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Thrombophilic Factors Do Not Predict Outcomes in Renal Transplant Recipients Under Prophylactic Acetylsalicylic Acid

L. Ghisdal[a], N. Broeders[a], K.-M. Wissing[a], A. Saidi[a], T. Bensalem[a], J. Mbaba Mena[a], A. Lemy[a], W. Wijns[b], O. Pradier[b], A.-D. Hoang[c], D. Mikhalski[c], V. Donckier[c], P. Cochaux[d], H. El Housni[d], M. Abramowicz[d], P. Vereerstraeten[a] and D. Abramowicz[a]

[a] *Renal Transplantation Clinic,* [b] *Laboratory of Hematology, Department of Clinical Pathology,* [c] *Department of Abdominal Surgery and Sub-Diaphragmatic Transplantation and* [d] *Department of Medical Genetics, ULB-Erasme Hospital, Brussels, Belgium*
* *Corresponding author: Lidia Ghisdal, lghisdal@yahoo.com*

A cohort of recipients of renal transplant after 2000 (N = 310) was prospectively screened on the day of transplantation and 1 month later for a panel of 11 thrombophilic factors to assess their effect on post-transplant outcomes. All patients received prophylactic acetylsalicylic acid, started before transplantation.

The rate of thromboembolic events or acute rejection episodes during the first posttransplant year (primary composite endpoint) was 16.7% among patients free of thrombophilic factor (N = 60) and 17.2% in those with ≥1 thrombophilic factor (N = 250) (p > 0.99). The incidence of the primary endpoint was similar among patients free of thrombophilic factors and those with ≥2 (N = 135), or ≥3 (N = 53) factors (16.3% and 15.1% respectively; p = 1) and in patients who remained thrombophilic at 1 month (15.7%; p = 0.84). None of the individual thrombophilic factor present at the day of transplantation was associated with the primary endpoint. The incidence of cardiovascular events at 1-year, serum creatinine at 1-year, 4-year actuarial graft and patient survival were not influenced by the presence of ≥1 thrombophilic factor at baseline (p = NS).

In conclusion, the presence of thrombophilic factors does not influence thromboembolic events, acute rejection, graft or patient survival in patients transplanted after 2000 and receiving prophylactic acetylsalicylic acid.

Key words: Acute allograft rejection, factor V Leiden, kidney transplantation, prothrombin gene mutation, thrombophilia, thrombosis

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Introduction

Graft vessel thrombosis is a serious but relatively rare complication after renal transplantation. It has been reported to occur in 0.5–7% of patients (1–5). The rate of other thromboembolic events such as deep venous thrombosis (DVT) and/or pulmonary embolism is about 5% during the first posttransplant year (6–8). In the general population, DVT and pulmonary embolism are associated with well-known inherited and/or acquired hypercoagulability conditions (9). Mutations in genes encoding coagulation factors result in either insufficient inhibition of the blood-clotting cascade (antithrombin, protein S, protein C and factor V Leiden) or increased clotting activity (prothrombin). High levels of factors VIII and IX are also associated with thromboembolic risk (9). Beside these inherited factors, antiphospholipid antibodies and lupus anticoagulant are the main acquired thrombophilic factors associated with an increased thromboembolic risk. Hyperhomocysteinemia is a thrombophilic factor that can either be inherited (e.g. methylenetetrahydrofolate reductase gene mutation) or acquired in several conditions, such as renal failure (9). Over the last decade, several studies have evaluated the impact of thrombophilic factors on outcomes after renal transplantation, such as thrombo-embolic events including arterial or venous graft thrombosis (7,10–12), acute rejection (11,13,14), cardiovascular events (15) or graft survival (13,14,16). However, the design and the heterogeneity of these studies make conclusions or recommendations difficult. First, these studies were retrospective, hence liable to potential biases. Second, several studies have been performed during the era of cyclosporine A (Sandimmun®, Novartis Pharma, Switzerland) and azathioprine, when rejection rates approached 50% and thromboembolic events were more frequent (10,11). Whether the conclusions drawn from these observations are still valid today is questionable. Third, available trials have evaluated only a limited number of thrombophilic factors. Therefore, patients considered as controls might have thrombophilic factors that were not searched for, thereby limiting the ability of these studies to detect an impact of such factors. Finally, perioperative anticoagulation and antiaggregation

treatments that may confound the analysis were not reported in previous observations.

