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Antithrombotic Management in Adult Kidney Transplantation: A European Survey Study

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Abstract
In kidney transplantation (KTx), renal graft thrombosis (RGT) is one of the main reasons for early graft loss. Although evidence-based guidance on prevention of RGT is lacking, thromboprophylaxis is widely used. The aim of this survey was to obtain a European view of the different thromboprophylactic strategies applied in KTx. An online 22-question survey, addressed to KTx professionals, was distributed by email and via platforms of the European Society for Organ Transplantation. Seventy-five responses (21 countries, 51 centers) were received: 75% had over 10 years' clinical experience, 64% were surgeons, 29% nephrologists, and 4% urologists. A written antithrombotic management protocol was available in 75% of centers. In 8 (16%) centers, respondents contradicted each other regarding the availability of a written protocol. Thromboprophylaxis is preferred by 78% of respondents, independent of existing antithrombotic management protocols. Ninety-two percent of respondents indicated that an anticipated bleeding risk is the main reason to discontinue chronic antithrombotic therapy preoperatively. Intraoperatively, 32% of respondents administer unfractionated heparin (400–10,000 international units with a median of 5,000) in selected cases. Despite an overall preference for perioperative thromboprophylaxis in KTx, there is a high variation within Europe regarding type, timing, and dosage, most likely due to the paucity of high-quality studies. Further research is warranted in order to develop better guidelines.

Introduction

Kidney transplantation (KTx) is the preferred treatment for end-stage renal disease (ESRD) [1]. Despite a big improvement in the graft and patient survival over time, occasional complications can lead to a poor outcome. Renal graft thrombosis (RGT) is a rare but serious complication, occurring approximately once in every 100 kidney transplants. It usually leads to a reduced function or even graft losses. Up to 45% of early graft

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loss is caused by thrombosis of the renal artery or vein [2]. A lot of effort is put into the prevention of RGT, and rapid detection is imperative as treatment options are limited to emergency surgery and attempting thrombectomy [3, 4]. Appropriate antithrombotic management in the perioperative kidney transplant period to prevent RGT seems therefore justified. In contrast to vascular surgery, where it is common practice to administer unfractionated heparin (UFH) prior to vascular clamping [5], there are no established protocols aimed at preventing RGT in KTx. The major general thrombosis prevention guidelines only address venous thromboembolism (VTE) and do not address specific issues of thrombosis at surgical sites [6, 7]. The European Association of Urology guideline for KTx recommends "to refrain from pharmacological prophylaxis after low-risk living donor KTx," which is based on a small randomized controlled trial [8, 9], a recommendation based on weak evidence, as acknowledged by the authors themselves. The European Renal Best Practice guideline recommends to not routinely use low-molecular-weight heparin (LMWH), UFH, or aspirin prior to transplantation. As a result, many differences concerning perioperative antithrombotic management exist between centers. In addition, a high variation in treatment strategies in postoperative thromboprophylaxis was observed when 35 French transplant centers were presented 4 clinical cases and asked what would be their standard practice in the first 48 h after KTx [10].

When deprived from evidence-based recommendations, it only seems reasonable to think that kidney transplant centers apply their own protocols which may or may not be based on evidence from other medical fields. Potentially, there could also be variation between different medical specialties, e.g., between vascular surgeons, abdominal surgeons, or urologists, based on long-existing dogmas in these individual fields. Given the observed lack of knowledge and uniformity, we conducted a questionnaire study to obtain a European cross-sectional view on the different antithrombotic management strategies applied in KTx.

Materials and Methods

Study Design

The survey (online suppl. information S1; for all online suppl. material, see www.karger.com/doi/10.1159/000521327) was conducted using Qualtrics survey software (Qualtrics, Provo, UT, USA). It was published online on September 16, 2019, and was accessible until October 31, 2019. In addition to sending invitations through email to members of Eurotransplant involved in KTx (n = 350), we communicated with participants of the ESOT Congress 2019 in Copenhagen, and the survey was featured in the October issue of *Grafts&Facts*, which was curated by the European Kidney Transplant Association (EKITA) and social media platforms of ESOT.

