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Published in:
Transplantation

DOI:
[10.1097/TP.0000000000004452](https://doi.org/10.1097/TP.0000000000004452)

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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2023

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

van den Berg, T. A. J., Nieuwenhuijs-Moeke, G. J., Lisman, T., Moers, C., Bakker, S. J. L., & Pol, R. A. (2023). Pathophysiological Changes in the Hemostatic System and Antithrombotic Management in Kidney Transplant Recipients. *Transplantation*, *107*(6), 1248-1257. Advance online publication. <https://doi.org/10.1097/TP.0000000000004452>

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Pathophysiological Changes in the Hemostatic System and Antithrombotic Management in Kidney Transplant Recipients

Tamar A.J. van den Berg, MD,^{1,2} Gertrude J. Nieuwenhuijs-Moeke, MD, PhD,³ Ton Lisman, PhD,^{1,2} Cyril Moers, MD, PhD,^{1,2} Stephan J.L. Bakker, MD, PhD,⁴ and Robert A. Pol, MD, PhD¹

Abstract. Nowadays, the main cause for early graft loss is renal graft thrombosis because kidney transplant outcomes have improved drastically owing to advances in immunological techniques and immunosuppression. However, data regarding the efficacy of antithrombotic therapy in the prevention of renal graft thrombosis are scarce. Adequate antithrombotic management requires a good understanding of the pathophysiological changes in the hemostatic system in patients with end-stage kidney disease (ESKD). Specifically, ESKD and dialysis disrupt the fine balance between pro- and anticoagulation in the body, and further changes in the hemostatic system occur during kidney transplantation. Consequently, kidney transplant recipients paradoxically are at risk for both thrombosis and bleeding. This overview focuses on the pathophysiological changes in hemostasis in ESKD and kidney transplantation and provides a comprehensive summary of the current evidence for antithrombotic management in (adult) kidney transplant recipients.

(*Transplantation* 2023;107: 1248–1257).

INTRODUCTION

Nowadays, the most prominent cause of early graft loss is renal graft thrombosis (RGT). Especially because immunological reasons for early graft loss have virtually vanished because advances in immunological techniques and immunosuppression. RGT, which predominantly originates from renal vein thrombosis, occurs in approximately 1% of transplanted grafts

(0.1%–0.3% in case of renal artery thrombosis) and usually results in a transplantectomy.^{1,2} Historically, patients with end-stage kidney disease (ESKD) were considered hypocoagulable with an increased bleeding tendency. In the early 80s, it was shown that the degree of anemia significantly contributed to bleeding time, and the subsequent introduction of recombinant erythropoietin and correction of anemia with hematocrit above 30%, resulted in significantly reduced bleeding time and severity of bleeding complications.³

More recently, several studies reported that chronic kidney disease (CKD) itself is a risk factor for thromboembolic events. Paradoxically, patients with ESKD (CKD stage 5) also show an increased bleeding tendency, as may be reflected by a 4% incidence of significant bleeding post-transplantation compared with 1% in general surgery,^{1,4} which is potentially due to profound pro- and anticoagulant changes in ESKD patients. Because of these alterations in the hemostatic system and the many confounding factors, patients with CKD/ESKD are often not included in clinical trials investigating the effect of anticoagulant therapy, which complicates decision-making for kidney transplant professionals.⁵ As a result, there are little to no reliable data for formulating evidence-based recommendations regarding perioperative antithrombotic therapy.⁶ To better understand the problems regarding antithrombotic management in kidney transplant recipients, this overview focuses on the pathophysiology of thrombosis and bleeding in ESKD and kidney transplantation and provides a comprehensive summary of the current evidence on antithrombotic management in (adult) kidney transplant recipients.

Received 25 May 2022. Revision received 17 September 2022.

Accepted 12 October 2022.

¹ Department of Surgery, University of Groningen, University Medical Center Groningen, the Netherlands.

² Surgical Research Laboratory, Department of Surgery, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands.

³ Department of Anesthesiology, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands.

⁴ Division of Nephrology, Department of Internal Medicine, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands.

The authors declare no conflicts of interest.

This research received no specific grants from any funding agency.

All authors contributed to the writing of the article. T.B. and R.P. wrote the initial draft.

Correspondence: Robert A. Pol, MD, PhD, Department of Surgery, University Medical Center Groningen, Hanzplein 1, Postbus 30 001, 9700 RB, Groningen, the Netherlands. (pol.chirurgie@gmail.com).

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ISSN: 0041-1337/20/1076-1248

DOI: 10.1097/TP.0000000000004452

GENERAL PHYSIOLOGY OF THE HEMOSTATIC SYSTEM

Platelet Activation

Platelets are the first responders in cases of acute inflammatory or hemostatic events. Under normal conditions, the endothelium expresses an antithrombotic phenotype. Negative signaling, for example, via nitric oxide (NO), counters the activation and adhesion of platelets near the endothelium.^{7,8} Trauma or inflammation can interfere with the integrity of the endothelium and cause activation of endothelial cells and exposure of the subendothelial matrix, resulting in platelet adhesion, activation, and aggregation (Figure 1).⁹ Activated platelets exocytose α -granules (containing, among others, platelet activating factor, platelet factor 4, von Willebrand factor [VWF], and stored proteins taken up from plasma) and dense (δ -) granules (adenosine triphosphate, adenosine diphosphate (ADP), and serotonin).¹⁰ Platelets also synthesize and release thromboxane A2 (TXA₂), which is a vasoconstrictor and a secondary platelet activating agent.

