Prophylactic antithrombotic management in adult and pediatric kidney transplantation: A systematic review and meta-analysis

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Abstract

Background: RGT is a major cause for early graft loss after KTx. Although evidence-based recommendations are lacking, aP is often used to prevent RGT. This systematic review aimed to determine the effectiveness and safety of aP in adult and pediatric KTx recipients.

Methods: MEDLINE, EMBASE, Cochrane Controlled Trials Register, conference proceedings, and electronic databases for trial registries were searched for eligible studies using search terms relevant to this review (April 21, 2020). The systematic review was carried out following the recommendations of the Cochrane Collaboration and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement.

Results: Twelve studies comprising 2370 patients (adult = 1415, pediatric = 955) were included, of which three were RCTs. The overall risk for developing RGT was lower in the group with aP compared with the control group (RR 0.24, 95% confidence interval 0.12–0.49). The antithrombotic drugs used were heparin (7/12), acetylsalicylic acid (2/12), a combination of both (2/12), and dipyridamole (1/12) with a high variability in timing, dosing, and mode of application. Adverse effects were reported rarely, with minor bleeding as the main complication. The non-randomized studies had significant risks of bias in the domains of patient selection, confounder, and measurement of outcomes.

Conclusion: Based on pooled analysis, aP seems to reduce the risk of RGT in KTx. However, the reliability of these results is limited, as the quality of the available studies is poor and information on adverse effects associated with aP is scarce. Additional high-quality research is urgently needed to provide sufficient data supporting the use of aP in KTx.

Keywords
antithrombotic prophylaxis, kidney transplantation, renal graft thrombosis, systematic review, thrombosis

Abbreviations: aP, antithrombotic prophylaxis; aPTT, activated partial thromboplastin time; ASS, acetylsalicylic acid; KTx, kidney transplantation; LMWH, low-molecular-weight heparin; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT, randomized controlled trial; RGT, renal graft thrombosis; ROB, risk of bias; RR, risk ratio; UFH, unfractionated heparin.

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1 | INTRODUCTION

Kidney transplant recipients are at risk for developing RGT. RGT is characterized by thrombus formation in either the renal artery or vein of the renal allograft and predominantly occurs within the first days after KTx. With a reported incidence of 0% to 6.1% in adults, and 0% to 13.0% in pediatric patients, RGT accounts for up to 10.0% of early graft failure.

In order to minimize the risk of renal graft loss due to thrombosis, aP is widely used in KTx. Current management strategies favor antplatelet and anticoagulant drugs. The clinical impact of aP for KTx recipients is still a matter of debate, primarily due to the paucity of available studies with partially conflicting results.9-11

In the absence of evidence-based recommendations and consensus guidelines, current antithrombotic strategies are often characterized by incongruent, non-standardized, and center-specific protocols for aP.12,13

Therefore, this systematic review and meta-analysis were performed to collate, summarize, and quantify the available evidence on beneficial and adverse effects of aP in adult and pediatric KTx recipients.

2 | MATERIAL AND METHODS

2.1 | Protocol

This systematic review was developed using guidance from the PRISMA statement and recommendations of the Cochrane Collaboration. The protocol was registered in the International Prospective Register of Systematic Reviews (http://www.crd.york.ac.uk/PROSPERO).

2.2 | Data sources

The electronic databases CENTRAL (Cochrane Central Register of Controlled Trials, Issue 4, 2020), MEDLINE, and EMBASE (from their inception to April 21, 2020) were searched without language restriction (search strategy in Table S1). Additionally, clinical trial registries (for ongoing or recently completed trials), available conference proceedings (Table S2), and reference lists of included studies and potentially relevant other articles were searched using predefined keywords.

2.3 | Eligibility criteria

All types of studies were included if they compared thromboprophylaxis with either placebo, no aP, or with different antithrombotic agents. Exclusion criteria were as follows: combined organ transplantation, ABO-incompatible KTxs, aP for other reasons than KTxs, and case reports with ≤3 participants.

2.4 | Outcomes

The primary outcome of interest was the event of RGT confirmed by ultrasound, angiography or any other equivalent imaging method, or by renal histology and graft loss, respectively.

Secondary outcomes were (1) thrombosis other than RGT, (2) thromboembolism, (3) adverse outcomes related to aP (bleeding, hematuria, surgical re-intervention, blood transfusions, heparin-induced thrombocytopenia, allergic reaction, peptic ulcer, and others), (4) serious adverse events (prolonged length of hospital stay, persistent or significant disability, life-threatening events, death), (5) graft function (based on estimated glomerular renal function/blood creatinine concentration), and (6) patient survival.