The survey consisted of 22 questions and took approximately 7–10 min to complete. It was structured into sections covering demographic information, such as country of employment, medical profession, and years of clinical experience in KTx and 3 further sections which focused on use of antithrombotic therapy (a) before, (b) during, or (c) after KTx. Respondents were asked whether there was a center-wide perioperative antithrombotic protocol for KTx or if they could decide on their own. Furthermore, they were asked to identify factors they would take into consideration when administering or discontinuing antithrombotic agents prior to or during the kidney transplant procedure. The survey was tested in advance by a panel of 5 transplant surgeons in order to enhance clarity and avoid ambiguity.

Statistical Analysis

Statistical significance was assumed in case of a two-sided $p < 0.05$. Continuous data are presented as mean ± standard deviation or median with interquartile range for continuous variables, depending on distribution of data. Categorical data are presented as the total with percentages (n [%]). Graphs were created, and statistical analyses were performed using R: A Language and Environment for Statistical Computing, version 3.5.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

All responses (n = 91) were collected in an electronic database and thoroughly checked for duplicates, incomplete responses, and missing data. Three of the entries were duplicates, and 13 responses were incomplete (less than 50% of the questions answered and could not be completed after follow-up email) and were therefore excluded from the dataset. A group of 75 responses were finally included and formed the basis for the analysis.

The 75 unique responses came from 21 countries, of which 17 were European and 4 came from outside of Europe (shown in Fig. 1). Respondents were employed in 51 different transplant centers. Fifty-six (75%) respondents had over 10 years' clinical experience, 48 (64%) were surgeons, and 22 (29.3%) nephrologists. Others included urologists (n = 3, 4%), 1 transplant coordinator (1.3%), and 1 pediatric nephrologist (1.3%). Availability of a written antithrombotic management protocol was reported by 56 (75%) respondents. In 8 (16%) centers, respondents contradicted each other regarding the availability of a protocol. Perioperative thromboprophylaxis is preferred by 51 (78%) of respondents independent of the availability of a protocol (Table 1).

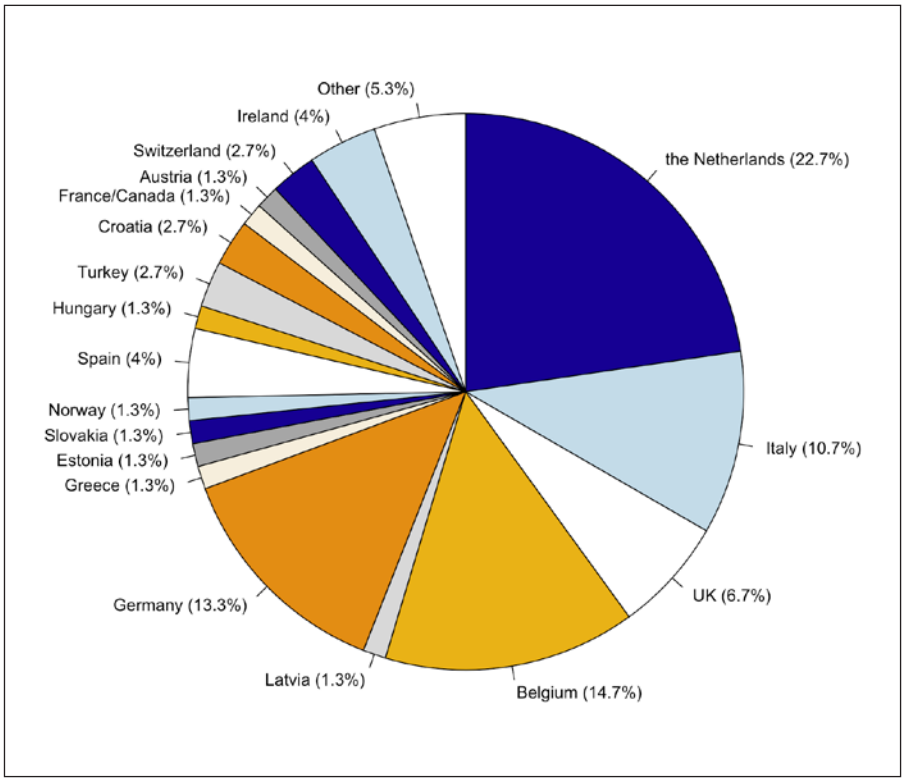

Fig. 1. Pie chart of the distribution of respondents among countries.

