REVIEW ARTICLE

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Assessment of thrombotic risk in renal transplantation

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ABSTRACT

Venous thromboembolism is a thrombotic complication that occurs in renal transplantation patients. Allograft thrombosis and death with a functioning graft are now the main causes of early graft and patient loss. The early thrombosis of renal allograft occurs in approximately 2-8% of transplants, and the risk of thrombosis is greater up to five months after transplantation. The nature of clotting activation in these patients is probably multifactorial. The contribution of thrombophilia as a risk factor for severe acute rejection and renal allograft thrombosis has only recently been recognised. Carriers of the Factor V Leiden mutation or prothrombin gene *G20210* polymorphism have a 3- to 4-fold increase in allograft thrombosis. Patients with systemic lupus erythematosus as the primary cause of end stage renal disease and patients with antiphospholipid antibody syndrome have a particularly poor outcome following renal transplant due to allograft loss or other vascular complications, suggesting measures to prevent thrombosis are imperative. Data for other hypercoagulable states such as hyperhomocystinaemia or the methylenetetrahydrofolate reductase gene *C677T* polymorphism are deficient. Screening of renal transplant candidates for thrombophilia is reasonable in patients with a history of venous thromboembolism or other risk factors, as the current evidence does not support routine screening of all patients. The American Society of Transplantation recommends screening high-risk patients and prophylatic perioperative anticoagulation for patients with thrombophilia and a history of thrombosis. Interventions to reduce thrombotic risk including heparin, warfarin, and aspirin have been evaluated in both selected high risk groups and unselected populations. Aspirin (75-150 mg/day) appears to reduce the risk of renal allograft thrombosis significantly with a low risk of bleeding. In high risk groups a longer period of heparin and maintenance with warfarin should be considered.

Key-Words:
Allograft thrombosis; renal transplant; thrombophilia.

INTRODUCTION

Renal transplantation provides the best long-term treatment for patients with end-stage renal disease (ESRD). There is an approximately 70% reduction in mortality within one year of transplantation[1]. This immediate benefit suggests a rapid change in cardiovascular risk due to resolution of the uraemic state. On the other hand, the outcome of renal transplant recipients (RTR) is largely influenced by the occurrence of thrombotic complications.

Renal transplant recipients are at an increased risk of venous thromboembolism, possibly due to an impaired fibrinolysis and a persistent hypercoagulable state[2]. Hypercoagulability following transplantation can be detected indefinitely[3]. The nature of clotting activation in these patients is probably multifactorial, related to not only classical but specific renal transplantation risk factors.

RENAL ALLOGRAFT THROMBOSIS

Allograft loss due to thrombosis is numerically small in absolute terms, but disastrous individually speaking. Historically, many early graft failures were related to hyperacute or aggressive acute rejection, but now many centres find this a diminishing cause of graft loss. Early allograft thrombosis and death with a functioning graft, usually due to cardiovascular disease, are now the principal causes of graft and patient loss, and require additional study and therapies to reduce these losses. Many centres are now reporting one-year graft survival rates in the order of 90-95%, and most graft failures in this period are related to allograft thrombosis[4].

The early thrombosis of renal allograft occurs in approximately 2-8% of transplants, and accounts for >25% of all early (90 days) graft loss[5]. Venous thrombosis is more frequent, usually occurring within the first two weeks, and is frequently accompanied by graft pain and swelling, sometimes with allograft rupture. Many of these early thrombosed grafts never have primary function, suggesting early venous occlusion. While arterial thrombosis is often painless and without swelling or rupture, thrombosis of both arterial and venous conduits can occur[5]. Previously, reviews of allograft thrombosis sought explanatory mechanisms for this catastrophic event (Table I). These studies identified environmental risks for thrombosis, not all of which are modifiable. Further, these studies could not fully explain the often random and unexpected early graft thrombosis.

