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ORIGINAL ARTICLE

Perioperative antithrombotic therapy does not increase the incidence of early postoperative thromboembolic complications and bleeding in kidney transplantation – a retrospective study

Tamar A. J. van den Berg[1], Robert C. Minnee[2], Ton Lisman[1], Gertrude J. Nieuwenhuijs-Moeke[3], Jacqueline van de Wetering[4], Stephan J. L. Bakker[5] & Robert A. Pol[1]

1 Department of Surgery, Division of Transplantation Surgery, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands
2 Department of HPB and Transplant Surgery, Erasmus Medical Center, Rotterdam, the Netherlands
3 Department of Anesthesiology, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands
4 Department of Internal Medicine, Division of Nephrology and Kidney Transplantation, Erasmus, Medical Center, Rotterdam, the Netherlands
5 Department of Internal Medicine, Division of Nephrology, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands

Correspondence
Robert A. Pol MD, PhD, Department of Surgery, Division of Vascular and Transplantation Surgery, University Medical Center Groningen, P.O. Box 30 001, 9700 RB Groningen, The Netherlands.
Tel.: 31 503613382;
fax: 31 503611745;
e-mail: pol.chirurgie@gmail.com

SUMMARY

Perioperative antithrombotic therapy could play a role in preventing thromboembolic complications (TEC) after kidney transplantation (KTx), but little is known on postoperative bleeding risks. This retrospective analysis comprises 2000 single-organ KTx recipients transplanted between 2011 and 2016 in the two largest transplant centers of the Netherlands. TEC and bleeding events were scored ≤7 days post-KTx. Primary analyses were for associations of antithrombotic therapy with incidence of TEC and bleeding. Secondary analyses were for associations of other potential risk factors. Mean age was 55 ± 14 years, 59% was male and 60% received a living donor kidney. Twenty-one patients (1.1%) had a TEC. Multiple donor arteries [OR 2.79 (1.15–6.79)] and obesity [OR 2.85 (1.19–6.82)] were identified as potential risk factors for TEC. Bleeding occurred in 88 patients (4.4%) and incidence varied significantly between different antithrombotic therapies ($P = 0.006$). Cardiovascular disease [OR 2.01 (1.18–3.42)], pre-emptive KTx [OR 2.23 (1.28–3.89)], postoperative heparin infusion [OR 1.69 (1.00–2.85)], and vitamin K antagonists [OR 6.60 (2.95–14.77)] were associated with an increased bleeding risk. Intraoperative heparin and antiplatelet therapy were not associated with increased bleeding risk. These regimens appear to be safe for the possible prevention of TEC without increasing the risk for bleeding after KTx.

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Key words
anticoagulation, bleeding, kidney transplant, risk factors, thrombosis

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Introduction

Renal graft thrombosis (RGT) is a serious complication after kidney transplantation (KTx) and a major risk factor for impaired graft function and graft loss [1]. Although RGT is rare, varying from 0.5% to 8% [1–5], it has high morbidity and mortality and accounts for up to 45% of graft loss in the first post-transplantation

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phase [2,6]. Known risk factors for RGT are donor age <6 or >60 years, recipient age <5 or >50 years, cold ischemic time (CIT) >24 h, atherosclerosis in the external iliac, common iliac or renal artery, right donor kidneys, prior peritoneal dialysis, diabetes mellitus, previous thrombosis in the recipient, technical difficulties and hemodynamic instability during transplantation [7]. RGT, deep venous thrombosis (DVT), and pulmonary embolisms (PE) are collectively known as thromboembolic complications (TEC). Incidence of TEC after KTx is reported to vary between 0.6% and 9.1% [8–11]. The wide ranges reported are because of the differences in study populations, with highest incidences found in pediatric KTx and lowest in studies involving living donor KTx [1–5]. In the KTx population, risk factors for DVT are age >40 years, diabetes mellitus, previous DVT and simultaneous pancreas–kidney transplantation [1,8,10,11]. Since more elderly patients with higher comorbidity are being transplanted, incidence of TEC is likely to increase [8,12]. In vascular surgery, intraoperative administration of heparin is common with the aim to avoid thrombus formation at the anastomoses and clamp sites [13,14]. In KTx, no consensus or protocol for antithrombotic prophylaxis exists. A common argument is the general belief that dialysis-dependent patients, in contrast to pre-emptive patients, are at greater risk for bleeding because of combined effects of uremia, residual effect of heparin used during dialysis and continuous platelet activation, and thus exhaustion, through contact with the dialysis membrane [15]. However, recent insights show that dialysis-dependent and pre-emptive patients have comparable hemostatic profiles preoperatively and are at risk of both bleeding and thrombotic complications [15–17]. Risk of thrombosis should always be carefully weighed against risk of bleeding, but evidence suggests that the benefits of antithrombotic prophylaxis to prevent postoperative thrombosis outweigh the risks of bleeding in procedures such as KTx [18]. The aim of this study was to assess early TEC and bleeding after KTx in relation to perioperative antithrombotic prophylaxis.

Materials and methods

Study population

This retrospective cohort analysis comprises all adult KTx recipients in two large tertiary university based hospitals in the Netherlands, the University Medical Center Groningen (UMCG) and the Erasmus Medical Center in Rotterdam (EMC), transplanted between 2011 and 2016. Exclusion criteria for this study were combined transplantations (36 patients), lack of data on antithrombotic therapy (eight patients), or inaccessible hospital records (13 patients). A total cohort of 2000 patients were further analyzed.