Procoagulant Mechanisms

Upon injury of the endothelium, subendothelial tissue factor (TF) initiates coagulation by complex formation with coagulation factor VIIa. Coagulation factors circulate in the blood in their inactive zymogen form and become activated during coagulation via a catalytic chain reaction. The TF-FVIIa complex activates FX or FIX, eventually leading to the formation of thrombin. Thrombin cleaves

fibrinogen to fibrin, which is cross-linked by FXIIIa.¹¹ Concomitant amplification of thrombin generation via the intrinsic pathway is established by thrombin activating FXI (Figure 2). Under certain pathological conditions, coagulation may also be activated by the contact activation system (also referred to as the intrinsic pathway of coagulation). Contact activation results in the generation of factor XIIa, which activates FXI (Figure 2).

Anticoagulant Mechanisms

Various serine protease inhibitors (serpins), such as antithrombin and activated protein C, regulate the coagulation cascade by either direct inhibition of coagulation factors (antithrombin) or inactivation of nonenzymatic cofactors involved in coagulation (activated protein C).

Fibrinolysis is induced when the zymogen plasminogen is activated by an endothelial tissue plasminogen activator (t-PA) and converts plasminogen to plasmin, which cleaves fibrin into degradation products, such as D-dimers. Fibrinolysis is also regulated by inhibitory proteins such as plasminogen activator inhibitor type 1 (PAI-1) and antiplasmin.

PATHOPHYSIOLOGICAL CHANGES IN HEMOSTASIS IN ESKD

Nondialysis-dependent CKD Stage 5

ESKD has a profound influence on hemostasis. Alone or in combination with renal replacement therapy, it disrupts the fine balance between procoagulation and

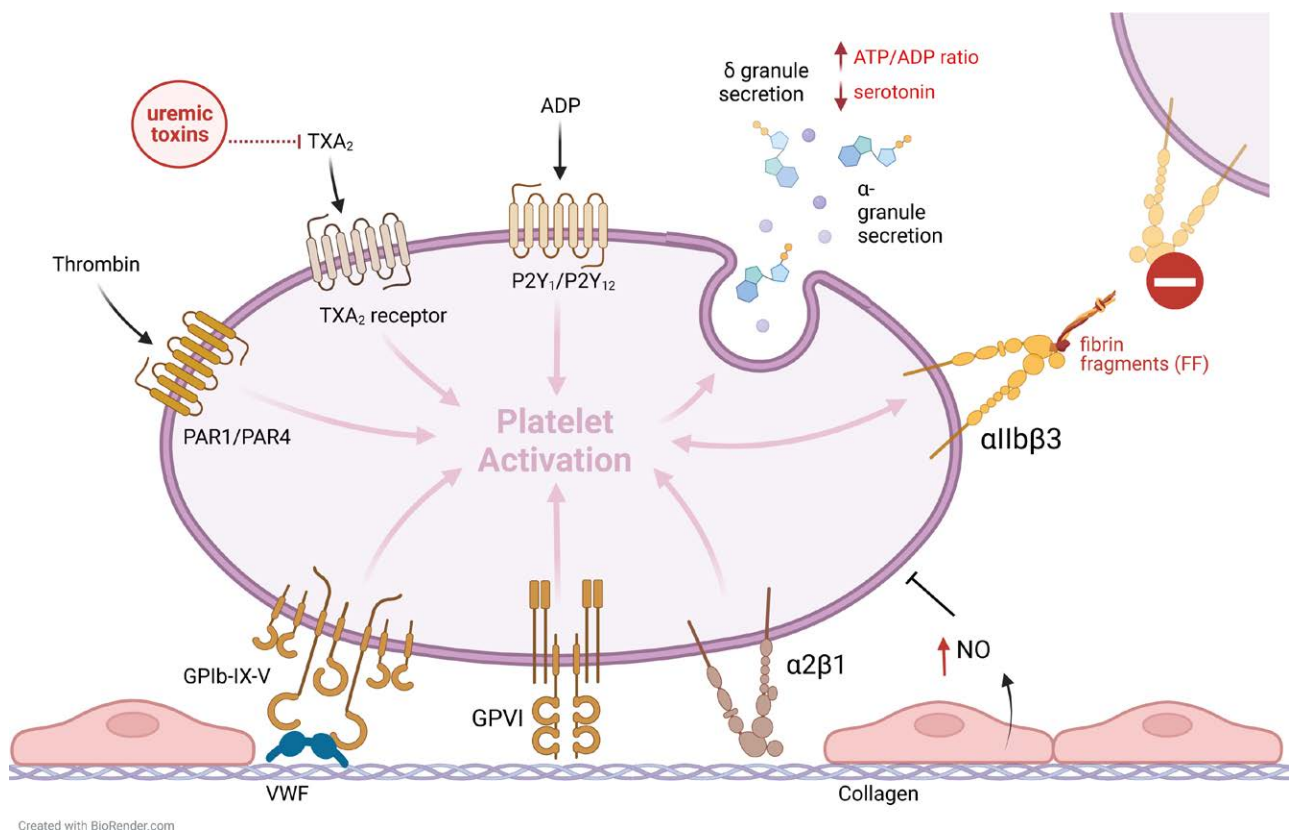


FIGURE 1. Platelet activation and disturbances due to ESKD and dialysis. ADP, adenosine diphosphate; ATP, adenosine triphosphate; ESKD, end-stage kidney disease; NO, nitric oxide; PAR, protease-activated receptor; TXA₂, thromboxane 2; VWF, von Willebrand factor.