Table I

Putative environmental risks factors for renal allograft thrombosis[3-5]

Previous personal or family history of venous thrombosis
Diabetes Mellitus
Systemic Lupus Erythematosus (SLE)
Peritoneal dialysis *vs.* haemodialysis
Extremes of donor and recipient age
Abnormal donor anatomy (right-sided kidneys, multiple vessels, atheroma)
Recipient morbidity (hypotension, sepsis)
Cyclosporin, OKT3
Rejection
Delayed graft function

Patients treated with peritoneal dialysis, as compared with haemodialysis, appear to exhibit more pronounced evidence of hypercoagulability, including increased platelet count, fibrinogen and PAI-1 and reduced albumin, which may reflect the protein losing state, analogous to nephrosis[3]. Recent data suggest that haemodialysis, but not peritoneal dialysis, has specific functional and structural impairment of platelet activity. These findings provide pathophysiological support for the epidemiological data identifying prior peritoneal dialysis as a risk factor for early allograft loss[6-8].

There is no uniform policy for prevention of allograft thrombosis, in part due to concern over risks of bleeding and lack of agreement over patients at highest risk. However, if we are to improve one-year graft survival to the magic 100%, the assessment of thrombotic risk must be taken into consideration in all renal transplant candidates.

VENOUS THROMBOEMBOLISM IN RTR

Venous thromboembolism (VTE) is a thrombotic complication that occurs in patients receiving renal transplantation. Approximately 6% of RTR develop deep vein thrombosis. A hypergoagulable state persists typically for four weeks after surgery, depending on the invasiveness and duration of the procedure. The risk of thrombosis is increased up to five months after transplantation[9]. In this population of high-risk patients there is probably an underestimation of the disease, in particular in relation to the occurrence of asymptomatic episodes. A high rate of asymptomatic VTE has been reported in RTR[10] and asymptomatic proximal deep vein thrombosis has been related to pulmonary embolism and mortality, thus indicating the clinical relevance of the diagnosis of these events.

Poli *et al.*[11] reported an elevated rate of recurrence in RTR who had a first episode of VTE after withdrawal of thromboprophylaxis, underlining that a previous VTE event in the RTR remains a persistent risk factor for the occurrence of new episodes. Alterations of haemostasis have been seen in relation to the immunosuppressive treatment used in these patients, in particular to calcineurin inhibitors. In addition, the occurrence of acute CMV infection is reported as a risk factor for the occurrence of VTE. Pretransplant dialysis modality, recurrent proteinuria and posttransplant erytrocytosis have also been associated with a hypercoagulable state[12]. The high

incidence of solid or haematological tumours in RTR is another important condition that predisposes to thrombosis. Poli *et al.*[10] reported an incidence of cancer of 25.5% in RTR who developed a first episode of VTE, compared to 6.7% in RTR without thrombotic complications. Surprisingly, there was no difference in recurrence rate for patients with and without cancer. In addition, there was no significant difference in the rate of recurrence in relation to renal function. The prevalence of thrombophilia markers was no different in patients with and without recurrence. The high incidence of recurrence in RTR confirmed the existence of a hypercoagulable state in these patients, and the lengthy time period over which recurrences occurred suggests an extensive persistence of this hypercoagulable state.

THROMBOPHILIA

Thrombophilia denotes an inherited or acquired hypercoagulable or pro-thrombotic state (see Table II)[13]. In patients with ESRD, thrombophilia is a risk factor for VTE and for many of the complications related to haemodialysis access. Recurrent vascular access thrombosis resulting in failure to continue maintenance haemodialysis therapy is the most common and important complication of a thrombotic state before renal transplantation[14]. A variety of thrombosis-favouring haematological changes occur in ESRD patients. Additionally, nontraditional risk factors for thrombosis, such as hyperhomocysteinaemia, endothelial dysfunction, inflammation, and malnutrition, exist in the majority of patients. Therefore, thrombotic events contribute substantially to the high morbidity and mortality in this population before and after renal transplantation.

