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The risk of thromboembolic events in kidney transplant patients

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Little is known about the risk of venous thrombosis following kidney transplant. To determine this we estimated the risk of thromboembolic events (TEs) in a cohort of consecutive patients who underwent kidney transplantation at a single tertiary care center over an 11-year period and calculated standardized incidence ratios (SIRs) for a first TE in kidney transplant recipients compared with the general population. We then performed a nested case–control study and compared patients with and without TEs to identify risk factors for thrombosis. Among 913 kidney transplant recipients (KTRs), 68 patients developed these events. The SIR for TEs in KTRs compared with the general population was 7.9 over the duration of follow-up. The risk was particularly higher in the first post-transplant year (SIR 26.1) but remained elevated afterward (SIR 5.2). Hospitalization, use of sirolimus, low hemoglobin level, and use of renin–angiotensin system inhibitors were independently associated with these events. When cases of TEs that occurred during hospitalization were excluded, the risk of these events remained elevated. The risk of TEs in KTRs was eightfold higher than in the general population but not fully explained by the increased risk associated with hospitalization. Our results underscore the important risk of thrombosis in patients who received a kidney transplant, making vigilance mandatory especially during hospitalization.

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Deep venous thrombosis (DVT) and pulmonary embolism (PE) are two phenotypes of the same thromboembolic disease. If untreated, this disease has a high mortality.[1] Earlier studies have documented an increased risk of thromboembolic events (TEs) after kidney transplantation (KT).[2,3] Although in the first months after transplantation the risk of TE can be related to the transplant surgery, there seems to be an increased long-term TE risk in kidney transplant recipients (KTRs).[4] The magnitude and the determinants of the increased TE risk after KT are poorly defined. Moreover, in the general population, a major risk factor for TE is hospitalization.[5] It remains unknown whether the relatively high frequency of hospitalization in KTRs may explain the persistently elevated TE incidence in this patient population.

Although traditional risk factors for TE such as age, history of TE, and malignancy[2,3] have been linked to TE in KTRs, little is known about the effect of transplant-specific factors on TE risk. Although various immunosuppressive agents have been shown to possess procoagulant effects,[6] their effect on TE risk in KTR is unknown. For example, although sirolimus, which is increasingly being used for maintenance immunosuppression in KTRs, has been linked to an increased TE risk in cardiac and lung transplant recipients, an association with TE in KTRs has never been shown.[7,8] A recent study reported that TE was more common in KTRs with low estimated glomerular filtration rate (eGFR <30 ml/min per 1.73 m^2) 1 year after transplantation compared with patients with better graft function.[9] In another report, the use of a vitamin D receptor activator in combination with dual renin–angiotensin system (RAS) inhibitor seemed to be protective for TE.[10] As most studies measured putative risk factors at the time of transplantation instead of measuring them at or close to the time of TE, a pathophysiologically relevant exposure time window is lacking from previous reports.[2,9]

Hence, we undertook the present study to determine the magnitude and the secular trends of the increased TE risk observed after renal transplantation as compared with the risk of TE in the general population. We also aimed to determine whether the increased risk was explained by an

increased probability of hospitalization in KTRs, and we identified risk factors for TE in this patient population.

RESULTS

The cohort consisted of 913 patients who had 979 renal transplantations. The median follow-up was 5.9 years (range 0–22), with a total of 6760 person–years (p–y). The mean age at transplantation was 47 (± 12) years, and 63% of patients were men. In all, 68 patients developed a TE (1.0/100 per year), among whom 42 were diagnosed with DVT alone, 21 with PE alone, and 5 with both DVT and PE. The thrombus was located in the proximal veins in 85% of the subjects with DVT. Nine patients had recurrent TE events. Among the first TE events, 84% were initially treated with unfractionated heparin followed by warfarin, and 9% were treated with unfractionated heparin alone. The mean duration of therapy was 5 months for DVT and 6 months for PE for patients treated with warfarin. The six patients undergoing heparin treatment had a treatment duration varying from 1 month to life long. Loss to follow-up occurred in 26 patients (2.8% of the cohort). Although only one subject died of his TE, patients who experienced a TE had an increased mortality risk (hazard ratio 2.1 (1.2–3.8)).