Patient charts were screened using the electronic hospital registries for baseline characteristics, surgical details, postoperative complications, patient and graft outcome and preoperative antithrombotic prophylaxis (Tables 1 and 2). Included were the following agents with their Anatomical Therapeutic Chemical (ATC) classification code: vitamin K antagonists (VKA; phenprocoumon B01AA04 and acenocoumarol B01AA07), low-molecular-weight heparin (LMWH; dalteparin B01AB04 and nadroparin B01AB06), platelet function inhibitors (clopidogrel B01AC04, aspirin B01AC06, dipyridamole B01AC07, carbasalate calcium B01AC08, prasugrel B01AC22 and ticagrelor B01AC24), novel oral anticoagulants (NOACs; dabigatran B01AE07, rivaroxaban B01AF01, apixaban B01AF02 and edoxaban B01AF03) and intraoperative unfractionated heparin (UFH) B01AB01.

For this study, the Medical Ethics Committee (MEC) of the UMCG granted dispensation from the Medical Research Involving Human Subjects Act (WMO) obligation (registration no. MEC2016.601) and this dispensation was submitted to and approved by the MEC of the EMC. Patient data were processed and stored according to the declaration of Helsinki – Ethical principles for medical research involving human subjects. The clinical and research activities are consistent with the Principles of the Declaration of Istanbul as outlined in the "Declaration of Istanbul on Organ Trafficking and Transplant Tourism."

Outcome measures

Primary outcome measures were associations of antithrombotic therapy with incidence of TEC and bleeding. Secondary analyses were for associations of other potential risk factors.

Surgical procedure and center-based immunosuppressive and antithrombotic protocol

Kidney transplantation was performed with either a living or deceased donor kidney (donation after brain death (DBD) or circulatory death (DCD)). According to the protocol within EuroTransplant, DBD donors received 20 000 IU of heparin prior to systemic

Table 1. Incidence of postoperative TEC and baseline characteristics.

Baseline characteristics of KTx patients Characteristics	Cases		
	No TEC	TEC ≤7 days	*P*-value
N	1979	21	
Gender			
Male (%)	1198	10	0.23
Age in years			
≥50	1304	12	0.40
Pre-emptive KTx	611	7	0.81
Dialysis-dependent KTx			
Hemodialysis	1035	9	
CAPD	330	5	0.32
Dialysis duration months	22 ± 27	18 ± 19	0.51
Ethnicity			
Non-Caucasian	264	1	0.50
ASA score	3 (3–3)	3 (3–3)	0.51
BMI in kg/m^2 ≥30	412	9	0.01
Baseline eGFR ≥10	604	6	0.83
CCI score	4 (3–6)	4 (3–6)	0.94
Co-morbidities			
Diabetes	400	5	0.60
SLE	26	1	0.25
Cardiovascular disease	465	4	0.80
Peripheral vascular disease	162	1	0.99
Hypertension	1171	11	0.70
DVT in medical history	71	1	0.77
Coagulation disorders	19	0	0.99
Bleeding disorders	6	0	0.80
Smoking at time of KTx	385	2	0.40
Diabetic nephropathy	269	4	0.47
N arteries >1	354	8	0.04
N veins >1	54	1	0.45
Blood loss (ml) ≥500	320	6	0.15
Intraoperative diuresis			
No	389	10	0.004
Donor type			
Living donor	1193	10	0.24
DBD	381	6	0.70
DCD	403	5	
Donor age (years) ≥60	693	11	0.10
Donor gender			
Male (%)	962	10	0.92
Right kidney	695	9	0.25
Ischemic times in min.			
1st WIT	5.7 ± 8.5	5.6 ± 5.7	0.71
CIT >24 h	14	1	0.03
2nd WIT	30.8 ± 13.6	36.3 ± 19.6	0.14
Preoperative Hb	7.4 ± 1.0	7.2 ± 1.1	0.23
Preoperative platelets	228 ± 85	213 ± 42	0.42
Antithrombotic therapy			
None	1344	15	0.73
Continued VKA*	52	1	0.40
APT†	388	2	0.56
Intraoperative UFH	193	2	0.71
APT + intraoperative UFH	28	1	0.27
Postoperative heparin infusion	632	5	0.43

Table 1. Continued.

Baseline characteristics of KTx patients Characteristics	Cases		
	No TEC	TEC ≤7 days	*P*-value
AB0 – blood group Incompatible	72	2	0.19
DGF	453	2	0.44

Shown are baseline characteristics in n (%). Ordinal data are given as median with IQR. Continuous data as mean ± SD.

N, number in group; CAPD, continuous ambulatory peritoneal dialysis; ASA, American society for anaesthesiologists; BMI, body mass index; eGFR, estimated glomerular filtration rate; CCI, Charlson Comorbidity Index; SLE, systemic lupus erythematosus; DVT, deep venous thrombosis; DBD, donation after brain death; DCD, donation after circulatory death; WIT, warm ischemic time; CIT, cold ischemic time; VKA, Vitamin K antagonists; APT, antiplatelet therapy; UFH, unfractionated heparin.

*Administration of VKA on day of transplantation was continued and INR not corrected.

†Administration of APT was continued at the day of transplantation. Second WIT was defined as the time from cold storage to recirculation (anastomosis time). CCI, which predicts the 1 year mortality for a patient, was scored for all recipients [34].