In an effort to address these methodological issues, we performed a prospective study to evaluate if a panel of 11 thrombophilic factors (9) tested at the day of transplantation and 1 month later were associated with thromboembolic events or acute rejection at 1 year posttransplantation. In addition, we collected data on postoperative anticoagulation and antiaggregation therapies in all patients.

Materials and Methods

Coagulation analyses

On the day of transplantation and 1 month after transplantation, three trisodic citrate-supplemented sample tubes (5 mL) and one ethylenediamine tetra acetic acid (EDTA)-supplemented sample tube (8 mL) were collected from each enrolled patient. Blood samples were drawn by peripheral vein puncture, within 1–3 h prior to transplantation, and 1 month later. The following analyses were performed: resistance to activated protein C, levels of antithrombin, protein C, protein S, factor VIIIc, factor IX and homocystein, lupus anticoagulant and antiphospholipid antibodies titers. Details concerning dosage methods and definition of the thrombophilic risk (cut-off values) based on standard laboratory values are summarized in Supporting Table S1. Other coagulation tests were routinely performed but not considered as thrombophilic factors (data not shown): prothrombin time, activated partial thromboplastin time (APTT), fibrinogen, D-dimers, thrombin time and euglobulin lysis time.

Genetic analyses

Blood was collected at the day of transplantation in a standard 3 mL EDTA-supplemented tube. Genomic DNA was extracted using a phenol:chloroform method. DNA samples were stored at 4°C. The determination of the following gene variants: factor V Leiden (G1691A) and prothrombin (G20210A) was performed as previously described in our center (17). GPIIIa (T1565C) polymorphism of the GPIIIa/IIb receptor was genotyped as previously described by Salido et al. (14). Homozygous as well as heterozygous status for any of the three variants were considered as a thrombophilic factor.

Subjects

Informed consent was obtained from all patients for DNA sampling and analyses. From September 2001 to December 2006, we enrolled prospectively 320 consecutive single renal transplantations performed on 317 adult recipients in our center. Among the 320 grafts, 169 had all the 11 thrombophilic factors tested, 102 had 10 factors tested, 15 had 9 factors tested, 24 had 8 factors tested and only 10 graft recipients had fewer than 8 factors tested at the day of transplantation. We decided to exclude the 10 grafts with >3 missing assays, leading to a cohort of 310 renal grafts. A second screening of thrombophilic factors was performed 1 month after transplantation in 251 out of 310 patients. The results of the screening were not available to clinicians at the time of transplantation and were not taken into account for individual anticoagulation prophylaxis. Prophylaxis with low-molecular-weight heparin (LMWH) was considered only in case of: (a) a clinical history of hypercoagulable state, such as repeated thromboses of vascular access for hemodialysis, or a history of DVT; (b) the presence of a lupus anticoagulant when associated with previous thrombosis; (c) a risk of graft vessels thrombosis, discovered at surgery (donor or recipient's vessel atheromatosis, multiple arteries or renal vein reconstruction), which in the opinion of the surgeon required prophylaxis. These patients received enoxaparin subcutaneously just after the surgical procedure, then once daily for a maximum of 1 week (2000–4000 anti-Xa U per day, according to patient weight and renal function). Enoxaparin was stopped in case of bleeding. Unfractioned heparin was used in rare cases (15 U/kg/h, then adapted for an APTT of 1.5-fold normal value). This prophylaxis was replaced by acetylsalicylic acid after 3–5 days. Acenocoumarol, which was taken by 9% of the patients, was discontinued before surgery and was resumed as soon as possible, unless the indication was the prevention of thrombosis of the hemodialysis catheter access. All patients received 100 mg of acetylsalicylic acid orally started before surgery and continued *ad vitam*. All patients wore elastic compression stockings (Kendall®) for the first posttransplant week. Immunosuppression consisted of tacrolimus (Prograft®, Astellas Pharma; target trough levels between 8 and 10 ng/mL during the first year) or cyclosporine A (Neoral®, Novartis Pharma; target trough levels between 100 and 150 ng/mL and C2: 600–900 ng/mL during the first year) with mycophenolic acid (Cellcept®, Roche Pharma, Switzerland; 2 g/day under tacrolimus; 2.5 g/day under cyclosporine A, dose adaptated according to clinical tolerance) and methylprednisolone. Most patients received antibody prophylaxis with either a monoclonal anti-IL-2 receptor antibody (basiliximab: Simulect®, Novartis Pharma, or daclizumab: Zenapax®, Roche Pharma, Switzerland) or rabbit antithymocyte antibodies (Thymoglobuline®, Genzyme Pharma, Cambridge, MA) according to their immunological risk (18).