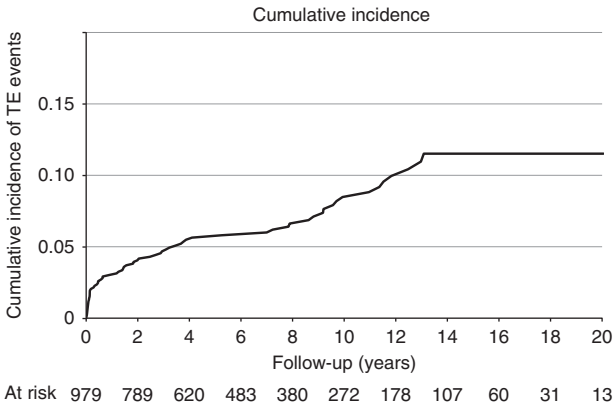

Figure 1 | Graph illustrating the cumulative incidence of TE events (left *y* axis) per year after renal transplantation (right *y* axis).

The risk of TE is elevated in the first year after KT but remains higher than that in the general population throughout follow-up

The cumulative incidence for TE at 1, 5, and 10 years after renal transplantation was 3.0, 5.8, and 8.4% (Figure 1). The standardized incidence ratio (SIR) was calculated based on age- and gender-stratified incidences. The SIR in KTRs compared with the general population was 7.9 (95% confidence interval (CI): 6.2–10.0) when averaged for the whole duration of post-transplant follow-up (Table 1).

To determine whether this increased risk was due to the transplantation itself, we calculated SIR for the first post-transplant year, and SIR for later time periods. When only the events and person–time of the first post-transplant year were considered, the SIR for TE in KTRs was 26.1 (95% CI: 17.6–37.5) compared with the general population. After the first post-transplant year, the SIR for TE in KTRs was 5.2 (95% CI: 3.8–7.1) compared with the general population, whereas this ratio was 4.3 (95% CI: 2.6–6.7) after 5 years and 3.9 (95% CI: 1.6–8.1) after 10 years (Figure 2). Our results suggest that the elevated TE risk observed in KTRs is mediated by the initial surgery. However, other factors likely contribute to the increased TE risk observed in our patient population, as the risk remains persistently elevated even after 5–10 years of follow-up.

Compared with the general population, KT conferred a similar increase in risk in both men and women. However, there was a disproportionate increase in TE risk associated with KT in younger compared with older patients (Table 1).

The risk of TE is partly but not fully explained by an increased probability of hospitalization in KTRs compared with the general population

We questioned whether the augmented TE risk in transplant patients was due to their frequent hospitalizations. When the cases and corresponding person–time that occurred during a hospitalization were excluded ($n = 20$), the SIR decreased to 5.6 (95% CI: 4.2–7.4). Hence, the risk of TE after KT is partly, but not fully, explained by the increased likelihood of KTRs to be hospitalized compared with the general

Table 1 | Thromboembolic events in kidney transplantation recipients and in the general population

	Kidney transplant recipients			Reference general population				
	Events	P–y	Rate per 1000 p–y	Events	P–y	Rate per 1000 p–y	SIR	95% CI
Overall	67[a]	6760.02	9.91	52,699	49,794,387	1.06	7.92	6.19–9.99
Women	26	2359.44	11.44	27,445	25,092,214	1.09	8.89	5.93–12.83
Men	41	4400.58	9.32	25,254	24,702,173	1.02	7.41	5.39–9.95
Within first year post transplantation	27	903.52	29.88	52,699	49,794,387	1.06	26.14	17.58–37.50
After first year post transplantation	39[b]	5541.14	7.04	52,699	49,794,387	1.06	5.23	3.77–7.08
Age 20–39 years	16	1289.11	12.41	9268	19,751,872	0.47	27.30	16.16–43.39
40–49	13	1739.08	7.48	10274	12,421,796	0.83	9.15	5.09–15.25
50–59	24	1992.72	12.00	15047	10,585,383	1.42	8.46	5.55–12.40
60–69	14	1394.95	10.04	18110	7,035,336	2.57	3.87	2.20–6.34

Abbreviations: CI, confidence interval; p-y, person–years; SIR, standardized incidence ratio.
[a]One case that occurred at the age of >70 was excluded because of the low number of patients in that age group.
[b]One case was classified in the >70 age group after 1 year of follow-up because of aging one year. This case was excluded.