Table II

Thrombophilic states[5-7,12-17,20]

Inherited thrombophilias
Factor V Leiden gene mutation
Prothrombin gene *(G20210A)* mutation
Protein C deficiency
Protein S deficiency
Antithrombin III deficiency
Elevated levels of coagulation factors
Acquired thrombophilias
Antiphospholipid antibodies
Lupus anticoagulant
Anticardiolipin antibody
Anti-β2-glicoprotein-1 antibody
Hyperhomocysteinaemia

The contribution of thrombophilia as a risk factor for severe acute rejection and renal allograft thrombosis has only recently been recognised[15-17]. Renovascular thrombosis after kidney transplantation, caused by inherited thrombophilia, was described for the first time by Koester *et al.*[18]. Here, protein S deficiency resulted in graft loss of two consecutive kidney transplants in the same patient. In fact, the majority of early thrombotic events after renal transplantation occur in patients with thrombophilia[19].

Recently, a number of thrombophilic (hypercoagulable) states have been identified through laboratory testing. These include antithrombin III deficiency, known for over 30 years, as well as deficiencies in protein C and protein S. Although these deficiencies are rare, factor V Leiden and prothrombin *G20210* mutations are fairly common[14]. Acquired coagulation defects are particularly common in patients with ESRD[15].

Inherited thrombophilia

Inherited thrombophilas are: deficiency of antithrombin III, protein C and S, factor V Leiden (FVL) mutation and prothrombin gene *G20210A* polymorphism. When thrombosis occurs beyond the age of 45 and is combined with a negative family history, a deficiency of ATIII, protein C or S is rather unlikely. FVL mutation and prothrombin gene *G20210A* polymorphism are known to predominantly cause thrombosis of the veins. Nonetheless, with concurrent risk factors such as smoking or metabolic dysfunction, thrombosis of the arteries may also occur.

The FVL mutation is responsible for more than 90% of cases related to activated protein C (APC) resistance and is the most common mutation associated with venous thrombosis in European populations (approximately 5% carriers)[21]. Heterozygosity for this mutant allele increases venous thrombotic risk 5- to 10-fold, and homozygosity approximately 80-fold[22]. Approximately 20-60% of patients presenting with their first venous thrombosis will have APC resistance, but conversely not all patients with APC resistance experience a clinical thrombotic

event. There are two types of assays available for diagnosis[23]. The APC resistance assay is a screening test for the APC-resistant phenotype, characterised by a minimal prolongation of the activated partial thromboplastin time in response to added APC. The most widely used DNA assay involves polymerase chain reaction amplification of the region containing the mutation followed by restriction fragment-length polymorphism analysis.

The prothrombin gene mutation is the second most common inherited thrombophilic disorder, found in 2-3% of the general population. A single nucleotide substitution *(G20210A)* of the prothrombin gene is associated with elevated plasma prothrombin levels and a 2- to 4-fold increased risk of venous thrombosis[23]. A heterozygous mutation is found in approximately 6% of patients with a first venous thrombotic episode and 18% of patients with recurrent thrombosis. Alone, it is a relatively mild risk factor, but the overall thrombotic risk increases markedly when it is combined with other inherited or acquired risk factors. Diagnosis requires DNA analysis, which usually involves polymerase chain reaction amplification followed by restriction fragment-length polymorphism analysis.

Deficiency of antithrombin III, protein C and S are inherited as autosomal dominant traits with protein C deficiency occurring in around 1:300 and antithrombin in 1:5000 of the general population[13]. While these deficiencies increase the risk of venous thrombosis approximately 20-fold, they are uncommon and account for only 6-8% of venous events in the general population[13].

Acquired thrombophilia

Antiphospholipid antibodies

Antiphospholipid antibodies (APA) comprise a heterogenous group of antibodies directed against proteins bound to phospholipids. These antibodies may have *in vitro* anticoagulant activity by interfering with the phospholipid surfaces on which coagulation depends, prolonging the activated partial thromboplastin time (aPTT). While these antibodies appear to impair coagulation *in vitro*, *in vivo* they are most often associated with thrombosis. The reduction in phospholipid surface prolongs the coagulation process and (paradoxically) promotes hypercoagulability. Antiphospholipid antibodies also promote platelet aggregation and endothelial activation and injury[13].

