (35.5)	12 (33.3)	26 (36.6)	0.832
Hypertension	91 (85)	29 (80.6.)	62 (87.3)	0.396
Diabetes mellitus	35 (32.7)	6 (16.7)	29 (40.8)	0.016
Dyslipidemia	50 (46.7)	12 (33.3)	38 (53.5)	0.065
Malignancy	10 (9.3)	3 (8.3)	7 (9.9)	1.000
Venous thrombosis	7 (2.7)	0 (0.0)	7 (9.9)	0.093
Thrombophilia	3 (2.8)	0 (0.0)	3 (4.2)	0.549
Pretransplant anticoagulation therapy, n (%)	3 (2.8)	0 (0.0)	3 (4.2)	0.549
Pretransplant antiplatelet therapy, n (%)	28 (26.2)	8 (22.2)	19 (26.8)	0.609
Serum albumin,[c] g/dL, mean ± SD	4.2 ± 0.5	4.2 ± 0.6	4.3 ± 0.5	0.235
Hemoglobin,[c] g/dL, mean ± SD	12.6 ± 1.6	13.2 ± 1.4	12.4 ± 1.6	0.006
Donor/recipient CMV serostatus,[d] n (%)				0.788
D^+/R^+	77 (72.6)	24 (66.7)	53 (75.7)	
D^-/R^+	17 (15.9)	7 (20.0)	10 (14.1)	
D^+/R^-	10 (9.4)	4 (11.4)	6 (8.5)	
D^-/R^-	2 (1.9)	1 (2.9)	1 (1.4)	
Recipient EBV (anti-EBNA IgG) positive serostatus,[e] n (%)	94 (96.9)	34 (100.0)	60 (95.2)	0.550
No. of HLA mismatches, median (IQR)	5 (4–5)	5 (4–5)	5 (4–5)	0.610
Induction therapy with rATG, n (%)	99 (92.5)	30 (83.3)	69 (97.2)	0.017
RRI,[f] mean ± SD	0.89 ± 0.09	0.88 ± 0.09	0.89 ± 0.01	0.531
Delayed graft function, n (%)	83 (31.8)	21 (58.3)	62 (87.3)	0.061
Time to graft function recovery, d, mean ± SD	16.3 ± 7.9	13.6 ± 5.6	17.5 ± 8.4	0.022

[a]Data on the BMI were only available for 79 donors.
[b]Data on the BMI were only available for 59 donors.
[c]At the time of transplantation.
[d]Data on donor/recipient CMV serostatus were not available for 1 patient.
[e]Data on recipient EBV serostatus were not available for 10 patients.
[f]Measured in the renal Doppler US examination performed within the first 24–72 h after transplantation.

BMI, body mass index; CMV, cytomegalovirus; D, donor; EBNA, Epstein-Barr nuclear antigen; EBV, Epstein-Barr virus; ESRD, end-stage renal disease; IQR, interquartile range; PRA, panel-reactive antibody; R, recipient; rATG, rabbit antithymocyte globulin; RRI, renal resistive index; US, ultrasound.

TABLE 2.

Comparison of demographics, donor characteristics, and recipient characteristics between KT recipients from uDCD donor who developed or did not develop graft venous thrombosis

