Improving Peri-operative Surgical Care in Kidney Failure Patients

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Statement of originality

This is to certify that to the best of my knowledge the content of this thesis is my own work. This thesis has not been submitted for any degree or other purposes.

I certify that the intellectual content of this thesis is the product of my own work and that all the assistance received in preparing this thesis and sources have been acknowledged.

Author Attribution

This thesis includes chapters that have been published (Chapter 2 and Chapter 3). I confirm, as the candidate, I was the principal investigator and primary author for all included works: with primary responsibility for study design, data collection, analysis, and manuscript preparation. The co-authors provided intellectual input and manuscript review during drafting.

Date: 08 Jan 2026

Dr Animesh Singla

Author's attribution – Supervisor Statement

The work presented in this thesis has been carried out by the author under the supervision of Professor Angela Webster, Dr Melanie Wyld, Dr Tess Cooper and Professor Henry Pleass, through the Sydney Medical School.

The author planned the research, participated in the design of the studies, managed and analysed the data, interpreted results, wrote and revised the manuscripts for submission to peer-reviewed journals, and wrote and compiled this thesis.

As supervisor for the candidature upon which this thesis is based, I can confirm that the authorship attribution statements above are correct.

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Professor Angela Webster

Ethical approval

The studies presented in Chapter 2 and 3 did not require ethics approval as all utilised data was present in the public domain.

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Use of Generative AI

Generative AI (ChatGPT) was utilised for final production of the thesis. The main utilisation of generative AI was to assist with grammar correction through the thesis and generating correct sentence structures in certain aspects of the thesis.

Abstract

Chapter 1: Introduction

Haemostasis in kidney failure is paradoxical: patients are simultaneously at risk of bleeding and thrombosis. Under physiological conditions, the vascular endothelium maintains an antithrombotic surface. Following vascular injury, platelet tethering to subendothelial collagen and von Willebrand factor (vWF) initiates adhesion. In kidney failure, uraemic toxins impair platelet adhesion, activation, and aggregation. Paradoxically, hypercoagulability arises from endothelial dysfunction, systemic inflammation, oxidative stress, and haemodialysis-induced platelet activation.

Peri-operative surgical care in patients with kidney failure has conflicting evidence supporting increased bleeding risk and/or thrombotic risk. For dialysis access surgery, this may result in access thrombosis and repeated intervention. In kidney transplantation, complications may include graft thrombosis, deep vein thrombosis and/or major life-threatening bleeding. There is limited information on peri-operative surgical factors that may play a role in improving outcomes and guiding future policies. In particular, the use of intra-operative unfractionated heparin remains one intervention with varied usage. Given the paradoxical altered haemostatic mechanisms, it is unknown what relative impact, if any, this intervention has for surgical outcomes.

This thesis aims to assess the role of intra-operative intravenous (IV) unfractionated heparin (UFH) bolus in impacting peri-operative outcomes in bleeding and thrombosis for kidney failure patients.

Chapter 2: Intravenous Unfractionated Heparin bolus in Autogenous Arteriovenous Access Surgery

This chapter assessed the impact of intra-operative IV UFH bolus in outcomes for autogenous surgical dialysis access creation. It presents the results of a systematic review and meta-analysis evaluating the role of intra-operative IV UFH bolus for arteriovenous fistula (AVF) creation. We identified seven randomised control trials (RCTs) with a total of 701 participants. The findings support the role of giving an intra-operative IV UFH in reducing incidence of AVF thrombosis, particularly for radio-cephalic AVF creation (Relative Risk, RR = 0.45, 95% CI 0.25 to 0.80). It also resulted in improved clinical patency in the follow-up period. Whilst bleeding complications were increased in the IV UFH group (RR = 2.7, 95% CI 1.42 to 5.17), these were mostly self-limited to small amount of ooze at the surgical site.

Chapter 3: Intravenous Unfractionated Heparin bolus in kidney transplants.

This chapter presents a systematic review and meta-analysis assessing the value in intra-operative IV UFH in kidney transplant recipients. There are disparate practices in kidney transplant recipients with regards to use of intra-operative IV UFH bolus in living and deceased donors. The study found three retrospective cohort studies, which included 1989 participants. The use of IV UFH compared to no heparin did not impact the incidence of graft thrombosis. Surprisingly, there was also no difference seen in bleeding complications or in incidence of delayed graft function. Further higher quality prospective studies in this area are required to enhance our understanding.

Chapter 4: Discussion/Conclusion

This thesis investigated the complex haemostatic disturbances observed in patients with renal failure undergoing surgery, with a specific focus on the peri-operative use of intraoperative intravenous (IV) heparin.

Across two review studies, this thesis evaluated the effects of intraoperative IV UFH bolus on thrombotic and bleeding outcomes in AVF surgery and kidney transplantation. Findings from the AVF cohort suggest that heparin use may reduce early thrombotic failure, particularly in radiocephalic fistulae and smaller-diameter anastomoses where thrombosis risk is highest. In kidney transplant recipients, while no statistically significant differences were observed in the overall population, the results indicate there may be potential benefit in anatomically complex cases, particularly those involving multiple accessory arteries. Importantly, bleeding complications in both systematic reviews were no different and overall lower than historically anticipated, likely reflecting improvements in modern medical and surgical care of renal failure patients.

Significant gaps in current evidence were identified, including the lack of high-quality randomized controlled trials in the use of IV UFH in adult kidney transplantation, heterogeneity in heparin dosing regimens, and the absence of reliable risk-stratification tools for balancing perioperative bleeding and thrombotic risk. Future research priorities include development of a Delphi consensus and a prospective randomized trial.

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List of Abbreviations

vWF	von-Willebrand factor
GP	Glycoprotein
TEG	Thromboelastogram
APTT	Activated thromboplastin time
IV	Intravenous
UFH	Unfractionated heparin
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
RCT	Randomised control trial
ANZDATA	Australian and New Zealand Transplant Registry
DGF	Delayed graft function
MTHFR	Methylenetetrahydrofolate reductase
ROTEM	Rotational thromboelastometry

Chapter 1: Introduction

Kidney failure is a leading cause of morbidity and mortality worldwide, with kidney transplantation offering superior survival, cardiovascular outcomes, and quality of life compared with chronic dialysis.[1,2] Haemostasis in kidney failure is paradoxical: patients are simultaneously at risk of bleeding and thrombosis.[3,4]

1.1 Normal Haemostatic Physiology

Under physiological conditions, the vascular endothelium maintains an antithrombotic surface through continuous release of nitric oxide, prostacyclin, and ecto-ADPase, which inhibit platelet adhesion and aggregation. Following vascular injury, exposure of subendothelial collagen and von Willebrand factor (vWF) facilitates platelet adhesion via glycoprotein (GP) receptors.[5]

Subsequent platelet activation triggers conformational change of integrin αIIbβ3 (GPIIb/IIIa), promoting fibrinogen binding and platelet aggregation. Parallel activation of the coagulation cascade, initiated via tissue factor exposure, results in thrombin generation and fibrin polymerisation, consolidating the platelet plug. This process is tightly regulated by endogenous anticoagulant pathways and fibrinolysis.[5,6]

1.2 Haemostatic Abnormalities in Kidney Failure

Bleeding Diathesis

The haemostatic defect in uraemia is primarily due to impaired platelet adhesion, activation, and aggregation. Uraemic toxins interfere with platelet receptor function and intracellular

signalling. Reduced thromboxane A_2 synthesis, impaired ADP release, and diminished cyclooxygenase and phospholipase A_2 activity contribute to attenuated platelet activation.[7,8]

Alterations in surface glycoproteins (notably GP Ib and GP IIb/IIIa) and reduced affinity for vWF further impair platelet–endothelial interactions. Carbamylation of platelet proteins has also been described, leading to reduced receptor function.[5]

Anaemia exacerbates the bleeding tendency by diminishing platelet margination and impairing platelet–vessel wall contact.[9]

Prothrombotic Tendency

Despite the bleeding phenotype, kidney failure is also associated with hypercoagulability. Endothelial dysfunction, systemic inflammation, and oxidative stress contribute to increased expression of adhesion molecules and tissue factor, reduced nitric oxide bioavailability, and decreased prostacyclin synthesis.[10,11]

Platelet activation may also be enhanced during haemodialysis due to contact with bioincompatible surfaces. Elevated levels of fibrinogen, factor VIII, and plasminogen activator inhibitor-1 have been reported, further predisposing to thrombosis.[10,11]

Loss of anticoagulant proteins (antithrombin, protein C, and protein S) in nephrotic-range proteinuria may further increase thrombotic risk. Autoantibodies such as antiphospholipid antibodies have also been described in dialysis patients, though their clinical significance remains uncertain. The result is imbalance that predisposes patients both to bleeding during surgical procedures and to vascular access or graft thrombosis in the perioperative period.

1.3 Clinical Implications

As previously described, the paradoxical haemostatic changes may lead to kidney failure patients being more prone to bleeding or thrombosis perioperatively. The clinical phenotype in these patients has been described in the literature in individual studies focusing on bleeding or thrombosis complications. It remains unclear whether any perioperative intervention or investigation may help to predict whether the patient are more likely to have a bleeding or thrombotic complication. Current perioperative guidelines do not recommend a routine testing for clinical bleeding or thrombosis risk in the absence of a pre-existing history.[12,13] Despite this, in the era of personalised medicine, and significant advances in our understanding of haemostatic mechanisms, there are potential investigations and therapies which may influence the aforementioned outcomes.

In studies assessing perioperative outcomes in dialysis access surgery, access thrombosis is reported in up to 50% distal autogenous access creations. Access thrombosis has normally been attributed to a technical problem when it occurs in the immediate perioperative period, recognising factors such as vessel size, post-operative oedema, and haemodynamic factors as playing a role. However, given the perturbations in haemostasis in patients with kidney failure, access thrombosis may in-fact may also relate to concurrent pro-thrombotic tendency in these individuals. This has implications for future management in these patients, for example, in the need for more complex access creation and in kidney transplantation. Several studies have implicated haemodialysis itself as a prothrombotic risk factors in access thromboses.[14,15] In a separate study, comparing haemodialysis patients to routine healthy subjects, there was presence of significantly elevated acquired thrombophilia via lupus antibodies and protein C/S deficiencies.[16,17] In addition to the perioperative surgical

outcomes, this prothrombotic state is supported by a plethora of literature indicating a significantly elevated deep vein thrombosis risk in patients with kidney failure, from 1.5 to 3.8x the general population.[13] In particular, patients with kidney failure with genetic thrombophilia markers have up to a 10x higher venous thromboembolism risk.[16]

The bleeding and thrombosis complications following more major surgery, including kidney transplantation can be more catastrophic leading to graft loss and major life-threatening bleeding. Transplant thrombosis has been extensively reported in the literature, with rates varying from 0.3 to 5%, with venous thrombosis being more common than arterial thrombosis.[18,19] Again, technical considerations have been the main causative attributable factor in the perioperative setting. However, more contemporary work has suggested genetic and acquired thrombophilias may play a greater role.[20,21] The presence of a thrombophilia is associated with 3.5 to 4x normal graft loss incidence. One study of 97 cadaveric kidney transplantations found 22% incidence of acquired or inherited thrombophilia, with a much higher incidence of acute rejection in the first 6 months in this group. Hyperhomocystemia (including MTHFR gene mutation) has also been implicated in thrombosis risk.[22]

Conversely, bleeding complications in kidney transplant recipients have also been reported, of up to 25% in one study.[23] Thromboelastrogram (TEG) studies have clearly documented an in-vitro abnormality with bleeding tendency in kidney failure patients which is reversed several days following kidney transplantations. In addition, studies analysing therapeutic anticoagulation in kidney failure have had conflicting data.[24,25] Lower activated thromboplastin time (APTT) targets in post-operative heparin infusion protocols have been suggested in kidney failure patients to achieve therapeutic effect, whilst bleeding scores such as HASBLEED have had variable success in predicting bleeding risk with chronic

anticoagulation.[27] Certainly, perioperative surgical bleeding risk remains elevated compared to the general population without kidney failure.

Given these conflicting clinical findings in the literature, effort to help predict bleeding and reduce thrombosis incidence may be a worthwhile endeavour. One intervention which has been sparsely investigated in this patient population has been the use of intra-operative intravenous (IV) unfractionated heparin (UFH) bolus. This is a mainstay of therapy in most vascular surgery procedures to reduce risk of downstream ischemia and acute vascular thromboses. Despite this there is little evidence of reducing complications, with the main historical study by Thompson et al. finding only a reduction in perioperative myocardial infarction risk with its use in open abdominal aortic aneurysm repairs prior to cross-clamping.[28,29] Given the paradoxical nature of bleeding and thrombosis in patients with kidney failure undergoing surgery IV UFH benefit or harm remains to be elucidated.

The overall aim of subsequent chapters will be to synthesise and analyse the literature on the role of IV UFH in two common procedures for patients with kidney failure; access creation and kidney transplantation. The findings may help inform future policies and allow for the development of a more robust study protocol to better investigate and improve our understanding of this paradoxical state for kidney failure patients.

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Chapter 2: A Systematic Review and Meta-analysis of Intra-operative Intravenous Unfractionated Heparin bolus in Autogenous Arteriovenous Access Surgery

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2.1 Abstract

Introduction: There is controversy over the balance of benefit to harm of intravenous unfractionated heparin (UFH) in the creation of autogenous fistulas. This review aimed to assess the efficacy and safety of intra-operative administration of intravenous UFH bolus during creation of autogenous venous access in kidney failure.

Methodology: MEDLINE, Embase, and CENTRAL were systematically searched for randomised controlled trials (RCTs) recruiting adults with kidney failure undergoing arteriovenous dialysis access surgery (PROSPERO CRD42022319502). Quality was assessed using the Cochrane Risk of Bias Assessment Tool. Outcomes: fistula patency, bleeding complications, fistula thrombosis and re-intervention rates. Relative and absolute effects were synthesised using a random-effects model as risk ratio (RR) with 95% confidence intervals (CI). Certainty of evidence was assessed using the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) approach.

Results: Seven RCTs (701 participants) were identified. Risk of bias was low or unclear in most domains. Using intravenous UFH compared to no heparin may reduce the risk of loss of fistula patency (6 studies, 548 participants, RR = 0.49, I^2 = 0%; low certainty evidence). The greatest benefit was for autogenous radio-cephalic fistula compared to other autogenous fistula formation (4 studies, 302 participants, RR = 0.45, I^2 = 0%; low certainty evidence). The risk of bleeding complications may be higher with intravenous UFH (7 studies, 698 participants, RR = 2.71, I^2 = 5%; low certainty evidence). The most common bleeding complications were haematoma formation (57%). Based on very low-certainty evidence, use

of intravenous UFH may also associated with a reduced risk of acute fistula thrombosis (7 studies, 698 participants, RR = 0.49, I^2 = 54%).

Conclusion: Using intravenous UFH bolus (compared to no heparin) during AVF creation, may improve early clinical patency and reduced thrombosis, but may result in more bleeding complications. Due to the low certainty of evidence, a contemporary multicentre RCT is needed to further assess the validity of this conclusion. This study should provide an update on the existing guideline in the literature.

Key Words: Dialysis access surgery, intravenous unfractionated heparin, fistula patency, randomised control trials

2.2 Introduction

Kidney failure is a leading cause of mortality across the world, as well as markedly reduced quality of life.[1] Arteriovenous access creation is the safest way to enable harm-minimised haemodialysis and is the mainstay of renal replacement therapy for those with kidney failure.[2] Despite this, autogenous fistula creation between native artery and vein is often complicated by failure or multiple re-interventions.[3] The cause for loss of primary patency often relates to patient risk factors and underlying flow-dynamics inherent with an arteriovenous fistula creation.