Data collection

Baseline characteristics, on the day of transplantation, were collected for all patients. A past history of thromboembolic and cardiovascular events was defined as: coronary heart disease with or without myocardial infarction, coronary artery bypass surgery (CABG) or percutaneous transluminal coronary angioplasty (PTCA), DVT, pulmonary embolism, nonhemorrhagic stroke and proximal or distal lower extremities arterial disease. The following data were collected at 1 year posttransplantation: (a) thromboembolic events defined as graft vessels thrombosis (venous or arterial), DVT or pulmonary embolism, (b) major cardiovascular events defined as coronary heart disease with or without myocardial infarction, CABG or PTCA, nonhemorrhagic stroke and proximal or distal lower extremities arterial disease, (c) acute rejection episodes (more than 95% biopsy-proven) and (d) renal graft function, evaluated by serum creatinine. Delayed graft function (DGF) defined as the need for dialysis during the first posttransplant week and data on graft and patient's survival were also collected.

Statistical methods

This is a prospective, single-center, observational, cohort study. The primary composite endpoint was the occurrence of either a thromboembolic event (graft vessel thrombosis, DVT or pulmonary embolism) or an acute rejection episode during the first posttransplant year. The secondary endpoints were: 1-year incidence of thromboembolic events; 1-year acute rejection rate; 1-year major cardiovascular events rate (see definition mentioned earlier); DGF; serum creatinine levels at 1 year; 4-year actuarial graft and patient survival and the rate of the primary composite endpoint among patients who have ≥1 thrombophilic factor at transplantation and at 1 month posttransplantation. Thrombophilic factors were analyzed in two different ways. First, the cohort was divided in two groups: the control group without the exposure of interest (no thrombophilic factor) and the exposed group of patients with at least one thrombophilic factor present. Patients without thrombophilic factor were compared to patients with ≥1 thrombophilic factor at the day of transplantation and to patients who still have ≥1 thrombophilic factor 1 month later. Second, the association of each individual thrombophilic factor with the primary composite endpoint was analyzed separately by comparing patients with the isolated thrombophilic factor to the patients free of thrombophilic factor. Categorical data were compared using the chi-square or Fisher's exact tests as appropriate. ANOVA was used to compare continuous data: one-way analysis was used for differences between group and two-way analysis for repeated measures ANOVA. In all cases, a bilateral p-value of less than 0.05 was used to reject the null

hypothesis. Univariate survival analyses were conducted according to the actuarial method and the Breslow–Gehan–Wilcoxon test was used to estimate the difference between the survival curves. Deviation from Hardy–Weinberg equilibrium was evaluated by the chi-square test for the three genetic variants. We could not perform an *a priori* sample size calculation to evaluate the power of the trial to detect significant differences between groups, because of the lack of published data on coagulation abnormalities prevalence in patients undergoing dialysis. An interim analysis was done in July 2006, after 220 patients have been enrolled. As the primary composite endpoint was virtually identical in patients with thrombophilic factors *versus* those free of thrombophilic factors, and unlikely to change with a larger cohort, the enrollment was stopped in December 2006.

