College of Health Sciences

School of Pharmacy

Department of Pharmacology and Clinical Pharmacy

Anticoagulation Outcomes and Associated Factors among Acute Kidney Injury Patients during Hemodialysis at Two Selected Hospitals in Addis Ababa, Ethiopia: A Prospective Study

By: Hanan Muzeyin (B.Pharm)

December, 2023

Addis Ababa, Ethiopia

College of Health Sciences

School of Pharmacy

Department of Pharmacology and Clinical Pharmacy

Anticoagulation Outcomes and Associated Factors among Acute Kidney Injury Patients during Hemodialysis at Two Selected Hospitals in Addis Ababa, Ethiopia: A Prospective Study

By: Hanan Muzeyin (B. Pharm)

A Thesis proposal Submitted to the Department of Pharmacology and Clinical Pharmacy, School of Pharmacy, College of Health Sciences, Addis Ababa University in Partial Fulfillment of the Requirements of a Master of Science Degree in Pharmacy Practice.

Under the supervision of:

Eskinder Ayalew (Assistant Professor), Tamrat Assefa (Assistant Professor), and Addisu Melkie (MD, Assistant Professor)

December, 2023

Addis Ababa, Ethiopia

Addis Ababa University

School of Graduate Studies

This is to certify that the thesis prepared by Hanan Muzeyin, entitled: ***"Anticoagulation Outcomes and Associated Factors among Acute Kidney Injury Patients during Hemodialysis at Two Selected Hospitals in Addis Ababa, Ethiopia: A Prospective Study"*** and submitted in partial fulfillment of the requirements for the Degree of Master of Pharmacy in Pharmacy Practice complies with the regulations of the University and meets the accepted standards concerning originality and quality.

Signed by the examining committee:

Examiners:

Internal: Beshir Bedru: Signature: _____ Date: _____

(B.Pharm, MSc, Assistant Professor of Clinical Pharmacy)

External: Hailu Chare: Signature: _____ Date: _____

(B.Pharm, MSc, Assistant Professor of Clinical Pharmacy)

Advisors:

Eskinder Ayalew: Signature: _____ Date_____

(B.Pharm, MSc, Assistant Professor of Clinical Pharmacy)

Tamrat Assefa: Signature: _____ Date_____

(B.Pharm, MSc, Assistant Professor of Clinical Pharmacy)

Addisu Melkie: Signature: _____ Date_____

(MD, Assistant Professor of Internal Medicine)

_____

Head, Department or Graduate Program Coordinator

Abstract

Anticoagulation Outcomes and Associated Factors among Acute Kidney Injury Patients during Hemodialysis at Two Selected Hospitals in Addis Ababa, Ethiopia: A Prospective Study

Hanan Muzeyin, Addis Ababa University, 2023

Background: During hemodialysis (HD), clots in the dialyzer reduce the effective surface area of the dialyzer and in extreme situations clots in the circuit may prevent treatment from continuing and result in loss of blood in the circuit. Anticoagulation is essential during HD to prevent clot formation the circuit without putting the patient at risk of bleeding.

Objective: The study aimed to assess anticoagulation outcomes and associated factors among Acute Kidney Injury (AKI) patients during HD at Tikur Anbessa Specialized Hospital (TASH) and St. Paul's Hospital Millennium Medical College (SPHMMC), Addis Ababa, Ethiopia.

Method: A prospective, multicenter observational study was conducted between October 1st, 2021, and March 31st, 2022, at TASH and SPHMMC in Addis Ababa, Ethiopia. The study included all AKI patients who were undergoing HD at least once during the study period. Descriptive statistics were used to summarize the data while multinomial logistic regression analysis was used to determine factors associated with clotting and bleeding.

Results: Data were extracted from 1010 HD procedures performed on 175 patients. Extracorporeal circuit clotting occurred in 34 patients in 39 (3.9%) dialysis sessions, and 27 patients in 29 (2.9%) sessions had experienced bleeding. The total number of HD sessions (AOR=1.932, 95% CI, 1.227-3.043) and blood flow rate (AOR=0.868, 95% CI, 0.812-0.928) showed a statistically significant association with clotting. Bleeding was associated with length of hospitalization (AOR=1.247, 95% CI, 1.053-1.478), serum creatinine at admission (AOR=1.886, 95% CI, 1.285-2.769), uremic signs and symptoms (AOR=0.092, 95% CI, 0.009-0.955), and use of an anticoagulant and/or antiplatelet drug (AOR=0.017, 95% CI, 0.001-0.446).