The use of intra-operative intravenous (IV) unfractionated heparin (UFH) is in routine practice in vascular surgery, for both endovascular and open vascular procedures. The rationale is to reduce potential thromboembolic complications associated with reduced downstream flow, particularly in the presence of occlusive arterial disease. Despite this, the evidence base for its use remains limited.[4] The role of intra-operative intravenous UFH in patients with kidney failure is less well established.[5] It is well recognised that these patients have significant uraemia-associated platelet dysfunction, which can result in prolonged bleeding times and increased perioperative surgical complications.[6,7]

Whilst there are recommendations for periprocedural management for patients on chronic antiplatelet or anticoagulant therapy, there is limited guidance on the use of intra-operative IV UFH in haemodialysis access surgery.[8] The 2018 European Vascular Access Clinical Practice Guidelines did not provide a specific recommendation regarding the use of IV heparin therapy in haemodialysis access surgery.[9] More recently, the 2023 European Antithrombotic clinical practice guidelines recommend against the use of IV heparin in haemodialysis access surgery (Class III, Level A).[10] Despite this, the use of intra-operative intravenous UFH remains widely divergent in practice, varying with speciality and institution.[8,11]

The aim of this review was to perform a rigorous synthesis on the efficacy and harms of intra-operative IV UFH bolus for access creation, following Cochrane methodology.

2.3 Methods

The protocol for this systematic review was registered on the International Prospective Register of Systematic Reviews (CRD42022319502). This study is reported in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta Analyses).[12]

Study eligibility criteria

We included randomised controlled trials (RCTs) assessing the role of intra-operative IV UFH in any dosage, compared to either no treatment or use of placebo (saline), in adults (≥18 years of age) with kidney failure undergoing access creation in autogenous arteriovenous dialysis access operations. We excluded studies of paediatric populations (age < 18 years) due to differences in vessel diameters and anastomosis techniques. We included studies of only new dialysis access creation and excluded studies of patients undergoing revision surgery due to differing risk profiles for access patency.

Outcomes

The primary outcome was loss of fistula patency at four to six weeks post access creation. The time-point of four to six weeks was chosen as this is the routine follow-up period used in clinical practice when assessing fistula patency. Fistula patency was defined by clinical assessment for thrill and bruit, and/or ultrasound assessment of the fistula. Loss of fistula patency was used rather than conventional primary patency, to keep direction of effect in outcomes consistent and to allow clinical interpretation of impact of IV UFH. A pre-planned

sub-analysis of primary outcome was performed for radio-cephalic fistula creation specifically.

The secondary outcomes were:

1) Clinically relevant bleeding complications: a composite endpoint defined as any clinically relevant bleeding issues including review for post-operative bleeding at site of fistula creation, need for blood transfusions, or post-operative haematoma. This definition also included any major bleeding events in terms of central nervous system or gastrointestinal bleeding.

2) Acute fistula thrombosis (from any cause) in the immediate (24 to 48hours) post-operative period.

3) Re-operation defined as the need for re-intervention on the fistula (for any cause) during the study follow-up period.

Search strategy

The search strategy was developed using pre-defined terms and adapted to each database. We searched MEDLINE via Ovid (1946 to present), Embase via Ovid (1947 to present) and Cochrane Central Register of Controlled Trials (CENTRAL) up until 5th November 2023 with no date or language restrictions. Using Boolean operators, the searches combined keywords and Medical Subject Heading (MeSH) when searching in the title, abstract, keywords, and MeSH fields. Additionally, grey literature search was performed in Google Scholar to retrieve potentially relevant articles. This search was not limited to English language or publication status. The comprehensive search strategy is shown in supplementary document. All attempts were made to contact the authors of the original study via email to

obtain missing data on risk of bias, patient demographics and outcomes. The comprehensive search strategy is outlined in *Appendix A.1*.

Study Selection and Data Extraction

We used Covidence software to screen titles and abstracts, followed by full-text review performed independently by two authors (A.S. and K.P.) and in case of disagreement, a consensus was reached by discussion.

Data extraction and outcomes

Two authors (A.S. and K.P.) independently performed the data extraction from eligible studies. Disagreements were resolved by a consensus and where any uncertainties arose, a third author (T.C.) assisted. Extracted data was collected by using a standardised piloted data collection Excel spreadsheet (Excel, Microsoft Corp, WA, US).

Risk of bias assessment

Each included study was independently assessed for quality by two authors (A.S. and K.P.) using the Cochrane Risk of Bias Assessment Tool (ROB 1.0).[12]

Statistical Analysis

For dichotomous outcomes, we used risk ratio (RR), with 95% confidence intervals (CI). Where continuous scales of measurement were required, we planned mean difference (MD) or standardised mean difference (SMD). A random effects model was applied due to inherent heterogeneity in study design and patient demographics regardless of the I^2. Interpretation of the heterogeneity was done through combination of visual inspection of forest plot and calculation of I^2 statistic, with confidence intervals for I^2 were calculated to improve

precision.[13] Heterogeneity amongst studies were considered low, moderate and high when $I^2 \leq 30\%$, $31\% < I^2 \leq 50\%$ and $I^2 > 50\%$ respectively.[14] All meta-analysis statistics was performed in Review Manager 5.3 software.[15]

Summary of findings and assessment of the certainty of the evidence

The main results of the review are presented as 'Summary of findings'. These present the key information relating to the certainty of evidence, the magnitude of the effects of using intravenous heparin and the sum of the available data for the main outcomes that we planned a priori: loss of fistula patency, fistula thrombosis, clinically relevant bleeding complications.

The 'Summary of findings' also includes an overall grading of the certainty of evidence for each outcome measure using GRADE (Grading of Recommendations Assessment, Development, and Evaluation) approach and was conducted with GRADEprofiler (Version 3.6).[16,17] The certainty of the body of evidence involves consideration of within-trial risk of bias (methodological quality), directness of evidence, heterogeneity, the precision of effect estimates, and risk of publication bias.

2.4 Results

Description of studies

The search of databases and additional sources identified a total of 512 records. After removal of duplicates, 506 records were screened for relevance based on title and abstract, of which 498 were removed. Eight full-text articles were reviewed of which seven studies (701 participants) were included in this review. The PRISMA study flow diagram is shown in Figure 2.1. The PRISMA checklist is outlined in *Appendix A.2.*

Study characteristics

A summary of the study characteristics including the baseline demographics of included studies is provided in *Appendix A.3* and *Appendix .4*. A summary of study outcomes and GRADE recommendations are provided in *Appendix A.5* and *Appendix A.6* respectively.

All seven studies were single-centre and took place in hospital settings in the United States of America, Nepal, Iran and Malaysia.[18-24] No studies were from European centres. Patient ethnicity and race were not included in the analysed studies.

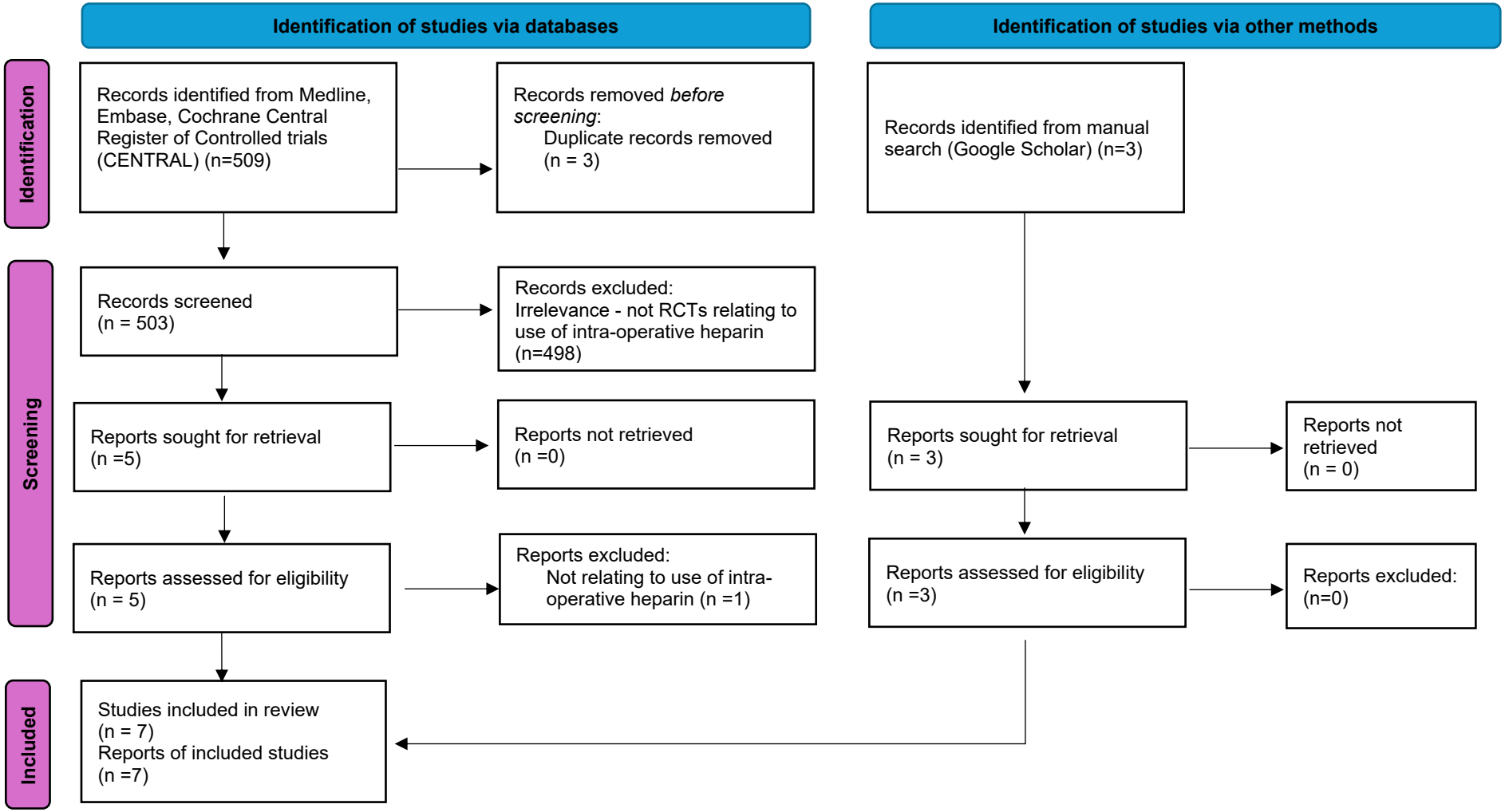


Figure 2.1: PRISMA diagram - Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram detailing study selection process in systematic review

All fistula creations were created using autogenous vein in forearm or upper arm. Four of the seven studies only compared radiocephalic AVFs,[18-20,22,23] while two studies analysed patients with either upper arm or forearm AVFs.[21,24] All anastomoses were performed with utilisation of vessel clamps. The treatment arms in all studies were randomised to receive a bolus of IV UFH prior to vessel clamping and anastomosis. Four studies used a standard 5000 international units (IU) bolus of heparin,[18-21] the remaining three used weight-based boluses ranging from 75 to 100IU/kg.[22-24] In five studies, the study personnel did not provide an alternative treatment to the patients randomised to the control/placebo arm. Two studies did report the placebo agent in the control arm: one study gave a saline bolus[21] and another gave heparinised saline bolus.[19]

The majority of studies reported follow-up at four to six weeks, which is the standard timeframe for first outpatient follow-up to assess patency and maturation.[18-20,22,24] One study only reported 24 hour follow-up[23] and one study only reported follow-up at two weeks.[21]

Risk of Bias

Figure 2.2 depicts the graphical summary of risk of bias assessment separated by each study. All studies were low risk for selection bias. However, allocation concealment process and blinding of participants and assessors were unclear in majority of studies (leading to unclear risk for selection, performance, and detection bias). Risk of attrition bias was judged to be low in all studies, with **Wang 2010** having the highest rate of 10% attrition.[24] Reporting bias was unclear in most studies as the trial protocol registration or published protocol could not be confirmed. There were no other major biases in any of the studies.

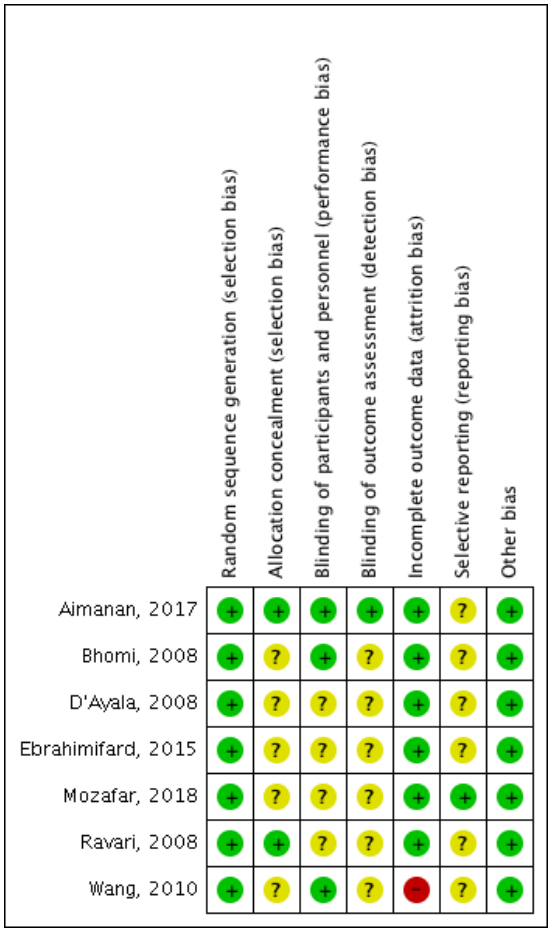


Figure 2.2: Risk of bias summary of all studies according to domain

Early Patency

Six of the seven studies reported patency of fistula beyond 24 hours.[18-22,24] **Mozafar 2018** only reported 24-hour post-operative patency.[23] **Ravari 2008** only reported two-week fistula patency,[21] while the remainder reported four- to six-week fistula patency.

Compared to no treatment, the use of IV UFH bolus prior to surgical anastomosis may be associated with a lower risk of loss of fistula patency (RR = 0.49, 95% CI 0.33 to 0.73, I^2 = 0%,) (Figure 2.3A). Combined loss of fistula patency across the six studies occurred with an incidence of 11.0% (n = 30) in patients receiving IV UFH and 23.6% (n = 65) with no treatment. Sub-group analysis for studies reporting on radio-cephalic fistula only (n = 4)

demonstrated a similar difference favouring patients receiving IV UFH (RR = 0.45, 95% CI 0.25 to 0.80, I^2 = 0% (Figure 2.3A).

Two studies reported 24 hour-patency. **Wang 2010** did not show any difference in patency between the two groups (100% for both).[24] **Mozafar 2018** showed better 24-patency in those receiving IV UFH versus those without (100% vs 92%, p = 0.03).[23]

The certainty of evidence for this outcome was low (*Appendix A.6*).