Variables	Graft venous thrombosis (N = 7)	No graft venous thrombosis (N = 100)	*P*
Donor age, y, mean ± SD	38.9 ± 16.1	43.6 ± 9.7	0.357
Male donor sex, n (%)	7 (100.0)	86 (86.0)	0.591
Donor serum creatinine, mg/dL, mean ± SD	11.4 ± 0.2	1.3 ± 0.3	0.192
Warm ischemia time, min, mean ± SD	131.0 ± 12.0	131.7 ± 21.0	0.930
Cold ischemia time, h, median (IQR)	15.1 ± 6.4	13.2 ± 4.6	0.320
Time ≥20 h, n (%)	2 (28.6)	13 (13.0)	0.258
Anatomical features, n (%)			
Right kidney	4 (57.1)	51 (51.0)	0.753
>1 renal vein	1 (14.3)	3 (3.0)	0.128
>1 renal artery	2 (28.6)	17 (17.0)	0.439
Recipient age, y, mean ± SD	45.3 ± 16.9	50.0 ± 10.5	0.493
Male recipient sex, n (%)	3 (42.9)	67 (67.0)	0.232
Recipient weight, kg, mean ± SD	73.6 ± 15.6	73.9 ± 16.4	0.950
Cause of ESRD, n (%)			
Glomerulonephritis	1 (14.3)	20 (20.0)	1.000
Diabetic nephropathy	2 (28.6)	25 (25.0)	1.000
Polycystic kidney disease	1 (14.3)	15 (15.0)	1.000
Nephroangiosclerosis	1 (14.3)	9 (9.0)	0.507
Chronic interstitial nephropathy	2 (28.6)	12 (12.0)	0.227
Vasculitis or autoimmune disease	0 (0.0)	4 (4.0)	1.000
Pretransplant dialysis, n (%)	7 (100.0)	100 (100.0)	1.000
Time on dialysis, mo, median (IQR)	14 (5–24)	20 (10–39)	0.416
Modality of dialysis, n (%)			0.613
Hemodialysis	5 (71.4)	82 (82.0)	
Peritoneal dialysis	2 (28.6)	18 (18.0)	
Previous transplantation, n (%)	0 (0.0)	8 (8.0)	1.000
Peak PRA ≥15%, n (%)	0 (0.0)	2 (2.0)	1.000
Pretransplant conditions, n (%)			
Current or previous smoking habit	2 (28.6)	36 (36.0)	1.000
Hypertension	6 (85.7)	85 (85.0)	1.000
Diabetes mellitus	2 (28.6)	33 (33.0)	1.000
Malignancy	2 (28.6)	8 (8.0)	0.128
Venous thrombosis	0 (0.0)	7 (7.0)	1.000
Thrombophilia	0 (0.0)	3 (3.0)	1.000
Serum albumin,[a] g/dL, mean ± SD	3.9 ± 0.9	4.3 ± 0.5	0.366
Hemoglobin,[a] g/dL, mean ± SD	12.9 ± 1.7	12.6 ± 1.6	0.627
CMV serological mismatch (D^+/R^-)[b], n (%)	1 (14.3)	9 (9.1)	0.650
Recipient EBV (anti-EBNA IgG) positive serostatus,[c] n (%)	7 (100.0)	87 (96.7)	1.000
No. of HLA mismatches, median (IQR)	5 (5–6)	5 (4–5)	0.172
Induction therapy with rATG, n (%)	5 (71.4)	94 (94.0)	0.085
Renal resistive index,[d] mean ± SD	0.95 ± 0.09	0.88 ± 0.09	0.071

[a]At the time of transplantation.
[b]Data on donor/recipient CMV serostatus were not available for 1 patient.
[c]Data on recipient EBV serostatus were not available for 10 patients.
[d]Measured in the renal Doppler US examination performed within the first 24–72 h after transplantation.
CMV, cytomegalovirus; D, donor; EBV, Epstein-Barr virus; EBNA, Epstein-Barr nuclear antigen; ESRD, end-stage renal disease; IQR, interquartile range; PRA, panel-reactive antibody; R, recipient; rATG, rabbit antithymocyte globulin.

did not develop RVT. Although not reaching statistical significance because of the low number of events, the proportion of recipients of grafts with >1 renal artery or vein was numerically higher in the group that developed RVT.

Prophylactic Anticoagulation

All the 71 patients analyzed in the anticoagulation group received weight-adjusted LMWH, although 12 of them (16.9%) were given unfractionated heparin during the first 72 h. The median activated partial thromboplastin time value in this group was 43 s (IQR, 41–44). The most commonly used LMWH was enoxaparin at a median daily dose of 40 mg (IQR, 40–40).

Anticoagulation was initiated at a median of 2 d (IQR, 2–3) after transplantation and maintained for a median of 12 d (IQR, 7–18). In 4 patients (5.6%), anticoagulation had to be prematurely stopped after a median of 5 d (IQR, 2.3–13) because of the development of a hemorrhagic complication, whereas in the remaining 67 patients, it was ceased once the RRI assessed in consecutive Doppler US examinations

TABLE 3.

