TITLE

Efficacy and safety of chemical thromboprophylaxis in renal transplantation – A systematic review

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ABSTRACT

Introduction

The benefit of administering chemical thromboprophylaxis to chronic kidney disease patients undergoing renal transplantation is unclear and no previous systematic review has addressed this as reflected by variations in national guidelines.

Methods

A literature search was performed using MEDLINE, Embase, Cochrane, CINAHL, World Health Organisation (WHO) International Clinical Trials Registry Platform and ClinicalTrials.gov databases to December 2019. Studies included participants undergoing renal transplantation only with no contra-indication to thromboprophylaxis, no history/clinical suspicion of acute organ rejection and those describing a form of chemical thromboprophylaxis intervention compared with another form, no intervention or placebo.

Results

Thirteen studies with 1600 patients were included. There was wide variation concerning type of thromboprophylaxis, time of onset, dosing and duration. Reports of symptomatic/asymptomatic venous thromboembolism and mortality were limited. Seven studies reported on renal allograft thrombosis. When comparing thromboprophylaxis to no intervention, there was no evidence of difference for thrombosis risk (risk ratio 0.2; [95% CI 0.01 – 4.63]), however all studies were underpowered to answer this question. Six studies reported on major bleeding but type of intervention, timing of onset and duration of thromboprophylaxis varied significantly, making it difficult to pool data for further analysis.

Conclusion

There is insufficient evidence to advise on efficacy and safety of chemical thromboprophylaxis in patients undergoing renal transplantation or to determine whether one chemical thromboprophylaxis is better than another thromboprophylaxis.

KEYWORDS

Thromboprophylaxis, renal transplant, thrombosis, end stage renal disease, low molecular weight heparin

INTRODUCTION

Renal transplantation is a gold standard treatment for stage 5 chronic kidney disease (CKD) - defined as reduction of glomerular filtration rate (GFR) to 15ml/min/1.73 m^2 or below, or patients receiving renal replacement therapy (i.e. haemodialysis or peritoneal dialysis). Data from different national registries show an increase in the number of transplant operations over the last decade (1-5).

CKD results in altered haemostasis (increased risks of both venous/arterial thrombosis) and bleeding (6-8). The increased risk of thrombosis, in particular venous thromboembolism (VTE) is thought to be due to an increase in both procoagulant factors as part of the chronic inflammatory process and anti-fibrinolytic proteins that inhibit clot breakdown (8-10). The increased risk of bleeding is due to several factors such as platelet dysfunction induced by uraemia, anaemia, thrombocytopenia and use of anti-platelet/anticoagulant agents during haemodialysis (8, 9, 11, 12).

VTE, comprising deep vein thrombosis (DVT) and pulmonary embolism (PE), is associated with significant short and long-term morbidity and mortality(13). For patients who undergo renal transplantation, the risk of VTE increases further due to surgery, patient-related risk factors (increasing age, obesity, immobility, thrombophilia, previous VTE etc.) and post-operative related risk factors, such as use of immunosuppressive medication (14). Further, these patients are also at risk of developing renal allograft vascular thrombosis (renal artery or renal vein) which is a major early complication post renal transplantation that often results in graft loss (7, 15, 16), causes of which are often attributed to surgical factors from damage to the renal vessels, twist on implantation or graft repositioning (17, 18).

As these patients represent a unique and challenging cohort with a predisposition to both thrombosis and haemorrhage chemical thromboprophylaxis (TP) may increase their bleeding risk, whilst its omission may increase their risk of VTE and graft thrombosis. The optimal approach to administering chemical TP during renal transplantation with regards to type and duration of anticoagulant that should be used is unknown (16). National guidelines (Table A1, appendix A) (19) on the use of chemical TP are mainly for general urology patients, with none of the recommendations being specific to renal transplant surgery.