Acute thrombosis

Seven studies reported acute fistula thrombosis.[18-24] **Bhomi 2008** and **Wang 2010** reported no events in either group in their follow-up.[17,23]

Compared to no treatment, the use of IV UFH bolus may be associated with significantly lower risk of acute fistula thrombosis (RR = 0.49, 95% CI 0.29 to 0.84, I^2 = 54%) (Figure 2.3B). The incidence of acute fistula thrombosis was 4.89% (n = 17) in those patients receiving IV UFH, and 10.6% (n = 37) in those patients receiving no treatment. In **D'Ayala 2008**, all thromboses (n = 3) were thought to be secondary to post-operative haematoma.[19] **Aimanan 2017** was the only study to report fistula thrombosis up to first week,[22] whilst remainder of studies reported immediate post-operative thrombosis.

The certainty of evidence for this outcome was very low (*Appendix A.6*)

Bleeding Complications

All seven studies reported outcomes on combined bleeding complications.[18-24] **Ravari 2008** reported zero events occurring within both groups in their follow-up.[21]

Compared to no treatment, the use of IV UFH bolus may be associated with significantly higher risk of bleeding complications (RR = 2.71, 95% CI 1.42 to 5.17, I^2 = 5%) (Figure 2.3C). Combined incidence of bleeding complications was 12.1% (n = 42) and 3.40% (n = 12) in patients receiving IV UFH versus no treatment respectively. All the clinical bleeding events in **Aimanan 2017**, **Ravari 2008**, and **Wang 2010** were from wound haematomas.[21,22,24] **D'ayla 2008** had 4 patients who received IV UFH who required blood transfusion.[18] The remainder of the clinical bleeding events were related to wound ooze.

The certainty of evidence for this outcome was low (*Appendix A.6*).

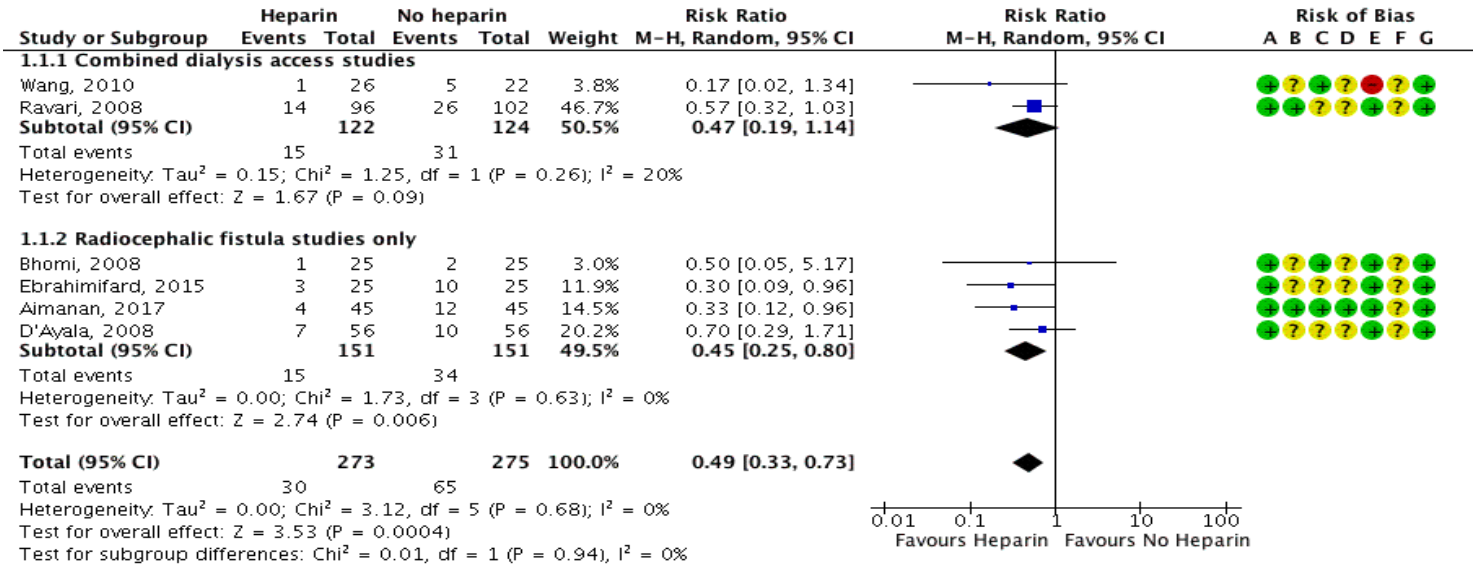
Re-operation

Due to small sample size, meta-analysis for this outcome was not possible. Two patients (n = 2) required re-operation, both had received IV UFH. One patient required evacuation of a haematoma,[24] and another required control of bleeding.[20] No patients who had an acute thrombosis event underwent re-intervention.

Publication Bias

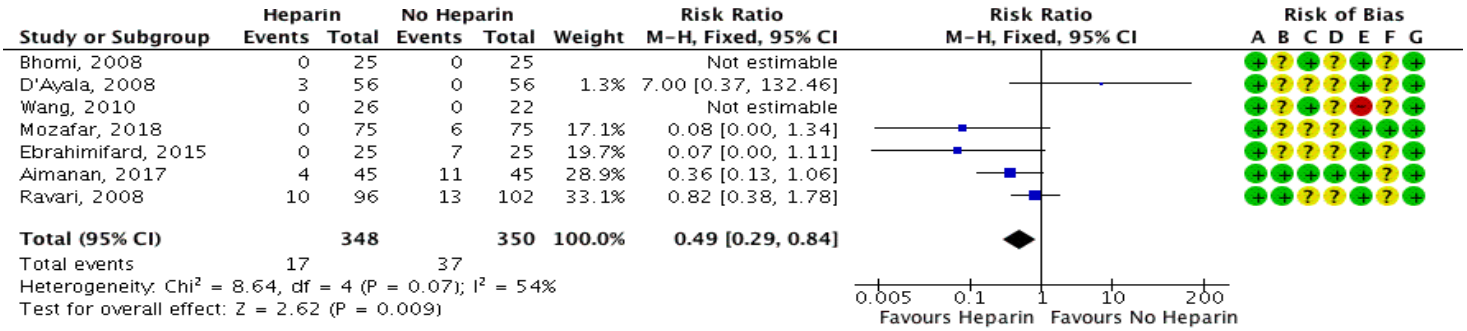
We planned to investigate publication bias if there were a minimum of ten studies for pairwise comparison. We only had seven studies and meaningful interpretation of funnel plots would have been limited and thus not performed.

3a) Loss of Fistula Patency



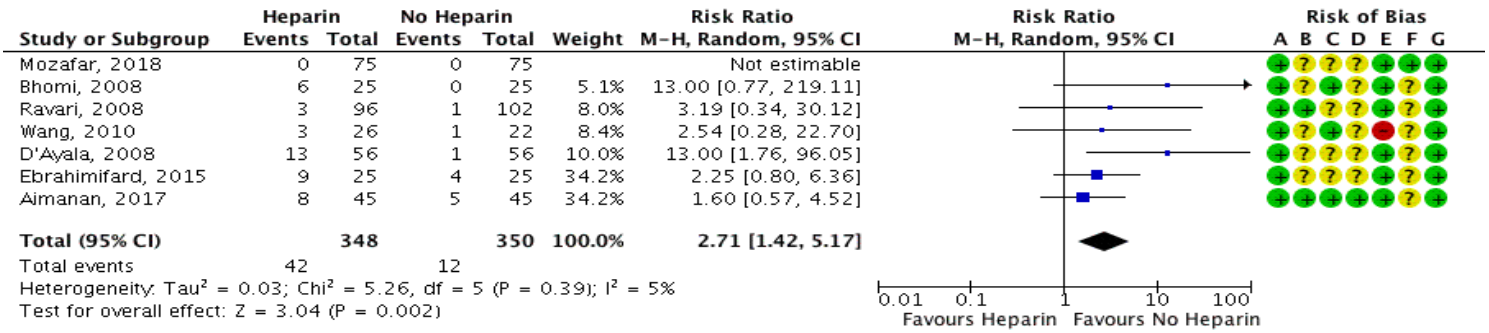
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

3b) Acute Fistula Thrombosis



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

3c) Bleeding Complications



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Figure 2.3: Forest plot of primary and secondary outcomes for IV UFH versus no heparin.
IV: intravenous; UFH: unfractioned heparin.

2.5 Discussion

Our study found intra-operative intravenous UFH bolus may improve early clinical patency for haemodialysis arteriovenous access creation, as measured by reduced risk of fistula loss at two to six weeks by 50%. The impact on patency with intravenous UFH was similar when sub-group analysis of radio-cephalic fistula was undertaken.

Surgical creation of arteriovenous fistula may be prothrombotic due to multiple factors including: an absence of vessel flow, tissue oedema, inflammation, and vessel spasm.[25] Use of intravenous UFH bolus may mitigate thrombosis risk by reducing the development of new platelet/fibrin deposition. The main anticoagulation effect of UFH is potentiation the action of antithrombin 3 (AT3), resulting in inactivation of thrombin and activated factor X (factor Xa).[26] As a result, this peri-operative anti-thrombotic effect may translate into the improved early clinical patency results seen in our study. One study by **Mozafar 2018** did support this hypothesis.[23] They found that even 24- hour patency was statistically significantly better between patients receiving intravenous UFH and those not receiving any treatment (0% vs 8%, $p = 0.03$).

Whilst improving early clinical patency, the use intravenous UFH may also be associated with an increase in clinical bleeding complications. It is well recognised that patients with end-stage renal failure suffer from uraemia. This results in significant platelet dysfunction, increased nitric oxide and prostacyclin levels, all of which increase bleeding tendency.[6,27] It is also likely, in the IV UFH group, the anticoagulation effect persisted beyond completion of the anastomosis.[28] Taken together, this may explain why there was such a high incidence of wound haematoma in the patients receiving IV UFH.

Only one study directly correlated wound haematoma with fistula patency, with all three acute thromboses occurring in the intravenous UFH group with wound haematoma.[23] In addition, all studies used therapeutic doses of intravenous UFH either at fixed bolus (5000 IU) or weight-based dose (80 to 100IU/Kg). These are very rarely used in clinical practice by surgeons due to accepted bleeding tendency for renal failure patients. Despite this, our meta-analysis revealed the overall acute fistula thrombosis risk was still 50% less likely in those receiving IV UFH. Except for one study where the AVFs with the wound haematoma (clinical bleeding) led to AVF failure; in all other studies, the clinical bleeding events were self-limiting and relatively minor.

The findings of this study provide potential support for the routine use of IV UFH bolus during the creation of autogenous AVFs. This is in contrast to the most recent 2023 European Antithrombotic Guidelines[9] which made a Class III (Level A) recommendation against the routine use of IV UFH. The recommendation was based largely on a previous systematic review published in The Journal of Vascular Access, by Smith et al.[29] Whilst this was a well-designed systematic review, it only included four of the seven studies from our study. Since then, three further RCTs have been published, which have significantly increased the sample size and events rates in both arms. Our study provides a more contemporary and complete synthesis of the knowledge on the topic. In addition, we have performed sub-group analysis for radio-cephalic fistula, where the patency difference was most pronounced. A more recent systematic review by Bahi et al. in 2021[8] was excluded from the guidelines. This study had a number of significant methodological flaws, including a lack of risk of bias assessment. This was a single author paper that did not follow best practice methods, making its conclusions unreliable.[8]

The practice of intravenous UFH has particular implications for radio-cephalic fistula. It is known that the short- and long-term patency and maturation rates for primary radio-cephalic fistula are inferior to more proximal arteriovenous access.[25] This is often due to combination of factors including calcified distal arteries in diabetics, small artery and vein diameter or diseased outflow contributing to non-maturation of main forearm cephalic vein.[26,27] Despite this, distal fistulas are often first choice in-order to preserve as much cannulation zone as possible. Improving patency with intravenous UFH bolus may reduce need for early re-intervention due to thrombosis, earlier time to access maturation and reduced time with temporary line placement for those needing imminent dialysis. This should translate into reduced length of stay in hospital, reduced costing, and overall, more cost-effective utilisation of resources.

The overall certainty of evidence was very low or low across most of the outcomes in our review. Despite inclusion of only randomised control trials, the appropriate participant and assessor concealment was unknown in most of the included studies. In addition, only one trial had an actual trial registration.[22] Imprecision was also a risk of bias in the included studies of this meta-analysis despite low I^2 values.

There are several limitations in this study which may have influenced the results. The meta-analysis had significant heterogeneity in several factors which may have added several confounders. In particular, the technique for access creation varied between studies. The dose of heparin varied across the studies, and without testing activated clotting time, the exact anticoagulation effect would not be discernible between the studies. Hydro-distention of the vein was utilised in four of the seven studies and not reported in the remainder. In addition, only two studies gave a ‘placebo’, whilst the remainder did not provide any treatment.

Finally, the use of antiplatelet therapy in these patients were not reported. This is likely to have a meaningful impact on both patency and bleeding risk.[30] Additionally, another intra-operative factor which may have influenced outcome was the utilisation of protamine for reversal of any anticoagulation effect. Without more specific patient level data (not reported in the studies), the impact of anti-platelet therapy or use of protamine in these patients could not be assessed. Finally, these patients often suffer several other comorbidities which may have confounded their bleeding risk including having anaemia, ischemic disease, anticoagulation for thrombophilia, and other chronic diseases. These were sparsely reported in the studies and thus may have been an additional confounder. Finally, there was generally limited follow-up across most of the studies. Thus, no conclusions can be made about longer-term patency or the functional maturation of these fistulae. We also acknowledge that overall event rates in the study were low. As a result, the observed difference in outcomes between our review and the earlier review[29] (with inclusion of more contemporary studies) may also be caused by a type 1 statistical error.

Despite these confounders, this is the only contemporary and comprehensive systematic review and meta-analysis combining all current randomised control trials assessing the role of IV UFH in autogenous access creation. More robust and higher quality RCTs are needed to validate the results of this review and assess the impact on AVF maturation.

2.6 Conclusion

This systematic review analyses the safety and efficacy of IV UFH bolus in patients undergoing autogenous arteriovenous fistula creation. Despite an increase in self-limited bleeding complications, the use of IV UFH bolus may be associated with improved early

clinical patency and reduced thrombosis risk. This was most pronounced in those undergoing distal radio-cephalic fistula formation.

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Chapter 3: Intra-operative Unfractionated Heparin for Kidney Transplantation: A Systematic Review and Meta-analysis

Publication details and contribution of authors

Singla A, Cai S, Hameed A, Pleass H, Cooper T, Wyld M, Webster A. Intra-operative unfractionated heparin (UFH) for kidney transplantation: a systematic review and meta-analysis. 2025. *Transplantation Reviews*, *Accepted for Publication.*

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AS: Study design, data collection, data analysis, data interpretation, drafting and revision of manuscript.

SC: Data collection, data analysis, data interpretation, and revision of manuscript.

AH: Data analysis, data interpretation, drafting and revision of manuscript.

HP: Data analysis, data interpretation, drafting and revision of manuscript

TC: Study design, data collection, data analysis, data interpretation, drafting and revision of manuscript.

AW: Study design, data collection, data analysis, data interpretation, drafting and revision of manuscript.

MW: Study design, data collection, data analysis, data interpretation, drafting and revision of manuscript.

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3.1 Abstract

Introduction: Balancing bleeding risk with graft thrombosis is a challenge in transplantation surgery. This systematic review assessed the efficacy and safety of intra-operative administration of intravenous (IV) unfractionated heparin (UFH) bolus during adult kidney transplantation.