Conclusion: A comparable number of circuit clotting was found when compared to other studies. However, it resulted in treatment interruptions and blood loss. Additionally, the study revealed a notable incidence of bleeding during HD, with most cases being minor.

Keywords: Acute kidney injury, Anticoagulation, Hemodialysis, Ethiopia.

Acknowledgments

To begin, I express my gratitude to the almighty ALLAH, whose guidance has been with me throughout my life. Next to this, I would like to thank my advisors Mr. Eskinder Ayalew, Mr. Tamrat Assefa, and Dr. Addisu Melkie for their continuous guidance throughout my thesis work. My gratitude goes to TASH and SPHMMC dialysis clinics and the nursing staff who were very cooperative and helpful in providing consistent assistance that enabled me to get patients' basic data. I extend my heartfelt gratitude to Addis Ababa University, College of Health Sciences School of Pharmacy for providing me with this educational opportunity. Additionally, I am deeply appreciative of my family members and friends for their invaluable guidance, patience, and unwavering support.

Table of Contents

Abbreviation and Acronyms

ACT	Activated clotting time
AKI	Acute kidney injury
aPTT	Activated partial thromboplastin time
CKD	Chronic kidney disease
ESRD	End stage renal disease
GI	Gastrointestinal
HD	Hemodialysis
HIT	Heparin-induced thrombocytopenia
ICU	Intensive care unit
LMWH	Low molecular weight heparin
RRT	Renal replacement therapy
SCr	Serum creatinine
SPSS	Statistical Package for Social Science
SPHMMC	St. Paul's Hospital Millennium Medical College
TASH	Tikur Anbessa Specialized Hospital
UFH	Unfractionated heparin

List of figures

List of tables

1. Introduction

1.1 Background

Hemodialysis (HD) is a treatment modality that filters out the waste products from the blood circulates outside the body of the patient through a machine that has special filters (Chawla *et al.*, 2011). Arteriovenous access is most frequently lost due to thrombosis, which accounts for 80%–85% of cases (Daugirdas, Blake and Ing, 2014). In HD, additional parts of the extracorporeal blood circuit besides the dialyzer are also thrombogenic. The tubing, arterial, and venous bubble traps, along with the needles or catheters used for vascular access play a role in thrombogenesis (Ross, 2011; Dirkes and Wonnacott, 2016). The arterial and venous bubble traps are highly prone to clot formation due to slower blood flow. In certain situations, blood stasis may occur, which is leading to the development of a thrombus. This can result in an early termination of the HD session, with insufficient dialysis dosage and potential blood loss (Fischer, 2007; Mhatre V. Ho, Ji-Ann Lee, 2012). Blood clots inside the circuit can result in blood loss and decrease solute removal (Dirkes and Wonnacott, 2016). Additionally, a limited filter lifetime increases treatment costs and workload (Srisawat *et al.*, 2010).

The dialyzer experiences a significant clotting rate of 5–10% during a 3- to 4-hour dialysis session when anticoagulants are not used. This may result in the dialyzer and blood tubing being lost, along with a loss of between 100 and 180 mL of blood. Anticoagulation-free dialysis, on the other hand, can be used as a substitute in patients who are moderately to highly susceptible to bleeding caused by anticoagulants. This is due to the fact that bleeding in these people can frequently have devastating outcomes (Daugirdas, Blake and Ing, 2014).

A delicate balancing act between under and over-heparinization is needed to provide the proper anticoagulation for HD to avoid extracorporeal circuit bleeding and clotting, respectively (Kessler, Moureau and Nguyen, 2015). To keep the dialyzer and venous chamber clear of blood cell debris and ensure timely hemostasis at the vascular access points after the session, it is crucial to use the minimal effective dose of anticoagulant (Fischer, 2007). Although these doses differ greatly between individuals and are dependent on both patient and HD factors, they are lower than what is required for complete anticoagulation. Insufficient anticoagulation may diminish the effectiveness of dialysis in clearing waste products from the blood (Ross, 2011).