perfusion and flushout. DCD and living donors do not receive any form of anticoagulation. After procurement, kidneys were flushed and perfused with cold University of Wisconsin solution (ViaSpan; DuPont, Wilmington, NC, USA; Belzer UW; Bridge to life, Columbia, SC, USA) and placed in either cold storage or using hypothermic machine perfusion (national protocol for all deceased donor kidneys since January 2016). No heparin was added to the perfusates (cold storage or machine perfusion). No subcutaneous heparin was given to recipients intraoperatively. KTx was performed according to local protocol and published before [19,20]. Multiple artery reconstruction was performed in either an end-to-end or end-to-side fashion in both centers. In some deceased donors, attachment to the aortic patch was possible and thus reconstruction was not needed and sometimes the second artery was too small, so it was sacrificed. At the UMCG, patients transplanted pre-emptively received 5000 IU UFH intravenously before clamping of the iliac vessels. In the UMCG, Mannitol is given prior to reperfusion. In both centers, no additional diuretics are administered. Intraoperative diuresis was defined as visible urine coming from the ureter before ureter-bladder anastomosis or through the urinary catheter in case of absent diuresis prior to surgery. All patients received induction therapy with basiliximab, or occasionally anti-thymocyte globulin, with exception of recipients with human leukocyte antigen (HLA) mismatch of 000. Maintenance immunosuppression consisted of prednisolone, mycophenolic acid, and tacrolimus. Between 2011 and 2013, patients at the EMC were treated with 12 000 IU/24 h of continuous UFH (without sequential APTT measurements) for 5 days after transplantation, starting 6 h postoperatively. In 2013, this protocol was changed and thereafter only recipients of a kidney with reconstruction of multiple arteries were treated with 12 000 IU/24 h of continuous UFH for 5 days. All patients who did not receive postoperative heparin infusion were given a prophylactic dose of 2850 IU LMWH s.c. as part of hospital protocol for immobilized patients, starting 6 h postoperatively. Three patients with history of heparin-induced thrombocytopenia were excluded from this protocol and some patients received therapeutic doses of LMWH, which was adjusted according to renal function.

Antithrombotic strategies

Antithrombotic therapy was divided into five groups: none (control group, CG; $n = 1333$), intraoperative UFH (UFH; $n = 195$), continued use of VKA ($n = 53$), continued use of antiplatelet therapy (APT; $n = 390$), and combined continued use of APT and UFH (APT + UFH; $n = 29$). Patients receiving dual APT ($n = 9$) were combined with patients receiving single APT and analyzed as one group. None of the patients used a NOAC at time of surgery. Continued use of VKA was defined as a preoperative INR > 1.5, which was not corrected and last administration was given at day of transplantation. Patients of whom VKA therapy was bridged with heparin were included in the VKA group ($n = 25$). VKA in the 18 patients with a living donor were ceased 3–5 days prior to transplantation and bridged with heparin. The seven patients with a deceased donor were first corrected for INR by Vitamin K/phytomenadione or prothrombin complex concentrate after admission to the hospital and then bridged with heparin. Twenty-nine patients of CG-group had a pre-transplant anticoagulation regime, but were adequately and timely corrected for INR prior to

Table 2. Incidence of postoperative bleeding and baseline characteristics.

Baseline characteristics of KTx patients Characteristics	Cases		
	No bleeding	Bleeding ≤7 days	*P*-value
n	1912	88	
Gender (%)			
Male	1157	51	0.63
Age in years			
≥50	1255	61	0.48
Pre-emptive KTx	581	37	0.02
Dialysis-dependent KTx			
Hemodialysis	1006	40	
CAPD	324	11	0.64
Dialysis duration months	22 ± 27	19 ± 24	0.32
Ethnicity			
Non-Caucasian	246	19	0.02
ASA score	3 (3–3)	3 (3–3)	0.06
BMI in kg/m^2 ≥30	410	11	0.04
Baseline eGFR ≥10	574	36	0.03
CCI score	4 (3–6)	5 (3–6)	0.02
Co-morbidities			
Diabetes	384	21	0.39
SLE	27	0	0.26
Cardiovascular disease	433	36	<0.001
Peripheral vascular disease	152	11	0.13
Hypertension	1129	53	0.82
DVT in medical history	68	4	0.56
Coagulation disorders	19	0	0.35
Bleeding disorders	6	0	1.00
Smoking at time of KTx	378	9	0.02
Diabetes nephropathy	256	17	0.11
N arteries >1	342	20	0.24
N veins >1	55	0	0.11
Blood loss (ml) ≥500	304	22	0.12
Intraoperative diuresis			
No	376	23	0.13
Donor type			
Living donor	1151	52	0.84
DBD	373	14	0.23
DCD	386	22	
Donor age (years) ≥60	664	40	0.04
Donor gender			
Male (%)	930	42	0.85
Right kidney	677	27	0.54
Ischemic times in min			
1st WIT	5.4 ± 7.0	5.7 ± 6.1	0.70
CIT >24 h	14	1	0.42
2nd WIT	31.1 ± 13.8	26.1 ± 11.0	0.001
Preoperative Hb	7.4 ± 1.0	7.3 ± 1.0	0.46
Preoperative platelets	228 ± 85	226 ± 75	0.94
Antithrombotic therapy			
None	1287	46	0.26
Continued VKA*	38	15	<0.001
APT†	370	20	0.44
Intraoperative UFH	190	5	0.15
APT + intraoperative UFH	27	2	0.37
Postoperative heparin infusion	593	44	<0.001

Table 2. Continued.

Baseline characteristics of KTx patients Characteristics	Cases		
	No bleeding	Bleeding ≤7 days	*P*-value
AB0 – blood group Incompatible	72	2	0.77
DGF	432	23	0.41

Shown are baseline characteristics in n (%). Ordinal variables are shown as median with interquartile range. Continuous variables are shown as mean ± SD.

N, number in group; CAPD, continuous ambulatory peritoneal dialysis; ASA, American society for anaesthesiologists; BMI, body mass index; eGFR, estimated glomerular filtration rate; CCI, Charlson Comorbidity Index; SLE, systemic lupus erythematosus; DVT, deep venous thrombosis; DBD, donation after brain death; DCD, donation after circulatory death; WIT, warm ischemic time; CIT, cold ischemic time; VKA, Vitamin K antagonists; APT, antiplatelet therapy; UFH: unfractionated heparin.

*Administration of VKA on day of transplantation, medication was continued and INR not corrected.

†Administration of APT was continued at the day of transplantation. Second WIT was defined as the time from cold storage to recirculation (anastomosis time).

surgery. In the APT group, two patients received platelet transfusion prior to surgery because clopidogrel was not discontinued.