Results

Baseline characteristics of patients and perioperative anticoagulation

On the day of transplantation, 250 patients had ≥1 thrombophilic factor and 60 patients were free of thrombophilic factor (prevalence: 80.6%). One month later, from the 250 patients with ≥1 thrombophilic factor at baseline, 140 patients still had ≥1 thrombophilic factor and 51 patients had no more thrombophilic factor. The prevalence of each single thrombophilic factor at baseline is detailed in Table 1. Genotype distribution of the three variants was in agreement with Hardy–Weinberg equilibrium. The most relevant demographic data at baseline and perioperative anticoagulation data are summarized in Table 2. Patients with ≥1 thrombophilic factor at baseline had significantly longer warm ischemia time, a higher HLA sensitization and had received more blood transfusions. The other characteristics and perioperative anticoagulation were similar in both groups. The mean doses of methylprednisolone (mPDS) at 1, 3, 6, 9 and 12 months, the proportion of patients free of steroids (cases: 16%, controls: 20%; $p = 0.48$) and the mean maintenance mPDS dose (cases: 0.059 mg/kg/day, controls: 0.052 mg/kg/day; $p = 0.3$) at 12 months were similar in both groups.

Table 1: Prevalence of single thrombophilic factors at the day of transplantation (N = 310)

Thrombophilic factor	Number of patients tested	Number (%) of patients with thrombophilic factor
Antithrombin	309	44 (14.2)
Protein C deficiency	301	39 (13.1)
Protein S deficiency	302	16 (5.3)
APC resistance	310	8 (2.6)
Factor VIIIc	309	63 (20.4)
Factor IX	214	3 (1.4)
Lupus anticoagulant	304	116 (38.2)
Antiphospholipid antibodies	286	77 (26.9)
PT (G20210A) variant	291	7 (2.4)
GPIIIa (T1565C) variant	289	86 (29.8)
FV (G1691A) variant	291	7 (2.4)

Impact of thrombophilic factors on thromboembolic events and acute rejection episodes at 1 year

During the first year posttransplantation, thromboembolic events or acute rejection episodes occurred in 53 transplant recipients in the whole cohort (17.1%). There were 11 (3.5%) thromboembolic complications: graft arterial thrombosis: N = 2, graft venous thrombosis: N = 1, DVT: N = 8. No patient experienced pulmonary embolism. Forty-three patients (13.9%) developed at least one acute rejection episode. One patient developed both a thromboembolic event and an acute rejection episode during the first year. The rate of thromboembolic events or acute rejection episodes (primary composite endpoint) was 16.7% (95% CI: 9.1–28.2%) in patients without thrombophilic factor and 17.2% (95% CI: 12.7–22.4%) in patients with ≥1 thrombophilic factor at baseline ($p > 0.99$). Thromboembolic events occurred in 5.0% of patients without thrombophilic factor and in 3.2% of patients with ≥1 thrombophilic factor at baseline ($p = 0.46$). The rate of acute rejection was 13.3% in patients without thrombophilic factor and 14.0% in patients with ≥1 thrombophilic factor at baseline ($p > 0.99$). Subgroup analyses were performed for the primary objective (Table 3). The incidence of the primary endpoint was similar among patients free of thrombophilic factor and those with ≥2 or ≥3 thrombophilic factors at baseline. Along the same line, among patients who still had ≥1 thrombophilic factor at 1 month posttransplantation, the incidence of the primary composite endpoint (15.7%), of thromboembolic events (2.1%) or acute rejection rates (13.6%) were similar to controls. Finally, no differences were observed for the composite primary endpoint between cases and control patients in subgroups who either received postoperative heparin, in those who did not, or in patients who were not treated by acenocoumarol at baseline. This last analysis was performed to investigate the possible bias associated with acenocoumarol intake, as this treatment is known to lead to reduced levels of both protein S and C, and to trigger false-positive lupus anticoagulant.

We could find no significant difference neither in the rate of thromboembolic events or acute rejection episodes nor in those outcomes considered separately, between patients with a single thrombophilic factor and patients without this thrombophilic factor at baseline (Table 4). After exclusion of patients under acenocoumarol at baseline, neither protein C or protein S deficiency, nor positive lupus anticoagulant had any significant impact on the occurrence of the primary endpoint.