Given the background predisposition to both thrombosis and bleeding in patients with CKD we undertook a systematic review of the literature to evaluate the effectiveness and safety of different pharmacological thromboprophylaxis agents in patients undergoing renal transplant surgery.
The primary objective was to assess the effectiveness and safety of a chemical TP agent (any type) with another form(s) of chemical TP or placebo or no intervention for preventing VTE after renal transplantation up to 3 months post-transplant. Secondary objectives looked at similar outcomes up to 12 months post-transplant. Mechanical TP strategies were not considered.

Types of chemical TP included one or more of the following: low-molecular-weight heparin (LMWH), unfractionated heparin (UFH), direct oral anticoagulant [DOAC], aspirin, fondaparinux and vitamin K antagonists (VKA).

METHODS

This review was prospectively developed, registered (PROSPERO CRD42018103137) and conducted in accordance with published guidelines described in the Cochrane Handbook (20). Reporting was per the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. Ethical approval was not required for this systematic review.

Search strategy and study selection

Databases were searched from inception to 16 December 2019: Pubmed (electronic publications), MEDLINE (Ovid SP), Embase (Ovid SP), Cochrane, CINAHL (Ebsco), World Health Organisation International Clinical Trials Registry Platform (apps.who.int/trialsearch) and ClinicalTrials.gov (clinicaltrials.gov). There was no restriction on language or year of publication. Reference lists of relevant studies were also searched, where appropriate (Search strategy, Appendix B).

All randomised trials controlled clinical trials, non-randomised studies, single and multiple intervention studies were considered. Systematic reviews were used to identify relevant studies. Recipients (any age and gender) who underwent renal transplantation (deceased/live donor) for any medical condition were included. All studies comparing a form of chemical TP (as listed above) to another chemical TP or no intervention or placebo were included.

Two review authors (RK and AZ) independently assessed all studies. To be eligible, studies had to (1) include participants (any age) who were undergoing renal transplantation only and had no contra-indication to TP e.g. a bleeding disorder, (2) did not have a history of acute organ rejection or clinical suspicion of the same, and (3) the study compared a form of chemical TP intervention to another form or no intervention or placebo. Studies were excluded if there was only a historical comparison arm because these studies are at critical risk of bias.

Outcome measures

Primary outcome measures were assessed up to 3 months post-transplant. These included effectiveness measures i.e. symptomatic VTE (deep venous thrombosis [DVT] and pulmonary embolism [PE]), confirmed by radiological examination such as venography, ultrasonography, ventilation-perfusion scan, CT scan or angiography, asymptomatic VTE or renal allograft thrombosis (arterial and venous) diagnosed by radiological examination as described above. Safety outcome measures included major bleeding defined as per International Society on Thrombosis and Haemostasis (ISTH) criteria (i.e. overt bleeding associated with a decrease in haemoglobin of ≥ 20g/L, transfusion of 2 or more units of blood or occurring at a critical site [intracranial, intra-spinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal, gastrointestinal]) (21) and mortality from major bleeding, VTE and all-cause (cardiovascular, other).

Secondary outcome measures were assessed up to 12 months post renal transplant. Clinically relevant non-major bleeding (not meeting criteria for major bleed but still requiring intervention) was also assessed as a secondary outcome.

Data Extraction and Quality Assessment

Data was independently extracted using a standardised form and any disagreements were resolved by either consensus or discussion with a third author (LG). The review authors were not blinded to names of authors, institutions, journals or the study outcomes. Attempts to contact authors (Broyer (22) and Murashima (23)) where data was only available in abstract form was made. No response was received from either author.

For randomized controlled trials (RCTs) risk of bias was assessed using Cochrane's risk of bias assessment tool for included randomised controlled trials (20). Items were classified into 'low risk', 'high risk', or 'unclear risk'. Consensus on the degree of risk of bias was through comparison of the review authors' statements. For non-RCTs, of bias was done using ROBINS-I tool. The quality of evidence was rated as 'low risk' (comparable to a well-performed randomized trial), 'moderate risk' (cannot be considered comparable to a well-performed randomized trial), 'serious risk' (study has some important problems), or 'critical risk' (study too problematic to provide useful evidence on the effects of intervention).