Thromboembolic and bleeding complications

After KTx, diagnoses of TEC were made based on clinical symptoms or laboratory abnormalities and confirmed with duplex imaging, renal scintigraphy or CT-scan. DVT, extending to the popliteal vein or more proximally, all cases of PE and thrombosis of the femoral artery, confirmed by radiological imaging ≤7 days after surgery, were counted as events. Furthermore, all radiologically or surgically confirmed cases of renal artery or renal vein thrombosis ≤7 days post-transplantation were counted as an event. Cases of postoperative bleeding ≤7 days were extracted from follow-up documentation. Clinical symptoms suspected for bleeding, i.e., pain due to compression or conjunctival pallor, had to be accompanied by either a sudden drop of hemoglobin, noticed by the treating physician, or compression on the graft as confirmed on imaging. Bleeding requiring further intervention, by blood transfusion, re-exploration or both, was then counted as event.

Statistical methods and analyses

Descriptive statistics were presented as mean ± standard deviation (SD) or median with interquartile range (IQR) for continuous variables and analyzed by student's *t*-test, ANOVA, Mann–Whitney *U* or Kruskal–Wallis test depending on distribution, evaluated by Shapiro Wilk-test. Categorical variables were presented as total with percentages (*n* (%)). Differences between patients with and without complications after transplantation were evaluated by Chi-square and/or Fisher's exact tests. Primary analyses focused on univariable regression analysis to determine relationship between perioperative antithrombotic therapy and incidence of TEC and bleeding. Secondary analyses focused on multivariable regression analysis to adjust for potential confounders. Results of the regression analyses were presented as odds ratio (OR) with 95% confidence interval (CI) and its corresponding *P*-value. Tests of significance are two-tailed with significance set at $P < 0.05$. A $P < 0.2$ in univariable analysis and/or known risk factors from the literature were added to the adjusted multivariable model. Hosmer–Lemeshow test was used to test fitness of the model. The model was considered fit when $P > 0.05$. Internal validation was performed using bootstrap sampling with 1000 resamples. Discrimination of the model was evaluated using Harrell's C-index. Incidence of TEC was analyzed as percent of patients experiencing TEC ≤7 days after transplantation. Time to TEC and time to bleeding were calculated from day of transplantation until day of diagnosis as described above. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS v22; IBM Corp, Armonk, NY, USA) and graphs were created using GRAPHPAD PRISM v5.04 (GraphPad Software Inc.©, La Jolla, CA, USA).

Results

Baseline characteristics and pre- and intraoperative parameters stratified for TEC and bleeding are shown in Table 1 (TEC) and Table 2 (Bleeding). Mean age of the total cohort was 54 ± 14 years and 60% of patients were male.

Incidences of TEC

Twenty-one patients (n = 21/2000, 1.1%) developed TEC ≤7 days after KTx. Fourteen (14/21, 67%) TEC developed in patients who did not receive any form of antithrombotic therapy and three (14%) in patients treated with APT. The groups VKA and APT+UFH each had one patient with an event of TEC (n = 1, 5%) (Fig. 1). Two patients (11%) receiving UFH had an event of TEC. Of all TEC, 19 were RGT, one case of arterial thrombosis was found in the common femoral artery (day 1) and in one case DVT occurred (day 7). Incidence of TEC did not vary between the treatment groups (P = 0.69). Median time for the development of TEC was 1 day (1–3) (n = 13, 62%) (Fig. 2).

Risk factors for TEC

Univariable analysis (Table 3) shows that KTx with multiple donor arteries increases the risk for the development of TEC by 2.8-fold [odds ratio (OR) 2.79 (95% CI: 1.15–6.79), P = 0.04]. For every recipient with a BMI > 30 kg/m^2, the added risk for developing TEC is almost threefold [OR 2.85 (95% CI: 1.19–6.82), P = 0.03]. Intraoperative diuresis was associated with decreased risk of TEC [OR 0.27 (95% CI: 0.11–0.65), P = 0.004]. A multivariable regression analysis could not be performed without the risk of underfitting the model owing to small numbers.

Incidences of postoperative bleeding

Postoperative bleeding occurred in 88 (4.4%) cases ≤7 days after transplantation. Fourty-six (52%) cases occurred in the control group, 15 (17%) in the VKA group, 20 (23%) in the APT group, five (6%) in the UFH group and two (2%) in the APT + UFH group (Fig. 3). Incidence of bleeding varied significantly between the treatment groups (P = 0.006). Of all patients with postoperative bleeding, 47 required surgical intervention with or without blood transfusion, and 17 required only a blood transfusion. Median time for development of bleeding was on the second postoperative day (1–4) (n = 45, 51%), with a peak on the first day (n = 36, 41%) (Fig. 2).

Risk factors for bleeding ≤7 days after transplantation

In univariable analysis (Table 4), continued use of VKA [OR 10.13 (95% CI: 5.33–19.52), P < 0.001] and postoperative continuous heparin infusion increased the risk [OR 2.22 (95% CI: 1.45–3.42), P < 0.001] for postoperative bleeding. Donor age >60 years [OR 1.60 (95% CI: 1.04–2.46), P = 0.04] was associated with a 1.6-fold increased risk. Being of non-Caucasian ethnicity increased the risk nearly twofold [OR 1.91 (95% CI: 1.13–3.24), P = 0.01] and patients suffering from CVD had a 2.4-fold increased risk [OR 2.41 (95% CI: 1.55–3.75), P < 0.001]. Furthermore, being pre-emptively transplanted increased the risk by 1.7-fold [OR 1.70 (95% CI: 1.10–2.62), P = 0.02] and every point increase on the American Society for Anaesthesiologists (ASA)-scale by 2.1-fold [OR 2.10 (95% CI: 1.04–4.23), P = 0.04]. A second warm ischemic time, defined as time from cold storage to recirculation (anastomosis time), >45 min [OR 0.46 (95% CI: 0.21–1.00), P = 0.04] and smoking [OR 0.46 (95% CI: 0.23–0.93), P = 0.03] reduced the risk of developing postoperative bleeding by more than half. Every increase of 5 kg/m^2 in recipient BMI decreased the risk by more than a quarter [OR 0.72 (95% CI: 0.52–0.99) P = 0.05].