Homocystein was analyzed separately, as 66% of our population had abnormally high values (≥16 μmol/L). Hyperhomocysteinemia was not significantly associated with the occurrence of the primary outcome.

Impact of thrombophilic factors on major cardiovascular events and graft function at 1 year

Nine major cardiovascular events (coronary heart disease: N = 5, proximal or distal lower extremities arterial

Table 2: Baseline characteristics of patients and peri-operative anticoagulation

Characteristics[1]	No thrombophilic factor (N = 60)	≥1 thrombophilic factor (N = 250)	p-Value
Previous history of thromboembolic or cardiovascular events: % with	15.0	16.4	>0.99
Sex of recipient: % male	60.0	66.8	0.36
Sex of donor: % male	65.0	53.2	0.11
Age of recipient	48.4 ± 1.8	47.6 ± 0.8	0.63
Age of donor	45.4 ± 1.9	46.0 ± 0.9	0.78
Origin of donor: % deceased	91.7	90.8	>0.99
Duration of dialysis (months)	32.0 ± 4	38.0 ± 3	0.35
Cold ischemia time (h)	14.7 ± 0.8	15.8 ± 0.4	0.25
Warm ischemia time (min)	29.0 ± 1.0	32.3 ± 0.6	0.014
Ethnicity (N)			
Caucasian	49	184	0.42
North African	7	35	
Black African	4	23	
Other	0	8	
Cause of end-stage renal disease (N)			
Glomerulonephritis	15	73	0.47
Nephroangiosclerosis/hypertension	11	33	
Chronic interstitial nephritis	15	39	
Polycystic kidney disease	4	24	
Diabetic nephropathy	4	21	
Other	7	28	
Uncertain	4	32	
Regrafts: % with	11.7	17.2	0.34
Panel reactive antibody: (% with)			
Current: >5%	1.7	15.6	0.002
Peak: >50%	0.0	9.2	0.01
Number of blood transfusion	1.0 ± 0.2	2.4 ± 0.4	0.049
Number of HLA mismatches			
Locus A	0.92 ± 0.08	0.89 ± 0.04	0.76
Locus B	1.02 ± 0.08	0.94 ± 0.04	0.38
Locus DR	0.82 ± 0.07	0.66 ± 0.04	0.06
Immunosuppression: (% with)			
Mycophenolate/Azathioprine/other	55/0/5	214/1/35	>0.99
Tacrolimus/Cyclosporin A/other	50/6/4	197/52/1	0.55
IL2R antagonist/ATG/none	38/9/13	165/40/45	0.81
Acenocoumarol: (% with)			
At the day of transplantation	5.0	10.0	0.32
1 month posttransplantation	6.7	5.2	0.66
Postoperative administration of: (% with)			
Low-molecular-weight heparin	31.7	40.7	0.24
Unfractioned heparin	3.3	3.6	>0.99

[1]Numerical data are shown as mean ± standard error of the mean (SEM).

disease: N = 4) occurred during the first year. The rate was similar in patients without thrombophilic factor (3.3%), in those with ≥1 thrombophilic factor at baseline (2.8%) and in those who still had ≥1 thrombophilic factor at 1 month (2.1%). No single thrombophilic factor was associated with major cardiovascular events (data not shown). The mean homocysteinemia level at transplantation was comparable in patients with or without cardiovascular events (21.7 ± 4.3 mg/dL *vs.* 23.7 ± 1.0 mg/dL; p = 0.76). Serum creatinine was stable during the first year in both groups. At 12 months, mean serum creatinine level was 1.3 (±0.4) mg/dL and 1.4 (±0.4) mg/dL in patients without and with ≥1 thrombophilic factor at baseline, respectively (p = 0.18). The rate of DGF was 10.0% and 11.2% in patients without and with ≥1 thrombophilic factor at baseline, respectively (p > 0.99).