Preoperative Discontinuation of Thromboprophylactic Agents

Vitamin K antagonists (69%), direct oral anticoagulants (79%), and at least 1 agent of dual antiplatelet therapy (81%) were most often discontinued prior to KTx. P2Y12 inhibitors such as clopidogrel or ticagrelor were stopped by 48% and 59%, respectively, and UFH by 45%. Dipyridamole (28%) and LMWH (30%) were discontinued by 1/3 of respondents. A minority considered it necessary to discontinue acetylsalicylic acid (11%) or carbasalate calcium (Ascal®, 15%). The main reason to discontinue thromboprophylactic agents preoperatively was the estimated risk of bleeding (92%). Other reasons reported were the risk of sensitization; subsequent donor-specific antibody development, when a blood transfusion would be required ($n = 1$); unclear indication for an antithrombotic agent ($n = 1$); the possible need for a post-transplant biopsy ($n = 1$); or missing indication ($n = 1$).

Administration of Thromboprophylactic Agents

Preoperatively, 31% start at least 1 thromboprophylactic agent, and 8% do so in selected cases. Intraoperatively, 24% routinely give thromboprophylaxis, and 33% prescribe thromboprophylaxis only in selected cases. Postoperatively, 80% give some form of thromboprophylaxis, and 9.3% only use thromboprophylaxis in selected cases (shown in Fig. 2). Preoperatively, 18% start with a LMWH and 12% with UFH infusion. Intraoperatively, 34% administer intravenous UFH in selected cases and 19% in all cases (Table 1). Doses varied between 400 and 10,000 international units, with a median of 5,000 (2,150) IU. Five of 36 (14%) varied the dose according to bodyweight, and 7/36 (19%) gave 5,000 IU (corrected for multiple responses from the same center). As it is more common to use UFH during vascular surgery, an analysis was performed to detect potential differences between medical specialists. Vascular surgeons ($n = 4/9$, 44%) did not administer intraoperative heparin more frequently than other specialists ($n = 33/66$, 50%) or general/transplant surgeons (23/39, 59%) or nonsurgical specialists in particular (10/23, 43%). Postoperatively, 51% prescribe subcutaneous LMWH, 21% aspirin, and 19% intravenous UFH.

Reasons to Prescribe New or Additional Antithrombotic Prophylaxis

History of VTE (74%), vascular reconstruction (64%), or atherosclerosis of the recipient (60%) was the most common reason to prescribe new or additional thromboprophylaxis (Table 2). In response to the question wheth-

Table 1. Preferences of respondents

	No, %	Yes, %	Sometimes, %
Prefers to use thromboprophylaxis	22	78	NA
Protocol present in the transplant center	25	75	NA
Preoperative stop of			
VKA	26	69	5
Clopidogrel	37	48	15
Ticagrelor	29	59	13
Aspirin	79	11	11
Ascal	75	15	10
Dipyridamole	55	28	17
Heparin	40	45	15
LMWH	57	30	14
One agent of DAPT	11	81	8
Both DAPT	80	13	7
DOAC	13	79	8
Reason to stop antithrombotic prophylaxis preoperatively	92 bleeding	0 protocol	8 other
Preoperative administration of			
Heparin	79	12	9
APT	86	7	7
LMWH	77	18	5
Intraoperative administration of			
Heparin IV	47	19	34
Heparin SC	93	4	3
LMWH	92	5	3
Postoperative administration of			
Heparin IV	56	19	25
Heparin SC	82	8	10
LMWH IV	93	6	1
LMWH SC	32	51	17
VKA	86	6	8
APT	76	8	15
Aspirin	51	21	27

VKA, vitamin K antagonist; LMWH, low-molecular-weight heparin; DAPT, dual antiplatelet therapy; DOAC, direct oral anticoagulants; APT, antiplatelet therapy; IV, intravenous; SC, subcutaneous.

er recipient status (preemptively transplanted or dialysis-dependent) influences decision-making to prescribe new or additional thromboprophylaxis, significantly more surgeons than nephrologists considered this important (17.4% vs. 0%, $p = 0.049$). There were no further differences in considerations regarding thromboprophylaxis between these 2 groups of specialists.