Methodology: We searched MEDLINE, Embase, and CENTRAL (from inception to May 2025) for comparative studies of any design recruiting adults undergoing living or deceased donor kidney transplantation (PROSPERO CRD42023391473), that examined intra-operative IV UFH as a perioperative intervention. Study quality was assessed using the Newcastle Ottawa Scale. Outcomes: Graft thrombosis (including subgroup analysis of arterial thromboses), bleeding complications, delayed graft function, and transplant nephrectomy. Relative and absolute effects were synthesised using a random-effects model as risk ratio (RR) with 95% confidence intervals (CI). Certainty of evidence was assessed using the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) approach.

Results: Three retrospective cohort studies (1989 participants) met inclusion criteria. Study quality was rated as 'fair' in two studies and 'good' in one study. There was no difference for graft thrombosis with intra-operative IV UFH (3 studies, 1989 participants, RR = 1.02, 95% CI 0.49 to 2.12, $I^2 = 0\%$, very low certainty evidence). Sub-group analysis also did not identify any difference for arterial thrombosis risk. Nearly all graft thromboses (17/23) resulted in transplant nephrectomy. IV UFH did not increase bleeding complications (3 studies, 1989 participants, RR = 1.29, 95% CI 0.78 to 2.13, $I^2 = 68\%$, very low certainty

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evidence). There was no difference in delayed graft function (2 studies, 461 participants, RR = 0.95, 95% CI 0.57 to 1.58, I^2 = 40%, very low certainty evidence).

Conclusion: Despite its common use in clinical practice, evidence supporting intra-operative IV UFH during kidney transplant surgery is sparce and of very low certainty. Current evidence does not demonstrate a reduction in graft thrombosis or delayed graft function demonstrated with intra-operative IV UFH, nor a clear increase in bleeding complications. High-quality prospective studies are needed to clarify the net clinical benefit of intra-operative UFH in kidney transplant surgery.

Key Words: kidney transplant, intravenous unfractionated heparin, graft thrombosis, bleeding

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3.2 Introduction

Kidney transplantation is the preferred treatment for people with kidney failure.[1] It is associated with significantly improved quality of life, and overall reduced morbidity and mortality compared with dialysis.[2,3] The surgical technique for kidney transplantation has changed little since its first description in early 1950s.[4] Despite overall excellent outcomes, a proportion of recipients experience early bleeding and/or thrombotic complications.[5] Recent analysis from the Australian and New Zealand Transplant Registry (ANZDATA) has reported that acute causes of graft loss account for 2.6% to 5.3% of graft failures (vascular, technical and hyperacute/acute rejection respectively).[6] Renal vein thrombosis and renal artery thrombosis are reported to occur in 1% and 0.5% of kidney transplants respectively[7,8], and graft salvage after vascular thrombosis is rare.[7]The reported incidence of major bleeding events post-kidney transplantation is 3% to 5%.[9,10]

Coagulation and haemostatic mechanisms are substantially altered in people with kidney failure.[11,12] These abnormalities are multifactorial and may be exacerbated by perioperative management during kidney transplantation.[13,14] There is considerable practice variation in the use of perioperative anti-thrombotic agents in kidney transplant recipients, particularly regarding the use of intra-operative intravenous (IV) unfractionated heparin (UFH), for which the evidence base remains limited. The only existing guideline, from the European Urology Association, recommends against routine use of any thromboprophylaxis prior to kidney transplantation, citing a lack of any high quality evidence.[15] Despite this, a recent European survey of practicing kidney transplant specialists found over one third administer intra0operative IV UFH, with doses varying from 400-10,000 International Units.[16] Practice variation appears to be influenced in part by the transplanting surgeon's training background. The rationale for intra-operative IV UFH is to reduce the risk of ischemic complications with

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temporary vascular occlusion and to limit microthrombi formation in kidney transplant recipients compared with no IV heparin.[17]

The aim of this study was to synthesise all published data evaluating the use of intra-operative IV UFH for kidney transplant recipients.

3.3 Methodology

The protocol for this systematic review was registered on the International Prospective Register of Systematic Reviews (CRD42023391473). This study is reported in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta Analyses) [18] (*Appendix B.1*).

Study Selection Criteria

We included all study designs comparing the role of intra-operative IV UFH with no intra-operative anticoagulation in adult recipients prior to vascular anastomosis of a kidney transplantation. Any study published in peer-reviewed journals and grey-literature were eligible. Studies involving multi-organ transplantation were excluded.

Search strategy

We searched pre-defined terms in MEDLINE via Ovid, Embase via Ovid and Cochrane Central Register of Controlled Trials (CENTRAL) from 1954 to May 2025. Using Boolean operators, the searches combined keywords with Medical Subject Heading (MeSH) when searching in the title, abstract, keywords, and MeSH fields (*Appendix B.2*). This search was not limited by language.

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The search and inclusion of articles were performed independently by two authors (A.S. and S.C.) and in case of disagreement, a consensus was reached by discussion with other authors.

Data Extraction and Outcomes

Two authors (A.S. and S.C.) independently abstracted data into a standardised template. Where data were unclear or detail not available in the published report, we attempted to contact study authors to obtain more information. Reviewers extracted study characteristics including: author, year, period of study, country, study design; and patient baseline demographics including: sex, co-morbidities, immunosuppression).

Primary outcome was occurrence of thrombotic complications of transplantation (arterial, venous or combined graft vessel thrombosis). We planned a sub-analysis of thrombosis by arterial and venous location.

The secondary outcomes were: Bleeding complications including post-operative blood transfusion, surgical revision due to bleeding complications or complicated haematuria; incidence of delayed graft function (defined as dialysis within he first week post transplantation)[19]; and graft loss (defined as graft nephrectomy or dialysis dependence)

Quality of study assessment

Each included study was independently assessed for bias by two authors using the Newcastle Ottawa Quality Assessment Scale.[20] The components included three domains: Selection, Comparability and Outcome. Quality of studies were rated according to the following scoring criteria across the domains: ≥ 7 stars as good, 4 – 6 as fair, and ≤ 3 as poor.

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Statistical Analysis

We compared intra-operative IV UFH with no UFH using IBM SPSS Statistics (version 12, SPSS Inc., Chicago, Il, USA). We used Chi-square tests for categorical data, and for continuous data used mean ± standard error (SE), and independent t-tests. Results were regarded as significant at $p < 0.05$.

For meta-analysis of dichotomous outcomes, we summarised with risk ratio (RR), with 95% confidence intervals (CI) and planned mean difference (MD) or standardised mean difference (SMD) if different scales were used for continuous outcomes. A random effects model was applied due to inherent heterogeneity in study design and patient demographics in included studies, regardless of the I^2. Interpretation of the heterogeneity was done through combination of visual inspection of forest plot and calculation of I^2 statistic. Heterogeneity amongst studies were considered low, moderate and high when $I^2 \leq 30\%$, $31\% < I^2 \leq 50\%$ and $I^2 > 50\%$ respectively.[21] As we expected a relatively small number of included studies in the meta-analysis, we calculated confidence intervals for I^2 to improve precision. All meta-analyses were performed in Review Manager 5.3 software (Cochrane Collaboration, Software Update, Oxford, UK).

Summary of findings and assessment of the certainty of the evidence

We present the main results of the review in the 'Summary of findings' tables. These present the key information relating to the certainty of evidence, the magnitude of the effects of using intravenous heparin and the sum of the available data for the main outcomes. We summarised the certainty of evidence considering within-trial risk of bias (methodological quality), directness of evidence, heterogeneity, the precision of effect estimates, and risk of publication

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bias, using the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) approach[22] with GRADEprofiler (Version 3.6).

3.4 Results

Three observational cohort studies, including 1989 participants, meet the inclusion criteria and were included in this review. No randomised trials were identified. The PRISMA study flow diagram is shown in Figure 3.1.

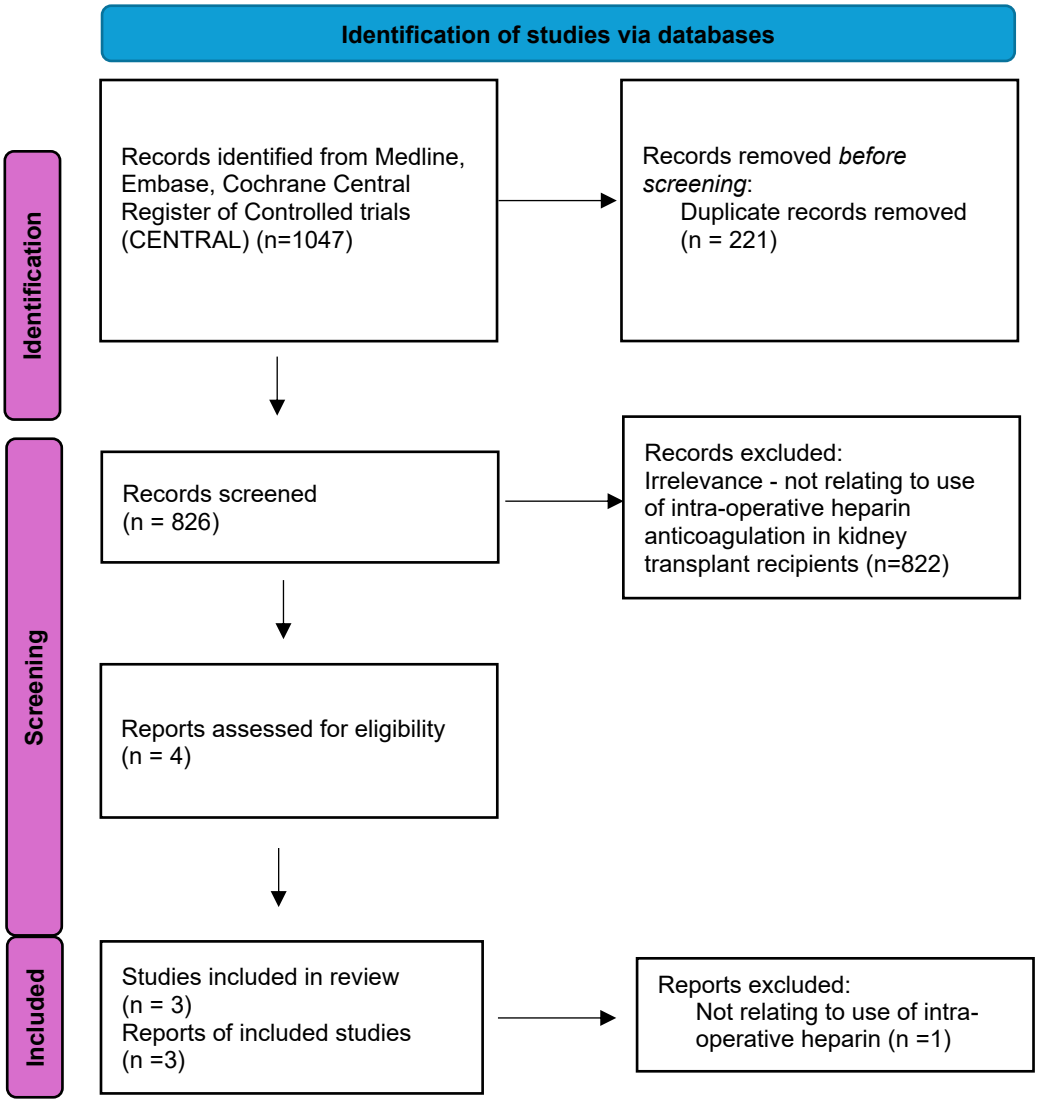

Figure 3.1: PRISMA diagram - Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram detailing study selection process in systematic review

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A summary of the study characteristics and baseline demographics of included studies is provided in Table 3.1 (further detail in *Appendix B.3*). The included studies were conducted in the Netherland, France and Ireland. A summary of study outcomes and GRADE assessments are provided in Table 3.2.

Two studies administered a standard 5000 International Units (IU) of intra-operative UFH prior to vessel clamping.[23,24] One study gave a weight-based dose (0.5mg/kg) for intra-operative UFH and exact conversion to international units could not be performed.[25] All of studies reported follow-up of at least one year.

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Table 3.1: Characteristics of the three retrospective cohort studies included in the review

Study (First author, year)	Country	Comparison				Sample size (n)	Mean age (Years)	Sex (% female)	Follow up (weeks)
		IV unfractionated heparin (IU)	n	No intra-operative anticoagulation	n				
Denize 2021	France	Weight-based*	51	No systemic anticoagulation	210	261	51.5	40	52
Van Den Berg 2019	Netherlands	5000	195	No systemic anticoagulation	1333	1528	NA	NA	52
Mohan 1999	Ireland	5000	100	No systemic anticoagulation	100	200	39.5	37	52

* 0.5 milligrams/kilogram.

IU: international units; UFH: unfractionated heparin; NR: not recorded; n: number.

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Quality of studies

Using the Newcastle-Ottawa Scale (NOS), one study was judged to be of good quality, and two studies were considered as fair (Figure 3.2).

For the selection domain, all three studies were rated fair with adequate selection, ascertainment and confirmation of absence of outcome of interest prior to study. None of the studies scored a point in representative cohort due to substantial variability of recipient factors that could influence outcomes.

For the outcome domain, all studies were rated good, with adequate assessment of outcomes and duration of follow-up. Both **Mohan 1999**[23] and **Vand den Berg 2019**[24] were graded as poor for comparability domain as cofounding factors in demographics were not accounted for. Only **Denize 2021**[25] rated good overall across all NOS domains.

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STUDY AND YEAR	SELECTION				COMPAR-ABILITY	OUTCOME			Quality of study†
	Representative cohort	Selection	Ascertainment	Outcome of interest not present prior to study		Assessment	Follow up long enough	Adequacy of follow up	
Denize 2021	-	*	*	*	**	*	*	*	Good
Mohan 1999	-	*	*	*	-	*	*	*	Fair
Vand de Berg 2019	-	*	*	*	-	*	*	*	Fair

Quality of studies adjudged by the following criteria - ≥7 as 'Good', 4-6 as 'Fair', and ≤ 3 as 'Poor'.
Maximum of 7 stars attributed to three sections as follows:
1) Selection (max four stars; one each for representative cohort, selection of non-exposed individuals, adequate ascertainment of exposure, demonstration that outcome of interest not present before the study)
2) Comparability (max two stars; one each for controlling age/sex/marital status, and for controlling other factors)
3) Outcome (max three stars; one each for adequate assessment of outcome, length of follow-up, and follow-up accounting for all or most subject

Figure 3.2: Study quality assessed by the Newcastle-Ottawa Scale (NOS) for studies included in the systematic review of outcomes

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Thrombotic complications

All three studies[23-25] reported thrombotic graft complications. There were 46 thrombotic complications across 1989 transplant recipients. The risk of thrombotic graft complications did not differ between those who received intra-operative IV UFH and those who did not (RR = 1.02, 95% CI 0.49 to 2.15, I^2 = 0%,) (Figure 3.3). Sub-group analysis also showed there was no difference in incidence of arterial thrombotic events for people receiving intra-operative IV UFH versus those without (RR = 0.82 95% CI 0.49 to 2.15, I^2 = 0%) (Figure 3.3).

Denize 2021 and **Mohan 1999** reported types of thrombotic graft failure.[23,25] In **Denize 2021**, most graft thromboses (63%, n = 12/19) were arterial, with half of these being in polar arteries. All polar artery thromboses were in the no IV UFH group.[25] In **Mohan 1999**, the arterial and venous thromboses were equally distributed (n = 5 each), with one patient having both arterial and venous thromboses.[23]

The certainty of evidence for this outcome was very low (Table 3.2).