Impact of thrombophilic factors on patient and graft survival

Four-year overall graft survival was 81.2% and 83.7% among patients with and without thrombophilic factor at baseline, respectively (p = NS). Four-year death-censored graft survival was 87.3% and 87.8% among patients with

Table 3: Subgroup analyses for the primary outcome

Subgroups (N)	Primary outcome present (%)	p-Value
No thrombophilic factor (60)	16.7	
≥2 thrombophilic factors at baseline (135)	16.3	1.0[1]
≥3 thrombophilic factors at baseline (53)	15.1	1.0[1]
Patients who still have thrombophilic factor at 1 month (140)	15.7	0.84[1]
Early postoperative administration of heparin (131)		
No thrombophilic factor (21)	19.0	0.78
≥1 thrombophilic factor (110)	23.6	
No postoperative administration of heparin (179)		
No thrombophilic factor (39)	15.4	0.59
≥1 thrombophilic factor (140)	12.1	
No acenocoumarol at baseline (281)		
No thrombophilic factor (57)	17.5	0.84
≥1 thrombophilic factor (224)	16.1	

[1]p-Value of the comparison with control group (no thrombophilic factor).

and without thrombophilic factor at baseline (p = NS). Four-year patient survival was 91.7% among patients with ≥1 thrombophilic factor and 95.9% among those free of thrombophilic factor at baseline (p = NS).

Discussion

The main result from this series is the lack of significant association between thrombophilic factors and the occurrence of thromboembolic events or acute rejection episodes during the first year posttransplantation. While the two most recent series also failed to show any detrimental effect of thrombophilic factors on acute rejection, thromboembolic events (6) or graft survival (19), some earlier studies have reported major deleterious impact of thrombophilic factors on acute rejection rates (11,13,14,20), thromboembolic events (7,10–12), cardiovascular events (15,21) and graft survival (13,14,16,20,22) after renal transplantation. Several factors probably contribute to explain these major differences in outcomes.

First, the incidence of both acute rejection and severe, cortico-resistant rejection was higher in earlier reports, when CsA-sandimmun® and azathioprine were used. The fact that activation of the coagulation cascade into the renal graft contributes to the most severe forms of rejection might explain the negative impact of thrombophilic factors on the incidence of severe rejection episodes leading to graft loss during the previous era of immunosuppression. The rejection incidence in the present cohort was less than 15%, similar to rates reported in recent multicenter trials where patients received quadruple immunosuppressive therapy with a calcineurin inhibitor, mycophenolic acid and antibody prophylaxis (23). The contributing role, if any, of thrombophilic factors might be harder to detect in this setting of low event rates.

Table 4: Impact of a single thrombophilic factor on thromboembolic events and acute rejection episodes rates at 1 year

Thrombophilic factor (number of patients with) at baseline[1]	Thromboembolic events or acute rejection episodes (%) Thrombophilic factor		Thromboembolic events (%) Thrombophilic factor		Acute rejection episodes (%) Thrombophilic factor	
	Present	Absent	Present	Absent	Present	Absent
Antithrombin (44)	11.4	16.7	2.3	5.0	9.1	13.3
Protein C deficiency (39)[2]	17.9	16.9	2.6	5.1	15.4	13.6
Protein S deficiency (16)[2]	31.3	16.9	6.3	5.1	25.0	13.6
APC resistance (8)	37.5	16.7	25.0	5.0*	12.5	13.3
Factor VIIIc (63)	9.5	16.7	3.2	5.1	6.3	13.3
Factor IX (3)	33.3	18.1	0	6.8	33.3	13.6
Lupus anticoagulant (116)[2]	18.1	10.9	4.3	3.6	13.8	9.1
Antiphospholipid antibodies (77)	18.2	14.0	3.9	2.0	14.3	14.0
PT (G20210A) variant (7)	42.9	17.9	14.3	5.3	28.6	14.3
GPIIIa (T1565C) variant (86)	15.1	18.2	1.2	5.4	14.0	14.5
FV (G1691A) variant (7)	28.6	17.9	14.3	5.3	14.3	14.3

*p = 0.1.[1]The number of controls in whom these assays were performed ranged between 55 and 60, except for factor IX (N = 44).
[2]After the exclusion of patients taking acenocoumarol at baseline (N = 29), a comparison of patients with thrombophilic factor with controls showed that protein C deficiency, protein S deficiency and lupus anticoagulant had no significant impact on the primary composite endpoint (protein C deficiency: 15.4% vs. 17.5%; p > 0.99, protein S deficiency: 25.0% vs. 17.5%; p = 0.63, lupus anticoagulant: 15.8% vs. 11.5%; p = 0.62, respectively).