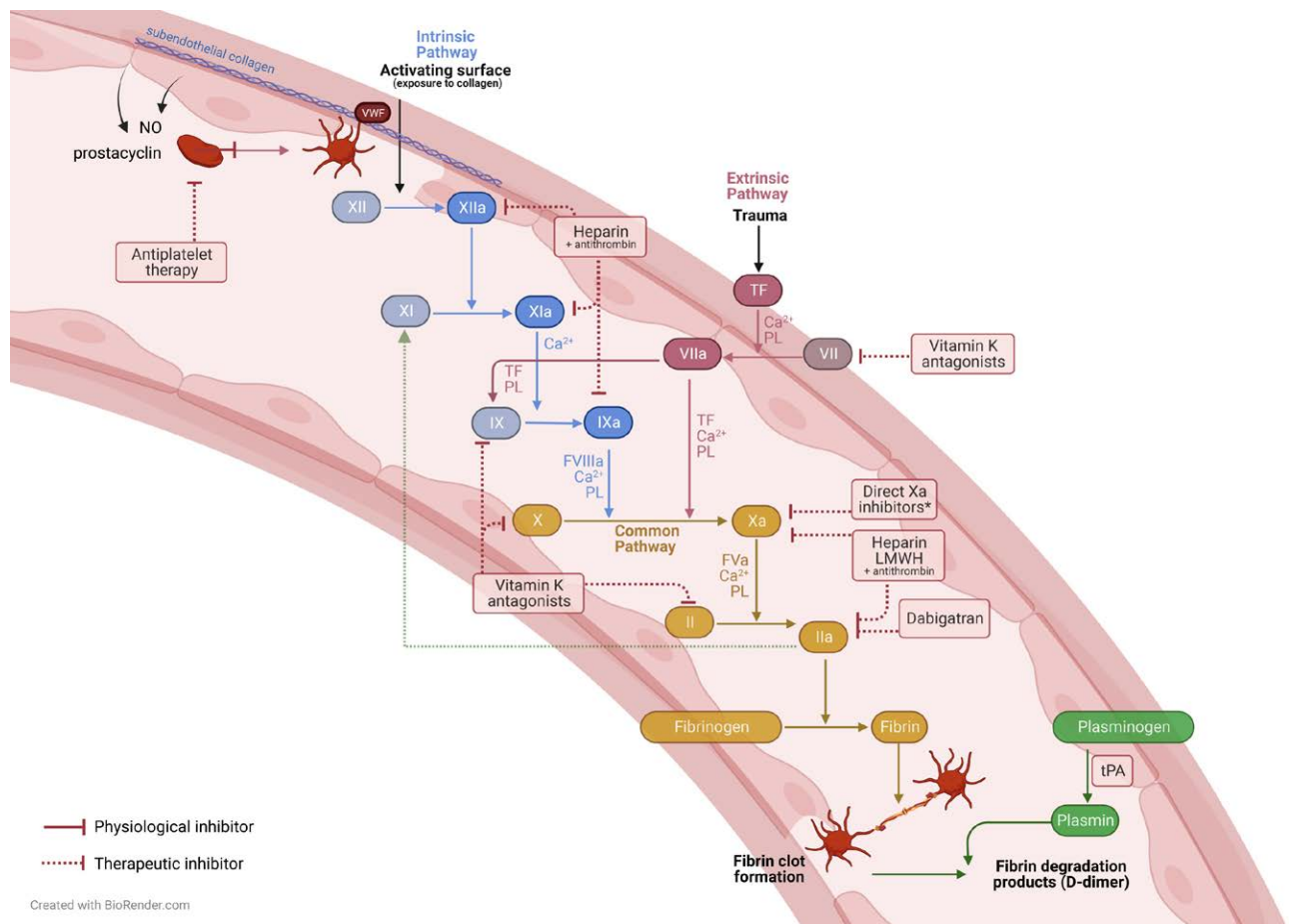


FIGURE 2. The process of clot formation and the coagulation cascade with sites of inhibition of antiplatelet and anticoagulant drugs. LMWH, low-molecular weight heparin; NO, nitric oxide; PL, phospholipids; TF, tissue factor; tPA, tissue plasminogen activator; VWF, von Willebrand factor.

anticoagulation mechanisms in the body, resulting in a bleeding tendency on one side and increased risk for thrombosis on the other. Because of reduced kidney filtration, pathophysiological changes in uremic patients include the accumulation of urea, which induces the production of mitochondrial reactive oxygen species, causing endothelial dysfunction,^{12,13} and the accumulation of uremic toxins, of which several have been shown to interfere with platelet function, by, for example, inhibiting TXA₂ synthesis.¹³ Furthermore, platelet δ -granules have a decreased ADP and serotonin content, and platelet-vessel wall interactions are impaired, because a decreased amount of GPIIb receptors and increased NO production.^{7,9,14}

Circulating fibrin degradation products,¹⁵ which are present in uremic patients, competitively bind to α IIb β 3, impairing platelet-to-platelet interaction. Anemia, which is frequent in ESKD patients, increases the risk of bleeding because of diminished platelet function caused by reduced vessel-wall interaction (as a result of a decreased number of erythrocytes pushing platelets towards the vessel wall), an impaired release of ADP stimulated by erythrocytes, and less scavenging of NO by hemoglobin.^{3,16} Higher VWF levels in uremic patients compensate the relative adhesion defect to some extent,¹⁷ but altogether, these interactions result in thrombocytopenia and a subsequently impaired primary hemostasis. Additionally, it is important to note that, on top of these changes in platelet function, many

ESKD patients experience volume overload associated with hypertension and cardiovascular disease and use antiplatelet therapy indicated for their primary disease or other (cardiovascular) comorbidities, which increase the risk of bleeding. On the other hand, increased levels of circulating fibrinogen and reduced fibrinolytic properties, caused by activation of the renin-angiotensin-aldosterone system, and endothelial cell damage, steer toward hypercoagulability.⁹ An extensive summary of the differential effects of renal failure and dialysis on hemostasis is presented in Table 1.