Bleeding Complications

All three studies reported bleeding complications.[23-25] There were 193 bleeding complications in 1989 transplant recipients. There was no difference in risk of bleeding complications with use of intra-operative IV UFH compared to without any IV UFH (RR = 1.21, 95% CI 0.84 to 1.73, I^2 = 23%) (Figure 3.3).

The majority of bleeding complications recorded in this analysis were due to the need for peri-operative blood transfusions in recipients. In addition, **Mohan 1999** reported peri-renal

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haematoma in two of their patients with venous thromboses, likely contributing to graft loss. **Denize 2021** reported on 8.4% (n = 22) patients requiring surgical intervention for bleeding.

The certainty of evidence for bleeding complications was rated as very low (Table 3.2).

Delayed Graft Function (DGF)

Across the included studies, 111 transplant recipients who experienced delayed graft function (DGF), corresponding to an incidence of 24%. There was no difference in DGF with the use of intra-operative IV UFH compared with no IV UFH (2 studies; RR = 1.05, 95% CI 0.63 to 1.75, $I^2 = 40\%$) (Figure 3.3).[23,25]

The certainty of evidence for delayed graft function was very low (Table 3.2).

Graft loss and Transplant nephrectomy

Graft loss was reported in **Denize 2021**[25] and **Mohan 1999**.[23] Across these two studies, there were 17 graft losses among 23 cases of main renal artery or main renal vein thrombosis, corresponding to a graft loss incidence of 3.61% in the overall cohort. In **Mohan 1999**,[23] all graft thromboses (n = 10) underwent transplant nephrectomy within 30 days of transplantation. In **Denize 2021**,[25] 7 transplant nephrectomies were performed during the 12 months of follow-up, with an additional 13 patients requiring dialysis by the end of the 12-month follow-up.

Publication Bias

We planned to assess publication bias using funnel plots however, the small number of included studies precluded meaningful evaluation of publication bias.

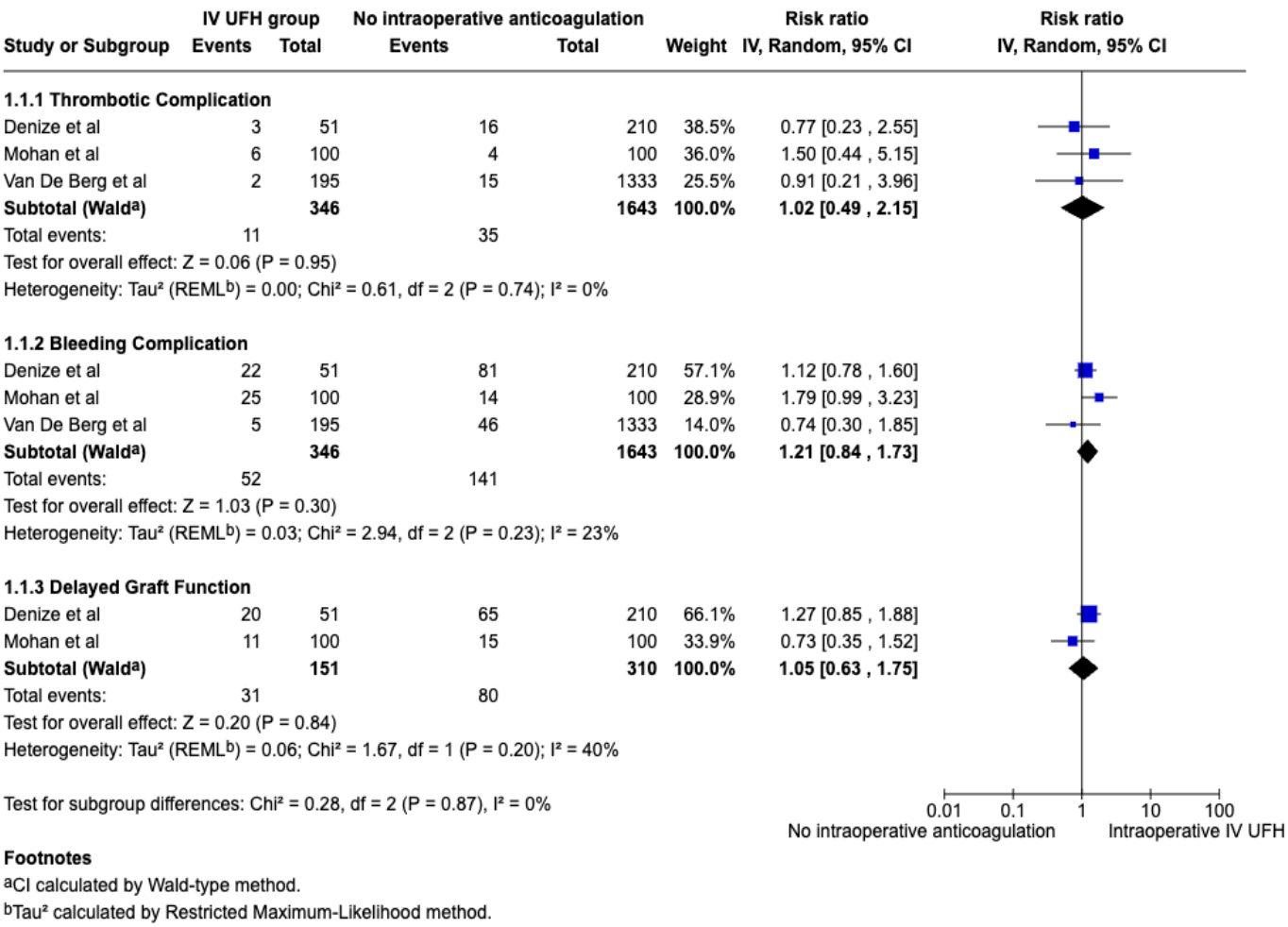

Figure 3.3: Forest plot of primary and secondary outcomes

Figure 1.1.1: Total thrombotic complications between intra-operative IV UFH vs no intra-operative anticoagulation.

Figure 1.1.2: Bleeding complications between intra-operative IV UFH vs no intra-operative anticoagulation

Figure 1.1.3: Delayed graft function between intra-operative IV UFH vs no intra-operative anticoagulation

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Table 3.2: GRADE Summary of findings

Intra-operative IV UFH compared to no intra-operative anticoagulation in adult kidney failure patients undergoing kidney transplantation

Patient or population: Adult kidney failure patients undergoing kidney transplantation living and deceased
Setting: In-patient
Intervention: Intra-operative IV UFH
Comparison: No intra-operative anticoagulation

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with no intra-operative anticoagulation	Risk with Intra-operative IV UFH			
Thrombotic complication	21 per 1,000	22 per 1,000 (10 to 45)	RR 1.02 (0.47 to 2.13)	1989 (3 non-randomised studies)	⊕◯◯◯ Very low[a,b,c]
Bleeding complication	105 per 1,000	135 per 1,000 (79 to 234)	RR 1.28 (0.75 to 2.22)	1989 (3 non-randomised studies)	⊕◯◯◯ Very low[a,b,c]
Delayed graft function	258 per 1,000	245 per 1,000 (147 to 415)	RR 0.95 (0.57 to 1.61)	461 (2 non-randomised studies)	⊕◯◯◯ Very low[a,b,c]

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: confidence interval; RR: risk ratio.

GRADE Working Group grades of evidence
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.
Explanations
a. retrospective cohort study with moderate risk of bias
b. study population significant mix in living and deceased donors. generalisability for routine deceased donor population limited
c. wide confidence intervals crossing the midline with low event rates

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3.5 Discussion

This systematic review of intra-operative IV UFH bolus found no significant differences in graft thrombosis or bleeding complications in retrospective cohort studies of adult patients with kidney failure receiving a kidney transplant. These findings are consistent with recent European guidelines which do not support routine use of intra-operative anticoagulation for adult kidney transplant recipients.[15]

Patients with kidney failure have a paradoxical haemostatic profile, characterised by both increased bleeding risk and increased thromboembolic risk due to altered haemostatic mechanisms.[11] The additional risk or benefit conferred by anticoagulants and anti-platelet therapy in transplant recipients is poorly defined.[26,27] Clinical studies assessing bleeding risk have found that compared with the general surgical population, patients with kidney failure who undergo kidney transplantation have higher bleeding rates at similar APTTs.[28] This likely relates to uraemia associated platelet and clotting factor dysfunction, reduced platelet production, and paradoxical consumption of coagulation factors.[29] Conversely, there are data supporting a higher peri-operative thromboembolic complication rate, reflecting a hypercoagulable state.[30] In particular, the incidence of antiphospholipid antibodies was reported to be up to 10% to 30% even among recipients without antiphospholipid syndrome.[31] In addition, studies have suggested the risk of venous thromboembolism remains post transplantation into the first post-operative year.[32,33]

Graft thrombosis due to arterial or venous occlusion is uncommon, with reported incidences between 1% to 6%.[7] A recent Cochrane Review which examined pharmacological strategies to prevent graft thrombosis,[26] concluded that there was a lack of high-quality evidence to guide specific antithrombotic regimens in abdominal organ transplant recipients. Another

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recent systematic review did not find a difference in the graft vascular thrombosis rates across various anti-platelet and anticoagulation regimens.[8] However, there was substantial heterogeneity in the study populations and overlap in preoperative and post-operative therapies. In that review, most thrombotic events occurred in the first month post-operatively. Our study found all graft thromboses occurred within the first 30 days post-transplant, supporting the concept that vascular graft thrombotic complications may be more strongly influenced by surgical and anatomical factors than by perioperative anticoagulation alone.

We did not find a higher incidence of perioperative bleeding complications in recipients who received IV UFH. One possible explanation is the heterogeneity in recipient population and transplant settings across the included studies. Furthermore, due to the way IV UFH and no IV UFH were reported in the included studies, it was difficult to differentiate living donor transplantation from deceased donor transplantation.

We also found no difference in the incidence of DGF between recipients who received IV UFH cohort and those who did not. Previous work by Van Den Berg and colleagues has suggested an important role for microthrombi in the pathogenesis of delayed graft function in both animal models and human clinical studies.[34] If microthrombi were a dominant contributor to DGF, intra-operative IV UFH might be expected to reduce DGF rates. However, our findings do not support this hypothesis. Moreover, the overall incidence of DGF in our review (24%) was lower than contemporary DGF rates of 30-40% in deceased donor transplantation from donation after cardiac death and neurological death.[6] The aetiology of DGF is multifactorial, including anastomosis time, cold and total ischemic time, donor characteristics and perioperative complications.[35] Further evaluation of these factors in

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relation to DGF within our meta-analysis was limited by incomplete reporting in the included studies.

Despite the included studies being graded as ‘fair’ or ‘good’ quality, the overall certainty of evidence was considered for all outcomes was very low. We identified no randomised control trials of intra-operative IV UFH in kidney transplant recipients. This may have introduced selection bias, as the decision to administer anticoagulation may have been influenced by the surgeons’ intra-operative assessment of clotting or bleeding tendency. Such treatment-by-indication bias could have led to a type II error, whereby a true difference between groups was not detected because patients at higher risk were more likely to receive IV UFH.

The role of intra-operative IV UFH in the context of multiple vascular anastomoses was of particular interest, but difficult to interpret. Only Denize 2021 reported specifically outcomes related to polar vessels. Interestingly, all polar artery thromboses which occurred in recipients who did not receive intra-operative IV UFH.[25] This may be more akin to paediatric kidney transplantation in terms of technique and vessel size. Systematic reviews in paediatric kidney transplantation have found that intra-operative or post-operatively thromboprophylaxis can reduce graft loss,[36,37] likely reflecting the impact of smaller vessel size and more technically demanding anastomoses. Although direct extrapolation to adult kidney transplantation is limited by differences in dosing and patient characteristics, our findings raise the possibility that intra-operative IV UFH may have a role in selected adult kidney transplants with multiple renal arteries. Prior studies have also examined the impact of different anastomotic techniques for multiple renal arteries on graft outcomes.[38]

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There are several limitations which we would like to acknowledge. Firstly, we acknowledge that there was wide temporal relationship with no statistical difference observed in only three studies in the meta-analysis. Despite no statistically significant difference being observed, we felt the meta-analysis still strengthens the review by providing pooled effect estimates, confidence intervals, and heterogeneity measures that cannot be derived from narrative synthesis alone. In addition, by highlighting the wide confidence intervals we showed quantitatively that there is an insufficiency data in this topic and highlight a significant literature gap.

We were unable to account for several confounders including technical considerations in anastomosis, the impact of living versus deceased donation, and variations in immunosuppression regimens. The included studies were conducted across different countries with different transplantation protocols which may limit generalisability of the results in our study for a specific population. The use of an end to end anastomosis to the internal iliac artery has lost favour and may increase recipient complication risk.[39] No specific mention of technique of anastomosis were included in two of the three studies.[23,24] In addition, one of the studies was conducted in the era of routine cyclosporine use.[23] Whilst they did not demonstrate any increase thrombosis risk, it is postulated that traditional cyclosporine-based immunosuppression was associated with increased thrombosis risk for transplant recipients.[40,41]

In addition, several medication related confounders were also not evaluated. Firstly, the impact of antiplatelet therapy in recipients is unclear. A recent meta-analysis by Lee et al, demonstrated a significantly increased risk of post-operative haemorrhage with dual antiplatelet therapy compared with single antiplatelet therapy, with relative risk of 1.58.[42] The

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influence of anti-platelet agents on outcomes in the included studies could not be assessed, as these data were not consistently reported. Similarly, we could not analyse haematological blood parameters such as APTT, activated clotting time, or thromboelastograms (TEG) results which might help identify higher risk patient who may benefit from intra-operative IV heparin.[43] Variation in the use of post-operative anticoagulation including therapeutic heparin or thromboprophylaxis dose heparin, was also not described by the included studies and therefore could not be incorporated into our analysis. Such variation may have contributed to the absence of observed differences in bleeding and thrombotic outcomes between groups.

Overall, our study suggests that whilst intra-operative IV UFH bolus prior to kidney transplantation appears safe from a bleeding perspective, its clinical benefit remains uncertain. The relatively low incidence of DGF observed, combined with the retrospective nature of the available studies, supports the likelihood of selection bias with a predominance lower-risk recipients. There is insufficient evidence to recommend routine use of IV UFH for all adult kidney transplant recipients. Well-designed prospective studies, ideally randomised control trials, are needed to clarify whether specific subgroups, such as those with multiple renal arteries or other high risk vascular features, derive benefit in terms of reduced graft thrombosis.

3.6 Conclusion

This review provides a systematic evaluation of intra-operative IV UFH in adult kidney transplantation. No major differences were observed in thrombotic or bleeding complications between recipients who received intra-operative IV UFH and those how did not, and there was no difference in the incidence of delayed graft function. The overall certainty of evidence

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was very low due to wide temporal trend and confidence intervals, highlighting the need for high-quality prospective studies to define the role of intra-operative IV UFH and to identify transplant recipients who may benefit from targeted anticoagulation strategies.

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Chapter 4: Discussion and Conclusion

4.1 Overview

The haemostatic balance in patients with kidney failure and dialysis represents a complex interplay between pro-haemorrhagic and pro-thrombotic factors, creating a paradoxical state with potential to significantly impact surgical outcomes.[1,2] This thesis investigated the complex haemostatic mechanisms in kidney failure patients undergoing minor and major surgery, with a focus on the role of intra-operative intravenous (IV) unfractionated heparin (UFH) bolus.