Discussion/Conclusion

Perioperative antithrombotic management in KTx against RGT is an ever-changing and frequently debated topic. The results of this survey show that the presence of a written protocol on perioperative antithrombotic management in KTx is neither universally present nor always acknowledged as in 8 centers, respondents contradicted each other. Nevertheless, the majority of KTx professionals prefer to use some form of perioperative thromboprophylaxis, even though evidence-based recommendations are lacking. UFH appears to be the most favored thromboprophylactic agent for intraoperative use, possibly due to its beneficial pharmacokinetic characteristics, such as a low half-life and the fact that it is not eliminated by the kidney [11, 12]. Dosing however varied considerably between 400 and 10,000 IU. Postoperatively, LMWH s.c. is the treatment of choice for the majority of respondents, which is in line with the American Society for Hematol-

Table 2. Reasons to optimize antithrombotic prophylaxis

	No, %	Yes, %
Age of the recipient	74	26
Age of the donor	91	9
ABO-incompatible KTx	89	11
Arteriosclerosis recipient	40	60
Arteriosclerosis of the graft	64	36
APPT and PTT	89	11
BMI of the recipient	74	26
BMI of the donor	99	1
Dialysis modality: hemodialysis or peritoneal dialysis	90	10
Gender of the donor	100	0
Gender of the recipient	99	1
Gut feeling	93	7
Habit of practice	91	9
Hemoglobin	93	7
History of VTE	26	74
INR of the recipient	99	1
Need for vascular reconstruction	37	63
Number of platelets	86	14
Preemptive KTx or dialysis-dependent	89	11
SLE	74	26
Vascular anatomy of the donor	63	37
I do not know	100	0
Other*	89	11

PTT, prothrombin time; BMI, body mass index; INR, international normalized ratio; SLE, systemic lupus erythematosus. * Other includes underlying conditions such as a mechanic heart valve, known coagulation disorders, increased cardiovascular risk, or diabetes.

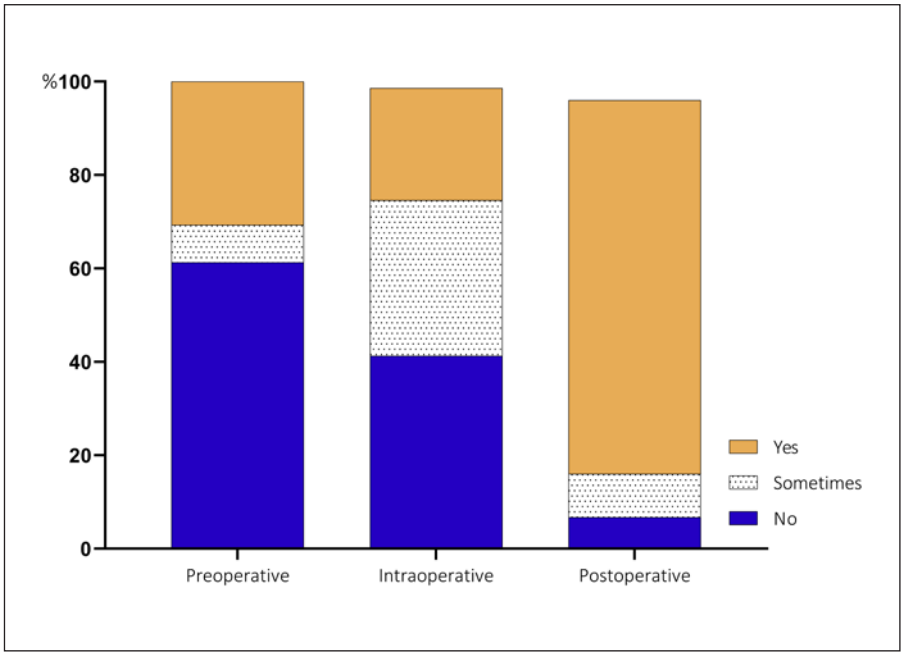

Fig. 2. Administration of new or additional thromboprophylaxis in the perioperative kidney transplant period. Data given in percentages.