Dialysis-dependent CKD Stage 5

Hemodialysis has been shown to affect hemostasis in 3 ways: it leads to (1) thrombocytopenia due to low-grade platelet activation resulting in release of α - and δ -granules following the passing through the dialysis membrane of the extracorporeal circuit, leading to “exhausted” platelets;²² (2) rebalancing by removing uremic toxins that, for example, inhibit TXA₂ synthesis, and by removing fibrin degradation products, which both disrupt platelet activation and thus primary hemostasis;^{9,15,23} and (3) procoagulant changes, such as circulating antiphospholipid antibodies in hemodialysis patients, and platelet activation with increased plasma levels of PAI-1 and several coagulation factors in peritoneal dialysis patients with hypoalbuminemia.^{9,24}

TABLE 1.**Differential effects of ESKD and dialysis on the coagulation system (modified from Nieuwenhuijs-Moeke¹⁸)**

Procoagulant	Anticoagulant
<p>Coagulation cascade</p> <ul style="list-style-type: none"> • ↑ fibrinogen level, associated with ↑ level of proinflammatory markers (eg, CRP, IL-6) • ↑ TF level • ↑ FXIIa and FVIIa, ↓ ATIII • Activation RAAS, associated with ↑ fibrinogen, ↑ D-dimer, ↑ PAI-1 • PD: ↑ PAI-1, ↑ levels FII and FVII up to FXII <p>Platelets</p> <ul style="list-style-type: none"> • PD: ↑ activity and ↑ count • ↑ phosphatidylserine (PS) exposure¹⁹ due to ↑ platelet activation, which stimulates binding of vit K-dependent coagulation factors. • ↑ p-selectin expression, activation of αIIbβ3 facilitating platelet–leucocyte interaction. Results in platelet activation, ROS formation, and increased thrombotic state • Elevated plasma levels of VWF¹⁷ <p>Endothelium</p> <ul style="list-style-type: none"> • Endothelial injury through hypoxia, thrombin, oxidants IL-1, TNF-α, IFN-γ, endotoxins... → loss of antithrombotic properties • Production of endothelial microparticles with surface exposure of PS, facilitating thrombin formation and TF, release soluble TF. MP also produced by other cells. • Homocysteine: inhibits thrombomodulin-dependant APC system → permanent activation of thrombin. Interferes with t-PA release → hypofibrinolysis <p>Antibodies</p> <ul style="list-style-type: none"> • Antiphospholipid antibodies: detectable in many HD patients, significance not clear²¹ • Increased ↑ prevalence APC/antiprotein S antibodies in HD patients with vascular access thrombosis, significance not clear 	<p>Coagulation cascade</p> <p>Platelets</p> <ul style="list-style-type: none"> • Uremic toxins: ↓ TXA2 → ↓ adhesion, ↓ aggregation, reversed by HD • ↓ function, disturbance α-granules: ↑ ATP/ADP ratio, ↓ serotonin content • ↑ Ca content, with disturbed intracellular flux • ↑ ATP release • Competitive binding of FDP bind to αIIbβ3 → ↓ adhesion, ↓ aggregation • Reduced collagen-induced platelet aggregation²⁰ • Continuous activation dialysis membrane (HD) <p>Platelet-vessel wall interaction</p> <ul style="list-style-type: none"> • ↓ GPIIb platelet receptors • Competitive binding of uremic toxin to αIIbβ3 → reduced binding to fibrinogen • Functional defect VWF-platelet interaction related to uremic toxins • Inhibition platelet aggregation by vasoactive substances: ↑ NO production by platelets • ↓ in anemia (less scavenging of NO by haemoglobin) <p>Medication</p> <ul style="list-style-type: none"> • Platelet aggregation inhibitors • Accumulation of LMWH, FXa inhibitors, thrombin inhibitors

ADP, adenosine diphosphate; APC, activated protein C; ATP, adenosine triphosphate; CRP, C-reactive protein; FDP, fibrin degradation products; GP, glycoprotein; HD, hemodialysis; IFN, interferon factor; IL-6, interleukin-6; LMWH, low-molecular-weight heparin; MP, microparticles; NO, nitric oxide; PAI, plasminogen activator inhibitor; PD, peritoneal dialysis; PS, phosphatidylserine; RAAS, renin-angiotensin-aldosterone system; ROS, reactive oxygen species; TF, tissue factor; TXA2, thromboxane 2; TNF, tissue necrosis; t-PA, tissue plasminogen activator; VWF, von Willebrand factor.

Interestingly, all kidney transplant recipients, regardless of dialysis modality, have been shown to have a comparable and procoagulant hemostatic state before transplantation.²⁵ A possible explanation for this might lie in the formation of neutrophil extracellular traps (NETs). These web-like structures, containing DNA, histones, and antimicrobial proteins, are expelled from neutrophils undergoing NETosis and are usually recruited in case of microorganism invasion. However, excessive formation of NETs has been described in CKD patients, hemodialysis, ischemia-reperfusion injury (IRI), and thrombosis.²⁶⁻²⁸ Hypothetically, the combined effects of CKD, hemodialysis, and IRI led to a more pronounced prothrombotic state in dialysis-dependent recipients than preemptive recipients.