Data synthesis

Where clinical and methodological characteristics of individual studies were sufficiently homogeneous, data were combined. Meta-analysis was not possible due to heterogeneity among trials. Results were presented narratively in tabular form.

RESULTS

Study selection and characteristics

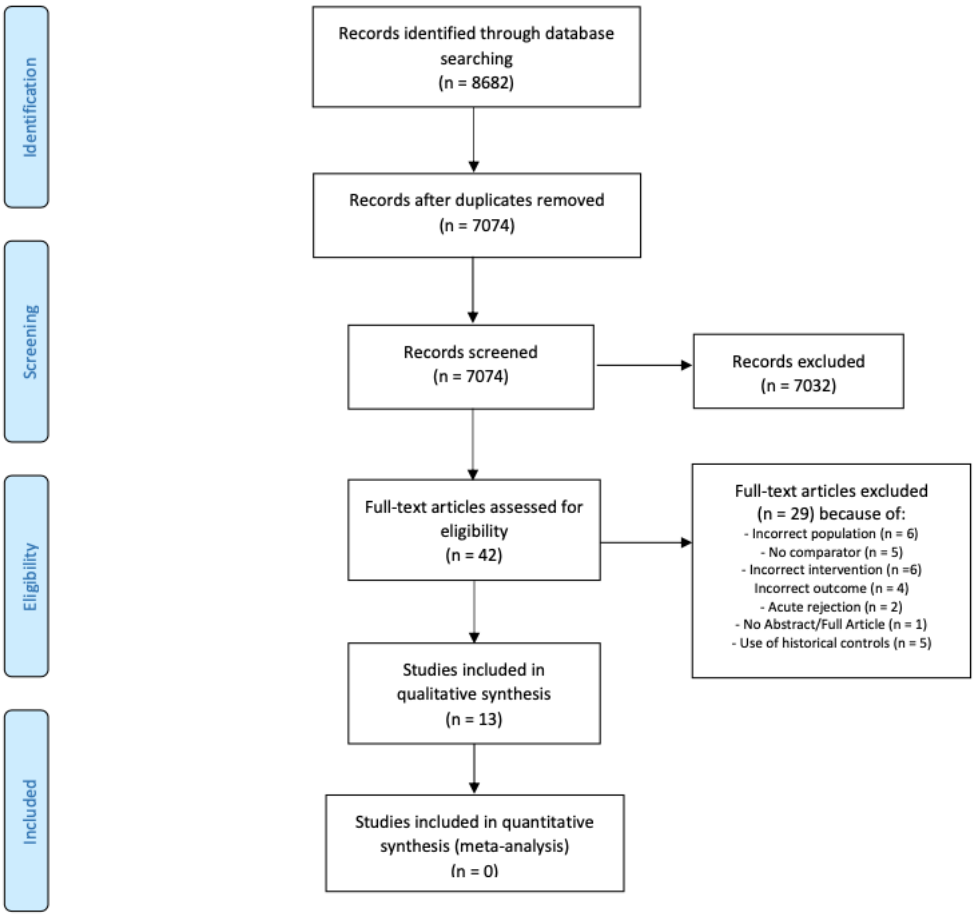
8682 citations were identified through database searching. After duplicate removal and screening by two independent authors 7032 records were excluded based on the abstract. Forty-two full text articles were reviewed and 13 identified as eligible (Figure 1). Of these, five were randomised trials (24-28), 1 was a non-randomised controlled trial (22) and 7 were cohort studies (19, 23, 29-33). There were no ongoing trials. Included studies were published between 1974 and 2016. The total number of patients in the included studies was 1600 (see Table A2, Appendix A).

Three studies (one RCT [n = 75] and two cohort studies [n = 688] patients) compared LMWH with UFH and no intervention (19, 28, 29). Three studies (one controlled trial [n= 115] and two cohort studies [n = 285]) compared LMWH with no intervention (22, 30, 32). Four studies (two randomised trials [n = 105] and two cohort studies [n= 518]) compared UFH with no intervention(25, 27, 31, 33). Two randomised trials (n = 113) compared warfarin with no intervention (24, 26) and 1 cohort study (n=87) compared aspirin with no intervention (31).