Multivariable regression analysis for postoperative bleeding ≤7 days

For multivariable adjusted analyses, the following variables were entered in the model: UFH, VKA, APT, postoperative heparin, non-Caucasian ethnicity of the recipient, pre-emptive KTx, presence of CVD, BMI per 1 kg/m^2 increase, donor age >60, intraoperative blood loss >500 ml, CIT per hour increase, smoking, presence of peripheral vascular disease (PVD) and diabetic nephropathy (Table 5). Hosmer–Lemeshow test showed fitness of the model (P = 0.98). The C-statistic of this model is 0.75, indicating a high degree of discrimination. Pre-existing CVD [OR 2.01 (95% CI: 1.18–3.42), P = 0.010], pre-emptive KTx [OR 2.23 (95% CI: 1.28–3.89), P = 0.005], continued use of VKA [OR 6.60 (95% CI: 2.95–14.77), P < 0.001] and postoperative heparin infusion [OR 1.69 (95% CI: 1.00–2.85), P = 0.049] remained independently associated with risk for postoperative bleeding ≤7 days after KTx. After adjustment for VKA therapy, which is indicated in certain cardiovascular conditions and could thus be a confounding factor, CVD remained a significant risk factor for bleeding [OR 2.46, (95% CI: 1.47–4.12), P = 0.001]. When patients with postoperative heparin infusion (n = 637) were removed from the equation, pre-emptive KTx remained associated with bleeding [OR 3.24 (95% CI: 1.42–7.41), P < 0.01]. Stratification for transplant center did not show significant difference in bleeding in the pre-emptively transplanted patients (P = 0.23).

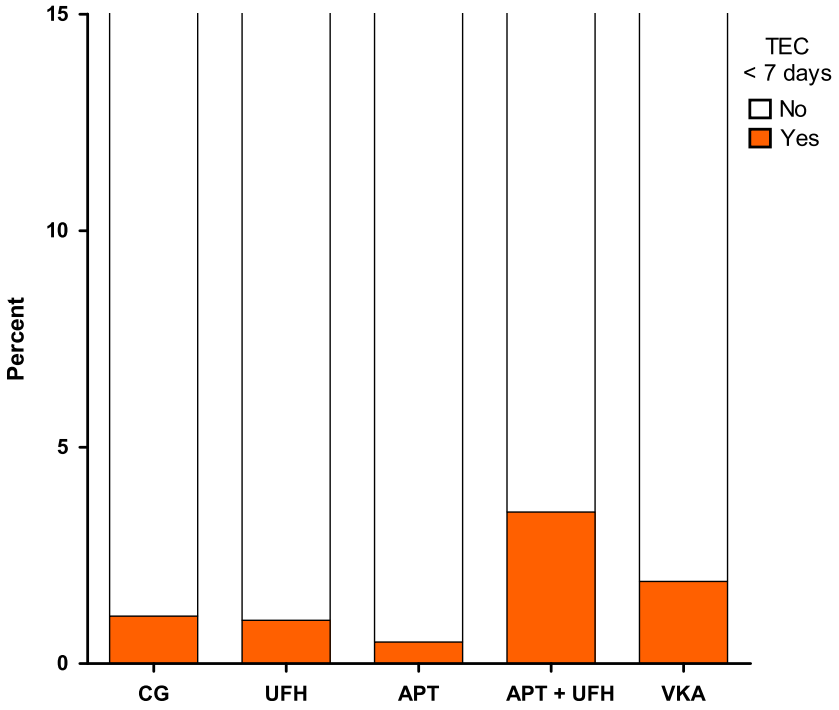

Figure 1 Incidence (%) of thromboembolic complications per treatment group. TEC, thromboembolic complications; APT, antiplatelet therapy; VKA, Vitamin K antagonists; UFH, unfractionated heparin (given intraoperatively).

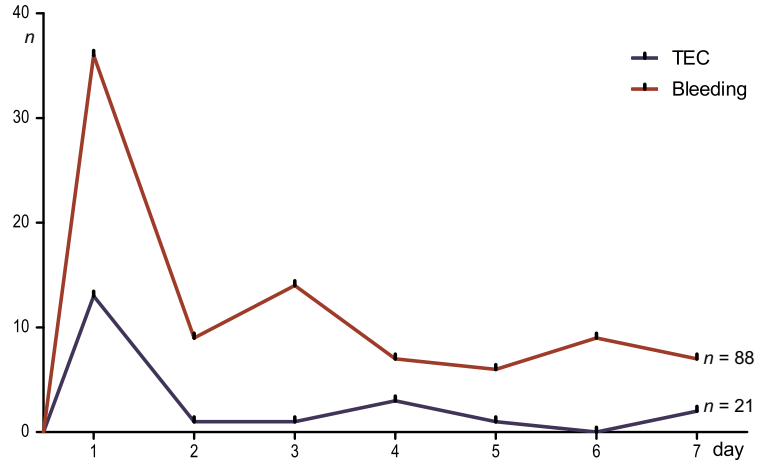

Figure 2 Number of TEC and bleeding per day after transplantation. *n*, number of group; TEC, thromboembolic complication.