Kidney Transplantation

During kidney transplantation, the alterations in pro- and anticoagulant properties of ESKD patients are further amplified. Activation of hemostatic processes as a result of surgical damage, IRI, and hemodilution contribute to

the aggravation of the preoperative hemostatic abnormalities and induce endothelial dysfunction.²⁹ Together with the obvious stasis/reduced blood flow due to clamping of the vessels, but also the possible torsion or kinking of the vessels, these conditions include all 3 prerequisites for thrombogenesis as recognized in Virchow's triad: vessel wall/endothelial injury, stasis, and hypercoagulability.³⁰ At the same time, vascular anastomoses, with the risk of anastomotic bleeding, together with acquired coagulation abnormalities secondary to hemodilution add to the already existing bleeding diathesis in kidney transplant recipients.³¹

Coagulation in Immune Response and Rejection

It has been generally accepted that the coagulation system and platelet activation are an integrated part of the innate immune system, which can be activated upon inflammation or trauma, such as IRI or donor-specific antibodies. Accumulation of platelet aggregates in graft rejection biopsies indicated that platelets could be a marker of graft rejection, but more recently, it was also

shown that they are active contributors.³² Platelets can contribute to graft rejection in several ways: by functioning as mediators for leukocytes and the damaged endothelium, and through glutamate receptor signaling, which accelerates T cell recruitment.^{33,34} Regarding the coagulation system, serpins such as thrombin, which activates proteinase-activated receptor-1, can contribute to a pro-inflammatory response. Furthermore, the coagulation and complement systems are closely intertwined. It has been shown that the complement system, and especially the alternative pathway, is activated in graft rejection and ischemia-reperfusion. Both C3 and C5 of the complement system can become activated through FIXa, FXa, FXIa, thrombin, and plasmin, and C1 can be activated by FXIIa. In turn, the complement system can contribute to a procoagulatory response by activating thrombin via components of the lectin pathway.³³ For a more comprehensive description on the interplay between coagulation and complement, we refer to an in-depth review from Oikonomopoulou et al.³³

PREVENTION AND TREATMENT OF THROMBOSIS IN KIDNEY TRANSPLANTATION

Most thromboembolic and bleeding events occur in the first days after transplantation and are most likely related to the surgical procedure.^{1,35} Over the years, several groups have studied known and unknown risk factors for thrombosis and bleeding in KTx patients compared with general surgery patients.³⁵⁻⁴⁰ High heterogeneity limits the possibility to perform thorough multivariate and meta-analyses, but several independent risk factors have been reported. These risk factors are given in Table 2. Well-known, nonmodifiable risk factors are the extremes of age and renal atherosclerosis in both donors and recipients, diabetic nephropathy, past

VTE events, and hemodynamic instability. Technical difficulty and longer cold ischemia (>24 h) are independent risk factors as well, but surgical difficulty is highly operator-dependent, and long cold ischemia can be actively avoided.^{36,37} Importantly, although CKD cannot be investigated as a potential risk factor in the kidney transplant setting (given the underlying disease of all patients), it was identified as an independent contributor to thrombosis in another setting.²¹

In addition, studies have described an apparent increased thrombotic risk and protection against bleeding for patients with obesity (BMI >30 kg/m²).^{1,36,56} Although BMI probably interacts with other patient characteristics, it is an important factor to include when identifying the patient at risk and for patient education.⁵¹ Especially considering the global obesity pandemic, patients with a high BMI are increasingly transplanted.⁵⁷ Many European centers use a BMI cutoff of 35 kg/m² and, in the United States, sometimes even 40 kg/m². Informed preoperative consent now often includes postoperative bleeding as one of the main complications, apart from rejection. The results presented here suggest that, in obese patients, more emphasis should be put on the occurrence of RGT rather than postoperative bleeding.

Inherited/Acquired Thrombophilia

An important risk factor for increased thrombotic risk is thrombophilia. Patients with thrombophilia have an inherited or acquired hypercoagulable state. Thrombophilia includes, among others, factor V Leiden, prothrombin G20210 mutations, protein C, S, or antithrombin III deficiency, activated protein C resistance, and antiphospholipid or anticardiolipin antibodies.^{40,58} In addition, auto-immune disease systemic lupus erythematosus (SLE) is associated with increased risk of vascular events, such as early atherosclerosis and both arterial and venous thrombosis. A vast amount of SLE patients have antiphospholipid antibodies, also called lupus anticoagulant (LA), which increases the risk for vascular events 6 times. LA negative SLE patients have a 10% to 20% risk of vascular events, compared with 40% of LA positive SLE patients.⁵⁹ Furthermore, acquired thrombophilia, such as LA, is common in ESKD patients, and certain predisposed individuals may encounter thrombosis in response to an external factor, such as transplant surgery.⁶⁰ Already, in 1998, patients with thrombophilia were shown to have a 3.5-fold increased risk for 1-y graft loss, related to both thrombosis and vascular rejection, and in 2001, it was shown that prophylactic anticoagulation of patients with hypercoagulable states due to thrombophilia showed a 2.6-fold reduction of the expected graft thrombosis incidence.⁶⁰ Detection of LA is possible through enzyme-linked immunosorbent assays. However, it is still debated whether routine screening for thrombophilia should be implemented. Anticoagulation should be considered in individuals with known thrombophilia, and postoperative monitoring for development of RGT should be done vigilantly.