Unfractionated heparin (UFH) is commonly employed as an anticoagulant during HD. Its extensive use over many years in medical practice, along with its favorable safety profile due to a brief half-life, supports its widespread adoption (Cronin and Reilly, 2010).The initial loading dose of 50 IU/kg UFH into the arterial access needle and the maintenance dose of 500 to 1500 IU of UFH/hr., given by continuous infusion, is recommended by the European best-practice guidelines for HD (European Best Practice Guidelines Expert Group on Hemodialysis, 2002). The recommendation is to use as little UFH as possible because the majority of acute kidney injury (AKI) patients are unwell and may require daily dialysis. If clot formation or bleeding does occur, a dose adjustment or even heparin-free dialysis may be necessary (Royal Liverpool and Broadgreen University Hospitals NHS Trust, 2015). There are currently new anticoagulation strategies that just target the extracorporeal circuit. However, none of the methods have been widely used because they are complicated and need more time and staff for administration and monitoring (Safadi *et al.*, 2017).

Because critically ill patients commonly have impaired coagulation and low platelet counts, systemic anticoagulants raise the risk of bleeding overall and considerably more so in these patients (Mhatre V. Ho, Ji-Ann Lee, 2012; Liang, 2016). Nonetheless, patients who are at risk of bleeding should not use strategies that cause systemic anticoagulation. The European Best Practice Guidelines suggest utilizing either regular saline flushing or localized citrate anticoagulation to provide HD without the need for systemic anticoagulation in this situation (European Best Practice Guidelines Expert Group on Hemodialysis, 2002). Periodic saline rinsing serves multiple purposes during dialysis. It allows for prompt treatment cessation or dialyzer replacement, while also enabling inspection of the hollow-fiber dialyzer for any signs of clotting. Additionally, some believe that regular saline rinsing may inhibit clot formation or reduce the propensity of dialyzers to clot (Daugirdas, Blake and Ing, 2014).

1.2 Statement of the problem

Up to 50% of critically ill patients in intensive care units (ICU) develop AKI. Renal replacement therapy (RRT) is now necessary for about 10–20% of all ICU patients (Hoste *et al.*, 2015). Due to the concomitant hemodynamic instability and various organ dysfunction, managing these patients on dialysis is challenging, and their mortality rates range from 50–70% (Mehta *et al.*, 2001). In low-resource countries, HD is the most prevalent, though its delivery is quite difficult (Liyanage *et al.*, 2015).

Blood clots in the circuit, known as filter clotting, were identified as the source of the patient's blood loss and the inability to continue dialysis. Both of which may have contributed to the patient's hemodynamic instability. In addition to alterations in venous and transmembrane pressures, it is characterized by blood that is stained with extremely dark shadows or black striations in the capillaries (Daugirdas, Blake and Ing, 2014). Anticoagulants are used to stop the circuit from clotting while minimizing the risk of bleeding for the patient (Mhatre V. Ho, Ji-Ann Lee, 2012; Shrewsbury and Telford NHS, 2017). In a clinical study conducted in Brazil, 19 patients (25.3%) experienced filter clotting during the trial, and this phenomenon occurred in 29 sessions (14.9%) (Albino, Balbi and Ponce, 2014). Another retrospective study that compared heparin-free HD with heparin use during HD showed that heparin-free HD was associated with a higher rate of HD circuit clotting (9.1% vs. 2.4%, $p = 0.019$), most requiring a change in the HD circuit (7.3% vs. 0.8%) (Liang, 2016).

Using anticoagulants during HD is common practice, although there are concerns regarding this because inpatients have a higher risk of bleeding. Major bleeding is more likely in dialysis patients compared to non-dialysis patients, and it has been demonstrated that oral anticoagulant or antiplatelet therapy can enhance this risk (Holden *et al.*, 2008; Chan *et al.*, 2009). A Canadian study found that the risk of major bleeding episodes per year of exposure was 0.8%, 3.1%, 4.4%, and 6.3% in HD patients taking neither warfarin nor aspirin, warfarin alone, aspirin alone, or the combination of warfarin and aspirin, with the majority of the bleeding coming from the gastrointestinal (GI) tract (Holden *et al.*, 2008). Since this area is not studied in our setup, the findings of this study will help to identify the outcomes related with anticoagulation in HD among AKI patients.

1.3 Significance of the study

This study was primarily designed to assess the treatment outcomes related to anticoagulation in patients undergoing HD. Anticoagulation is a major aspect of treatment for patients undergoing HD. There is limited information available about anticoagulation-related outcomes and associated factors among AKI patients on HD in Ethiopia.