Discussion

To our knowledge, we report on the largest series focusing on postoperative thromboembolic and bleeding complications after KTx. We identified a 1.1% incidence of early TEC and 4.4% bleeding complications. This is lower than reported in the literature [8–11,21,22]. High BMI and multiple donor arteries were associated with increased risk for TEC. Pre-emptive KTx, use of VKA, CVD, and postoperative heparin infusion were independent risk factors for early (re-)bleeding. Interestingly intraoperative heparin, APT, or the combination were not associated with an increased risk. TEC or bleeding occurred mostly within the first days after KTx, with the majority on the first postoperative day, which has been reported before [21]. TEC in the first post-transplant week, were predominantly RGT, whereas DVT and PE were rare or absent. Because KTx recipients are reported to have a sevenfold higher risk of venous thromboembolism compared to the general population, which confers an increased risk of graft loss and even death [9,23], our results can help in identifying the patients most at risk and provide a starting-point for prospective studies in order to develop preventive strategies. Since therapeutic options for RGT are scarce, antithrombotic prophylaxis may decrease this risk.

While some data considering antithrombotic prophylaxis in KTx exist, these reports are limited by their

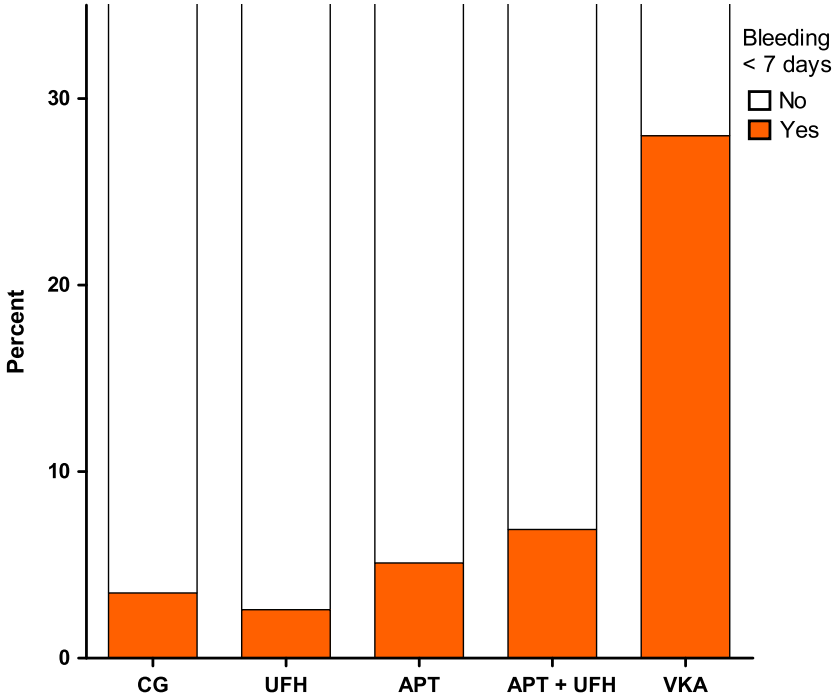

Figure 3 Incidence (%) of bleeding per treatment group. APT, antiplatelet therapy; VKA, Vitamin K antagonists; UFH, unfractionated heparin (given intraoperatively).

sample size. Therefore, a clear answer as to whether antithrombotic therapy increases bleeding risk had yet to be found. Pawlicki *et al.* [22] reported an association between increased risk for bleeding and antithrombotic prophylaxis, but this study was limited by sample size (n = 67), and suboptimal methodology: hematomas of ≥4 cm, with or without graft compression were scored as bleeding events. In general, hematomas of ≥4 cm are common after KTx and rarely have any clinical relevance. Our inclusion criteria for bleeding were stricter, and therefore the incidence of postoperative bleeding was relatively low compared to other studies (4.9–25.4%) [21,22]. The incidence is reported to decline to 0.2–1.9%, if only a reoperation is considered clinically relevant [24]. Considered all above, our incidence seems to be an accurate representation of clinically relevant bleeding after KTx. High BMI was found to be associated with increased risk for TEC, while it reduced the risk for bleeding. It is known that obesity leads to hypercoagulability and several explanations for this finding have been considered. Patients with higher BMI could have more space for bleeding and would therefore be less likely to develop bleeding with compression on the graft or high body weight could possibly tamponade the bleeding [21,25]. Difficulty in performing duplex ultrasound on obese patients could lead to underreporting of bleeding, although our inclusion criteria for bleeding should have been able to identify these patients as well. The higher volume of surrounding tissue could also lead to impaired blood flow and thus increase the risk for thrombosis by twofold. Contradictory results have been reported regarding the increased risk for TEC (especially renal artery thrombosis) in case of multiple donor arteries [7,26,27] and this finding might therefore be of less significance in a multivariable model. Another study on bleeding risks after perioperative anticoagulation concluded that the utilization of antithrombotic prophylaxis does neither increase the incidence nor the risk for bleeding in the perioperative period, except for postoperative heparin infusion [28]. Heparin infusion, starting within 24 h after surgery, has been associated with an increased risk for bleeding before [29], as in our analysis, whereas the prophylactic use of heparin (5000 IU s.c. twice daily) is reported to be safe [30]. Others reported an increased risk of bleeding after continued VKA therapy as well, but concluded that the indication for VKA therapy was nonmodifiable in certain patients [31]. We can concur this finding since all patients on continued VKA therapy in our analysis had a vital indication for anticoagulation therapy, i.e., due to paroxysmal atrial fibrillation with high CHA2DS2-VASc scores. In all cases, the treating physicians were aware of the possible complications and deemed discontinuing preoperatively as more threatening than the risk of a postoperative bleeding. Aside from VKA therapy, often indicated in certain cardiovascular diseases, CVD was associated with an increased risk for bleeding, even after correction for VKA or APT, most likely explained

Table 3. Univariable analysis for possible risk factors for TEC.