Effectiveness and safety outcomes in both study groups

Variables	Overall cohort (N = 107)	Nonanticoagulation group (N = 36)	Anticoagulation group (N = 71)	*P*
Effectiveness outcomes (cumulative incidence in the first 2 wk after transplantation)				
Graft venous thrombosis by month 1, n (%)	7 (6.5)	7 (19.4)	0 (0.0)	<0.001
Primary graft nonfunction, n (%)	9 (8.4)	7 (19.4)	2 (2.8)	0.006
Graft lost, n (%)	11 (10.3)	7 (19.4)	4 (5.6)	0.041
Safety outcomes (cumulative incidence during the transplant hospitalization)				
Macroscopic hematuria, n (%)	17 (15.9)	2 (5.6)	15 (21.1)	0.049
Hematoma, n (%)	46 (42.9)	16 (44.4)	30 (42.2)	0.823
Blood product transfusion requirement, n (%)	35 (32.7)	7 (19.4)	28 (39.4)	0.050
No. of units of packed RBCs transfused per patient, median (IQR)	3.0 (2.5 – 3.7)	2.0 (2.0 – 3.0)	4.0 (2.2 – 7.0)	0.080
Major hemorrhagic complication requiring surgical intervention, n (%)	10 (9.3)	6 (16.6)	4 (5.6)	0.639
Length of transplant hospitalization, d, median (IQR)	21 (18 – 26)	19 (15.3 – 22)	23 (18 – 29)	0.007

IQR, interquartile range; RBC, red blood cell.

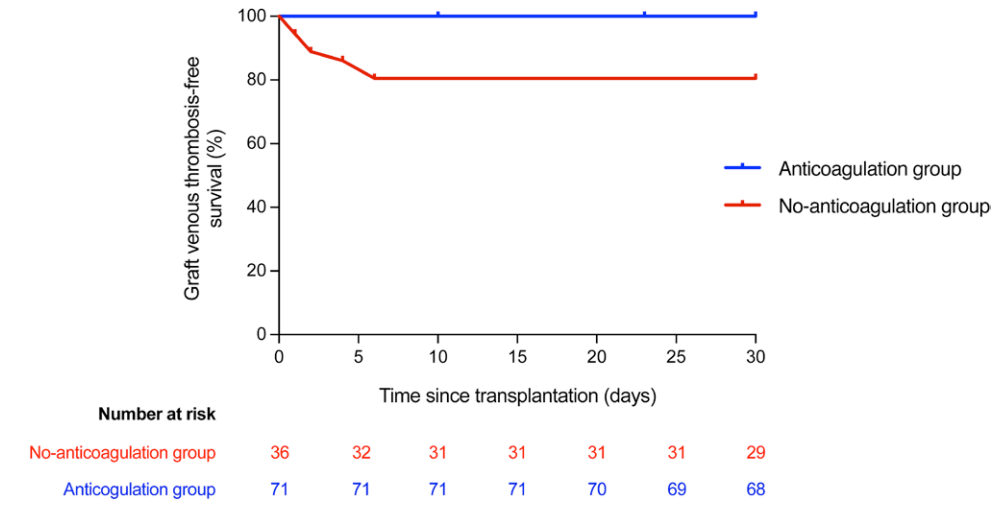

FIGURE 2. Comparison of graft venous thrombosis-free Kaplan-Meier survival curves between both study groups (log-rank $P < 0.001$).

performed weekly returned to <0.8. Therefore, prophylactic anticoagulation was not withheld in any of the patients who only developed hematuria or hematoma. These cases were managed with blood transfusion (if required) and weekly imaging follow-up until the hematoma was resolved.

There were some differences in terms of demographics and clinical characteristics between both groups (Table 1). As compared with the nonanticoagulant group, donors in the anticoagulation group were older (38.6 ± 11.7 versus 45.9 ± 8.5 y; $P = 0.002$) and less likely to be men (97.2% [35/36] versus 81.7% [58/71]; $P = 0.032$), and had lower body mass index; (28.3 ± 3.0 versus 26.2 ± 2.7 kg/m^2; $P = 0.015$). The anticoagulation group had a higher prevalence of male recipients (50.0% [18/36] versus 73.2% [52/71]; $P = 0.020$) and diabetes (16.7% [6/36] versus 40.8% [29/71]; $P = 0.016$), higher body mass index (24.6 ± 6.1 versus 27.9 ± 5.1 kg/m^2; $P = 0.045$), and were more likely to receive induction therapy with rabbit antithymocyte globulin (rATG; 83.3% [30/36] versus 97.2% [69/71]). Three patients had a documented cause of thrombophilia, all within the anticoagulation group. Overall, 28 patients were receiving antiplatelet therapy before transplantation, with no significant differences between both groups (22.2 [8/36] versus 26.8% [19/71] in the nonanticoagulation and anticoagulation groups, respectively; $P = 0.609$).