This study aims to provide valuable information about the risks and benefits of anticoagulation in this population. The findings can be utilized to develop evidence-based guidelines for anticoagulation in AKI patients undergoing HD. This study will also benefit healthcare professionals and researchers by offering new insights into the problem and helping to shape clinical practices related to anticoagulation in HD.

Considering the large number of AKI patients receiving HD, the findings of this study will be crucial for the early identification and application of preventive measures against bleeding and thrombotic events. Overall, this study has the potential to make a significant contribution to the knowledge base on anticoagulation for AKI patients on HD and improve the care of these patients.

2. Literature Review

2.1 Acute Kidney Injury

The Acute Dialysis Quality Initiative (ADQI) group created a system for the diagnosis and classification of a wide variety of acute renal failure through a large expert consensus (Bellomo *et al.*, 2004). The term RIFLE (Risk, Injury, Failure, Loss of kidney function, and End-stage renal disease) refers to the growth coming up with various Risk, Injury and Failure; and the two outcomes classes Loss and End-Stage Renal Disease (ESRD). The three categories of severity are characterized in terms of changes in serum creatinine (SCr) or urine production where almost all of each criterion is used. The two outcome parameters, Loss and ESRD, are specified by the period of renal function loss (Kellum *et al.*, 2012).

Crucially, by describing acute renal function syndrome more generally, the RIFLE requirements go beyond acute renal failure. The word "acute kidney injury/impairment" has been suggested to represent the full range of the condition from mild improvements in renal disease markers to the need for renal RRT (Mehta *et al.*, 2007). The definition of AKI, as established by RIFLE, therefore introduces a new framework. AKI is neither an acute tubular necrosis nor a kidney failure. Rather, it covers both and also contains other, less severe, conditions. In fact, as a syndrome, it involves patients without real kidney disease but with functional disability due to physiological requirements. The inclusion of these kinds of patients in the AKI category is conceptually desirable since these are specifically the patients who may benefit from early diagnosis. Even so, this ensures that AKI requires both accident and/or disability (Kellum *et al.*, 2012).

Until now, various definitions of AKI have emphasized either a rapid rise in SCr (indicating a decline in the glomerular filtration rate) or a significant reduction in urine output. Recently, there has been growing interest in exploring urinary and blood biomarkers that could potentially detect AKI at an early stage, even before SCr levels show an increase (Hewitt, Dear and Star, 2004). Despite the promise of numerous biomarkers in revolutionizing our understanding of AKI, most clinical studies have been limited to single-center settings. Consequently, the prognostic and predictive value of these biomarkers remains unverified across diverse populations. As a result, the definitions and categorizations of AKI still center around changes in SCr and urine output (Himmelfarb and Ikizler, 2007).

The RIFLE parameters incorporate severity levels based on alterations in SCr or urine production, along with relevant clinical criteria. Preliminary evidence indicates that implementing RIFLE criteria within the ICU setting provides valuable prognostic insights across most studies (Chuang *et al.*, 2001). The AKI network recently put up a simpler approach that simply considers an increase of more than 0.3 mg/dl (>25 mmol/l), a rise of more than 50% in SCr, or an occurrence of oliguria, which is defined as urine output less than 0.5 ml/kg/hr. for more than 6 hours (Hoste and Kellum, 2006; Himmelfarb and Ikizler, 2007).

2.2 Anticoagulation Practice in HD among AKI Patients

The administration of heparin and the treatment plan are crucial components of dialysis medication. The variable pharmacokinetics of UFH and its limited therapeutic range can pose challenges in determining appropriate dosing strategies. In clinical practice, both active partial thromboplastin time (aPTT) and activated clotting time (ACT) are employed to evaluate the anticoagulant effect of UFH (Warkentin *et al.*, 1995). At elevated serum levels of heparin necessary for effective anticoagulation during extracorporeal therapies, the aPTT yields inconsistent outcomes. When monitoring UFH anticoagulation using aPTT, it is advisable to establish a reagent-specific therapeutic range based on blood heparin levels (Hattersley *et al.*, 1983; Østerud and Bjørklid, 2006).