ogy (ASH) 2019 guideline recommendations for prevention of VTE in hospitalized patients after major general surgery [6] and is possibly not specifically directed against prevention of RGT. It appears that some form of patient-tailored thromboprophylaxis against RGT might already be applied by a fair share of respondents as the answer "sometimes" was given quite often, which, together with the reasons mentioned to add new or additional thromboprophylaxis, might indicate that patient characteristics influence decision-making. Need for vascular reconstruction, a history of VTE, or atherosclerosis of the recipient were the most frequently given reasons to prescribe new or additional antithrombotic prophylaxis in specific patients. A history of VTE or atherosclerosis of the recipient is a known risk factor for RGT. Vascular reconstruction has to date not been identified as a risk factor, but contradictory results have been reported regarding the increased risk for thrombosis in grafts with multiple renal arteries [4, 13, 14]. Furthermore, it could be considered a technical difficulty, which has been identified as an independent risk factor [4].

One of the more striking results of our survey is that more surgeons consider the preemptive or dialysis-dependent state of recipients as a reason to adjust the antithrombotic therapy accordingly compared to nephrologists (17.4% vs. 0%), although we are not able to differentiate at which end the additional thromboprophylaxis is applied. Furthermore, even though we did not perform a formal analysis due to low numbers, we observed that general/transplant surgeons tend to administer intraoperative heparin more often compared to vascular surgeons (58% vs. 44%), which is surprising, given the routine use of UFH in arterial vascular surgical procedures [5]. Both observations could have been biased by the center, when the protocol involves intraoperative UFH administration to preemptive recipients. However, there is also a possibility that among specialists, certain ideas and dogmas prevail over evidence-based medicine, an assumption that gains strength when the necessary evidence is limited. Only a few prospective studies on interventions to prevent RGT are available, as confirmed by a recent systematic review [15], and these provide little evidence. Furthermore, the scarce number of retrospective studies also draws conflicting conclusions [3, 9, 11, 16]. This survey further illustrates the high variation in antithrombotic management strategies in adult KTx, as a result of the paucity of high-quality studies. A similar problem has been observed in pediatric KTx [12].

Most respondents seem to adhere to the ASH 2019 guideline to prevent VTE from postoperative immobilization, considering KTx as major general surgery. In this guideline, major surgery is defined as "any surgical intervention that carries greater than minimal risk, is performed in the operating room, and requires specialized training." According to this definition, KTx certainly qualifies as major surgery, with moderate/high risk for developing postoperative VTE according to the Caprini score [17] or Rogers score [18], due to venous reconstruction and the duration of surgery (generally over 45 min). Risk factors for VTE and RGT do not completely coincide, but there is reason to believe that both VTE and RGT have a common pathophysiology. However, there is an important nuance that distinguishes kidney recipients from general surgery patients. Physiologically, the hemostatic system consists of an equilibrium between endogenous pro- and anticoagulatory processes. In kidney transplant recipients, ESRD and renal replacement therapy have a profound influence on hemostasis, which unsettles this equilibrium, resulting in a paradoxical situation with bleeding tendencies and an increased risk of thrombosis. In uremic patients, among other changes such as in platelet-vessel wall interactions, platelet alpha-granules are disturbed, resulting in thrombocytopathy and subsequently in impaired primary hemostasis. Additionally, hemodialysis can contribute to bleeding due to continuous contact of platelets with the dialysis membrane and due to the added heparin in the dialysis circuit. However, by clearing uremic toxins from the system, hemodialysis also has the potential to mitigate platelet abnormalities. Paradoxically, increased levels of circulating fibrinogen and impaired fibrinolysis, together with endothelial cell damage in ESRD, which causes the endothelium to lose its antithrombotic properties, result in increased risk of thrombosis [19]. These complex changes to the hemostatic state of ESRD patients complicate protocolizing antithrombotic management in KTx. This is illustrated by the fact that KTx is not specifically addressed in thrombosis prevention guidelines, although several risk factors for RGT have been identified [4, 13]. The European Renal Best Practice guideline, which dates back to 2014, makes a moderate evidence recommendation to not use LMWHs, UFH, or aspirin prior to transplantation to prevent RGT. The recommendation is based on studies not powered ($n < 200$) for the incidence of RGT, which occurs in about 1 of 100 kidney transplant recipients [3]. It underlines the difficulty of drawing up guidelines with the limited literature and evidence. Until further evidence is presented, preferably in a large ran-