There is a high variability in reported rates and titres of APA in patients receiving dialysis and continuing controversy over their significance. The prevalence of APA in patients awaiting renal transplantation is more than 10%[23]. Fortunately, the rate of clinical events is far less than the frequency of thrombophilic states. The most common antigenic target is β2-glicoprotein-1, but other phospholipids-binding proteins may be involved[24]. Antiphospholipid antibodies are divided into two broad categories defined by the laboratory test used to detect them. Anticardiolipin antibodies are detected by solid phase immunoassay. Solid phase assays are also available for anti-β2-glicoprotein-1 antibodies, which may be more specific for the clinical complications of the antiphospholipid-antibody syndrome (APS). Indeed, anti-β2-glicoprotein-1 antibodies in patients with APS may predict recurrent vascular events[13]. Lupus inhibitors are autoantibodies that interfere with phospholipids-dependent clotting assays. Testing for APA should include immunologic assay for anticardiolipin autoantibodies and multiple coagulation assays for lupus inhibitors, because only 50% of patients with the APS have both types of antibodies[24]. Lupus inhibitors, high-titre IgG anticardiolipin antibodies (>40 GPL), and anti-β2-glicoprotein-1 antibodies are most strongly associated with thrombosis and other clinical manifestations of the syndrome.

The APS is defined by a history of arterial and venous thrombosis, thrombocytopaenia or recurrent pregnancy loss, and laboratory evidence of persistent APL. In addition to arterial and venous thromboembolism, patients with APS may develop a thrombotic microangiopathy with microvascular thrombosis. This can occur acutely or as a more chronic process, resulting in slowly progressive organ failure[25]. Patients with primary APS have clinical complications in the absence of another underlying disorder, but the syndrome also occurs secondary to other disorders such as lupus. Antiphospholipid antibodies are found in approximately one-third of patients with lupus, and 50% to 70% of these patients may develop the complications defining the syndrome. Antiphospholipid

antibodies occurring transiently in association with infections or medications, and the low-titre antibodies found in 1% to 10% of normal individuals are usually clinically insignificant.

Hyperhomocysteinaemia

Homocysteine, a normal by-product generated during the metabolism of methionine, is metabolised by two major pathways: the transsulfuration pathway, which converts excess homocystein to cystathionine; and the remethylation pathway, which recycles homocystein to reform methionine. Several key enzymes in these pathways require vitamin B_{12}, vitamin B_6, folic acid, or a combination of these as essential cofactors. Hyperhomocysteinaemia may result from defects or deficiencies of the enzymes involved in homocystein metabolism, or deficiencies of their vitamin cofactors[26]. The most common genetic cause of mild hyperhomocysteinaemia is a point mutation (*C677T)* in the methylenetetrahydrofolate reductase *(MTHFR)* gene, which results in a variant thermolabile enzyme with reduced activity for the remethylation of homocysteine, usually in the setting of suboptimal folate levels. Deficiencies of folate, vitamin B_{12}, or vitamin B_6, are the most common acquired causes of hyperhomocysteinaemia. Homocysteine levels are also elevated in ESRD patients and up to 90% of RTR, even in those with good graft function[24]. Indeed, homocysteine correlates inversely with renal function and folate levels in the majority of studies[27,28]. Hyperhomocysteinaemia is strongly correlated with arterial vascular disease. The risk of coronary artery disease is three times higher with plasma homocysteine levels exceeding 30µmol/l. Hyperhomocysteinaemia also increases the risk of venous thrombosis[9]. The risk is even higher when hyperhomocysteinaemia is combined with another thrombophilic disorder.