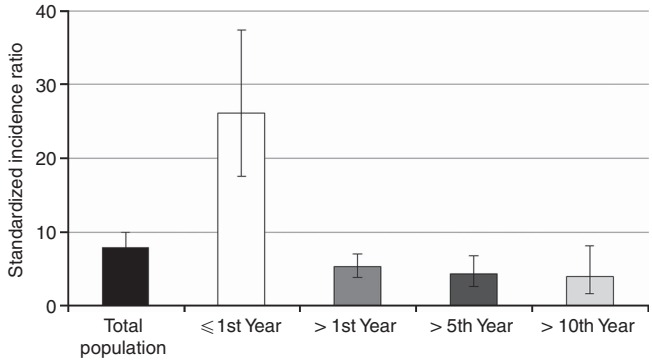

Figure 2 | Standardized incidence rate ratios and 95% CI for the first thromboembolic event in kidney transplantation patients compared with the general population for 'total' follow-up and within the first year and after 1, 5, and 10 years of transplantation.

population. In an attempt to verify whether the increased TE risk was due to factors known to provoke thrombosis, we excluded patients with TE during hospitalization, patients with recent trauma or surgery, and patients with a malignancy history. The SIR decreased but remained high (4.6, 95% CI (3.3–6.3)), indicating that the incidence of 'unprovoked' TE is increased after KT. To determine other potential risk factors for TE in our patient population, we turned to a nested case–control study design within our cohort of KTRs.

Hospitalization, anemia, and use of sirolimus are associated with an increased risk of TE, whereas the use of RAS inhibitors is associated with a decreased likelihood of TE in KTRs

We identified 68 cases who were matched to 260 controls. Controls were cohort members who did not have TE and were alive at the time of the corresponding TE of the case. Table 2 shows the population characteristics of the case–control study.

Cases and controls were similar in patient and transplantation characteristics. Approximately 92% were Caucasian. Both groups had a similar history in terms of TE before transplantation and smoking. The occurrence of malignancy after transplantation was more frequent in patients with TE than in control patients, although malignancy before transplantation occurred similarly in both groups. Among the patients who were hospitalized at the time of the index date, the proportion who received prophylactic subcutaneous heparin at any time during hospitalization was 42% in cases and 58% in controls ($P = 0.3$). We did not observe a lower incidence of TE after 2003, the year when a thrombosis prophylaxis protocol was introduced for the transplant hospitalization. eGFR was lower and proteinuria more frequent among patients with TE compared with controls. In addition, anemia, use of sirolimus, and hospitalization at the index date were more frequent, whereas the use of RAS inhibitors was lower in patients with TE compared with controls.

Table 2 | Patient characteristics

	Total cohort ($n = 328$)	TE ($n = 68$)	Control ($n = 260$)	*P*-value
Men (%)	203 (62)	41 (60)	162 (62)	NS
Mean age in years (s.d.)	50 (11)	50 (11)	49 (12)	NS
Median cold ischemia (min) (IQR)	810 (624–1020)	750 (538–960)	840 (653–1035)	NS
Living donor (%)	42 (13)	6 (9)	36 (14)	NS
Induction (ATG or anti-IL2 receptor blockade) (%)	164 (50)	30 (44)	134 (52)	NS
Smoking (past or present) at transplantation (%)	77 (23)	17 (25)	60 (23)	NS
TE before transplantation (%)	8 (2)	3 (4)	5 (2)	NS
Malignancy before transplantation (%)	17 (5)	5 (7)	12 (5)	NS
Malignancy after transplantation (%)	18 (6)	8 (12)	10 (4)	<0.05
Mean hemoglobin (mmol/l) (s.d.)	7.7 (1.2)	7.3 (1.2)	7.8 (1.2)	<0.01
Mean hemoglobin (g/dl) (s.d.)	12.4 (19.9)	11.8 (19.6)	12.6 (19.8)	<0.01
Mean eGFR (ml/min per 1.73 m^2) (s.d.)	57 (22)	50 (22)	58 (21)	<0.05
Median proteinuria (g/l) (IQR)	0 (0–0.2)	0.05 (0–0.9)	0 (0–0.2)	<0.05
Aspirin use (%)	61 (19)	8 (12)	53 (20)	NS
RAS blocker use (%)	109 (33)	15 (22)	94 (36)	<0.05
CNI use (%)	301 (92)	56 (82)	245 (94)	<0.05
Sirolimus use (%)	35 (11)	13 (19)	22 (9)	<0.05
Steroids use (%)	252 (77)	60 (88)	192 (74)	<0.05
Mycophenolate mofetil use (%)	232 (71)	42 (62)	190 (73)	NS
Azathioprine use (%)	27 (8)	8 (12)	19 (7)	NS