UFH is commonly used as the anticoagulant of choice in most maintenance HD units within the United States. However, in Western Europe, low molecular weight heparin (LMWH) is the preferred standard for this purpose, although it is not widely accepted in the United States for the same indication (Hoffman and Monroe, 2005). UFH remains the preferred choice in the United States due to its practical ease of use, protective properties, and cost-effectiveness. While coating tubes and dialyzers with heparin is now feasible, systemic anticoagulation with heparin is still typically necessary. However, the additional expense associated with this innovation does not justify its widespread adoption. Both UFH and LMWH can lead to adverse effects, including heparin-induced thrombocytopenia, hypertriglyceridemia, and hyperkalemia (Hattersley *et al.*, 1983). It is unclear if osteoporosis is a significant consequence, as vitamin D deficiency, secondary hyperparathyroidism, age, and fatigue are conflicting factors. When UFH causes harm or hence it is considered unsafe, e.g. after the emergence of heparin-induced thrombocytopenia, its use of direct thrombin inhibitors, regional citrate anticoagulation, citrate dialysate, and heparin-free dialysis may be necessary (Cronin and Reilly, 2010).

In patients undergoing HD, systemic anticoagulation may be inappropriate. This includes patients who have recently undergone surgery, biopsies, or other invasive procedures within the last 48 hours, as well as those with GI bleeding, potential cranial trauma, or pulmonary contusion. Additionally, systemic anticoagulation should be avoided in cases of heavy bleeding to prevent exacerbation. Alternative approaches should be considered for these patients to prevent coagulation within the extracorporeal circuit (Ross, 2011).

Heparin-free HD is now the most popular form of dialysis for patients with a high risk of bleeding. This technique was originally designed used in patients with a high risk of bleeding (Sanders, Taylor and Curtis, 1985). In the no-heparin HD procedure, the extracorporeal circuit is primed with 2000 to 5000 units of UFH during the recirculation phase of dialysis system preparation. Prior to initiating dialysis therapy, heparinized saline is flushed from the saline circuit to prevent the patient from receiving an inadvertent heparin bolus (Schwab *et al.*, 1987). During the course of treatment, the blood flow rate is swiftly raised to over 300 mL/min and maintained at this level throughout. At intervals of approximately 15 to 30 minutes, a saline bolus of 30 to 50 mL is introduced into the arterial side of the circuit. These saline infusions effectively cleanse the fiber strands within the dialyzer, preventing clot formation and ensuring smooth functioning (Schwab *et al.*, 1987; Ross, 2011).

In high-risk patients, one of the initial strategies to prevent clotting involves regional anticoagulation using heparin and protamine. This method involves infusing UFH continuously into the arterial limb of the extracorporeal circuit, along with a simultaneous infusion of protamine just before the blood is returned to the patient (Tolwani and Wille, 2009). In regional anticoagulation, routine monitoring of ACT is performed using arterial and venous lines. Adjustments are made to the infusion rates of heparin and protamine to maintain the ACT within the extracorporeal circuit at around 250 seconds, while ensuring that the ACT of the blood returning to the patient remains at the baseline pre-dialysis level (Ridel *et al.*, 2005).

Some other type of regional anticoagulation includes the continuous injection of trisodium citrate solution into the arterial extremity of the extracorporeal circuit. Regional citrate anticoagulation has been shown to minimize the frequency of bleeding in high-risk patients relative to regular heparin protocols (Janssen MJ, Deegens JK, Kapinga TH, Beukhof JR, Huijgens PC, van Loenen AC, 1996; Jarraya *et al.*, 2010). Citrate binds to ionized calcium in the blood and is an effective inhibitor of coagulation. The citrate-calcium complex is partly

extracted by the dialyzer. This removal is improved when calcium-free dialysate is used. Calcium chloride is mixed into the venous return line to neutralize the effects of any remaining citrate (Janssen MJ, Deegens JK, Kapinga TH, Beukhof JR, Huijgens PC, van Loenen AC, 1996). The citrate infusion rate is regulated to allow the ACT to stay in the arterial limb at approximately 200 seconds. Plasma calcium levels must be monitored regularly and the calcium chloride infusion must be continuously modified to avoid hypocalcemia or hypercalcemia (Flanigan *et al.*, 1996).

LMWH was used as an option for UFH for HD anticoagulation. LMWHs have an average molecular mass ranging from 4 to 9 kDa and are formed by managed fractionation of heparin (Schrader *et al.*, 1988; Lohr and Schwab, 1991). Their lighter weight creates more predictable pharmacokinetics, making their dosing easier than UFH. LMWH attaches antithrombin and inhibits the Xa factor. The anticoagulant effect of LMWH can be controlled by evaluating the function of the anti-factor Xa in the blood of the patient. LMWHs are costly but have usually not been shown to be preferable to heparin due to dialysis-related bleeding or other risks (Lim, Cook and Crowther, 2004; Davenport, 2009).