Antiplatelet and anticoagulant therapies are, in accordance with their function and purpose, known risk factors for the occurrence of bleeding complications. However, reports investigating the actual risks or benefits of continuing prophylactic or therapeutic antithrombotic therapy in KTx patients are scarce. There are no randomized controlled

TABLE 2.
Transplant-specific risk factors

Renal graft thrombosis	Postoperative bleeding
CKD ⁴¹	Use of vitamin K antagonists ^{1,42}
Identified inherited/acquired thrombophilic factor ^{21,43}	Postoperative heparin infusion ^{1,39,44}
Donor age <6 and >60 ^{37,45,46}	Preemptive kidney transplantation ¹
Recipient age <5 and >50 ⁴⁷	Cardiovascular disease ¹
Peritoneal dialysis ^{21,40,48,49}	Longer pretransplant dialysis ⁵⁰
Atherosclerosis in external iliac, common iliac, or renal artery (both donor and recipient) ^{37,50}	Lower body mass index ^{36,51}
Re-transplantation ⁴⁸	<i>Univariate risk factors</i>
Diabetic nephropathy ^{38,48,52}	Longer CIT ³⁶
Hemodynamic instability ^{38,39}	Deceased donor type ³⁶
Technical difficulty ^{37,38}	ECD transplants ³⁶
<i>Univariate risk factors</i>	
Right donor kidney ^{a,37}	
Multiple donor arteries ^{1,37,53}	
CIT >24 h ^{40,46}	
Higher body mass index ¹	
Acute cytomegalovirus infection ^{54,55}	

^aConflicting reports. Probably most related to technical difficulty.³⁸
CKD, chronic kidney disease; CIT, cold ischemic time; ECD, extended criteria donor.

trials that sufficiently assess the efficacy of anticoagulant/antiplatelet therapy in preventing RGT, and retrospective reports are insufficiently powered to draw solid conclusions. Furthermore, different definitions, for example, what is considered significant bleeding, were used, which makes it difficult to compare studies. Current literature is more focused on the (un)safety of antithrombotic drugs, because of the higher incidence of bleeding complications, than the beneficial effects of preventing thrombosis.

Antiplatelet Therapy

In CKD patients, thromboembolic prevention is mainly managed with acetylsalicylic acid, its derivative carbasalate calcium (best known as Ascal), and P2Y₁₂-inhibitors, such as clopidogrel and ticagrelor, but CKD stage 4 of 5 patients are often underrepresented in studies investigating antiplatelet therapies.⁷ Some patients receive dual antiplatelet therapy, in which case most centers stop one of these before transplantation, but single antiplatelet therapy is generally continued.⁶¹ Hernandez et al reported 6% more bleeding complications in patients on antiplatelet therapy, but emphasized the importance of additional risk factors, such as complicated bench surgery.⁶² Our group analyzed and published a series of 2000 kidney transplant recipients and found no increased bleeding risk when antiplatelet therapy was continued.¹ Eng et al. also found no effect of preoperative clopidogrel on bleeding risk, although this might be biased by a low number of events (2 of 10 in a total cohort of 327 patients).⁵⁰ Additionally, Grotz et al showed that low-dose acetylsalicylic acid (aspirin) was associated with improved graft function, longer graft survival, and less proteinuria and hematuria.⁴⁴ As mentioned above, continuation of antiplatelet therapy must, however, be weighed against other risk factors, such as preexisting cardiovascular disease or expected high blood loss.¹

Anticoagulants

Anticoagulants that are subscribed can be roughly divided into 3 groups: heparins, vitamin K antagonists (VKA, coumarins), and direct oral anticoagulants (divided into direct FXa inhibitors and direct thrombin [FIIa] inhibitors). Heparins (including low-molecular weight) are used by several transplant centers to prevent RGT, whereas other anticoagulant or antiplatelet therapies are often prophylactically used for other indications, but may contribute to the prevention of RGT.⁶¹

Heparins

Heparin is a glycosaminoglycan that is naturally produced in all vertebrates and was discovered in 1916. Its clinical application was developed by Gordon Murray and Charles Best around the late 1930s,⁶³ and already, in these early days, Murray investigated its application in preventing RGT.⁶⁴ It now exists in 2 forms: unfractionated heparin (UFH), with a mix of polysaccharide chains, and low-molecular weight heparin (LMWH), existing of shorter polysaccharides.

UFH

UFH potentiates antithrombin III to inhibit several coagulation factors: mainly FXa and FIIa but, to a lesser extent, also FXIIa, FXIa, FIXa, and FVIIa (Figure 2). It has a short half-life of approximately 30 min, and although it can be

given safely in patients with CKD, ESKD patients with an eGFR <15 mL/min do require a dose reduction of 33%.⁶⁵ It is preferably administered intravenously, and its effects can be reversed quickly and completely by administering protamine sulfate. Clearance is mainly through endothelial cells and the reticuloendothelial system (phagocytic cells) and, to a lesser extent, through renal excretion.^{66,67} Side effects of UFH include bleeding and reduced platelet count. More severe is the occurrence of heparin-induced thrombocytopenia in selected individuals, which actually may result in thrombosis. Its bioavailability is unpredictable because of a selective binding to positively charged surfaces, which requires activated partial thromboplastin time monitoring.

For its use in kidney transplantation, Ng et al⁶⁸ investigated different heparin protocols in the posttransplant period. Although therapeutic use of UFH showed an increased incidence of significant postoperative bleeding, administration of a prophylactic dose (5000 international units [IU]) subcutaneously was not associated with increased bleeding, a finding consistent with our previously mentioned analysis of 2000 KTx recipients, even in combination with preoperative antiplatelet therapy.¹ Another small retrospective analysis also showed that kidneys from patients treated with 5000 IU UFH intravenously, before reperfusion, had less microthrombi than the no-heparin group.⁶⁹ Although its effectiveness remains unclear, it appears that prophylactic doses of UFH (eg, 5000 IU intraoperatively) can be safely used without increasing the incidence of significant postoperative bleeding.^{1,56,68,70} Interestingly, heparin and other heparinoids have also been shown to inhibit parts of the complement system, which is directly linked to the coagulation system and an important factor for IRI and antibody-mediated rejection.^{71,72} A recent nonhuman primate study showed that targeted inhibition of complement together with heparin significantly reduced delayed graft function after brain death donation.⁷³