domized controlled trial, as was also suggested by the ERBP, performing a consensus study following a (modified) Delphi approach [20–22], which enhances collective decision-making, could be a first step to tackling this problem. With a round table of experts in the field of KTx, an integral consensus on the use of perioperative antithrombotic therapy against RGT could be developed, even though proper meta-analyses cannot be performed yet.

Some limitations to this survey ought to be discussed. We report on responses on the use of thromboprophylaxis against RGT from 51 transplant centers and 21 countries. It was challenging to adequately reach the practitioners in charge of the antithrombotic strategy in the kidney transplant community. This is further exemplified by the fact that Spain, which has had the highest number of organ donors in the world for years [23], is fairly underrepresented in this study with just 3 respondents, representing only 5% of kidney transplant centers. This could also have caused an underrepresentation of urologists, which by our knowledge perform most of the KTxs in, e.g., Spain, Portugal, and France. Furthermore, there were multiple responses from the same hospital. Since the survey focuses mostly on personal opinions, whether or not in accordance with existing evidence and since responses were from different specialisms and not always consistent, the responses were, if not stated otherwise, analyzed separately. Furthermore, there was a large variance in coverage of kidney transplant centers per country. For example, we received at least 1 response from all Dutch kidney transplant centers (100%) and from 6 of 7 Belgian centers (86%), but only 13% of Italian centers were covered (online suppl. Table 1) [24, 25]. In our opinion, these limitations did not compromise our results as the high variance between practices became already apparent in the current study and confirms our suspicion and the need to establish uniform protocols. Finally, the list of reasons to apply antithrombotic prophylaxis prior to transplantation could have been more extensive as diabetes mellitus, which is a known risk factor for RGT, was mentioned by some respondents but was not given as an option in the survey, as well as increased cardiovascular risk and known coagulation disorders. These factors should be kept in mind when determining a patient's risk of developing RGT.

Despite the overall preference for thromboprophylaxis in KTx, there is a high variation within Europe regarding type, timing, and dose of thromboprophylaxis, most likely due to a paucity of high-quality studies. Future research should focus on the safety, interactions, and contraindications of available thromboprophylactic agents in KTx, in order to develop better guidelines for the prevention of RGT, specifically applied to the coagulation potential or deficiency, in this patient cohort. Guidelines will unlikely be based on "one-size-fits-all" principles but would rather steer toward a patient-tailored management plan based on agreed principles.

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Statement of Ethics

Data were processed and stored according to the principles of the Declaration of Helsinki, and research activities followed the principles of the Declaration of Istanbul. Participation in this survey was voluntary and anonymous, and communication with respondents was restricted to those who gave consent to contact them in case of missing data. The study was conducted according to the rules and regulations of the medical Ethical Committee of the UMCG and the Dutch law. Because this did not concern a study with patients, no formal approval was required.

Conflict of Interest Statement

The authors of this manuscript have no conflicts of interest to declare.

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Author Contributions

T.A.J.B., T.L., F.J.M.F.D., and R.A.P. contributed to conceptualization; T.A.J.B. and R.A.P. contributed to methodology; T.A.J.B., F.J.M.F.D., R.C.M., and R.A.P. contributed to data collection; T.A.J.B. contributed to data analysis and visualization; T.A.J.B., T.L., and R.A.P. contributed to writing – original draft preparation; and T.A.J.B., T.L., F.J.M.F.D., C.M., S.J.L.B., and R.A.P. contributed to writing – review and editing.

Data Availability Statement

The data presented in this study are available on request from the corresponding author. The data are not publicly available for privacy reasons.

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