Second, we observed a lower rate of thromboembolic events in the present cohort, in contrast with previous reports (10,11). Again, the contributing role, if any, of thrombophilic factors might be harder to detect in this setting of low event rates. Nevertheless, we and others (6) observed numerically more thromboembolic events among patients affected with factor V Leiden and prothrombin mutation (three-fold). This is not surprising, as these two thrombophilic factors carry an increased risk of DVT of eight- and three-fold, respectively, in the general population (24). The low absolute number of patients affected with these two mutations in our cohort probably precluded the association to reach statistical significance.

It is noteworthy that studies showing major impact of thrombophilic factors on thromboembolic events (7,10–12) did not report on the perioperative use of antiaggregant or anticoagulant therapies, which can obviously interfere with the occurrence of such events. Here, for the first time, we provide systematic data on perioperative anticoagulation and antiaggregation therapies. Acetylsalicylic acid was prescribed before transplantation to all patients. While the lack of a control group not taking aspirin precludes any definite conclusion about the possible beneficial impact of acetylsalicylic acid on thromboembolic events, its efficacy in the setting of renal transplantation has been suggested in previous retrospective studies (4,25). Heparin was administered in the early posttransplant period to approximately one-third of the patients. Of note, the clinicians who prescribed heparin were not aware of the thrombophilic factors screening results and the proportion of patients receiving heparin was similar among patients with thrombophilic factor and controls. Therefore, we feel that the administration of heparin did not bias the results.

In our cohort, the seemingly high global prevalence of thrombophilic factors (80.6%) is related to the fact that we tested for the majority of acquired or inherited thrombophilic factors (9) simultaneously, which has not been done previously. The prevalence of each individual thrombophilic factor we report here is within the range reported by others (6,11,14,19–21,26–30). These prevalences are higher than those observed in the general population (except for FV, prothrombin and GPIIIa genetic variants). This suggests that most of these factors are acquired with end-stage renal disease and/or dialysis conditions (use of heparin, of oral anticoagulant, liver disease, presence of auto-antibodies, nephrotic syndrome). Contrary to the general population, dialysis-associated thrombophilic factors do not appear to confer any increased thrombotic risk in the setting of renal transplantation. One limitation of our study is that we did not perform a second assay to control for positive lupus anticoagulant and antiphospholipid antibodies. While this would have been desirable, the prevalence we found with this single assay was similar to the figures usually reported in dialysis patients (21,26–30). This suggests that our population was not biased toward an overrepresentation or underrepresentation of patients with these two thrombophilic factors.

Several specific thrombophilic factors deserve some comments. The (T1565C) polymorphism of GPIIIa, conveying increased platelet aggregability, was shown to be associated with acute coronary thrombosis in the general population (31) and with more acute rejection episodes, poorer renal graft function and survival in one study (14). We were unable to confirm such associations in our cohort. Unlike previous studies, we measured homocystein levels instead of methylenetetrahydrofolate reductase (MTHFR) (C677T) genotyping. Available evidence suggests that it is the increased homocystein that carries the cardiovascular risk rather than the MTHFR status (32,33). Nevertheless, we did not find any association between hyperhomocysteinemia at baseline and cardiovascular events.

In summary, we observed that the prevalence of thrombophilic factors is much higher than in the general population. However, thrombophilic factors detected in dialysis patients were not significantly associated with thromboembolic events or acute rejection after renal transplantation in patients under acetylsalicylic acid prophylaxis. While these findings might be different for recipients of combined pancreas and renal grafts, our results do not support a systematic screening before renal transplantation.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1 Coagulation analysis details

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