LMWH

LMWHs also inhibit FXa but target thrombin (FIIa) much less efficiently than UFH (Figure 2). LMWHs include, among others, enoxaparin, dalteparin, tinzaparin, and nadroparin and are often used as VTE-prophylaxis, for example, in patients with increased PADUA scores.⁷³ The half-life of LMWHs is approximately 4h; it has a greater bioavailability than UFH, requires less monitoring, and can be prescribed to both inpatients and outpatients. It is renally eliminated, which, in CKD patients, at least requires empirical dose adjustment of enoxaparin because of increased bleeding risk.⁷⁴ The effects of LMWHs can only partly be reversed by protamine, which is more effective at reversing the activity of heparins toward thrombin than toward factor Xa. It is advised to monitor anti-Xa activity when deviating from weight-adjusted dosing.⁷⁵

VKAs (Coumarins)

The most famous coumarin, warfarin, was originally developed as a rodenticide in 1948. It was approved for human use in 1954 and quickly complemented heparin and dicoumarol (for which it took too long to reach a therapeutic effect for practical use) in the clinic under

the name Coumadin.⁷⁵ It has a half-life between 24 and 58 h. Later, acenocoumarol and fenprocoumon were developed, with a shorter and longer half-life, respectively.⁴² Coumarins inhibit the posttranslational modification that is required to synthesize vitamin K-dependent coagulation factors FIX, FX, FVII, and FII and protein C and protein S (Figure 2). They have a narrow therapeutic window and interact with certain foods and many other drugs, including antiplatelets and corticosteroids.^{68,76} For ESKD patients, the international normalized ratio target should be lowered because reduced kidney function is associated with significantly increased bleeding risk.⁷⁷ Furthermore, it is associated with the progression of vascular calcification through inhibition of vitamin K-dependent matrix gla protein, which inhibits vascular calcification.⁷⁸ Many kidney transplant recipients are on a VKA-regimen because of cardiovascular comorbidities, and most transplant professionals discontinue its use or bridge with heparin before transplantation, which, in deceased donor KT_x, is not always possible from a time perspective.⁶¹ Whereas Eng et al. found no effect of warfarin on bleeding risk, several other studies show that VKAs are an independent risk factor for severe postoperative bleeding with a nearly 7-fold increased risk.^{1,50,56,75} However, patients on VKA usually have a vital indication, for example, high CHA₂DS₂-VASc score, which makes it difficult to adjust the treatment or dosage.

Direct Oral Anticoagulants

More recently introduced anticoagulants are direct thrombin and FXa inhibitors. They inhibit serine proteases of the common pathway (Figure 2). For CKD stages 1 to 3, these are safe, but for CKD 4 or 5, results are poor and conflicting.⁷⁹ The half-time of dabigatran, a direct thrombin inhibitor, is severely influenced by renal function because this compound is 85% renally cleared. Therefore, dabigatran is contraindicated in CKD patients. Direct FXa inhibitors (rivaroxaban, edoxaban, and apixaban) have a half-life between 5 and 12 h and are only partially cleared through renal excretion, but it is expected that this half-life is prolonged in severe CKD stages as well.⁶⁵ The effects of rivaroxaban and apixaban can be reversed by administering andexanet alfa, which is a highly expensive antidote with a mean cost varying between \$24 000 and \$48 400 per patient.⁸⁰

Surgical Treatment of RGT

RGT can present as sudden anuria, pain in the surgical region (mostly in the case of renal graft vein thrombosis), and decline in renal function. When renal graft vein thrombosis progresses, pain, swelling, and redness can extend to the ipsilateral leg. Most renal graft thromboses result in transplantectomy,¹ but, when caught early, surgical treatment can be attempted, although success rates are low. There are some reports describing successful surgical thrombectomy, whereas others achieved resolution of the thrombus using intraarterial fibrinolysis with recombinant t-PA or urokinase.^{81,82} Klepanec et al described a case of acute renal graft artery thrombosis successfully treated by rheolytic thrombectomy, using a rapid-lysis technique with an XG Angiojet catheter and

catheter-directed t-PA,⁸³ which can also be applied to renal graft vein thrombosis.⁸⁴

MANAGEMENT AND TREATMENT OF POSTOPERATIVE BLEEDING

Postoperative bleeding can manifest in various degrees of severity. It may originate from the anastomoses, the perirenal tissue, or the recipient's surgical field. In the immediate postoperative period, gross hematuria or small perigraft or wound hematomas frequently occur.⁸⁵ Hematuria usually resolves in a few days and can be managed conservatively or with short-term bladder irrigation and attention to existing antithrombotic therapy.⁸⁶ It has been shown that the Lich-Gregoir technique significantly lowers the prevalence of hematuria requiring intervention compared with the Politano-Leadbetter or U-stitch (1.7% versus 4.1% and 7.2%).⁸⁷ Small hematomas without graft compression are often detected upon ultrasonography, are rarely of clinical significance, and will eventually resolve without intervention.⁸⁶ Significant postoperative bleeding, requiring blood transfusion and/or surgery, occurs in 0.2% to 4.4% of recipients and is associated with a higher risk of graft loss.^{1,35,88} Known risk factors for postoperative bleeding are given in Table 2. Surgical drain placement in high-risk patients, such as recipients with continued VKA therapy or when surgical hemostasis was already difficult, is an efficient way to detect sentinel bleeding before severe bleeding occurs. Daily duplex imaging and control of hemoglobin levels postoperatively also aid in early detection. A recent study also showed the predictive value of the HAS-BLED score in kidney transplant recipients on anticoagulant therapy, which can aid in identifying patients at increased risk for severe bleeding.⁵⁶