Abbreviations: ATG, anti-thymocyte globulin; CNI, calcineurin inhibitor; eGFR, estimated glomerular filtration rate; IL2, interleukin 2; IQR, interquartile range; NS, nonsignificant; RAS, renin–angiotensin system; TE, thromboembolic events.

Table 3 | Risk of thromboembolic events among renal transplant recipients

	Univariate model	Multivariate model
TE before transplantation	2.4 (0.6–10.0)	—
Induction therapy	0.6 (0.3–1.4)	—
Malignancy after transplantation	3.9 (1.3–11.7)	2.5 (0.7–8.4)
eGFR <60 ml/min per 1.73 m^2	1.7 (0.9–3.0)	—
Proteinuria >1 g/l	2.0 (0.8–5.0)	—
Hemoglobin <6.7 mmol/l	3.8 (1.9–7.7)	2.3 (1.0–5.0)
CNI	0.3 (0.1–0.7)	0.5 (0.2–1.3)
Sirolimus	2.7 (1.3–5.7)	3.0 (1.3–7.0)
Steroids	3.7 (1.5–9.0)	2.5 (0.9–7.3)
Aspirin	0.5 (0.2–1.1)	—
RAS inhibitor	0.4 (0.2–0.9)	0.5 (0.2–0.9)
Hospitalization	8.7 (3.4–22.4)	10.3 (3.5–30.5)

Abbreviations: CNI, calcineurin inhibitor; RAS, renin–angiotensin system; TE, thromboembolic event.
Conditional logistic regression odds ratios and 95% confidence intervals.

In univariate analyses, malignancy after transplantation (odds ratios (OR) 3.9 (95% CI: 1.3–11.7)), lower hemoglobin level (OR 3.8 (95% CI: 1.9–7.7)), sirolimus use (OR 2.7 (95% CI: 1.3–5.7)), steroid use (OR 3.7 (95% CI: 1.5–9.0)), and hospitalization at the index date (OR 8.7 (95% CI: 3.4–22.4)) were associated with TE (Table 3). The use of RAS inhibitors was inversely associated with TE (OR 0.4 (95% CI: 0.2–0.9)) as was calcineurin inhibitor use (OR 0.3 (95% CI: 0.1–0.7)).

Aspirin use and renal function parameters, such as eGFR or proteinuria, were not associated with TE. The use of induction therapy, biopsy-proven rejection, and donor type (living vs. deceased) were not associated with TE. In multivariate analyses, risk factors for TE included low hemoglobin levels (OR 2.3 (95% CI: 1.0–5.0)), sirolimus use (OR 3.0 (95% CI: 1.3–7.0)), and hospitalization (OR 10.3 (95% CI: 3.5–30.5)). The use of RAS inhibitors was associated with a lower TE risk (OR 0.45 (95% CI: 0.21–0.98)).

DISCUSSION

To our knowledge, this is the first detailed study to date to describe TE risk after KT. We observed that KTR patients have a risk of TE that is eightfold higher than that of the general population. The risk was highest in the first year after transplantation but remained elevated in the following years. Although a greater probability to be hospitalized partly explained the higher incidence of TE in KTR compared with the general population, these patients remained at greater risk even when hospital-acquired TE cases were excluded. Hospitalization was the strongest risk factor for TE in our cohort and was associated with a 10-fold increased risk for TE. Other risk factors were sirolimus use and low hemoglobin levels. RAS inhibition seemed to have a protective effect for TE. Although not related to the thrombotic event *per se*, we observed an increase in mortality among patients with TE, suggesting that this group had a greater comorbidity burden.