The timing of initiation of TP was reported in three randomised trials (24-26) and four non-randomised trials (non-RCTs) (29, 30, 32, 33). The duration of TP treatment ranged from 7-180 days. Patient follow-up varied between studies from 2 weeks to 48 months (in the intervention arm).

A summary of the general characteristics of all included studies is provided in Table 1. Data from two studies (30, 31) were not included in further analysis as follow up of the specific interventions was very different and likely to be misinterpreted.

Figure 1: *PRISMA study flow diagram*



Date of Search: 16-18th January 2019 (Updated 16th December 2019)

PRISMA Statement (34)

***Table 1**: General Characteristics of Included Studies*

Author	Year	Country	Multi-centre	Sample Size	Intervention (Dose)	Comparator (Dose)	Onset of TP	Duration of TP	Follow-up Period
RANDOMISED CONTROLLED TRIALS									
Osman (28)	2007	Egypt	No	75	LMWH (3500iu OD)	UFH (5000iu BD) No Intervention	NS	1 week	2 weeks
Barnes (24)	1974	United Kingdom	Yes (x3)	54	Warfarin (dose adjusted to maintain the prothrombin time between 2 to 3 times normal	No Intervention	Clinician discretion (diuresis/no longer on dialysis)	6 months	6 months
Horvath (25)	1975	Australia/New Zealand	No	36	UFH (2500iu pre-op then continuously q12h)	Placebo	Immediately pre-op	17 days	16 months
Mathew (26)	1974	Australia	No	54	OAC (dose adjusted to maintain the prothrombin time between 2 to 2.5 times normal) + Dipyridamole (25mg QDS, increased in steps to 100mg QDS by end of week 3)	No Intervention	As soon as clinically possible - mean delay 17 days	NS	OAC + Dipyridamole: Mean 33.5 months (no range given) No Intervention: mean 29.6 months (no range given)
Ubhi (27)	1989	United Kingdom	No	69	UFH (5000iu BD)	No Intervention	NS	7 days/fully mobile	30 days
CONTROLLED TRIAL									
Broyer (22) *Abstract Only*	1991	France	No	67	LMWH (dose NS)	No intervention	NS	NS	NS
COHORT STUDIES									

Pawlicki (29)	2011	Poland	No	67	UFH Intra-op (2500iu then 10000-15000iu continuous infusion)	LMWH (dose NS) No Intervention	UFH: intra-op LMWH: NS	UFH: 2 days LMWH: 2-4 days	14 days
Ng (19)	2016	Canada	No	547	Prophylactic heparin (variable doses; 5000iu OD, 5000iu BD, 5000iu q8h)	Treatment heparin (dose NS) No Intervention	NS	Prophylactic heparin: mean 5.6 days Treatment heparin: mean 3.1 days	NS
Bakkaloglu (30)	2012	Turkey	No	50	LMWH (40mg OD)	No Intervention	1 day pre-op	First post-op week	LMWH: mean 11 days (9-26) No intervention: mean 21 days (13-38)
Esfandiar (31)	2012	Iran	No	87	UFH (50u/kg q8h) + ASA (5mg/kg three times/week)	No Intervention	NS	Heparin, 7 days + ASA, 3 months	Heparin + ASA: 24 or 48 months (unclear) No intervention: 170 months
Lundin (32)	2002	Sweden	No	120	LMWH (variable doses and formulations; 20mg OD, 40mg OD, 2500iu OD, 5000iu OD)	No Intervention	Peri-op	Mean 10.4 days (10-47)	47 days
Kusyk (33)	2005	Australia	No	326	UFH (500-1000iu/hour)	No Intervention	Median 8 days (1-14)	NS	2 weeks
Murashima (23) *Abstract Only*	2010	USA	No	48	Heparin + warfarin	Heparin + Aspirin Heparin No intervention	NS	NS	NS