In a cross-sectional study conducted in Spain to investigate HD anticoagulation, a total of 6093 patients and 2 pediatric units were included. Among these units, 48.3% were affiliated with the public health system, while the remaining 51.7% were part of the private health system. The patient survey involved 758 randomly selected patients from the 78 HD units mentioned earlier. Among adult HD units, the majority (70.2%) utilized both types of heparin, with 19 units (21.8%) exclusively using LMWH and 7 units (8%) exclusively using UFH. Common criteria for LMWH use included medical indications (83.3% of HD units) and ease of administration (29.5%). Key methods for dosage adjustment included circuit clotting (88.2% of units), bleeding from vascular access after disconnection (75.3%), and patient weight (57.6%). The distribution of heparin forms was as follows: UFH (44.1%), LMWH (51.5%), and heparin-free dialysis (4.4%). Antiplatelet agents were administered to 45.5% of patients, while 18.4% received oral anticoagulants. Notably, 4.4% of patients experienced bleeding complications in the previous week, and 1.9% suffered thrombotic complications. Bleeding events were more frequent in patients on oral anticoagulants (P=.001), but no significant correlation was found between the type of heparin used and bleeding or thrombotic complications (Herrero-Calvo *et al.*, 2012).

In a retrospective cohort study involving 41,425 incident HD patients over 5-year follow-up, researchers explored whether the use of warfarin, clopidogrel, and/or aspirin impacted survival. Within the first 90 days of chronic HD initiation, the prescribing rates were as follows: warfarin (8.3%), clopidogrel (10.0%), and aspirin (30.4%). When compared to the 24,740 patients who did not receive any of these medications, the analysis revealed the following hazard ratios (HRs) for mortality: warfarin: HR 1.27 (95% CI 1.18 to 1.37); clopidogrel: HR 1.24 (95% CI 1.13 to 1.35), and aspirin: HR 1.06 (95% CI 1.01 to 1.11). Interestingly, the increased mortality risk associated with warfarin or clopidogrel use persisted even in stratified analyses. Similar findings were obtained from the covariate-and propensity-adjusted time-variate study, which accounted for longitudinal changes in prescribing. In addition, the matching between the treatment center and the attending physician showed similar correlations between prescribing and mortality. These studies concluded that warfarin, aspirin, or clopidogrel prescriptions are linked to higher mortality among patients with HD (Chan *et al.*, 2009).

In a U.S. study involving inpatient HD without anticoagulation, the HD access methods for these patients were as follows: catheters were used in 45%, native AV fistulas in 40%, and grafts in 15%. The average blood flow during treatments was 378 ± 46 mL/min. In 5% of cases, arterial and venous blood lines were accidentally reversed. Only 4 out of 400 treatments (1%) experienced clotting in the dialysis circuit. Factors associated with clotting included lower achieved blood flow (225 ± 50 mL/min vs. 379 ± 44 mL/min), higher arterial bloodline pressures (−198 ± 24 mmHg vs. −151 ± 45 mmHg), and the reversal of arterial and venous access lines. Remarkably, an anticoagulation-free protocol allows inpatient HD to be safely performed in adults using various access methods, with minimal risk of circuit coagulation (Sahota and Rodby, 2014).

In a retrospective cohort study conducted in Belgium, intermittent HD without systemic anticoagulation was evaluated. This approach involved using a heparin-grafted AN69ST dialyzer in combination with citrate-enriched dialysate. The study found that this method resulted in fewer clotting complications compared to published outcomes of anticoagulation-free intermittent HD strategies. These alternative strategies included saline flushes, heparin-coated dialysate alongside normal dialysate, or regional citrate anticoagulation with calcium-coated dialysate. Interestingly, the frequency of circuit coagulation in this cohort was higher than what was originally observed for regional citrate anticoagulation with calcium-free dialysate (François *et al.*, 2014).

2.3 Complications Related to Anticoagulation Use in HD among AKI Patients

Heparin, being an anticoagulant, primarily poses the risk of bleeding. Although there have been instances of bleeding in individuals undergoing long-term HD with heparin, limited large-scale studies have demonstrated that heparin significantly elevates the bleeding risk in this population. Specifically, GI bleeding is a common occurrence among HD patients, but no well-executed research has conclusively linked heparin to an increased risk of GI bleeding (Wasse *et al.*, 2003).