Risk factors for Thromboembolic complications (Univariable analysis using Enter method of binary logistics.)	Odds ratio (95% CI)	*P*-value
AB0-incompatible	2.69 (0.61–11.81)	0.19
Preoperative VKA therapy (not stopped, INR not corrected)	3.76 (0.49–29.04)	0.25
Preoperative antiplatelet therapy	0.68 (0.20–2.33)	0.78
Intraoperative heparin	0.46 (0.06–3.47)	0.71
Postoperative heparin infusion	0.67 (0.24–1.83)	0.43
Arteries >1	2.79 (1.15–6.79)	0.04
Blood loss >500 ml	2.05 (0.75–5.58)	0.23
CAPD (yes)	1.55 (0.56–4.25)	0.38
Coagulation disorder (yes)	0.99 (0.99–0.99)	1.00
Cold ischemic time per 1 h increase	1.08 (0.98–1.20)	0.14
DGF (yes)	0.56 (0.16–1.91)	0.44
Diabetic nephropathy (yes)	1.50 (0.50–4.48)	0.52
Donation of the right kidney	1.71 (0.68–4.33)	0.25
Donor age (<60 vs. >60)	2.04 (0.86–4.82)	0.10
Donor gender (female)	1.69 (0.71–3.99)	0.23
Donor (deceased)	1.67 (0.71–3.95)	0.24
Deceased donor type (DBD)	1.27 (0.38–4.19)	0.70
DVT medical history (yes)	1.34 (0.18– 10.15)	0.54
Ethnicity (non-white)	0.34 (0.05–2.55)	0.50
Intraoperative diuresis (yes)	0.27 (0.11–0.65)	0.004
Pre-emptive transplantation (yes)	1.12 (0.45–2.79)	0.81
Recipient age (≥ 50)	0.69 (0.29–1.65)	0.40
Recipient BMI (≥30)	2.85 (1.19–6.82)	0.03
Recipient gender (female)	1.69 (0.71–3.99)	0.23
SLE (yes)	3.76 (0.49–29.04)	0.25
Smoking (yes)	0.45 (0.10–1.94)	0.40
Time on dialysis (per 1 year increase)	0.89 (0.63–1.26)	0.51
Second warm ischemic time (≥ 45 min)	1.79 (0.65–4.97)	0.23
Recipient BMI per 5 kg/m^2 increase	0.96 (0.50–1.84)	0.90
Charlson comorbidity index score per 1 point increase	0.86 (0.61–1.20)	0.37
ASA score per 1 point increase	1.17 (0.32–4.23)	0.81

Odds ratio is presented with 95% confidence interval (CI). An OR above 1.00 implies an increased risk compared to its equivalent. An OR below 1.00 corresponds to a decreased risk. *P*-value <0.05 was considered statistically significant.

VKA, vitamin K antagonists; INR, international normalized ratio; CAPD, continuous ambulatory peritoneal dialysis; DGF, delayed graft function; DBD, donation after brain death; DVT, deep venous thrombosis; BMI, body mass index; SLE, systemic lupus erythematosus; ASA, American society of anaesthesiologists.

by the technical challenges of transplanting patients with a high burden of CVD. A previous study mentioned that pre-emptive KTx is protective against thrombosis [32]. Interestingly, we saw an increased risk for bleeding in our pre-emptively transplanted cohort. After adjusting for intraoperative heparin, predominantly given to pre-emptive patients in one center, pre-emptive transplantation remained an independent risk factor. To our knowledge, the general argument to refrain from anticoagulation during KTx is often the belief that patients on dialysis, in contrast to pre-emptive patients, are considered hypocoagulable, because of the residual effect of heparin used during dialysis and the continuous activation of platelets through contact with the dialysis membrane. However, uremic toxins, which influence platelet function, develop in all patients with renal failure and recent insights have shown that dialysis could even lead to reduced risk of bleeding due to removal of these uremic toxins [15,16]. Surgical aspects, such as cross-clamping and anastomoses of vessels, may also overcome the theoretically guarding effects of uremia against thrombosis [8]. Therefore, dialysis-dependent patients are at risk of both bleeding and thrombotic complications. Recent analysis has

Table 4. Univariable analysis for possible risk factors for postoperative bleeding.

Risk factors for bleeding (Univariable analysis using Enter method of binary logistics)	Odds ratio (95% CI)	*P*-value
AB0-incompatible	0.59 (0.14–2.45)	0.77
Preoperative VKA therapy (not stopped, INR not corrected)	10.13 (5.33–19.25)	<0.001
Preoperative antiplatelet therapy	1.23 (0.74–2.04)	0.44
Intraoperative heparin	0.55 (0.22–1.36)	0.19
Postoperative heparin infusion	2.22 (1.45–3.42)	<0.001
Arteries >1	1.35 (0.81–2.26)	0.24
Blood loss ≥ 500 ml	1.50 (0.90–2.49)	0.12
CAPD (yes)	0.70 (0.37–1.34)	0.28
Cold ischemic time per 1 h increase	1.06 (1.00–1.12)	0.05
DGF (yes)	1.23 (0.75–2.00)	0.41
Diabetic nephropathy (yes)	1.55 (0.90–2.67)	0.11
Donation of the right kidney	0.86 (0.53–1.38)	0.54
Donor age (≥ 60)	1.56 (1.02–2.40)	0.04
Donor gender (female)	1.11 (0.72–1.71)	0.63
Donor (deceased)	1.05 (0.68–1.62)	0.84
Deceased donor type (DBD)	0.66 (0.33–1.31)	0.23
Duration dialysis (per 1 year increase)	0.93 (0.80–1.08)	0.36
Ethnicity (non-white)	1.88 (1.11–3.18)	0.02
Intraoperative diuresis (yes)	0.68 (0.41–1.12)	0.13
Pre-emptive (yes)	1.66 (1.08–2.57)	0.02
Recipient gender (female)	1.11 (0.72–1.71)	0.63
Recipient age (>50)	1.18 (0.75–1.88)	0.48
Second warm ischemic time (≥45 min)	0.45 (0.21–0.98)	0.04
Smoking (yes)	0.46 (0.23–0.92)	0.02
Recipient BMI per 5 kg/m^2 increase	0.73 (0.53–1.01)	0.05
Charlson comorbidity index score per 1 point increase	1.06 (0.93–1.21)	0.36
ASA score per 1 point increase	2.14 (1.06–4.31)	0.03
Cardiovascular disease	2.37 (1.53–3.67)	<0.001
Peripheral vascular disease	1.65 (0.86–3.18)	0.13
Recipient BMI >30 kg/m^2	0.52 (0.28–0.99)	0.04

Odds ratio with 95% confidence interval (CI). An OR above 1.00 implies an increased risk compared to its equivalent. An OR below 1.00 corresponds to a decreased risk. $P < 0.05$ was considered statistically significant.