Effectiveness Outcomes

The use of prophylactic anticoagulation was associated with lower 2-wk cumulative incidence rates of RVT (19.4% [7/36] in the nonanticoagulation group versus 0.0% [0/71] in the anticoagulation group; $P < 0.001$) and PNF (19.4% [7/36] versus 2.8% [2/71], respectively; $P = 0.006$). Graft loss was also less common in the anticoagulation group (19.4% [7/36] versus 5.6 [4/71]; $P = 0.041$; Table 3).

The 2-wk survival free from RVT was lower in the nonanticoagulation group than in the anticoagulation group (80.6% versus 100.0%, respectively; log-rank test $P < 0.001$; Figure 2). The competing risk analysis with nonthrombotic causes of PNF as the competing event confirmed the higher risk of RVT in the nonanticoagulation group ($P = 0.0001$; Figure 3).

The use of prophylactic anticoagulation was confirmed to act as a protective factor for the development of RVT in the univariate analysis (HR: 0.005; 95% CI, 0.0001-6.311; $P = 0.147$), as was induction therapy with rATG and delayed

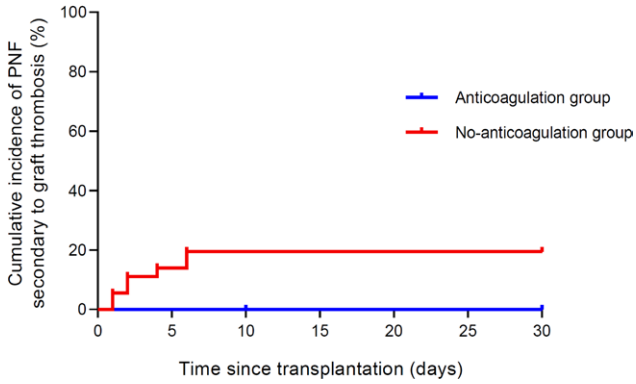

FIGURE 3. Competing risk analysis for the development of PNF secondary to renal graft venous thrombosis in both study groups with nonthrombotic causes of PNF as the competing event (*P* = 0.0001). PNF, primary graft nonfunction.

initiation of tacrolimus (HR: 0.175; 95% CI, 0.034-0.903; *P* = 0.037), whereas the pretransplant history of malignancy increased the risk of this complication (HR: 4.329; 95% CI, 0.839-22.336; *P* = 0.080; Table 4).

There were no significant differences between the non-anticoagulation and anticoagulation groups in 1-y patients (94.3% versus 97.2%; log-rank *P* = 0.535) and death-censored graft survival rates (80.5% versus 91.4%, respectively; log-rank *P* = 0.076; Figure 4).

Safety Outcomes

Regarding safety outcomes, the cumulative incidence of macroscopic hematuria (5.6 [2/36] versus 21.1% [15/71]; *P* = 0.049) and the requirement of blood product transfusion (19.4% [7/36] versus 39.4% [28/71]; *P* = 0.050) were higher in the anticoagulation group. The median number of packed RBC units transfused was also higher (2 [IQR, 2–3] versus 4 [IQR, 2.2–7] units; *P* = 0.080). In detail, 2 patients (2.8%) that received prophylactic anticoagulation required massive transfusion. There were no significant differences in the incidence of hematoma (44.4% [16/36] versus 42.2% [30/71]; *P* = 0.823) or major hemorrhagic complications requiring surgical intervention (16.6% [6/36] versus 5.6% [4/71]; *P* = 0.639) between both groups (Table 3). None of these complications led to graft loss or recipient death.

Patients in the anticoagulation group who were already on anticoagulation or antiplatelet therapy before transplantation were more likely to develop hematuria (36.3% [8/22] versus 12.0% [6/44]; *P* = 0.016), with no differences in the incidence of other adverse events.

DISCUSSION

In the present retrospective observational study comprising 107 KT recipients from uDCD donors with high RRI in the Doppler US examination performed within the first 24–72 h after transplantation, the use of prophylactic anticoagulation resulted in a significant reduction in the incidence of PNF attributable to RVT. Although this strategy was associated with an increased incidence of macroscopic hematuria and higher transfusion requirements in comparison with the preceding period of no anticoagulation, there were no cases of attributable graft loss or mortality.