Subgroup and sensitivity analyses were planned to be performed as prespecified.

2.5 | Study identification and selection

The literature search was conducted by pairs of reviewers (SB, MW). Conflicts were resolved by a third reviewer (MZ). In case of studies reporting results in more than one publication, the most recent and comprehensive article was selected. If studies included data on patients in whom eligibility criteria for the review were unclear or additional information was needed, study authors were contacted to obtain required data. The full texts of identified studies were analyzed by three authors (SB, MZ, MW). Studies ineligible for inclusion in the review were excluded with reasons.

2.6 | Data extraction

Two authors (SB, MZ) carried out data extraction by using a standard data extraction form including baseline characteristics and outcomes. Any disagreements were resolved by consensus or, if necessary, by a third party (MW). Further information required from the original authors was requested by written correspondence.

2.7 | Quality assessment

The Cochrane risk of bias (RoB) tool (RoB 2 for randomized controlled trials [RCT] and ROBINS-I for non-randomized studies) was used to appraise included studies, which was done by three independent reviewers (SB, KB, MW).

2.8 | Data synthesis and analysis

The RR was calculated from the number of events in each group using a Random effects model and the Mantel-Haenszel method. Heterogeneity was investigated using forest plots and the I² statistic. Sensitivity analyses were carried out to assess the statistical
effect of a trial design. The investigation of publication bias was estimated by funnel plots.\textsuperscript{23,24} All data were transferred into R 3.6.3., and statistical analysis was performed using the additional package meta 4.12-0.\textsuperscript{25}

3  |  RESULTS

3.1  |  Search results

The selection process for the studies included in the systematic review and meta-analysis is presented in Figure 1. After removing 1829 duplicates, the search strategy yielded 6361 records. From these identified studies, 113 full-text articles were retrieved for full-text review after title and abstract screening. 101 studies were excluded with reason (Table S3) leaving 12 studies (six pediatric and six adult studies) fulfilling the criteria for inclusion in the systematic review and meta-analysis.\textsuperscript{8-11,26-33} No additional studies were found in available clinical trial registries, conference proceedings, and reference lists. Additional data were retrieved by personal communication.

3.2  |  Study and participant characteristics

Details of the 12 included studies (RCTs [3/12], retrospective [6/12], and prospective cohort studies [2/12], one study with unclear recruitment) with a total of 2370 patients (male: 64.0%, where reported) are displayed in Table 1 (further details are presented in Table S4). The pediatric studies (n = 6) included 955 patients and the adult studies (n = 6) 1415 patients. The RCTs (adult patients only) used either heparin (2/3) or dipyridamole (1/3). In two studies, pretransplant screening for thrombophilia was reported. Ten studies reported to follow a center-specific transplant protocol. Three studies excluded patients with increased risk for thrombosis (young age, intraoperative complications, graft with multiple vessels, among others) or history of thrombosis. Trials were predominantly conducted at tertiary hospitals in the UK, USA, and Europe between 1989 and 2019. Statistical power analysis was lacking in all but two studies. Insufficiently reported data of the individual studies resulted in changing denominators of the study findings.

3.3  |  Characteristics of antithrombotic management strategies

3.3.1  |  Anticoagulants and antiplatelets

Heparin was the preferred drug for aP (9/12) including low-molecular-weight heparin (LMWH; 3/12) and unfractionated heparin (UFH; 3/12), followed by acetylsalicylic acid (ASS; 4/12) and dipyridamole (1/12).
| Study Design     | Study Cohort | Participants | Female % | Type and Mode of aP | Timing of aP | Screening for Thrombophilia |
|------------------|--------------|--------------|----------|---------------------|--------------|----------------------------|
| Al Midani, 2019  | Pediatric    | 328          | 37       | ASS, oral           | Intraoperative | Yes (subgroup starting 2000) |
| Bakkaloglu, 2012 | Adult        | 50           | Not reported | Heparin (LMWH), mode not specified | Preoperative | Not reported |
| Broyer, 1991     | Pediatric    | 140          | Not reported | Heparin (LMWH), subcutaneous | Preoperative | Not reported |
| Dubow, 2016      | Pediatric    | 90           | Not reported | Heparin, mode not specified | Postoperative | Yes |
| Esfandiar, 2012  | Pediatric    | 87           | 40       | Dual therapy (heparin + ASS), mode not specified | Postoperative | Not reported |
| Kim, 2019        | Pediatric    | 56           | 38       | Heparin (UFH), intravenous | Intraoperative or postoperative | Not reported |
| Murphy, 2001     | Adult        | 226          | Not reported | Dual therapy (heparin, subcutaneous + ASS, oral) | Preoperative | Not reported |
| Nagra, 2004      | Pediatric    | 254          | 33       | Heparin (UFH), subcutaneous | Intraoperative | Not reported |
| Osman, 2007      | Adult        | 75           | 31       | Group A: heparin (LMWH), subcutaneous, Group B: heparin (UFH), subcutaneous | Postoperative | Not reported |
| Robertson, 2000  | Adult        | 955          | Data not separable | ASS, mode not specified | Preoperative | Not reported |
| Schulze, 1990    | Adult        | 40           | Not reported | Dipyridamole, initially: intravenous, after day 4: oral | Intraoperative | Not reported |
| Ubhi, 1989       | Adult        | 69           | Not reported | Heparin, subcutaneous | Not specified | Not reported |
3.3.2 | aP strategies