Over the course of follow-up, 7.4% of patients who received a KT at out center experienced a TE. Previous studies have reported on TE risk following KT, with incidence estimates ranging between 0.6 and 25%.[11–13] Comparison between incidence rates are of limited value because of the differences in follow-up and mortality rates between different cohorts. There is also variability in the use of TE prophylaxis between the studies. In 1998, an incidence of 6.4% was reported in a retrospective study by using graduated compression stockings as TE prophylaxis.[2] In another study that actively screened asymptomatic KTR for TE, the incidence was 9.1% using 3 months of low-dose subcutaneous unfractionated heparin or low-molecular-weight heparin.[3] However, the clinical importance of asymptomatic TE remains uncertain. The major limitation of the previous studies is that they did not report follow-up times for their patients or cumulative incidence rates after KT, nor did they compare the risk with that of the general population. We observed a cumulative incidence at 5 years of 5.8% and an eightfold risk compared with the general population.

The highest number of TEs were previously described in the first month after transplantation, and these studies have suggested that the incidence remains high until the fifth month after transplantation.[2,4] Our results suggest that the risk is high in the first year after transplantation, and although it decreases in subsequent years, it remains significantly elevated. In the general population, the increase in TE incidence with age is well known; however, in KTRs, the incidence in younger and older patients is similar. Moreover, young transplanted patients had an impressive increased TE risk compared with the low incidence of TE in this age group in the general population (Table 1).

Our results underline the importance of hospitalization in TE risk. In the general population, in the year following hospitalization, the risk of TE was fivefold compared with that of nonhospitalized subjects.[14] Our data indicate that hospitalization has an impressive impact in KTRs, as they experienced a 10-fold increase in risk during hospitalizations. We validated these results by taking hospitalization within the 2 months before the index date (compared with TE during hospitalization). Hospitalization increased the risk of TE sixfold by enlarging the time frame of hospitalization (OR 6.2, 95% CI 2.4–15.8).

In our cohort, among the patients who were hospitalized at the time of the index date, the proportion of prophylactic heparin use was lower in those who developed TE versus those who did not. Although this suggests that subcutaneous heparin may have exerted a protective role on the development of TE during hospitalization, the difference did not reach statistical significance. This could be due to the relatively low number of subjects who were hospitalized.

We show that an increased probability of hospitalization in KTRs does not solely explain the increased TE risk observed in KTRs compared with the general population. Other factors have a role in the development of thrombosis. The prothrombotic effect of different immunosuppressive agents has been extensively studied. Cyclosporine is associated with a hypercoagulable state *in vitro*,[15] although this was not confirmed *in vivo*.[16] Cyclosporine use was not associated with TE in the present study. Recently, an association between steroid use and TE risk in the general population was reported.[17] This relationship is possibly because of a steroid-related increase in different clotting factors.[18] Our univariate analyses showed an increased TE risk with steroid use. However, this association lost its significance in the multivariate model. Sirolimus has previously been linked to TE in other clinical contexts. An increased incidence of hepatic arterial thrombosis was observed in liver transplant patients treated with sirolimus in combination with cyclosporine.[19] *In vitro*, sirolimus is associated with collagen-induced platelet aggregation.[20] Sirolimus also increases prothrombotic tissue factor expression in endothelial cells.[21,22] Recent studies in lung and cardiac transplantation reported an increased TE risk associated with sirolimus use.[7,8] In renal transplantation, one study looked at the risk in relation to sirolimus. No increase in TE risk with a sirolimus–cyclosporine-based regimen compared with an azathioprine–cyclosporine combination was documented.[23] However, the conclusions of this retrospective study are limited by its small sample size. Given the low rate of sirolimus use in our study, more studies are needed to draw a definitive conclusion on the relationship between sirolimus and thrombosis in KTRs.