THROMBOPHILIA AND RENAL ALLOGRAFT THROMBOSIS

In 1997, retrospective data from the Oxford Transplant Centre reported a 6% prevalence of FV Leiden in 300 transplant recipients. Carriers of the FVL mutation had a 4-fold increase in allograft thrombosis which accounted for 20% of primary allograft loss[15]. There was no increased risk of arterial thrombosis in carriers of the FVL mutation. In 1998, Fischereder *et al.* described a high prevalence of thrombophilia of 14% (FVL mutation 8%, Lupus anticoagulant 5%, protein S deficiency 1%) in 132 patients[29]. Patients identified with a thrombophilic risk had a 3.5-fold increased risk of graft loss at 1 year, although it is unclear whether this represented thrombotic or combined thrombotic/rejection graft loss. Heidenreich *et al.*[30] evaluated 97 transplant recipients and noted that 21 had an acquired or inherited thrombophilic risk (FVL mutation n=10, protein C, S, or antithrombin III deficiency n=11). The thrombophilic group had a significantly greater risk of early acute (particularly vascular) rejection compared with patients without thrombophilia ($p<0.017$), and two patients heterozygous ($p<0.05$) for FVL mutation lost grafts because of venous thrombosis and vascular rejection.

Fischereder *et al.*[31] and Heidenreich *et al.*[32] in retrospective and prospective studies, respectively, have confirmed that the *G20210* mutation of the prothrombin gene is associated with an increased risk of allograft loss. Fischereder[31] analysed 270 patients who received 311 allograft renal transplants and identified nine patients heterozygous for the *G20210A* mutation in the prothrombin gene. Carriers had a median allograft survival of 5 *vs.* 12 years for patients homozygous for the normal *G20210* allele with a 3-fold increase in graft loss due to thrombosis. In a prospective analysis of 165 renal allograft recipients, Heidenreich *et al.*[32] found 19 carriers (11.5%) of the FVL mutation and six (3.6%) carriers of the *G20210A* mutation. The risk of acute graft loss was 16% in FVL carriers and 50% in *G20210A* heterozygotes. There was a significantly increased risk of rejection, especially vascular rejection in both groups, and graft loss was related with vascular thrombosis and/or severe acute rejection.

Reports of adverse outcome following renal transplantation in patients with detectable APA were described. Ducloux *et al.*[23] detected a very high prevalence of posttransplant APA (28%) in RTR, most of whom could be demonstrated to have these APA while on dialysis. There was approximately a 3-fold increase in venous (peripheral) and arterial thrombotic risk in those with APA, but only one graft was lost due to thrombosis. Vaidya *et al.*[33] determined the prevalence of anticardiolipin antibodies in 502 ESRD patients recipients awaiting transplantation.

A high titre of anticardiolipin antibodies was found in 19% of patients, 23 of whom had a prior history of lupus, thrombosis, thrombocytopaenia, or thrombotic microangiopathy. Eleven of these 23 patients received renal transplants with (four patients) or without (seven patients) concomitant anticoagulation therapy. Of the four patients who received anticoagulation therapy, three retained their grafts. All of the seven patients transplanted without anticoagulation therapy lost the graft within 1 week as a result of renal thrombosis. Patients with systemic lupus erythematosus as the primary cause of ESRD and patients with APS have a particularly poor outcome following renal transplant from allograft loss or other vascular complications, suggesting that measures to prevent thrombosis are imperative in these conditions.

Ducloux *et al.*[34] identified hyperhomocysteinaemia (homocysteine levels >15µmol/l) as an independent risk factor for cardiovascular disease. Each micromolar increase in homocysteine was associated with a 6% increase in relative risk of a cardiovascular event. Heidenreich *et al.*[32] reported that in homozygous carriers of the T allele of the methylenetetrahydrofolate reductase (*MTHFR*) gene (10.3%) had an increased risk of rejection, but not of graft loss. On the other hand, Hagen[35] provided evidence that homocysteine levels did not influence patient or graft survival. In fact, no study has evaluated the potential effect of hyperhomocysteinaemia on the risk of graft or other thrombotic complications in RTR.