Despite the fact that recently reported experiences confirming the favorable results of KT from uDCD, the high rate of PNF (from 10% to 12.3% across different programs) remains a major concern, with approximately half of the cases secondary to the renal vein or intragraft thrombosis unrelated to surgical complications.[3,4] Although the occurrence of graft thrombosis may be driven by patient- or transplant-related factors, the process of uDCD itself entails a number of predisposing conditions for this complication.[5,6] It is well established that the grafts from this type of donor have severe ischemia/reperfusion injury, which would account for the increased risk of delayed graft function and RVT. Hypoxia upregulates the synthesis of tissue factors by endothelial cells and the influx of leukocytes, whereas endothelial injury promotes platelet activation, adhesion, and aggregation, releasing thromboxane A2. Finally, complement activation during the reperfusion process may lead to the formation of microthrombi within the allograft.[5,6,14] The most common histological findings in cases of PNF are glomerular, arteriolar, and arterial thrombosis with fibrinoid necrosis in arteriole and arterial walls in both kidneys of the same donor.[4] Studies based on animal models and following cardiac arrest in humans have confirmed the pathogenic role played by the activation of the clotting cascade.[15,16] A pig model of extended uDCD revealed that the presence of fibrin and fibrinogen after cardiac arrest largely disappeared with thrombolytic treatment based on Lys-plasminogen and alteplase, which restored histology and graft function.[15] In contrast, some authors have described a posttransplant hypercoagulable state because of impaired fibrinolysis and protein C activation, which could increase the risk of thrombotic complications, including renal graft thrombosis.[17-21] In contrast to other groups that use hypothermic regional perfusion, all uDCD donors in our program are routinely treated with sodium heparin at the time of normothermic extracorporeal membrane oxygenation initiation.[2,4]

The ischemia/reperfusion injury causes important renal vasoconstriction that the high RRI would reflect in the early

TABLE 4.

Univariate analysis of risk factors present at the time of transplantation associated with the occurrence of renal graft venous thrombosis

Variable	Graft venous thrombosis (N = 7)	No graft venous thrombosis (N = 100)	*P*	Univariate		
				HR	95% CI	*P*
Anticoagulation group, n (%)	0 (0.0)	71 (71.0)	<0.001	0.005	0.0001-6.311	0.147
Induction therapy with rATG and delayed initiation of tacrolimus, n (%)	5 (71.4)	94 (94.0)	0.085	0.175	0.034-0.903	0.037
Pretransplant diagnosis of malignancy, n (%)	2 (28.6)	8 (8.0)	0.128	4.329	0.839-22.336	0.080

CI, confidence interval; HR, hazard ratio; rATG, rabbit antithymocyte globulin.