We observed an inverse association between hemoglobin and TE risk. This was an unexpected finding, given the relationship between erythrocytosis and TE in polycythemia vera and in post-transplant erythrocytosis.[24] We hypothesize that the relationship is probably a reflection of the greater comorbidity burden and/or inflammation that are associated with having lower hemoglobin, which may in turn increase the TE risk. However, given the retrospective nature of the study, we had no biological material to study the link between anemia, inflammation, and TE. The association between low hemoglobin and TE risk may also be explained by a greater probability of blood transfusions in patients with anemia, although we had no information on the latter. Blood transfusion is a risk factor for TE[25] possibly because stored transfused red blood cells exhibit greater adhesion to endothelial cells with sequestration in the lung.[26]

Chronic kidney disease increases the TE risk possibly by a combination of an increase in proteins implicated in the development of thrombosis,[27] and the increased state of inflammation and endothelial damage.[28,29] Some reports have previously suggested that albuminuria is associated with TE.[30,31] In the present study, neither impaired renal function nor the presence of proteinuria increased the TE risk. However, our observations are limited by an imprecise, semiquantitative measurement of proteinuria (dipstick analyses), which may have precluded a difference to be observed.

We observed a protective effect of RAS inhibition on TE. The RAS contributes to a prothrombotic state. Angiotensin II stimulates the production of adhesion factors and plasminogen activator inhibitor-1 and induces thrombosis. RAS is associated with plasminogen activator inhibitor-1 increase, and ACE inhibition improves the fibrinolytic balance.[32,33] In the PERTINENT study, ACE inhibition reduced d-dimer in patients with stable coronary artery disease over a 1-year follow-up.[34] We believe that in our cohort RAS blockade exerted its protective effect independent of reduction in proteinuria, as forcing proteinuria in the regression model did not modify the point estimates for the relationship between RAS inhibition and TE risk. However, this apparent protective effect may be due to immeasurable time bias resulting from imprecisions in information on in-hospital medication use in the database.[35] Prospective studies with more precise determination of proteinuria are needed to clarify this issue.

In conclusion, we have shown that the risk of TE events is eight times higher in KTRs compared with the general population. The risk is particularly strong in the first year after transplantation, remains elevated even after many years of follow-up, and is not fully explained by the greater probability of KTRs to be hospitalized. Given that hospitalization increased the risk of TE by a factor of 10, clinicians should consider anticoagulant prophylaxis in renal transplant patients.

MATERIALS AND METHODS

Study design

First, we performed a retrospective cohort study of KTRs who received a kidney allograft between 1 January 1990 and 31 December 2010 at the Centre Hospitalier de l'Université de Montréal. Subjects who had received dual organ transplantation (combined liver–kidney or pancreas–kidney) were excluded. Patients entered the cohort on the date of transplantation and were followed up until TE, death, graft loss, retransplant, or 31 March 2012, whichever occurred first. We then performed a case–control study nested within our cohort to determine the risk factors for TE. The choice of a nested case–control study design allowed us to take into account the biologically relevant time windows of exposure for transient risk factors while providing an unbiased estimate of the hazard ratio when risk set sampling is performed.

Data collection

To obtain information on TE, we used the electronic clinical database of the Centre Hospitalier de l'Université de Montréal that includes all KTRs who received a graft at our center since 1980. In our center, ~80 KTs are performed each year. The data on patient history, transplantation characteristics, medication use, and clinical outcomes are entered prospectively by a dedicated medical technologist. It includes data on hospitalization and from the outpatient clinic.

To obtain information on TE in the general population, we used the Q−VTE cohort formed by linking two provincial administrative health-care databases in the province of Québec: the Maintenance et exploitation des données pour l'étude de la clientèle hospitalière database, which comprises summary information on the diagnoses for all hospital admissions, collected on summary sheets at the time of hospital discharge, and the health-care services database of Régie de l'Assurance Maladie du Québec (RAMQ), which contains information on all physician reimbursement claims for services provided to Québec residents.[36] The RAMQ databases were previously validated for the diagnosis TE.[37]

Measurements

The main outcome was first TE after KT. Second TE events were not considered in our analyses. TE was defined as symptomatic DVT and/or PE after renal transplantation. The diagnosis of DVT was based on objective confirmation by contrast venography, Doppler ultrasound, or magnetic resonance venography. The diagnosis of PE required objective confirmation by pulmonary angiography, spiral (helical) CT scanning with intravenous contrast, or ventilation perfusion scan with a high probability for PE.