SCREENING FOR THROMBOPHILIA

Should all patients receiving a kidney transplant be screened for thrombophilia? Allograft thrombosis, although uncommon, is potentially preventable. Screening is worthwhile if simple and inexpensive, and if identification of a recognised risk allows the use of an effective intervention to reduce that risk. However, measures to reduce allograft thrombosis have not been validated in controlled randomised trials.

There is currently no consensus on the selection of patients for thrombophilia testing. Screening is reasonable in patients with a history of venous thromboembolism or other risk factors[7-9,19,20,37], as the current evidence does not support routine screening of all transplant candidates (Table III).

Table III

Clinical and laboratory markers of patients at increased risk of renal allograft thrombosis[7,8,9,19,20,37]

Clinical features
History of ≥2 arteriovenous access thromboses
Prior allograft thombosis
Personal and/or family history of VTE
Multiple miscarriages
Collagen vascular disease such as systemic lupus erythematosus
Autoimmune disease
Antiphospholipid antibody syndrome (APS)
Cerebrovascular and/or cardiovascular disease in young patients (less than 45 years old)
Laboratory evaluation
FVL gene mutation
Prothrombin gene *(G20210A)* mutation
MTHFR gene (*C677T)* mutation
Protein S, C and ATIII deficiencies
Antiphospholipid antibodies (lupus anticoagulant, anticardiolipin antibody, anti-β2-glicoprotein-1 antibody)
Homocysteinaemia

Pretransplant screening should involve clinical stratification for thrombotic risk factors, followed by laboratory evaluation for the presence of a hypercoagulable state if criteria are met. Patients with a history of ≥2 arteriovenous access thromboses, prior allograft thombosis, personal or family history of VTE, multiple miscarriages, collagen vascular disease such as systemic lupus erythematosus, autoimmune disease, previous APS and young patients (less than 45 years old) with cerebrovascular and/or coronary artery diseases are considered to be at high risk. These patients should be tested for activated protein C resistance, FVL gene mutation, prothrombin gene (*G20210A*) mutation, MTHFR gene (*C677T*) mutation, protein S deficiency, protein C deficiency, and ATIII deficiency, APA (lupus anticoagulant, anticardiolipin antibody, anti-β2-glicoprotein-1 antibody) and homocysteinaemia. Baseline prothrombin time/international normalised ratio (INR) and aPTT should be drawn prior to the surgery.

Clinical risk stratification of RTR with known or suspected hypercoagulable state has been performed by Irish[13] and Morrisey *et al.*[20] The severity of the underlying hypercoagulable state was estimated from laboratory and clinical parameters. Patients were then risk stratified based on the severity of the preceding clinical event and the presence of any serologic abnormalities. What constitutes a

significant clinical event is somewhat subjective. Patients identified in a higher clinical risk group, or with previous evidence for thrombosis, should be considered for individualised testing and prophylaxis[13,20]. Peritoneal dialysis and diabetes are clinical groups which epidemiological review suggests are at higher risk (Table IV)[6-8].

Table IV

Clinical risk stratification of RTR with suspected hypercoagulable state[13,20]

High risk patients
Antiphospolipid antibody syndrome (APS).
One or more clinical features suggestive of a hypercoagulable state and laboratory evidence of thrombophilia (see Table III).
Patients at risk
Clinical features suggestive of a hypercoagulable state (excluding APS), without laboratory evidence for thrombophilia (see Table III).
Peritoneal dialysis.
Diabetes Mellitus.
Nephrotic syndrome.
Low risk patients
No suspicion of hypercoagulable state.

THERAPEUTIC INTERVENTION

Two studies have used aspirin for prevention of renal allograft thrombosis. The Oxford group[37] prescribed aspirin 75 mg/day for 1 month to all patients from July 1991 onwards, and compared the allograft thrombosis rate with a historic control group. The rate of allograft thrombosis prior to aspirin prophylaxis was 5.6% and after the introduction of aspirin prophylaxis 1.2% (p<0.01). Similarly, the Leicester group[38] introduced aspirin 150 mg/day from the first postoperative day for up to 90 days and 5000U of unfractionated heparin twice daily for 5 days. The investigators reported a reduced rate of thrombosis when compared with historic controls (0% *vs.* 5%; p=0.03). Both treated and untreated groups reported no significant bleeding problems and no restriction upon biopsy requirements. The investigators recommended aspirin as routine practice.