Point-of-care viscoelastic hemostatic tests, such as thromboelastography (TEG) or rotational thromboelastometry (ROTEM) can be used intraoperatively to assess bleeding or thrombotic risk, but data are mainly available from cardiac and liver transplantation surgery. Analyses with ROTEM have shown that ESKD patients, and especially those on peritoneal dialysis compared with hemodialysis, have reduced fibrinolytic properties and thrombin generation capacity, which have been demonstrated with standard laboratory studies, as well.^{25,89} In kidney transplantation, a recent study has shown that high dose-tPA TEG measurements were positively correlated with renal function on the first postoperative day, indicating that it might be beneficial to pair kidneys with known micro-thrombi and recipients with good functioning fibrinolysis.⁹⁰ However, it remains unclear whether TEG could be predictive of adverse outcomes or give directions for a targeted intervention. In cardiac surgery, activated clotting time (ACT) is used to manage the effect of heparin preoperatively; however, this may be unpredictable in kidney transplantation because haemodilution may prolong ACT. Furthermore, it is still discussed whether the available point-of-care devices to measure ACT are reliable and interchangeable.^{91,92}

WHERE DO WE STAND?

Kidney transplant recipients are at risk for both RGT and postoperative bleeding as a result of various hemostatic

changes caused by ESKD, dialysis, and the surgical procedure. A recent European survey among kidney transplant specialists concluded that it remains challenging to identify patients at risk and that there is a need for high-quality studies regarding antithrombotic management in kidney transplantation.⁶¹ Owing to the paucity of such studies, major thrombosis guidelines have to rely on low-grade evidence, resulting in weaker recommendations and subsequently in varying approaches to antithrombotic management, even within individual centers. What we know now is this: either all available anticoagulant drugs are associated with bleeding, or, if not, their effect on thrombosis reduction has not yet been demonstrated, even if they appear safe. However, postoperative bleeding is readily detectable, and several treatment options are available, whereas RGT usually results in graft loss. Nevertheless, kidney transplant recipients are regularly refrained from antithrombotic treatment. Overall, there seems to be evidence to indicate that intraoperative administration of prophylactic doses (eg, 5000 IU) of UFH before reperfusion is safe and can aid in decreasing the thrombotic risk.^{1,68-70} Antiplatelet therapy, including acetylsalicylic acid, carbasalate calcium, dipyridamole, clopidogrel, and ticagrelor, can be continued safely with minimal risk of postoperative bleeding.^{1,44,50} Continuation of VKAs or continued infusion of therapeutic doses of heparin postoperatively result is significantly associated with bleeding risk.^{1,50,56,75}

Future Studies

This overview highlights the complex changes in the hemostatic system of kidney transplant recipients and the deleterious effect of RGT, warranting appropriate antithrombotic therapy. For the near future, a Delphi study, in which kidney transplant experts draft a guideline based on a general consensus, could offer a solution for the center-wide differences in antithrombotic therapy. That is, at least until adequate randomized controlled trials or well-powered retrospective studies are conducted on which robust recommendations can be based. Most recently, the same approach has led to a consensus for hemostatic management in liver transplantation.⁹³ In the end, we do not only want to prevent RGT, but also the unwanted activation of the coagulation cascade and connected systems of inflammation and injury, without compromising on safety. It is clear that a one-size-fits-all approach does not apply to the ESKD population. However, we should be cautious of persisting dogmas about the bleeding tendency of patients with impaired renal function because they might benefit from anticoagulant therapy as well. It is evident that changes already occur in the donor, and future studies should focus on discovering which kidneys would benefit from intervention. It could, for example, be essential to pair donor kidney and recipient based on the recipients' fibrinolytic capability, as proposed by Walker and colleagues.⁹⁰ Furthermore, now that several studies have concluded that it is safe, future studies should focus on the effect of intraoperative heparin on thrombotic risk. Considering the inhibition of parts of the complement system by heparin and other heparinoids, such trials could function as a double-edged sword, and also provide information on incidence of delayed graft function and antibody-mediated rejection.

New Antithrombotic Drugs

A real solution might be provided by the development of more suitable drugs. Current anticoagulants mainly block proteases of the common pathway and thus affect all 3 stages of the coagulation process: inhibition, propagation, and amplification. As a result, bleeding complications remain a serious side effect. However, coagulation factors in the intrinsic pathway, such as FXI, appear to be key players in thrombosis but have a minimal role in bleeding, and thus, intrinsic coagulation factors are suggested to be suitable targets for effective and relatively safer anticoagulant drugs.⁹⁴

Many research groups work on FXI(a), as evidenced by a large number of patents,^{95,96} and several have already moved on to different stages of clinical trials. For example, the AXIOMATIC-TKA and ANT-005 TKA trials showed superior DVT prevention by FXIa-inhibitor milvexian and anti-FXI antibody abelacimab in patients undergoing total-knee arthroplasty compared with enoxaparin.^{97,98}

Several studies investigating the efficacy of FXI(a)-inhibitors Ionis FXI-LRx (NCT04534114), MK-2060 (NCT05027074), and osocimab (NCT03787368 and NCT04523220) in ESKD patients are currently planned or running. In the PACIFIC-AF study, asundexian (BAY2433334) was compared with apixaban in atrial fibrillation patients and showed a reduced bleeding risk in favor of asundexian. Although the differences between groups were small and the study was not powered to report on thrombosis incidence, these results are very promising, especially because 29% of the patients enrolled had CKD.⁹⁹

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