The role of intra-operative IV UFH bolus in impacting bleeding and thrombotic outcomes following surgery in kidney failure patients has been poorly investigated in the literature. A challenge to conducting adequately powered studies in this specific patient population is the relatively low event rate of these complications. Additionally, the unpredictable timing of transplant surgery means planning and executing trials is not easy.[3,4] Nonetheless, the considerable variation in clinical practice across different institutions and geographical regions underscores the urgent need for evidence-based practice guidelines.[5,6]

4.2 Key findings: intra-operative heparin in arteriovenous fistula creation and kidney transplantation

This thesis highlighted the role of intra-operative IV UFH administration during AVF creation for haemodialysis. The findings suggest that IV UFH does likely have a beneficial role in reducing AVF thrombosis complications, with the most prominent benefits observed for radiocephalic AVFs. This represents an important clinical finding, as intra-operative IV heparin

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bolus administration appears to confer particular benefit in procedures involving smaller vessel diameters, where the risk of early thrombotic failure is highest. The findings presented in Chapter 2 suggest that prophylactic intra-operative heparin may address this vulnerability by preventing platelet adhesion and thrombus formation during the critical perioperative period. The mechanistic rationale for UFH's protective effect in smaller vessel anastomoses relates to fundamental principles of vascular biology and haemodynamics.[7,8] During surgical manipulation and anastomosis creation, endothelial injury occurs, exposing subendothelial collagen and von Willebrand factor which serve as potent stimuli for platelet adhesion.[9] In smaller diameter vessels, the higher shear stress environment further promotes platelet activation through shear-induced conformational changes in vWF and the GPIb-IX-V receptor complex.[10,11] Additionally, the reduced flow rates in smaller vessels create conditions conducive to thrombin generation and fibrin formation.[12] Intra-operative IV UFH administration, by enhancing antithrombin III activity and inhibiting multiple coagulation factors (particularly thrombin and factor Xa), can effectively interrupt this prothrombotic cascade during the critical anastomotic period.[13,14]

In Chapter 3, I investigated the role of IV UFH bolus in kidney transplant recipients. Whilst I found no evidence of benefit or harm, studies were limited. By systematically mapping the existing evidence, I revealed a substantial evidence-practice gap and identified key areas of uncertainty that warrant prospective evaluation.

4.3 Bleeding risk assessment and the paradoxical thrombotic state

Interestingly, the bleeding complications observed in both AVF creation and kidney transplantation procedures with IV UFH bolus administration were not as pronounced as initially

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suspected based on traditional views of uraemic bleeding tendency.[15,16] This observation may point to the overall paradoxical thrombotic risk that is increasingly recognised to be present in patients with kidney failure and who are dialysis dependent.[17,18] The bleeding complications following AVF formation noted in Chapter 2 were small in magnitude and generally self-limiting, typically manifesting as minor haematoma formation or prolonged oozing that resolved with conservative measures. In kidney transplant recipients, we did not observe any increase in bleeding risk associated with intra-operative heparin use, as measured by transfusion requirements, reoperation for bleeding, or post-operative haemoglobin decline. The lack of bleeding complications in kidney transplant recipients is important given the significantly added morbidity associated with blood transfusion or take-back surgery.

The contemporary understanding of haemostasis in kidney failure has evolved considerably from earlier concepts that emphasised primarily the bleeding diathesis associated with uraemia.[19,20] While it is well-established that uraemic toxins can impair platelet function through multiple mechanisms – including defective platelet endothelial interactions, reduced platelet adhesion, and altered release of platelet-derived mediators—recent evidence has highlighted the concurrent presence of multiple prothrombotic factors.[21,22] These include elevated levels of fibrinogen, factor VIII, and vWF; reduced levels of natural anticoagulants such as protein C and protein S; impaired fibrinolysis; and chronic inflammation with associated endothelial dysfunction.[23-25] This complex haemostatic profile creates a state of "uremic thrombosis" that may partially offset the bleeding tendency, particularly in the perioperative setting where surgical stress and acute phase responses further shift the balance toward hypercoagulability.[26,27]

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Furthermore, the improving management of uraemia through modern dialysis techniques may have reduced the clinical significance of uraemic bleeding in contemporary practice.[28,29] The relatively low bleeding risk observed in our studies was surprising but may reflect these advances in the overall management of kidney failure patients.

4.4 Literature gaps and research implications

This thesis highlights significant gaps in evidence for everyday common clinical procedures and practice. Despite the clinical importance of these procedures and the unique haemostatic challenges posed by kidney failure, high-quality randomised controlled trials examining anticoagulation strategies in kidney transplantation sphere remain scarce. The very low certainty evidence in kidney transplants consists primarily of observational studies with heterogeneous populations, variable heparin protocols, and inconsistent outcome definitions and reporting, limiting the ability to draw definitive conclusions.

Key areas requiring further investigation include:

- Uncertainty on the true benefit or harm of IV UFH bolus during kidney transplantation
- Optimal IV UFH dosing and potential need for reversal is yet to be defined
- Alternatives to IV UFH including intra-operative subcutaneous UFH, antiplatelet agents or other heparnoids
- Better patient risk stratification strategies to identify thrombotic or bleeding phenotype in kidney transplant recipients.

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4.5 Clinical and policy implications

The results of this thesis may have direct impact on both future guideline development and practical clinical application in the management of kidney failure patients undergoing surgery. Currently, the only existing guidelines specifically addressing the value of intra-operative IV UFH bolus relate to AVF access creation, with the Kidney Disease Outcomes Quality Initiative (KDOQI) and European Renal Best Practice (ERBP) guidelines recommending against routine IV heparin use based on limited evidence.[30,31] These recommendations drew largely on older studies with methodological limitations and may not reflect current surgical techniques, patient populations, or our evolving understanding of uraemic haemostasis.

This thesis provides updated evidence to support reconsideration of the role of IV UFH bolus use in the European and other international vascular access guidelines. The findings suggest that a more nuanced, risk-stratified approach may be warranted, particularly for procedures involving smaller vessels where thrombotic risk is highest. Rather than a blanket recommendation against IV UFH bolus use, guidelines might consider endorsing selective UFH administration based on vessel characteristics, patient-specific thrombotic risk factors, and surgical complexity.

In addition, for kidney transplant recipients, this thesis identified a key literature gap highlighting the need for more nuanced risk stratification strategies to define bleeding and thrombosis risk. In the age of personalised medicine, better predictive models are urgently needed such as those which have been developed for stroke risk in atrial fibrillation (CHADS2VASC) and bleeding in AF (HASBLEED). Independent of the utilisation of IV UFH, risk stratification may improve our understanding of graft thrombosis and bleeding risks

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4.6 Future research directions

I demonstrated uncertainty for IV UFH use in patient selection, perioperative testing including the use of viscoelastic testing, timing and dosing of heparin, reversal strategies, and management of concurrent oral anticoagulant/antiplatelet therapy.

The evidence based I mapped was most sparse for UFH in kidney transplantation. I suggest future research in two stages: firstly, a structured expert Delphi consensus process to help refine clinical questions and secondly a subsequent randomized controlled trial.

Part 1: Delphi consensus process

The aim of Part 1 would be to achieve international expert consensus on key components of perioperative haemostatic management in kidney transplantation, with a specific focus on:

1. Patient-specific factors that might impact the balance between bleeding and thrombotic risk
2. Laboratory investigations that should be routinely performed preoperatively
3. Indications, timing, and dosing of intra-operative IV heparin across different clinical scenarios
4. Indications for reversal of heparin at the end of surgery
5. The role and implementation of viscoelastic testing (ROTEM/TEG) to guide UFH use
6. Perioperative management of antiplatelet agents and direct oral anticoagulants

Delphi structure will be grouped by domains, with the aim of arriving at consensus for:

1. **Risk stratification** – clinical and imaging factors influencing bleeding versus thrombosis

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2. **Laboratory testing** – standard coagulation assays, platelet function tests, viscoelastic testing
3. **Heparin use** – whether to use heparin routinely versus selectively; recommended dose range (e.g. 50 to 100 U/kg); timing (at clamp versus pre-reperfusion); monitoring strategy
4. **Reversal** – indications, dosing, and timing of protamine; how to incorporate ROTEM/TEG results
5. **Concomitant therapies** – perioperative interruption or continuation of antiplatelet agents and direct oral anticoagulants, including thresholds for delaying surgery
6. **Endpoints and outcomes** – which clinical and haemostatic endpoints should define 'success' for a heparin RCT (e.g. graft thrombosis, major bleeding, transfusion, DGF, ROTEM signatures)

Part 2: Pragmatic randomised controlled trial

With results from the Delphi survey, I will design a prospective randomized trial to evaluate intra-operative IV heparin on early thrombotic and bleeding outcomes in renal transplantation (Figure 4.1). I would draw on strengths of Australian and New Zealand trial and transplant infrastructure, using a pragmatic, registry-based, multicentre approach. The design would closely mirror the BEST-Fluids trial, which successfully leveraged a registry platform to conduct a large-scale RCT in renal transplantation.[32]

The trial will be conducted at renal transplant centres in Australia and New Zealand that contribute to the Australia and New Zealand Dialysis and Transplant (ANZDATA) Registry. All adult and paediatric recipients (≥ 20 kg) of kidney transplants—both living and deceased

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donor—will be screened for eligibility. Provisional inclusion criteria would include**:** people undergoing kidney transplantation (living or deceased donor), weighing ≥ 20 kg and with capacity to provide informed consent or consent from a legal guardian.

Exclusion criteria would include: known heparin-induced thrombocytopenia, active major bleeding or severe coagulopathy (e.g. INR > 2.5 or platelets < 40×10^9/L), known thromobophilia or requirement for chronic anticoagulation/bridging heparin therapy, or undergoing multi-organ transplantation (e.g. kidney–pancreas).

Provisionally, the intervention would be a single bolus of UFH (within an allowed range of 50 to 100 U/kg as determined by the Delphi consensus and local practice) administered IV immediately prior to clamping for the vascular anastomosis. The comparator would be an equivalent volume of 0.9% saline administered at the same time point.

Based on Delphi consensus, I may include provision for protamine administration at the discretion of the anaesthetist or surgeon in response to haemodynamic instability, diffuse bleeding, or viscoelastic evidence of excessive anticoagulation. Based on Delphi findings, I will also clarify any ROTEM/TEG sample testing strategy and timing.

All other aspects of intra-operative and post-operative care, including fluid management, blood products, immunosuppression, and thromboprophylaxis, will follow local practice and existing guidelines, consistent with the pragmatic design.

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Nested within the clinical trial, there may be opportunity for a 'study within a trial' (SWAT). SWAT design could be used to further assess mechanistic processes for the role of IV UFH and point of care innovations. TEG utilisation may offer better understanding of haemostatic physiology. Viscoelastic testing offers several advantages over traditional coagulation assays in this context. These tests provide rapid results (typically within 10 to 20 minutes) that can inform intra-operative decision-making, unlike conventional tests that require 45 to 60 minutes processing for results.[33] Second, viscoelastic tests assess the entire coagulation process from clot initiation through fibrinolysis, providing a more comprehensive picture of haemostatic function than isolated factor levels or platelet counts.[34] Third, these tests can identify specific defects (e.g. factor deficiency, platelet dysfunction, hyperfibrinolysis) that may guide targeted therapy.[35] Finally, viscoelastic testing has been shown to reduce transfusion requirements and improve outcomes in other surgical settings, including cardiac surgery and liver transplantation, suggesting potential applicability to kidney transplantation.[36,37]

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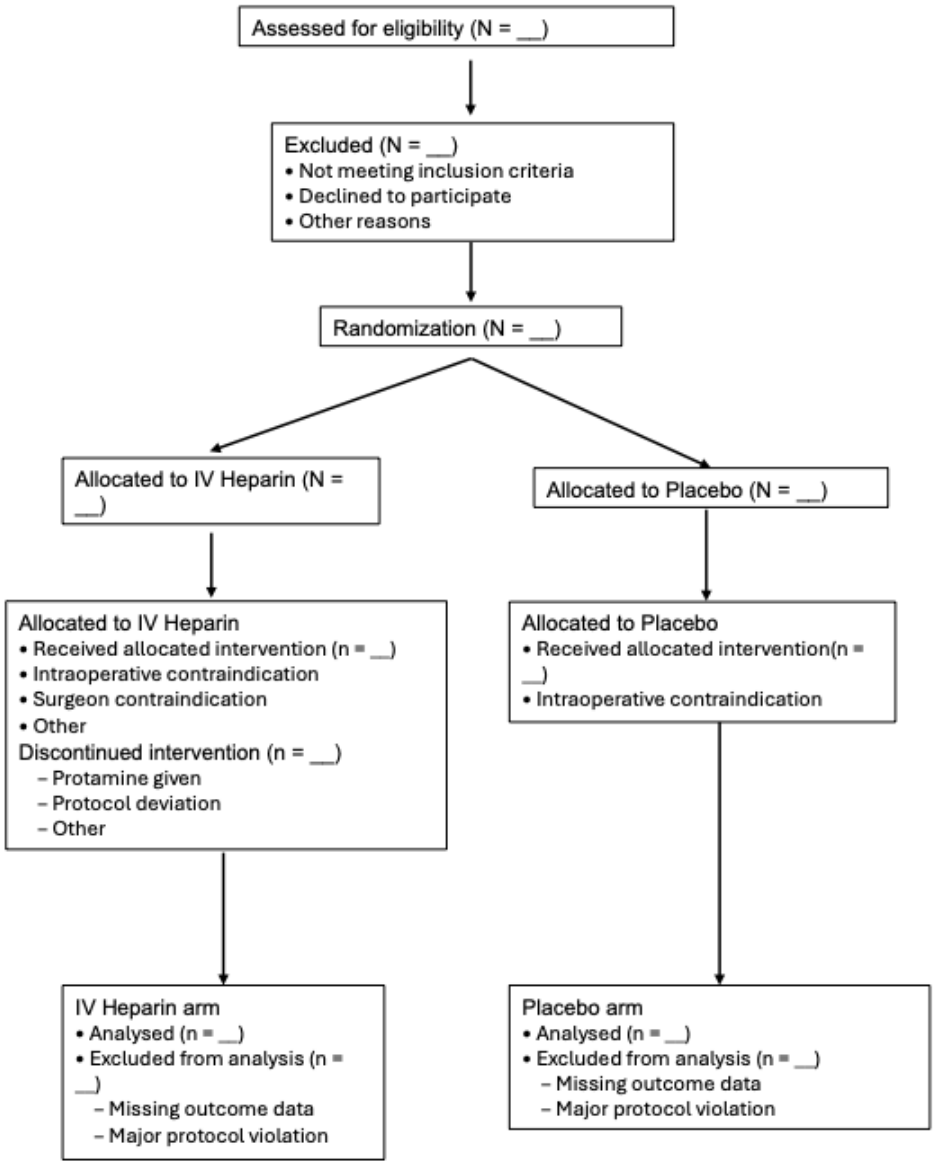

Figure 4.1: CONSORT diagram of a potential RCT design

4.7 Personal Research Development and Lessons Learned

The process of conducting this research as a part-time higher research degree has provided valuable insights into the challenges and rewards of balancing clinical duties with academic pursuits. Maintaining a regular schedule and dedicated time commitment to research proved essential for making consistent progress, despite competing unpredictable clinical responsibilities

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and the inevitable interruptions inherent in medical practice. The discipline of setting aside protected time for research activities including literature review, data collection and analysis, manuscript preparation, and meetings with supervisors, was critical to my successful completion of this thesis.