Friedman *et al.*[39] developed a clinical risk factor algorithm and tested only patients at risk of a hypercoagulable state. They instituted a programme of unfractionated heparin and long-term oral anticoagulation with warfarin in those patients with high clinical risk and a thrombophilic state. They identified a small group at high risk and achieved a 60% reduction in allograft thrombosis, compared with historic rates; however, they noted a very high haemorrhagic (wound) complication rate. Morrissey *et al.*[20] reported on 235 consecutive renal allograft recipients who were screened for thrombophilia based upon an initial clinical algorithm of thrombotic risk. They identified eight (3.4%) patients at risk using their criteria. Six of these patients were noted to have APA. Two had no detectable laboratory abnormality. No patients had either the FVL gene or *G20210A* gene mutation. Perioperative heparinisation was used in all eight patients and no allograft thromboses occurred in those eight patients or the remaining patients without clinical risk who did not receive heparin. Two patients had bleeding complications requiring intervention. Two patients not identified as at risk experienced deep vein thrombosis – one had acquired protein C deficiency and another APA. Mathis *et al.*[36] reported on 725 consecutive renal transplant recipients who were screened for thrombophilia based on the clinical algorithm of thrombotic risk reported previously by Friedman *et al.*[39]. Twenty-eight (3.86%) patients received unfractionated heparin to prevent renal thrombosis. Eighteen patients (64.3%) had clinically important bleeding. Among postoperative characteristics, higher maximum aPTT (p=0.052) trended toward a significant association with bleeding. They concluded that the optimal aPTT ratio appears to be 1.5-1.9 to prevent thrombosis and limit bleeding risk.

Alkhunaizi *et al.*[40] treated 120 adult kidney recipients with dalteparin 2500U Units daily (low risk group) for the period of hospitalisation only, or 5000U daily (high risk group) for at least one month. High risk was defined as a hypercoagulable state (15%) or multiple vessels (31%). There were no allograft thromboses and no major haemorrhagic events.

All of the studies linking thrombophilic disorders to renal transplant complications are retrospective in design, and an accurate assessment of risk will require prospective studies. Until these studies are carried out, the American Society of Transplantation recommends screening high risk patients and prophylatic perioperative anticoagulation for patients with thrombophilia and a history of thrombosis[41]. An algorithm for managing patients with thrombophilia who undergo renal transplantation in our institution

Table V

Proposal of therapeutic intervention to prevent renal allograft thrombosis[20,36-41]

High risk patients (see Table IV)	Unfractionated heparin[(a)], followed by oral anticoagulation for up to 6 months.
Patients at risk (see Table IV)	Unfrationated heparin in low-dose, followed by prophylactic enoxaparin for up to 6 months[(b)] or Aspirin 100 mg/day for up to 6 months
Low risk patients (see Table IV)	No prophylaxis

(a) unfractionated heparin starting 1–12 hours after the surgery, 10UI/Kg/h without a bolus dose, and APTT of approximately 50 seconds is targeted. Dose adjustment is based on aPTTs performed every 6 hours. Warfarin is started after it is certain that no further surgical procedures will be required and is continued long term. Heparin is discontinued when the INR has been 2–3 for 2 days.

(b) unfractionated heparin starting 1–12 hours after the surgery, 100-300UI/h without a bolus dose, and APTT less than 42 seconds is targeted. Dose adjustment is based on aPTTs performed every 6 hours. Unfractionated heparin is discontinued and enoxaparin 20 mg subcutaneously is started after it is certain that no further surgical procedures will be required and is continued long term. Enoxaparin is administered for up to 6 months.

is suggested in Table V. Continuous assessment of each patient's ongoing risk of thrombotic and bleeding events is essential for their safety.

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