VKA, vitamin K antagonists; INR, international normalized ratio; CAPD, continuous ambulatory peritoneal dialysis; DGF, delayed graft function; DBD, donation after brain death; BMI, body mass index; ASA, American society of anaesthesiologists.

shown that pre-emptively transplanted patients and dialysis patients have a comparable ability for platelet and coagulation activation prior to transplantation [17]. Therefore, differences might be found in platelet function, which could be worse in pre-emptive patients compared to dialysis-dependent patients than previously thought, since they do not benefit from the potentially beneficial effect of hemodialysis on platelet dysfunction.

A few limitations of this study need to be addressed. First, due low events numbers, multivariable analysis for TEC was not feasible without leading to under fitting the model and thus a detailed analysis of potential risk factors is missing. Considering our incidence, a similar multivariable analysis as performed for bleeding, would require nearly 8000 KTx recipients. Second, because of the retrospective study design and relatively low incidence, potential confounding risk factors may have been missed. A randomized study or propensity-matched cohort would probably have given a more robust outcome. However, given the many confounders and low incidences, this requires many patients, making a prospective study very challenging. Despite the skewed distribution in our study, we present the largest series with data from a real-world experience and provide reliable insights into risk factors for both TEC and bleeding after KTx. Third, postoperative antithrombotic therapy was not included in this study except for 5-day heparin infusion. When preoperative anticoagulants were stopped, reinitiation usually did not take place within 1–2 days after KTx, unless vital indications for anticoagulation stated otherwise. Since most TEC or bleeding occurred within the first postoperative day, we expect

Table 5. Multivariable regression analysis for risk factors for postoperative bleeding within 7 days after kidney transplantation.

Risk factors for bleeding (Multivariable analysis using Enter method of binary logistics)	Odds ratio (95% CI)	*P*-value
Intraoperative heparin	1.22 (0.43–3.45)	0.711
Vitamin K antagonists	6.60 (2.95–14.77)	<0.001
Postoperative heparin infusion	1.69 (1.00–2.85)	0.049
Antiplatelet therapy	1.51 (0.80–2.85)	0.204
Ethnicity of the recipient (non-Caucasian)	1.85 (0.98–3.49)	0.058
Pre-emptive transplantation	2.23 (1.28–3.89)	0.005
BMI per 1 kg/m^2 increase	0.93 (0.87–0.98)	0.011
Donor age >60	1.63 (0.99–2.69)	0.054
Intraoperative blood loss >500 ml	1.60 (0.91–2.83)	0.103
Cold ischemic time per 1 h increase	1.02 (0.97–1.06)	0.450
Smoking at time of transplantation	0.39 (0.17–0.89)	0.025
Cardiovascular disease	2.01 (1.18–3.42)	0.010
Peripheral vascular disease	1.36 (0.62–3.01)	0.446
Diabetic nephropathy	0.86 (0.42–1.76)	0.680

Odds ratio with 95% confidence interval. All factors adjusted for risk factors in the table. $P < 0.05$ was considered statistically significant.

CI, confidence interval; BMI, body mass index.

that this would not have significantly affected our results. Furthermore, DVT and PE might have required a longer follow-up until 30 days post-transplant, considered a reported cumulative risk [33]. In this study, we aimed at analyzing early postoperative complications in relation to perioperative antithrombotic prophylaxis.

Our results show that continued APT and intraoperative heparin do not increase the incidence of bleeding after KTx and that it is safe to use these agents in order to prevent early postoperative TEC. We advise that VKA should only be continued in patients with a vital indication for anticoagulation. Despite the significantly increased risk, patients using VKA should not be refrained from KTx, but instead should be monitored closely for early signs of postoperative bleeding, with i.e., daily duplex imaging in the first five postoperative days and prophylactic placing of surgical drains seems advised. Postoperative heparin infusion should be refrained from, as several studies have now reported increased bleeding risk with unclear advantages for prevention of TEC. There is still a lot of uncertainty about the use of antithrombotic prophylaxis during KTx. A cutoff point based solely on dialysis dependence seems very arbitrary and unfounded because pre-emptive patients also have a poor kidney function, with the associated risks of an impaired coagulation. Perhaps new criteria should be established in which a high-risk group is defined who would benefit most from antithrombotic prophylaxis perioperatively. Given the dogmas that prevail, we hope this study will add new insights and data into this long-standing and recurrent problem. Further research is needed to investigate the adjusted risk factors for early TEC and the possible additional advantages of intraoperative heparinization during KTx.

Authorship

TAJB: conceptualization, research design, methodology, data collection, data analysis, funding acquisition, visualization, writing- original draft preparation, writing – review and editing. RCM: conceptualization, methodology, data collection, resources, writing- original draft preparation, writing – review and editing. TL: methodology, writing- original draft preparation, writing – review and editing. GJNM and JW: data collection, writing- original draft preparation, writing – review and editing.. SJLB: data collection, methodology, funding acquisition, writing- original draft preparation, writing – review and editing. RAP: conceptualization, research design, methodology, resources, data collection, writing- original draft preparation, writing – review and editing.

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Conflicts of interest

The authors have declared no conflicts of interest.

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