The MPhil program provided an opportunity for comprehensive training. I had options of coursework study in both qualitative and quantitative research methodologies, enhancing my capability to critically appraise existing literature, design rigorous studies, and appropriately analyse complex datasets.

Particularly valuable was the opportunity to complete 12 units of coursework study in health economics (PUBH5312 and PUBH5317) which has helped me develop health economic evaluation skills, including cost-effectiveness analysis and decision-analytic modelling, which I hope to develop further in my future career. I hope to incorporate health economic evaluation into the trial I have proposed above, recognising the increasingly importance of resource constraints and value-based healthcare.

An unexpected but highly rewarding aspect of this research journey was the opportunity to co-author publications and supervise junior doctors undertaking similar research-style projects. My experience equipped me for a mentorship role, combining my clinical expertise with my new research skills. I was able to guide junior researchers, including MD students, through the research process: from formulating research questions and designing studies to analysing data and preparing manuscripts for publication. These experiences have reinforced the importance of

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fostering the next generation of clinician-scientists and have enhanced my own understanding of research principles through the process of teaching others.

The collaborative nature of this research, involving interactions with surgeons, nephrologists, anaesthesiologists, haematologists, epidemiologists and statisticians, has also highlighted the value of multidisciplinary approaches to addressing complex clinical questions.

The diverse perspectives and expertise contributed by team members from different specialties enriched my learning, enhanced the research process and will undoubtedly inform my future approach to clinical investigation.

4.8 Conclusion

This thesis highlighted the significant literature gap in our understanding of how to better predict and manage bleeding and thrombotic risk in kidney failure patients, particularly in the context of the common procedures of AVF formation and kidney transplantation. I showed that despite the critical importance of optimizing perioperative haemostatic management to improve outcomes in this vulnerable population, high-quality evidence to guide clinical decision-making remained limited. The heterogeneity in current clinical practice reflects this uncertainty and underscores the need for new and better rigorous comparative effectiveness research.

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Appendices

Appendix A and B contain the supplementary documents for Chapter 2 and Chapter 3, respectively.

Appendix A.1: Comprehensive search strategy

Databases:
EBM Reviews - Cochrane Database of Systematic Reviews <2005 to November 1, 2023>
EBM Reviews - ACP Journal Club <1991 to October 2023>
EBM Reviews - Cochrane Clinical Answers <October 2023>
EBM Reviews - Database of Abstracts of Reviews of Effects <1st Quarter 2016>
Embase Classic+Embase <1947 to 2023 November 03>
Ovid MEDLINE(R) ALL <1946 to November 03, 2023>

#	Query	Results from 5 Nov 2023
1	exp heparin/	250,291
2	exp anticoagulant agent/	1,078,497
3	exp fistula/ or exp arteriovenous fistula/	257,058
4	exp arteriovenous shunt/ or exp vascular access/	43,890
5	exp anastomosis/	305,090
6	(avf or avg).tw.	23,414
7	(randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or clinical trials as topic/ or randomly.ab. or (crossover or cross-over).tw. or cross-over studies/ or trial.ti.	3,456,492
8	(intraop* or operat* or periop*).mp. [mp=ti, ab, tx, kw, ct, hw, tn, ot, dm, mf, dv, kf, fx, dq, bt, nm, ox, px, rx, ui, sy, ux, mx]	4,172,422
9	anticoagulation.mp.	175,979
10	(systemic heparin or systemic anticoagulation).tw.	4,529
11	angioaccess.mp.	476
12	3 or 4 or 5 or 6 or 11	550,131
13	1 or 2 or 9 or 10	1,139,778
14	12 and 13	33,590
15	8 and 14	6,340
16	7 and 15	509
17	remove duplicates from 16	506

https://ezproxy.library.usyd.edu.au/login?url=http://ovidsp.ovid.com/ovidweb.cgi?T=JS&NEWS=N&PAGE=main&SHAREDSEARCHID=6O1CVgizdegvfpVLeFolJvebgZRjPUaLfCWkgeRhGgBvjdfJFXh0xG3FQiA2kCIop

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Appendix A.2: PRISMA checklist of items in systematic reviews (2020)

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Title, page 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Abstract, pg 4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Introduction, pg 6, lines 100-123
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Introduction, pg 6, lines 125-127
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Methods, pg 7, lines 133-139
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Methods pg 8, lines 158-167
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Supplementary material Table 3
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Methods pg 7-8,
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Methods pg 8, lines 169-178
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Methods pg 7 lines 141-156
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Methods pg 7 lines 141-156
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Methods pg 8, lines 180-182
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Methods pg 9, lines 184-193
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Methods pg 18, lines 174-178
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Methods, pg 9, lines 184-193
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Table 1 and 2
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software	Methods pg 9, lines 184-193

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Section and Topic	Item #	Checklist item	Location where item is reported
		package(s) used.	
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Methods pg 9, 184-193 Results pg 13, lines 297-300
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Nil
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Methods pg 8, lines 180-182
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Methods pg 9, lines 195-205
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Results, pg 9-10, lines 208-215. Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Figure 1
Study characteristics	17	Cite each included study and present its characteristics.	Table 2, Table 3
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Figure 2
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Results pg9-13 lines 208-300, Table 1-3, Figure 3
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Figure 2
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Results pg9-13 lines 208-300, Figure 3
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Figure 2-3
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Nil
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Figure 2, Supplementary 3
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Table 3
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Discussion, pg 13-16, lines 302-383
	23b	Discuss any limitations of the evidence included in the review.	Discussion, pg 350-376
	23c	Discuss any limitations of the review processes used.	Discussion, pg 350-376
	23d	Discuss implications of the results for practice, policy, and future research.	Abstract, pg 4 What this paper

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Section and Topic	Item #	Checklist item	Location where item is reported
			adds paragraph pg 3, discussion pg 14-15, lines 332-348
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Methods Pg7, lines 128-131
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Yes
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Nil
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	cover material pg 3, no sources of funding
Competing interests	26	Declare any competing interests of review authors.	cover material pg 3, no competing interests
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Yes – upon request

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

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Appendix A.3: Characteristics of included studies and risk of bias assessments with rationale

Wang, 2010

Study characteristics		
Methods	• Study Design: RCT • Study duration and follow-up: April 2007 to Nov 2009, follow-up to 30 days post-operatively	
Participants	Setting: Hospital Country: United States of America Inclusion Criteria • Patients needing haemodialysis access >18 years age, patients suitable for autogenous AVF Baseline Characteristics • Number: Intervention group (22); control group (26) • Mean age ± SD (years): Intervention group (51.8 ±2.8); control group (50.1±2.5) • Sex (M/F): Intervention group (14/12); control group (10/12) • Comorbidities: Hypertension, T2DM Exclusion Criteria • Allergy to heparin, lactating females or positive pregnancy test within 24 hours of creation	
Interventions	Intervention group • Intravenous Heparin administered 2 minutes before clamping artery • Dose 75 units/Kg Control group • Did not receive any medication Follow-up details: • At 30 days post-operatively • Patency diagnosed clinically by presence of palpable thrill	
Outcomes	Outcomes reported immediate post-operatively and 30 days: • Patency • Bleeding • Haematoma • Re-interventions	
Notes	• Approved by University of South California Health Sciences Institutional review board • Funding declaration: Not reported • Conflict of interest: Not reported • Publication type: Full-text article	
BIAS	AUTHOR'S JUDGEMENT	SUPPORT
Random Sequence Generation (Selection Bias)	Low Risk	"double-blinded, randomised control trial"
Allocation Concealment (Selection Bias)	Unclear Risk	No details on allocation process
Performance Bias	Low Risk	"double-blinded"
Detection Bias	Unclear Risk	No details on how post-operative assessment was performed
Attrition Bias	High Risk	5 patients lost in follow-up
Reporting Bias	Unclear Risk	No comment on trial registration
Other Bias	Low Risk	No other bias concern

Bhomi, 2008

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Study characteristics		
Methods	• Study Design: RCT • Study duration and follow-up: April 2005 to July 2007, follow-up to 6 weeks post-operatively	
Participants	Setting: Hospital Country: Nepal Inclusion Criteria • Patients needing haemodialysis access >18 years age, native AVF, Only R-C first fistulas Baseline Characteristics • Number: Intervention group (25); control group (25) • Mean age ± SD (years): Intervention group (48 ±2.6); control group (50±2.2) • Sex (M/F): Intervention group (14/11); control group (13/12) • Comorbidities: Hypertension, T2DM, hyperlidemia, and coronary artery disease Exclusion Criteria • If previous revision of surgery, if not radiocephalic fistula	
Interventions	Intervention group • Intravenous Heparin administered 2 minutes before clamping artery • Dose 5000 IU Control group • Did not receive any medication Follow-up details: • At 6 weeks post-operatively • Patency diagnosed clinically by useful function of access	
Outcomes	Outcomes reported immediate post-operatively and 30 days: • Patency • Bleeding • Haematoma • Re-interventions	
Notes	• Approval by ethics not reported • Funding declaration: Not reported • Conflict of interest: Not reported • Publication type: Full-text article	
Notes	• Approved by University of South California Health Sciences Institutional review board • Funding declaration: Not reported • Conflict of interest: Not reported • Publication type: Full-text article	
BIAS	AUTHOR'S JUDGEMENT	SUPPORT
Random Sequence Generation (Selection Bias)	Low Risk	"patients were randomised to receive systemic heparin or not"
Allocation Concealment (Selection Bias)	Unclear Risk	Unclear on allocation process
Performance Bias	Low Risk	Unclear if surgeons or participants were blinded and how
Detection Bias	Unclear Risk	Unclear if assessor was blinded
Attrition Bias	Low Risk	No loss of patients
Reporting Bias	Unclear Risk	No access to trial registration
Other Bias	Low Risk	No other concerns

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D'Ayala, 2008

Study characteristics		
Methods	• Study Design: RCT • Study duration and follow-up: July 2004 to March 2006, follow-up to 3 months post-operatively	
Participants	Setting: Hospital Country: United States of America Inclusion Criteria • Patients needing haemodialysis Baseline Characteristics • Number: Intervention group (57); control group (58) • Mean age $\pm$ SD (years): Intervention group 62(± 1.8); control group (60± 1.8) • Sex (M/F): Intervention group (33/29); control group (31/29) • Comorbidities: Hypertension, T2DM, hyperlidemia, and coronary artery disease Exclusion Criteria • If revision of previous surgery	
Interventions	Intervention group • Intravenous Heparin administered 2 minutes before clamping artery • Dose 5000 IU Control group • Heparinised saline irrigation Follow-up details: • At 30 days and 3 months post-operatively	
Outcomes	Outcomes reported immediate post-operatively and 30 days: • Patency • Bleeding • Haematoma • Re-interventions	
Notes	• Approval by ethics not reported • Funding declaration: Not reported • Conflict of interest: Not reported • Publication type: Full-text article	
BIAS	AUTHOR'S JUDGEMENT	SUPPORT
Random Sequence Generation (Selection Bias)	Low Risk	"patients were randomised to receive systemic anticoagulation…or no systemic heparin"
Allocation Concealment (Selection Bias)	Unclear Risk	No information on allocation concealment
Performance Bias	Unclear Risk	No information on blinding
Detection Bias	Unclear Risk	No information on assessor blinding
Attrition Bias	Low Risk	No loss of patients
Reporting Bias	Unclear Risk	No information on trial registration
Other Bias	Low Risk	No other concerns

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Ravari, 2008

Study characteristics		
Methods	• Study Design: RCT • Study duration and follow-up: Nov 2003 to May 2005, follow-up to 2 weeks post-operatively	
Participants	Setting: Hospital Country: Iran Inclusion Criteria • Native AVF creation. Only R-C or B-C fistulas Baseline Characteristics • Number: Intervention group (96); control group (102) • Mean age $\pm$ SD (years): Intervention group (48 ± 14.5); control group (48.5 ± 16.4) • Sex (M/F): Intervention group (60/36); control group (63/29) • Comorbidities: Not reported Exclusion Criteria • If revision of previous surgery, prior surgery at site, positive coagulopathy or vasculitis	
Interventions	Intervention group • Intravenous Heparin administered before clamping artery • Dose 5000 IU Control group • No medication given Follow-up details: • At 2 weeks post-operatively by clinical examination by thrill and bruit	
Outcomes	Outcomes reported immediate post-operatively and 30 days: • Patency • Bleeding • Haematoma • Re-interventions	
Notes	• Approval by ethics committee • Funding declaration: No funding but support of Sina Hospital, Research and Department Centre • Conflict of interest: No conflict of interest • Publication type: Full-text article	
BIAS	AUTHOR'S JUDGEMENT	SUPPORT
Random Sequence Generation (Selection Bias)	Low Risk	"patients were randomly divided into two groups"
Allocation Concealment (Selection Bias)	Low Risk	"randomisation was achieved using sealed envelopes"
Performance Bias	Unclear Risk	No information on blinding
Detection Bias	Unclear Risk	No information on assessors being blinded
Attrition Bias	Low Risk	No loss of patients
Reporting Bias	Unclear Risk	No information on trial registration
Other Bias	Low Risk	No other concerns.

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Ebrahimifard, 2015

Study characteristics		
Methods	• Study Design: RCT • Study duration and follow-up: Nov 2003 to May 2005, follow-up to 6 weeks post-operatively	
Participants	Setting: Hospital Country: Iran Inclusion Criteria • Native AVF creation. Only R-C fistula Baseline Characteristics • Number: Intervention group (25); control group (25) • Mean age $\pm$ SD (years): Intervention group (57.5 ± 15.8); control group (53 ± 13) • Sex (M/F): Intervention group (15/10); control group (17/8) • Comorbidities: Diabetes, Hypertension, Glomerulonephritis, Pyelonehpritis, Polycystic kidney disease Exclusion Criteria • If candidates for fistula reconstruction at other location, prior fistula surgery, anticoagulant consumption, or vasculitis	
Interventions	Intervention group • Intravenous Heparin administered before clamping artery • Dose 5000 IU Control group • No medication given Follow-up details: • At 3 and 6 weeks post-operatively	
Outcomes	Outcomes reported immediate post-operatively and 6 weeks: • Patency • Bleeding • Haematoma • Re-interventions	
Notes	• Ethics approval not stated • Funding declaration: No funding statement but support of center of Shahid, Modarres hospital • Conflict of interest: No provided in text • Publication type: Full-text article	
BIAS	AUTHOR'S JUDGEMENT	SUPPORT
Random Sequence Generation (Selection Bias)	Low Risk	"the patients were enrolled and randomly divided in two groups"
Allocation Concealment (Selection Bias)	Unclear Risk	Unclear on allocation concealment
Performance Bias	Unclear Risk	Unclear on performance bias by surgeons and participants
Detection Bias	Unclear Risk	Unclear on assessor bias
Attrition Bias	Low Risk	No loss of patients
Reporting Bias	Unclear Risk	No information on trial registration
Other Bias	Low Risk	No other information

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Mozafar, 2018

Study characteristics		
Methods	• Study Design: RCT • Study duration and follow-up: April 2011 to Sep 2012, with follow-up at24 hours post-operatively	
Participants	Setting: Hospital Country: Iran Inclusion Criteria • Native AVF creation. Only R-C fistula Baseline Characteristics • Number: Intervention group (75); control group (75) • Mean age $\pm$ SD (years): Intervention group (52.37 ± 15.78); control group (54.63 ± 19.71) • Sex (M/F): Intervention group (54/21); control group (36/39) • Comorbidities: Diabetes, Hypertension, smokers Exclusion Criteria • Contraindication to anticoagulation, being candidates for AVG or central line placement	
Interventions	Intervention group • Intravenous Heparin administered before clamping artery • Dose 100IU/Kg Control group • No medication given Follow-up details: • At 24 hours post-operatively	
Outcomes	Outcomes reported immediate post-operatively and 24 hours • Patency • Bleeding • Haematoma • Re-interventions	
Notes	• Trial registration with clinicaltrials.gov database (ID NCT02493504) • Funding declaration: No funding in study • Conflict of interest: No conflict declared. Ethics not declared • Publication type: Full-text article	
BIAS	AUTHOR'S JUDGEMENT	SUPPORT
Random Sequence Generation (Selection Bias)	Low Risk	"patients were randomised"
Allocation Concealment (Selection Bias)	Unclear Risk	Unclear on allocation concealment
Performance Bias	Unclear Risk	Unclear on surgeons/participant blinding
Detection Bias	Unclear Risk	Unclear on assessor blinding
Attrition Bias	Low Risk	No loss of patient
Reporting Bias	Low Risk	No information on trial registration
Other Bias	Low Risk	No other concerns.