Four different aP strategies were identified in the included studies: (1) single use of heparin (UFH or LMWH; 7/12); (2) single use of ASS (2/12); (3) single use of dipyridamole (1/12); (4) combined use of heparin and ASS (2/12). The mode of application differed between the trials and was reported by nine studies: heparin subcutaneously (5/12), heparin intravenously (1/12), oral ASS (2/12), dipyridamole intravenously, and per os (1/12).

3.3.3 | Dosing and therapeutic drug monitoring

The dosing of heparin was varying independent of the mode of application. ASS was administered at a dose between 75 and 150 mg once daily for adult studies and 1 mg/kg bodyweight for pediatric studies. Drug monitoring of aP was done for heparin in four out of 12 studies with three studies measuring activated partial thromboplastin (studies using UFH) time and one study measuring anti-factor Xa levels (study using LMWH).

3.3.4 | Timing of aP

aP was started either preoperatively (4/12), intraoperatively (3/12) or postoperatively (3/12; within 24 h after KTx). In one study, patients were either receiving aP intraoperatively or immediately postoperatively, and one study was not reporting precise timing of aP. The overall application period for aP ranged from 7 days to 3 months (median 8 days), and in terms of the individual drugs: heparin: 5 to 21 days (median 7 days), ASS: 1 to 3 months (median 1 month). No information was available for dipyridamole.
### 3.4 | Main outcome

The overall RR for developing RGT was 0.24 (95% confidence interval [CI] 0.12–0.49) in the group with aP compared to the control group, with a low to moderate heterogeneity ($I^2 = 36.0\%$, $p = .12$; Figure 2A). Figure 3 shows the stratification for the main outcome RGT to pediatric (RR 0.19 [95% CI 0.07–0.54], $n = 995$) and adult patients (RR 0.31 [95% CI 0.08–1.16], $n = 1415$).

In total, 102 of 2370 patients (4.3%) indicated a RGT (intervention group: 21/1254 [1.7%] and control group: 81/1116 [7.3%]). The incidence of RGT was 6.2% in the pediatric population (intervention group: 13/542 [2.4%] and control group: 46/413 [11.1%]) compared with 3.0% in the adult population (intervention group: 8/712 [1.1%] and control group: 35/703 [5.0%]). The RGT was diagnosed within the first 2 weeks after KTx (range 2–16 days). All patients with RGT subsequently lost the graft. Differentiation between arterial and venous thrombosis was not possible due to lack of information.

### 3.5 | Secondary outcomes

The following prespecified secondary outcomes were reported by the included studies: Bleeding complications (10/12), requirement of red cell blood transfusions (7/12), requirement of surgical re-exploration due to bleeding (8/12), thrombosis other than RGT (6/12), graft function determined by creatinine (3/12), graft survival (4/12), death (3/12), heparin-induced thrombocytopenia (2/12), peptic ulcer (4/12), and hospital stay (1/12). A narrative description of the reported data is presented in Table S5. Comparative analyses of the secondary outcomes were not possible due to insufficient reporting quality, inconsistent definitions of the outcome criteria between the individual studies and lack of numerical data.

### 3.6 | Subgroup analyses

The following subgroup analyses were carried out: adult studies after exclusion of dipyridamole (RR 0.21 [95% CI 0.09–0.46], $n = 1375$), patients stratified to the prophylactic anticoagulant or antiplatelet agent (single use of heparin (RR 0.25 [95% CI 0.08–0.76], $n = 734$; Figure 2B); single use of ASS (RR 0.17 [95% CI 0.08–0.38], $n = 1283$; Figure 2C); combined drug use of heparin and ASS (RR 0.14 [95% CI 0.02–1.09], $n = 313$), and mode of application (heparin subcutaneously (RR 0.40 [95% CI 0.14–1.13], $n = 538$).