For the nested case–control study, cases were defined as patients having a first TE event during follow-up. Controls were selected randomly from the cohort who were free from TE and at risk for developing TE at the time of case diagnosis (index date). Individual matching was used. For each case, up to four controls were randomly selected from the cohort who were of the same age (±5 years) and gender, had the same date of transplantation (±1 year) and duration of follow-up after transplantation (±1 day), and who were alive and without TE on the date of TE diagnosis of the corresponding case (or index date). We chose to match on age and gender because these are important risk factors for TE in the general population, and as a result we considered them as potentially strong confounders.[38,39]

Independent variables collected at the time of transplantation included age, gender, dialyses modality and duration of dialysis, cold ischemic time, type of donor, induction therapy, smoking (current or past), history of malignancy or TE events, and diabetes. In

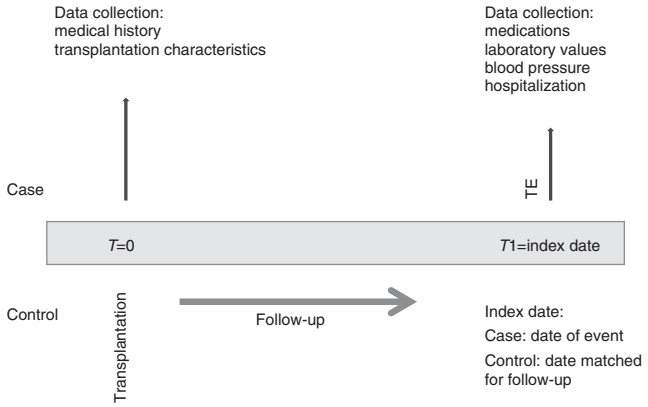

Figure 3 | Study outline.

addition, to collect data for transient risk factors in biologically pertinent time windows of exposure, we attributed an index date for all patients as described above (Figure 3). Independent variables collected in the days/weeks preceding the index date were body mass index, blood pressure, laboratory values (hemoglobin the lowest quartile <6.7 mmol/l), hematocrit, and serum creatinine to calculate eGFR using the CKD-epi formula[40]), proteinuria (measured by semiquantitative measurement (dipstick analyses)), medication use (including anticoagulant and antiplatelet agents), malignancy since transplantation date, and hospitalization at the index date. We validated the association of TE and hospitalization with information on hospitalization in the 2 months before the TE.

Since 2003, all KTR patients are prescribed unfractionated heparin thromboprophylaxis following transplantation (twice daily 5000 U subcutaneous heparin), which is usually discontinued at the time of hospital discharge. Before 2003, the decision to prescribe and/or discontinue TE thromboprophylaxis following transplantation was made by treating physicians. For hospital admissions that were unrelated to the initial transplant procedure, the prescription of thrombosis prophylaxis was left to the discretion of the treating physician for the entire study duration.

Statistical analyses

Normally distributed variables are presented as the mean and s.d., and non-normally distributed variables as the median with interquartile range (25th and 75th percentile). Categorical variables are summarized using proportions. We calculated cumulative incidence rates for TE at 1, 5, and 10 years after transplantation in our cohort. As the mortality in renal transplant recipients is relatively high, we corrected the cumulative incidence for the competing risk of death. For both the cohorts of KTRs and the general population, age- and gender-specific incidence rates and associated 95% CI were calculated using achieved age during follow-up, and as a result patients contributed person–time in different age categories while aging during follow-up.[35] Second, SIRs were computed. For SIR calculation, we performed an indirect standardization (age- and gender-adjusted). Ninety-five percent CIs are provided. Risk factors for TE were identified using a multivariate conditional logistic regression model. The statistical software of SPSS (IBM statistics 19) was used and the significance level was set at 5%.

DISCLOSURE

All the authors declared no competing interests.

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