TP, thromboprophylaxis; UFH, unfractionated heparin; LMWH, low molecular weight heparin; ASA, aspirin; NS, not stated; OAC, oral anticoagulant; q8h, every 8 hours; q12h, every 12 hours; OD, once a day; QDS, four times a day; BD, twice a day

Quality Assessment

RCTs

All RCTs were assessed to be at high risk of bias (Figure 2). Risk of bias assessment, addressing renal allograft thrombosis and major bleeding was also done for cohort studies using the ROBINS-I tool. All except for two studies [29,30] (where data was only available in abstract form) were assessed as serious risk (Figure A1, Appendix A).

Figure 2: *Risk of Bias Assessment Using Cochrane Methods for RCTs*

	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other sources of bias	Overall
Barnes (1974)	-	-	X	-	-	X	-	X
Horvath (1975)	-	-	+	+	-	X	-	X
Mathew (1975)	X	X	X	X	-	X	-	X
Ubhi (1989)	X	X	X	X	-	X	X	X
Osman (2007)	-	+	X	X	-	X	X	X

Judgement: X High; - Unclear; + Low

Primary outcomes (up to 3 months)

Effectiveness

Because of different TP agents and comparators, analysis of outcomes has been presented separately for studies comparing a single chemical TP agent versus no intervention/placebo (or active treatment versus no intervention) and a single chemical TP agent versus one/more other interventions (or active treatment versus another treatment).

Venous thromboembolism (VTE)

Active treatment versus no treatment

Symptomatic VTE

One cohort study (Table 2) reported on symptomatic VTE and this was a single centre retrospective study comparing UFH (n=10) with no intervention (n=310). No patients developed symptomatic VTE in the UFH arm; the number developing VTE in the no treatment arm was not reported. Follow-up was short at 2 weeks (33).

Asymptomatic VTE

No study reported on this outcome.

Active treatment versus another treatment

Symptomatic VTE

No study reported on this outcome.

Asymptomatic VTE

One RCT (28) comparing UFH (n=25) or LMWH (n= 25) with no treatment (n=25) reported no cases of VTE in any intervention arm (Table 2). Details of how this outcome was assessed radiologically were not specifically stated. Follow-up was 2 weeks.

***Table 2**: Number of participants with VTE*

ACTIVE TREATMENT VERSUS NO TREATMENT†				
Symptomatic VTE				
Author/Year	**Intervention Type (n)**	**Rates of VTE**	**Follow-up Period**	**Certainty of evidence (GRADE^)**
Kusyk (2005) (33)	No Rx (310)	NS	2 weeks	⊕⊖⊖⊖ Very Low
	UFH (16) then LMWH (10)	0		
ACTIVE TREATMENT VERSUS ANOTHER TREATMENT*				
Asymptomatic VTE				
Author/Year	**Intervention Type (n)**	**Rates of VTE**	**Follow-up Period**	**Certainty of evidence (GRADE^)**
Osman (2007) (28)	No Rx (25)	0	2 weeks	⊕⊖⊖⊖ Very Low
	LMWH (25)	0		
	UFH (25)	0		
VTE, venous thromboembolism; UFH, unfractionated heparin; Rx, treatment; LMWH, low molecular weight heparin; NS, not stated				

* Symptomatic VTE not reported by any study in this category

† Asymptomatic VTE not reported by any study in this category

^ GRADE Working Group grades of evidence used to assess certainty of evidence for all outcome measures (35):

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty:	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty:	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty:	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Renal allograft thrombosis

Seven studies (two RCTs (27, 28), 1 controlled trial (22) and 4 cohort studies (23, 29, 32, 33)) reported on the proportion of participants who developed renal allograft thrombosis (Table 3). Only one cohort study (29) did not report the outcome per intervention arm.

Active treatment versus no treatment

In the controlled trial(22), there were higher numbers of renal allograft thromboses in the no treatment arm (12.3%) compared to the treatment arm (LMWH) (2.1%). The length of follow-up was not described.