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Aimanan, 2018

Study characteristics		
Methods	• Study Design: RCT • Study duration and follow-up: April 2011 to Sep 2012, with follow-up at 6 weeks with ultrasound	
Participants	Setting: Hospital Country: Malaysia Inclusion Criteria • Minimum age 18 years, vessel diameter 2mm, r-c fistula only Baseline Characteristics • Number: Intervention group (45); control group (45) • Mean age $\pm$ SD (years): Intervention group (54.6 ± 13.5); control group (54.6 ± 12.5) • Sex (M/F): Intervention group (28/17); control group (26/19) • Comorbidities: Diabetes, Hypertension Exclusion Criteria • Warfarin therapy, platelet count<100, history of coagulopathy, pregnant patients, active GI bleeding	
Interventions	Intervention group • Intravenous Heparin administered before clamping artery • Dose 80IU/Kg Control group • 10ml saline Follow-up details: • At 24 hours post-operatively and 6 weeks post-operatively	
Outcomes	Outcomes reported immediate post-operatively and 6 weeks • Patency • Bleeding • Haematoma • Re-interventions	
Notes	• Ethics approval gained • Funding declaration: No funding in study • Conflict of interest: No conflict declared • Publication type: Full-text article	
BIAS	AUTHOR'S JUDGEMENT	SUPPORT
Random Sequence Generation (Selection Bias)	Low Risk	"double blinded randomised control trial"
Allocation Concealment (Selection Bias)	Low Risk	"patients were given two envelopes"
Performance Bias	Low Risk	"on the day of surgery, the drug or saline was prepared by the assigned medical officer"
Detection Bias	Low Risk	"the week one assessment was carried out by the investigator"
Attrition Bias	Low Risk	No drop out
Reporting Bias	Unclear Risk	No comment on trial registration
Other Bias	Low Risk	No other concerns

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Appendix A.4: Characteristics of the included studies

Study (First author, year)	Country	Study design	Comparison				Sample size (n)	Mean age (Years)	Sex (% Female)	Follow up (Weeks)
			IV UFH (IU)	n	No Heparin Group	n				
Aimanan 2017	Malaysia	RCT	Weight-based[3]	45	Saline bolus	45	90	55.6	40	4
Bhomi 2008	Nepal	RCT	5000	25	NR	25	50	49	46	6
D'Ayala 2008	USA	RCT	5000	56	Heparinised Saline bolus	56	112	61	37	12
Ebrahimifard 2015	Iran	RCT	5000	25	NR	25	50	55	36	6
Mozafar 2018	Iran	RCT	Weight-based[2]	75	NR	75	150	53.5	40	NA[4]
Ravari 2008	Iran	RCT	5000	96	NR	102	198	61.5	38	2
Wang 2010	USA	RCT	Weight-based[1]	26	NR	22	48	51.0	50	4

[1] 75 International units/kilogram. 2 100 International units/kilogram. 3 80 International units/kilogram. 4 24 hour follow-up
RCT, Randomised Control Trials; IU, International Units; UFH, Unfractionated Heparin; NR, Not Recorded

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Appendix A.5: Summary of outcomes

Outcome 1: Loss of Fistula Patency[1]		
Study	IV UFH	No Heparin
Aimanan 2017	4	12
Bhomi 2008	1	2
D'Ayala 2008	6	7
Ebrahimifard 2015	3	10
Mozafar 2018	NA[4]	NA[4]
Ravari 2008	14	26
Wang 2010	1	5
Outcome 2: Acute Fistula Thrombosis[2]		
	IV UFH	No Heparin
Aimanan 2017	4	11
Bhomi 2008	0	0
D'Ayala 2008	3	0
Ebrahimifard 2015	0	7
Mozafar 2018	0	6
Ravari 2008	10	13
Wang 2010	0	0
Outcome 3: Clinical Bleeding[3]		
	IV UFH	No Heparin
Aimanan 2017	8	5
Bhomi 2008	6	0
D'Ayala 2008	13	1
Ebrahimifard 2015	9	4
Mozafar 2018	0	0
Ravari 2008	3	1
Wang 2010	3	1

[1] 4-6 week patency, either on clinical examination or ultrasound. [2] Thrombosis of fistula in the perioperative period.
[3]Requiring review for oozing, blood transfusions or post-operative wound hematoma. [4]Only reported 24 hour patency.

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Appendix A.6: GRADE Summary of Findings Table

Question: Intravenous Heparin compared to No intravenous heparin in dialysis access creation
Setting: In-patient Setting

Certainty assessment							№ of patients	Effect			Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intravenous Heparin	No intravenous heparin	Relative (95% CI)	Absolute (95% CI)	
Loss of Fistula (follow-up: range 2 weeks to 6 weeks; assessed with: frequency)											
6	randomised trials	serious[a]	not serious	not serious	serious[b]	none	30/273 (11.0%)	65/275 (23.6%)	RR 0.49 (0.33 to 0.73)	12 fewer per 100 (from 16 fewer to 6 fewer)	⊕⊕◯◯ Low
Acute fistula thrombosis (reported as acute peri-operative thrombosis)											
7	randomised trials	serious[a,c]	serious[d]	not serious	serious[b]	none	17/348 (4.9%)	37/350 (10.6%)	RR 0.49 (0.29 to 0.84)	5 fewer per 100 (from 8 fewer to 2 fewer)	⊕◯◯◯ Very low
								0.0%		0 fewer per 100 (from 0 fewer to 0 fewer)	
Bleeding complications (transfusion, haematoma or clinically significant wound ooze)											
7	randomised trials	serious[a]	not serious	not serious	serious[b]	none	42/348 (12.1%)	12/350 (3.4%)	RR 2.71 (1.42 to 5.17)	6 more per 100 (from 1 more to 14 more)	⊕⊕◯◯ Low

CI: confidence interval; RR: risk ratio

Explanations
a. There was possible risk of bias due to several unclear domains in many studies in the meta-analysis including two large studies and several of the smaller studies
b. Very small events rates leading to large confidence intervals and potential impercision
c. Large number of unclear domains which may have risk of bias on outcome
d. Despite narrow confidence interval and direction of effect favouring heparin, I2 was 43%.

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Appendix B.1: Comprehensive search Strategy

Databases:
Database:
EBM Reviews - Cochrane Database of Systematic Reviews <2005 to May 14, 2025>
EBM Reviews - ACP Journal Club <1991 to April 2025>
EBM Reviews - Database of Abstracts of Reviews of Effects <1st Quarter 2016>
EBM Reviews - Cochrane Clinical Answers <April 2025>
EBM Reviews - Cochrane Central Register of Controlled Trials <April 2025>
EBM Reviews - Cochrane Methodology Register <3rd Quarter 2012>
EBM Reviews - Health Technology Assessment <4th Quarter 2016>
EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016>
Embase Classic+Embase <1947 to 2025 May 16>
Ovid MEDLINE(R) ALL <1946 to May 16, 2025>

#	Query	Results from 18 May 2025
1	(anticoagulation* or intravenous heparin* or unfractionated heparin*).mp. [mp=ti, ot, ab, tx, kw, ct, sh, fx, hw, tn, dm, mf, dv, kf, dq, bt, nm, ox, px, rx, an, ui, sy, ux, mx]	220,769
2	kidney transplantation*.mp. [mp=ti, ot, ab, tx, kw, ct, sh, fx, hw, tn, dm, mf, dv, kf, dq, bt, nm, ox, px, rx, an, ui, sy, ux, mx]	294,775
3	1 and 2	1,047
4	remove duplicates from 3	826

EBM Reviews - Cochrane Database of Systematic Reviews <2005 to November 1, 2023>
EBM Reviews - ACP Journal Club <1991 to October 2023>
EBM Reviews - Cochrane Clinical Answers <October 2023>
EBM Reviews - Database of Abstracts of Reviews of Effects <1st Quarter 2016>
Embase Classic+Embase <1947 to 2023 November 03>
Ovid MEDLINE(R) ALL <1946 to November 03, 2023>

https://access.ovid.com/custom/redirector/index.html?dest=https://go.openathens.net/redirector/sydney.edu.au?url=http://ovidsp.ovid.com/ovidweb.cgi?T=JS&NEWS=N&PAGE=main&SHAREDSEARCHID=3jCl3FtqrpI97Ixnz3Iu3B8Zhx5Ln9TasbfxK2X3CLjnKMCHrJpQ1sFZEO5yVhv6x

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Appendix B.2: PRISMA checklist of items in systematic reviews (2020)

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Title, page 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Abstract, pg 4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Introduction, pg 5, lines 95-123
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Introduction, pg 6, lines 122-123
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Methods, pg 6, lines 130-135
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Methods pg 7, lines 137-148
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Supplementary document 1
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Methods pg 6-8,
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Methods pg 6-8,
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Methods pg 7 lines 158-165
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Methods pg 7 lines 141-156
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Methods pg 8, lines 169-173
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Methods pg 8, lines 175-192
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Methods pg 18, lines 174-178
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Methods, pg 7-8
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Table 1 and 2 Figure 1
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software	Methods pg 8, lines 175-191

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Section and Topic	Item #	Checklist item	Location where item is reported
		package(s) used.	
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Methods pg 8, 175-191
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Nil
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Methods pg 8, lines 180-182
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Methods pg 9, lines 193-200
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Figure 1
Study characteristics	17	Cite each included study and present its characteristics.	Table 2, Table 3
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Table 2, Figure 2
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Results pg12-14 Table 1-3, Figure 3
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Table 2, Figure 2
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Results pg9-13 lines 208-300, Figure 3
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Figure 2-3 Discussion Pg 16-19
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Nil
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Figure 2, Supplementary 3
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Table 3
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Discussion, pg 15
	23b	Discuss any limitations of the evidence included in the review.	Discussion, pg 15-17
	23c	Discuss any limitations of the review processes used.	Discussion, pg 17
	23d	Discuss implications of the results for practice, policy, and future research.	Abstract, pg 4 What this paper adds paragraph pg 3, discussion pg 14-15, lines

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Section and Topic	Item #	Checklist item	Location where item is reported
			332-348
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Methods Pg6, lines 127
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Yes
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Nil
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	cover material pg 2, no sources of funding
Competing interests	26	Declare any competing interests of review authors.	cover material pg 2, no competing interests
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Yes – upon request

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

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Appendix B.3: Characteristics of included studies and risk of bias assessments with rationale

Denize, 2021

Study characteristics	
Methods	• Study Design: Retrospective Cohort study • Study duration and follow-up: April 2011 to Nov 2015, follow-up to 52 weeks
Participants	Setting: Hospital Country: France Inclusion Criteria • Patients needing kidney transplantation • Adult Baseline Characteristics • Number: Intervention group (51); control group (210) • Mean age $\pm$ SD (years): Intervention group (50 ± 15); control group (53 ± 15) • Sex (M/F): Intervention group (29/51); control group (128/210) • On haemodialysis : Intervention group (38/51), control group (165/210) Exclusion Criteria • Not reported
Interventions	Intervention group • Intravenous Heparin administered before venous clamping • Dose 0.5mg/Kg • Post-operative IV heparin used in those on antiplatelet therapy Control group • Did not receive any intraoperative anticoagulation • Post-operative anticoagulation varied depending on pre-operative factors Follow-up details: • To 1 year
Outcomes	Outcomes reported immediate post-operatively and 30 days: • Vascular thrombosis • Bleeding – haematoma, blood transfusion, complicated macroscopic haematuria
Notes	• Study conducted followed Decleration of Helsinki 1975, revised 2013 • Statement stating study followed institutional ethics • Funding declaration: Not reported • Conflict of interest: Not reported • Publication type: Full-text article

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Vand de Berg 2019

Study characteristics	
Methods	• Study Design: Retrospective cohort study • Study duration and follow-up: 2011 to July 2016, follow-up to 52 weeks
Participants	Setting: Hospital Country: Netherlands Inclusion Criteria • Patients needing kidney transplantation • Adult Baseline Characteristics • Number: Intervention group (195); control group (1333) • Age, sex and dialysis frequency divided by outcomes rather than via use of Intraoperative heparin versus without • Difficult to know if it may impact confounders Exclusion Criteria • Nil described
Interventions	Intervention group • Intravenous Heparin administered before venous clamping • Dose 5000 IU • Post-operative anticoagulation varied depending on pre-operative factors Control group • Did not receive any intraoperative anticoagulation • Post-operative anticoagulation varied depending on pre-operative factors Follow-up details: • 52 weeks post-operatively
Outcomes	Outcomes reported immediate post-operatively and 30 days: • Thromboembolic complications • Bleeding complications
Notes	• Medical Ethics Committee (MEC) of the UMCG granted dispensation from the Medical Research Involving Human Subjects Act (WMO) obligation (registration no. MEC2016.601) and this dispensation was submitted to and approved by the MEC of the EMC. • Clinical and research activities consistent with Principles of the Decleration of Istanbul • Funding declaration: Not reported • Conflict of interest: Not reported • Publication type: Full-text article

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Mohan 1999

Study characteristics	
Methods	• Study Design: Retrospective cohort study • Study duration and follow-up: Jan 1 1994 to December 1 1995, follow-up to 52 weeks
Participants	Setting: Hospital Country: Ireland Inclusion Criteria • Patients needing kidney transplantation • Adult Baseline Characteristics • Number: Intervention group (100); control group (100) • Mean age ± SD (years): Intervention group (42); control group (37) • Sex (M/F): Intervention group vs control group not reported • On haemodialysis : Intervention group vs control not reported • No PRA>60%: Intervention (10/100) vs control (20/100) • Mean HLA mismatch: Intervention (2.7) vs control (2.9) Exclusion Criteria • Nil described
Interventions	Intervention group • Intravenous Heparin administered before venous clamping • Dose 5000 IU • Post-operative anticoagulation varied depending on pre-operative factors Control group • Did not receive any intraoperative anticoagulation • Post-operative anticoagulation varied depending on pre-operative factors Follow-up details: • 52 weeks post-operatively
Outcomes	Outcomes reported immediate post-operatively and 30 days: • Thromboembolic complications • Bleeding complications
Notes	• Ethics not reported • Funding declaration: Not reported • Conflict of interest: Not reported • Publication type: Full-text article