### 3.7 | Sensitivity analyses

Sensitivity analyses were carried out for the following prespecified criteria: studies published after 2003 (RR 0.20 [95% CI 0.06–0.67),

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**Figure 3** Subgroup analysis of aP on RGT incidence in pediatric and adult population. (A) Pediatric studies. (B) Adult studies. Antithrombotic strategy: heparin monotherapy if not indicated otherwise (*ASS monotherapy, #ASS + heparin dual therapy, §dipyridamole monotherapy)
n = 940), studies published in the USA/Canada (RR 0.09 [95% CI 0.01–0.63], n = 146), studies without small sample sizes (RR 0.22 [95% CI 0.10–0.53], n = 1903), studies without low methodological quality (RR 0.24 [95% CI 0.08–0.70], n = 1026), and studies with RCT design (RR 1.08 [95% CI 0.05–22.03], n = 184).

### 3.8 | Heterogeneity and publication bias

A random effects model was used for meta-analysis. There was low to moderate statistical heterogeneity between studies for the main outcome RGT. The major sources of clinical heterogeneity between studies were selection of study participants, insufficient reporting of confounders, and measurement of outcomes. The included studies showed an asymmetric appearance with a prominent gap in the right lower bottom corner, suggesting a publication bias likely (Figure S1).

### 3.9 | Risk of bias

The RoB was assessed for each study and across all studies. The overall RoB of the included RCTs is presented in Figure 4 (further details for individual RCTs and non-RCTs are available in the Figures S2 and S3A,B). For the majority of the individual studies, the domains “confounding,” “selection of participants,” or “measurement of outcomes” were classified of being at serious or critical risk, resulting in an overall high risk of bias in 10 out of 12 included studies.

### 4 | DISCUSSION

This systematic review and meta-analysis including cohort studies and RCTs quantified the impact on the intervention effect of aP in pediatric and adult KTx. aP with an anticoagulant or antiplatelet drug either alone or in combination was associated with a lower risk of developing RGT in KTx recipients.

Expectedly, heparin was the primary drug of choice which may arise from a combination of the following conditions: The possibility of intravenous application in already existing (central) venous lines, short-term pharmacokinetic effects, and the availability of an antidot leading to the consequently lower attributive risk of non-controllable bleeding complications.26,31,34

ASS was the second most frequent used drug for aP. Albeit the use of ASS in the prevention of RGT seems to be slightly superior to heparin, the fact that only two studies were available for the single drug use of ASS, the deduction from this finding cannot be made.30,35 Thereby, it remains unclear whether antiplatelet drugs offer net advantages over anticoagulant regimens, which resembles the body of evidence in other areas of application.26,37

Two studies used heparin and ASS simultaneously for a short time period without demonstrating beneficial effects in contrast to single drug use.28,30 However, this may be more due to the study design than to inferior effectiveness of these drugs when used in combination. The same applies to the non-superior effects of heparin if it was used subcutaneously.

Not surprisingly, all included studies commenced aP in the peri- or early postoperative phase due to the fact that the majority of RGT occur within the first days following KTx.3 Despite this evidence and that most reported RGT of the included studies were within the time frame of 1 week after KTx, aP was often administered for a much longer period. While heparin was often used for 1–2 weeks following KTx, ASS was not rarely continued for several weeks, which may be traced back to the more convenient oral application of ASS compared with the preferred subcutaneous injection of heparin. However, taking into consideration associated risks and harms of the different anticoagulant and antiplatelet drugs, this management strategy of prolonged use of aP needs to be critically scrutinized.1,2 Furthermore, the prolonged use of aP is questionable, as there are numerous other factors related with both early and late RGT which cannot be modified by anticoagulants and antiplatelets.28

Within this context, it is also a remarkable finding that only few studies utilized drug monitoring with respect to potential subtherapeutic dosing, safety aspects, and risk of prescribing errors.39
Different dosing regimens and variable routes of drug administration hinder the comparability of the outcome measures, particularly for the most often used heparin with hypothetically available drug monitoring.40

Studies reporting on side effects and complications of aP only were not considered to be relevant for the study objective. Although the majority of the trials provided some information about bleeding complications or other adverse effects associated with aP, it was not possible to make a reliable overall statement due to the imprecise reporting of these outcome parameters. However, it is of utmost importance to carry out a critical assessment of the benefit-risk balance for aP as for any other medical intervention, and therefore, further studies need to address this issue for a better-informed decision-making in the daily clinical routine.41,42