Three cohort studies reported the number of participants developing renal allograft thrombosis per treatment arm; only two studies reported similar follow-up times for both study arms(32, 33). None of the studies adjusted the results to account for confounding factors (Table 3).

Three trials (25, 27, 28) (one (25) which reported outcomes beyond 3 months, see Table A3, Appendix A) comparing UFH with no intervention showed no evidence of a difference for thrombosis risk between the arms (risk ratio 0.2; [95% CI 0.01 – 4.63]). However, all three studies were small with a high risk of bias. Meta-analysis was not possible for this outcome as the patient follow up periods were very different.

Only two studies compared a TP versus another TP treatment, both were of small size (Table 3) reporting very low rates of renal artery thrombosis within 2 weeks.

Table 3: *Renal Allograft Thrombosis*

Author/Year	Intervention Type (n)	Dose of Intervention	Renal Allograft Thrombosis n (%)	Follow-Up Period	Certainty of evidence (GRADE^)
ACTIVE TREATMENT VERSUS NO TREATMENT					
RCT					
Ubhi 1989 (27)	UFH (32)	5000iu	0	30 days	⊕⊖⊖⊖ Very Low
	No Rx (37)	N/A	2 (5.4%)		
Controlled Trial					
Broyer 1991 (22)	LMWH (47)	NS	1 (2.1%)	NS	Unclear
	No Rx (73)	N/A	9 (12.3%)		
Cohort Studies					
Kusyk 2005 (33)	UFH (16)	500-1000iu/hr	0	2 weeks	⊕⊖⊖⊖ Very Low
	No Rx (310)	N/A	3 (0.9%)		
Lundin 2002 (32)	LMWH (56)	Variable: 20mg OD, 40mg OD, 2500iu OD, 5000iu OD	0	47 days	⊕⊖⊖⊖ Very Low
	No Rx (64)	N/A	1 (1.6%)		

Murashima (2010) (23)	Variable: Heparin + warfarin; Heparin + aspirin; Heparin (16)	NS	1 (6.3%)	NS	Unclear
	No Rx (32)		6 (18.8%)		
ACTIVE TREATMENT VERSUS ANOTHER TREATMENT					
RCT					
Osman 2007 (28)	No Rx (25)	N/A	0	2 weeks	⊕⊖⊖⊖ Very Low
	LMWH (25)	3500iu OD	0		
	UFH (25)	5000iu BD	0		
Cohort Studies					
Pawlicki 2011 (29)	UFH intra-op then LMWH (11)	2500iu then 10000-15000iu infusion	1* (1.5%)	14 days	⊕⊖⊖⊖ Very Low
	LMWH (8)	NS			
	No Rx (48)				

RCT, randomised controlled trial; ASA, aspirin; UFH, unfractionated heparin; Rx, treatment; SC, sub-cutaneous; LMWH, low molecular weight heparin; APT, anti-platelet therapy; OAC, oral anticoagulant; NS, not stated; N/A, not applicable; q8h, every 8 hours; q12h, every 12 hours; OD, once a day; QDS, four times a day

Safety – Major Bleeding

Six studies, 1 RCT (28) and 5 cohort studies (19, 23, 29, 32, 33), reported the number of participants with major bleeding as per ISTH criteria (21). See Table 4.

Active treatment versus no treatment

All 3 cohort studies (23, 32, 33) reported higher bleeding rates in the intervention arms. However, each study used a different form of intervention, different timing of onset and different duration of treatment (where stated). Only 1 (32) reported on resultant graft loss because of bleeding.

Active treatment versus another treatment

Three studies (1 RCT and 2 cohort studies) compared LMWH with UFH. The RCT reported a 4% major bleeding rate in the LMWH arm (n = 25) and no major bleeding event in the UFH arm (n = 25) (28). Of the two cohort studies, one reported a bleeding rate of 3% (8/266) in participants who received prophylactic heparin and 46% (6/13) in those who received treatment doses of heparin (19). The second study reported a 63.6% (7/11) rate for the UFH arm (2500iu given intra-op then 10000-15000iu continuous infusion for 2 days) and 50% (4/8) for LMWH (dose not stated) (29).