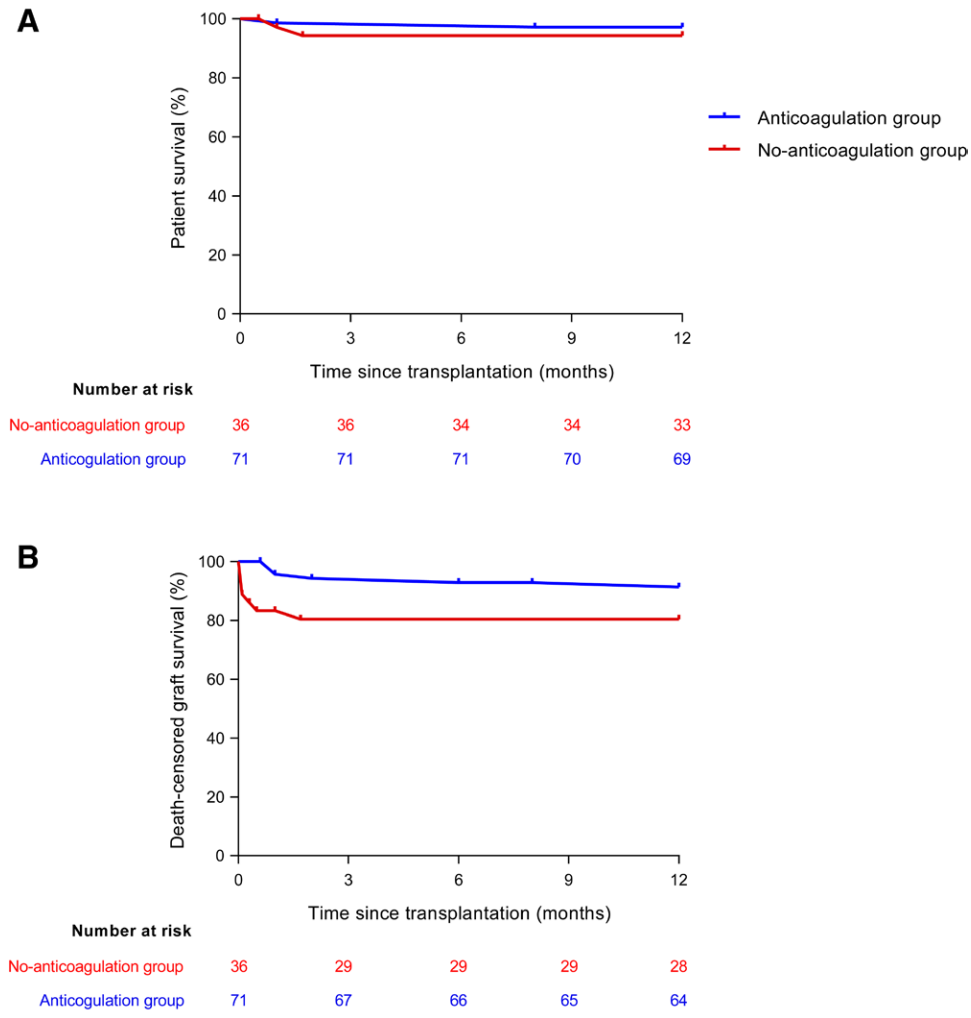

FIGURE 4. Comparison of Kaplan-Meier patient (A) and death-censored graft survival (B) between both study groups (log-rank $P = 0.535$ and 0.076, respectively).

Doppler US examination. Indeed, increased RRI may act as a nonspecific risk marker of RVT, presumably because of the slowing of blood flow in arterioles and, finally, in the main renal vein. We hypothesize that prophylactic anticoagulation may reduce this major cause of PNF in this specific KT population.[9] In support of this notion, only acute tubular necrosis with no evidence of thrombotic microangiopathy was found in renal graft biopsies performed before implantation or 1–2 wk after transplantation in the anticoagulation group (data not shown).

Although anticoagulation therapy is universally accepted in KT recipients with a documented hypercoagulable state,[5,22-26] no consensus has been reached on the prophylactic use to decrease the incidence of graft thrombosis.[6] A number of randomized clinical trials have evaluated this intervention.[27-29] Of note, 2 of them were performed in the 70s and 80s with cyclosporine-based immunosuppression regimens and different donor selection policies, thus limiting the generalizability of the results to the current practices.[27,28] The remaining trial was restricted to non–high-risk KT recipients from living donors and found no significant differences in the incidence of graft vascular thrombosis, thromboembolic events, or graft function at the expense of a significant decrease in the hemoglobin level in the group that received unfractionated heparin.[29] Further studies are retrospective in nature and mainly focused on the occurrence of adverse events (typically bleeding).[22,30,31] This wide heterogeneity in clinical practice with regard to prophylactic anticoagulation was noted in a survey of clinical practice performed in transplantation centers in France.[32] In addition, a recent systematic review concluded that it remains unclear whether heparin decreases the risk of early graft thrombosis, whereas low certainty evidence suggests that the use of unfractionated heparin may increase the risk of major bleeding after KT.[33]

Studies specifically aimed at evaluating the role of prophylactic anticoagulation in KT recipients from uDCD donors are eventually absent. In the experience reported herein, anticoagulation initiated within the first 24–72 h after transplantation in the presence of high RRI was associated with a reduced risk of RVT. With RRI measured by a noninvasive tool such as the Doppler US examination, we were able to stratify the risk of RVT in the immediate posttransplant period (ie, first 24–72 h) to guide the indication of anticoagulation.[7-9] Although increased Doppler RRI is a nonspecific finding that may be present in other conditions, such as acute graft rejection or pyelonephritis, its presence early after KT suggests the development of acute tubular necrosis as a result of

severe ischemia/reperfusion, which has been described as a risk factor for graft RVT.[5,9] We set the cutoff value to define high Doppler RRI based on early experience in our uDCD program (June 2005 to October 2009). Although the performance of such a threshold was not formally validated, the fact that no KT recipients with an early RRI of <0.8 developed RVT, either in the preintervention or in the intervention period, would support its high negative predictive value (data not shown). To minimize the risk of adverse events, the Doppler US examination was repeated weekly, and prophylactic anticoagulation was stopped as soon the RRI was <0.8. This strategy resulted in a median duration of anticoagulation of 12 d.