From our point of view, preventing RGT represents the main reason for aP in renal transplant patients. For that reason, trials focusing on other types of thrombosis or embolisms were not considered relevant for the study objective. A recently published systematic review assessing the efficacy and safety of aP in renal transplant patients included patients with any type to thromboembolism.43 As a consequence of the different eligibility criteria, included studies for the outcome RGT were partially different to our systematic review: however, the authors also assumed that aP may reduce the rate of RGT but were unable to draw final conclusions on the benefits and harms of aP in KTx due to the heterogeneity of currently existing data.43

The risk for developing RGT is assumed to be higher in children than in the adult population. The RGT incidence as well as the more frequent occurrence of RGT in children in the included study populations were comparable to previously published data. Several modifiable and non-modifiable factors such as surgical challenges due to small donor and recipients may play a pivotal role.44-46 This consideration might support the observation that the suggested benefit of aP in KTx recipients could not be demonstrated anymore when children were excluded. Contrariwise, if the single study using dipyridamole was not considered for inclusion, aP still seems to be superior compared to the control group which counteracts the hypothesis of superior effectiveness in pediatric patients only.

Of note, after excluding studies with a non-randomized controlled design, the intervention and control group showed no differences. However, this observation might be rather due to the poor quality of the RCTs with moderate to high risk of bias than a true estimated effect of the intervention. All other sensitivity analyses did not affect the overall results.

Interestingly, although the study population showed a highly clinical heterogeneity without addressing adequately potential confounders, the statistical heterogeneity of the included studies was only low to moderate. The overall risk of bias, however, was mostly classified as "high" in both, cohort studies and randomized controlled trials, predominantly due to selection of participants, measurement of outcomes, and confounding. Furthermore, the funnel plot shows an asymmetric appearance with a gap in the right bottom corner, which suggests the presence of unpublished studies without intervention effects of aP.47 This finding is even more important as realistic estimates of the effect of aP in KTx recipients derived from the included studies seem to be very difficult. Therefore, the true effect of intervention may be substantially different. The critical judgment of the quality of the studies may not be only traced back to the fact that many studies were initiated before the Consolidated Standards of Reporting Trials (CONSORT) conditions (http://www.consort-statement.org/).

Taking into account all these critical issues, the generalizability of the findings of this systematic review and the applicability in the daily clinical routine may not be thoroughly advocated. Notwithstanding, this systematic review and meta-analysis provide not only a critical appraisal of the current available evidence but also reveal critical issues in the current widespread practice of aP in KTx recipients. For that reason, it may serve as a precursor for the implementation of high-quality clinical trials to overcome the limitations of previous studies.

Given the numerous confounding factors associated with renal transplantation, well-designed randomized controlled trials would provide the most reliable clinical evidence. However, there are some limitations that should be considered, such as small sample sizes reducing the power of the analyses, difficulties in detecting serious rare adverse effects, and the increasingly high costs and time constraints.48 Most of all, it seems probably difficult to find a consensus on an aP protocol among potential participating KTx centers. The first important step toward resolving ongoing controversies about the efficacy and safety of aP could be an agreement for a harmonized and common aP protocol among KTx centers with comparable aP strategies in the past. Based on this consensus protocol, it would at least be possible to establish larger prospective clinical trials taking into account the following criteria: Predefined risk-adjusted selection of the patients with a matched control group (e.g., risk of thrombophilia, age, gender, underlying renal disease, immunosuppressive regimen, renal transplant size-mismatch among others), precise definition of the aP management protocol (including timing, drug choice, dosage, mode of application, drug monitoring), comprehensive reporting about associated harms and risks. In addition, the primary outcome RGT needs to be assessed objectively ensured by an adequate imaging method or histological diagnosis.

5 | CONCLUSION

The findings from this systematic review and meta-analysis might suggest that aP could reduce the risk of RGT in KTx recipients. However, based on the poor quality of the data and the incongruent management protocols for aP, recommendation cannot be made in favor or against the use of aP in adult and pediatric KTx. Notwithstanding, the presented data clearly demonstrate the urgent need of future high-quality clinical trials and a common built consensus between KTx centers for an aP intervention protocol.
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AUTHORS’ CONTRIBUTIONS
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DATA AVAILABILITY STATEMENT
All data relevant to the study are included in the article or uploaded as supplementary information.

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**SUPPORTING INFORMATION**

Additional supporting information may be found online in the Supporting Information section.

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