Findings have been summarised in Table 4.

Table 4: *Major Bleeding*

Studies	Intervention Type (n)	Major Bleeding (ISTH Criteria)	Resultant Graft Loss	Follow-Up Period	Certainty of evidence (GRADE^)
ACTIVE TREATMENT VERSUS NO TREATMENT					
Cohort Studies					
Kusyk (2004) (33)	UFH (16)	10 (62.5%)	NS	2 weeks	⊕⊖⊖⊖ Very Low
	No Rx (310)	11 (3.5%)	NS		
Lundin (2002) (32)	LMWH (56)	4 (7.1%)	0	47 days	⊕⊖⊖⊖ Very Low
	No Rx (64)	3 (4.7%)	0		
Murashima (2010) (23)	Variable: Heparin + warfarin; Heparin + aspirin; Heparin (16)	5 (31.3%)	NS	NS	Unclear
	No Rx (32)	2 (6.3%)			
ACTIVE TREATMENT VERSUS ANOTHER TREATMENT					
RCT					
Osman (2007) (28)	No Rx (25)	0	N/A	2 weeks	⊕⊖⊖⊖ Very Low
	LMWH (25)	1 (4%)	0		
	UFH (25)	0	N/A		
Cohort Studies					
Ng (2016) (19)	No Rx (268)	9 (3.4%)	NS	NS	⊕⊖⊖⊖ Very Low
	Prophylactic Heparin (266)	8 (3%)			
	Rx Heparin (13)	6 (46.2%)			
Pawlicki (2011) (29)	UFH intra-op then LMWH (11)	7 (63.6%)	1 (9%)	14 days	⊕⊖⊖⊖ Very Low
	LMWH (8)	4 (50%)	1 (1.8%) (NS if prophylactic heparin or no Rx)		
	No Rx (48)	6 (12.5%)			

RCT, randomised controlled trial; UFH, unfractionated heparin; Rx, treatment; LMWH, low molecular weight heparin; NS, not stated; N/A, not applicable

Mortality

Of the two cohort studies (19, 29), which reported on mortality rate, only one, described this per intervention arm (29). See table 5.

Table 5: *Mortality*

Studies	Intervention type (n)	Mortality	Follow-Up Period	Certainty of evidence (GRADE^)
ACTIVE TREATMENT VERSUS ANOTHER TREATMENT				
Cohort Studies				
Pawlicki (2011) (29)	UFH intra-op then LMWH (11)	0	14 days	⊕⊖⊖⊖ Very Low
	LMWH (8)	0		
	None (48)	0		
Ng (2016) (19)	None (268)	3 (NS which group)	NS	⊕⊖⊖⊖ Very Low
	Prophy Heparin (266)			
	Rx Heparin (13)			

RCT, randomised controlled trial; UFH, unfractionated heparin; Rx, treatment; LMWH, low molecular weight heparin; NS, not stated

Secondary outcomes (up to 12 months)

Due to the low number of studies reporting on the efficacy and safety outcomes beyond 3 months, and heterogeneity between studies in the intervention types, duration of TP and follow up period, conclusions on secondary outcomes are difficult to evaluate (see Tables A3 and A4, Appendix A).

DISCUSSION

Bleeding and thrombosis are outcomes that are critical to the success of renal transplant surgery. Current national and international guidelines on post-operative thromboprophylaxis are aimed at patients undergoing general urological procedures and do not specifically address the additional challenges of renal transplantation. Our systematic review, which is the first in the literature, revealed that the evidence base for making recommendations on thromboprophylaxis after renal transplant surgery is very poor.

Main Findings

In this systematic review, we identified 13 studies (5 RCTs, 1 controlled trial and 7 cohort studies) to assess the efficacy and safety of a chemical thromboprophylaxis strategy for VTE prevention post renal transplant surgery.