The evidence derived from the present study is limited by a number of factors, with its retrospective and nonrandomized design as the main limitation. Our results are prone to a type 2 error because of the relatively small number of patients included. We compared 2 consecutive periods, before and after the recommendation of tailored anticoagulation was implemented in our institutional protocol. Nevertheless, the attending team of nephrologists, urologists, transplant coordinators, and vascular radiologists remained unchanged throughout the study period, and no additional changes in surgical or graft preservation techniques were implemented. There were some baseline imbalances between both study groups in terms of donor age and sex, whereas recipients who received prophylactic anticoagulation were older, heavier, and more likely to have diabetes. Although all these factors act as risk factors for RVT,[5] the tested intervention was useful to effectively prevent this complication. In addition, there were no differences in other factors that have been also suggested to increase the thrombotic risk, such as cold or warm ischemia times.[5] In contrast, we observed an apparently protective role for rATG induction with delayed initiation of tacrolimus. Although T cell–depleting agents decrease the incidence of acute rejection, all the patients included had low immunological risk and we observed no cases of RVT associated with rejection in the nonanticoagulation group. We alternatively hypothesize that the delayed onset of tacrolimus therapy in KT recipients from uDCD donors may play a role in this apparent protective effect.[5] No details on intrarenal Doppler venous and arterial flow patterns were collected. In addition to the mentioned between-group differences, the impact of unmeasured confounding cannot be ruled out. For instance, although the Doppler US revealed no cases of stenosis of the main artery or vein of the graft, we did not collect details on the presence of thrombosis in accessory renal vessels.

The assessment of the potential impact of prophylactic anticoagulation on the occurrence of RVT could have been confounded by the competitive effect of other causes of PNF. Because this concern cannot be adequately controlled by conventional multivariable adjustment, we confirmed our findings through a competitive risk analysis. This approach is the best option when an individual is exposed to ≥2 causes of graft failure, with subsequent difficulties for causal attribution.[34]

Prophylactic anticoagulation was not entirely exempt from adverse events. We found an increased incidence of macroscopic hematuria and blood product transfusion requirement, although the incidence of major hemorrhagic complications requiring surgical intervention was similar between both groups. The higher number of RBC units transfused per patient may confer an increased risk of de novo donor-specific antibodies. It should be noted that patients at the highest risk of bleeding received unfractionated heparin instead of LMWH during the first days to make easier the dose adjustment and the rapid reversion of the anticoagulation effect with protamine sulfate if needed. In addition, the requirement of surgical revision because of hemorrhagic complications was overall uncommon in the cohort (<10%). Patients in the no-anticoagulation group had a numerically higher rate of hemorrhagic complications requiring surgical intervention (16.6% versus 5.6%) that did not reach statistical significance, although the uneven distribution of events may explain this apparent excess risk because of chance, low number of patients and the nonrandomized design. Finally, particular caution should be exerted among patients who are already receiving anticoagulation or antiplatelet therapy before transplantation because of the higher risk of hematuria observed although the antiplatelet agent was typically discontinued during the transplant hospitalization.

To our knowledge, ours is the first study to suggest a protective effect of prophylactic anticoagulation on the risk of RVT and associated PNF among KT recipients from uDCD identified by the presence of an increased RRI in the early Doppler US examination. Direct comparison with previously reported series is hampered by heterogeneity in the clinical characteristics of the patient population (eg, high versus low thrombotic risk or inclusion of DBD donors) and methodological design.

In conclusion, prophylactic anticoagulation in selected KT recipients from uDCD donors with an early (within the first 24–72 h after transplantation) Doppler RRI of ≥0.8 may reduce the PNF rate associated with RVT. In addition, no red flags were apparent in terms of an increased risk of hemorrhagic complications associated with the use of anticoagulation. The benefit derived from this strategy should be ideally confirmed in the controlled setting of an intervention study.

ACKNOWLEDGMENTS

The authors thank Mr Bello, Ms Cebrián, Ms Delgado, Ms Nuño, Ms Rodríguez, Ms Vázquez, and Ms Vereda for their assistance in the clinical management of recruited patients, as well as the involved staff from the Departments of Nephrology, Urology, Abdominal Surgery and Intensive Care Medicine of the Hospital Universitario "12 de Octubre." They also thank Gregorio Romero for his invaluable help and advice.

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