Overall, the rate of symptomatic and asymptomatic VTE for both comparisons (i.e. thromboprophylaxis versus no thromboprophylaxis, and versus another active treatment) were poorly reported, and of those studies where this was reported, there was no evidence that thromboprophylaxis versus no treatment, or another thromboprophylaxis treatment, reduces VTE risk. It is important to note that the sample sizes of studies that did report on VTE rates were small and underpowered to answer this question. Although more studies reported on the rates of renal allograft thrombosis, due to heterogeneity of studies and different timing of follow up, we were unable to perform a meta-analysis. For both primary and secondary efficacy outcomes, due to the limited number of studies, we were not able to establish if one chemical thromboprophylaxis is better than another thromboprophylaxis.

The definition of major bleeding varied between studies with only six fulfilling the ISTH criteria. Of the studies that compared active treatment versus no treatment, 2 RCTs (whose follow up was beyond 3 months) comparing LMWH and UFH versus no intervention reported higher numbers of major bleeding events in the TP arm (UFH 22.2%, and LMWH 4%) compared to no intervention where no major bleeding was reported. However, both trials were small, had different follow-up periods and used different TP doses. For active treatment versus

another treatment comparison, only 3 reported on major bleeding of which only one was an RCT and this was underpowered to answer this question.

Completeness, Applicability and Quality of Evidence

None of the studies reported losses to follow-up and it is assumed there were no missing outcomes. A few studies had long follow-up durations and it is questionable if the outcomes in these were attributable to the intervention.

None of the studies included in this review were powered to answer the efficacy or safety outcomes of TP against either another TP, no intervention or placebo. The poor quality of the evidence rated as low to very low for all RCTs means that the results for outcomes assessed in this review cannot be applied to clinical settings.

The RCTs included in this review were primarily single site, with a small sample size and lacked blinding of participants and personnel. As a result, the quality of evidence (using the GRADE system) for the RCTS was rated as low to very low. All were judged using Cochrane risk of bias assessment as high risk.

Strengths and Limitations

To our knowledge, there are no other published systematic reviews describing the efficacy and safety of different chemical thromboprophylaxis strategies in patients undergoing renal transplantation surgery. A recent review on prophylaxis of pulmonary embolism in renal transplant patients (36) similarly concludes a lack of evidence to determine effective prophylactic strategies in this population. However, there are notable differences between these two reviews. We have conducted a systematic review rather than a literature review, our review question is more specific and assesses efficacy (incidence of both symptomatic and asymptomatic VTE including renal allograft thrombosis) and safety (bleeding and mortality) and we have assessed the risk of bias of individual studies and overall quality of evidence.

The RCTs had small sample sizes (all less than 100 patients). To answer our objectives, we grouped studies into two wide groups (active treatment versus another treatment and active treatment versus no treatment). However, we recognise that within these groups there is heterogeneity with regards to type of TP, dosing, duration and outcome measures. Further, unpublished or non-indexed studies within the grey literature were not searched for, so there is a risk of missing data.

We excluded a number of cohort studies from analysis as intervention arms were compared with historical non-intervention arms. Much has changed in terms of surgical expertise during transplant surgery, immunosuppressive regimens used post-transplant, VTE assessment and monitoring, and post-operative care (e.g. recommendation for earlier mobilisation), and we felt that reported changes in outcomes could not be solely attributed to introduction of the intervention.

CONCLUSION

There is a lack of good quality evidence to determine whether chemical thromboprophylaxis is efficacious and safe post-renal transplantation surgery. Compared to no thromboprophylaxis, there was some evidence that thromboprophylaxis may reduce the rate of renal allograft thrombosis, but this may be associated with increased risk of bleeding. However, these conclusions must be interpreted with caution due to heterogeneity in study design, type, and onset/duration of thromboprophylaxis between studies, highlighting the need for future large-scale randomised controlled trials to determine the risk benefit ratio of the various thromboprophylaxis options in renal transplantation surgery.

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DISCLOSURE

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

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