In a study by Yang et al., it was observed that the incidence of acute non-variceal upper GI bleeding in dialysis patients remained unchanged from 1998 to 2007, despite a decline in GI bleeding among the non-dialysis population. The authors speculate that the increased use of antiplatelet or anticoagulant medications over time, possibly due to the growing preference for HD over peritoneal dialysis, could be associated with this phenomenon. However, it's important to note that the study lacked specific information about drug usage, preventing a direct test of this hypothesis. Additionally, other factors within the dialysis population, such as aging and a higher prevalence of comorbidities, may also contribute to this observed pattern (Yang *et al.*, 2012).

The risk of stroke in patients who are new to dialysis (incident dialysis patients) is 5.4 times higher compared to the general population (Seliger *et al.*, 2003). Although data are limited, it suggests that heparin is not a significant contributor to the risk of cerebral hemorrhage. A recent study in Japanese long-term HD patients reported an incidence of 8.7 cerebral hemorrhage events per 1,000 patient-years (Kawamura *et al.*, 1998). Among patients who experienced cerebral hemorrhage, there was no discernible difference in the heparin dosage administered to those who had the incident versus those who did not. Similarly, no significant distinction was observed between patients who survived the hemorrhage and those who did not. Surprisingly, approximately 85% of patients had the hemorrhagic event more than 6 hours after their HD session concluded. Considering that heparin has a relatively short half-life of approximately 1 hour, its unexpected association with cerebral hemorrhage in this population raises questions. Furthermore, the size of hematomas did not vary based on the duration since the last HD session, further suggesting that heparin did not contribute significantly to exacerbating the condition.

HD patients face a risk of ophthalmological bleeding due to higher rates of diabetes and hypertension. In a study involving 66 HD patients with diabetic retinopathy who received heparin during dialysis, there was no evidence of increased bleeding issues related to vitrectomy. This finding contrasts with rates observed in studies of diabetic patients not undergoing dialysis therapy (Del *et al.*, 2019). In other study, a patient with sudden hyphema had recently been administered 10,000 IU of heparin alongside dialysis. However, among 66 other participants undergoing HD who received equal or higher doses of heparin, no complications were observed. Although the dataset is limited, it suggests that heparin does not elevate the risk of ophthalmological bleeding (Mhatre V. Ho, Ji-Ann Lee, 2012).

HIT is a serious adverse reaction associated with heparin use. HIT has two forms: HIT type I, which is milder and HIT type II. In HIT type I, heparin binds to platelets, activating and depleting them. This typically occurs within the first 4 days of heparin therapy and is commonly observed in patients undergoing HD. Importantly, no antibodies are produced, and discontinuing heparin therapy is not recommended (Chong, 1988; Davenport, 2008). In recent years, several studies have demonstrated that the emergence of heparin-induced antibodies, even in the absence of thrombocytopenia, is linked to a 2- to 7-fold increase in morbidity and mortality among patients undergoing HD. The prevalence of these antibodies in HD patients can be as high as 17%, making it a potentially significant factor influencing patient outcomes (Mureebe *et al.*, 2004; Peña De La Vega *et al.*, 2005; Carrier *et al.*, 2008). In a Japanese study involving incident HD patients, the daily dosage of heparin required for the production of heparin-induced antibodies and HIT has not been specifically documented. Interestingly, the dosage of heparin administered to patients who developed HIT was not significantly different from that given to patients who did not experience HIT (Wasse *et al.*, 2003).

Hypoaldosteronism with resulting hyperkalemia is a common side effect of UFH (Edes and Ettayapuram, 1985). Heparin reduces aldosterone levels by affecting both the quantity and responsiveness of angiotensin II receptors in adrenal glomerulosa cells. Although no specific studies have investigated the potassium differences in long-term HD patients who do not receive heparin, it is likely that HD patients are often hyperkalemic due to kidney failure. Additionally, given the reduced glomerular filtration rate in this population, the renal impact of aldosterone is minimal. Importantly, the potassium dialysate dose can be adjusted to resolve any hyperkalemia that may be correlated with heparin, making this a less clinically important side effect for HD patients (Carrier *et al.*, 2008).

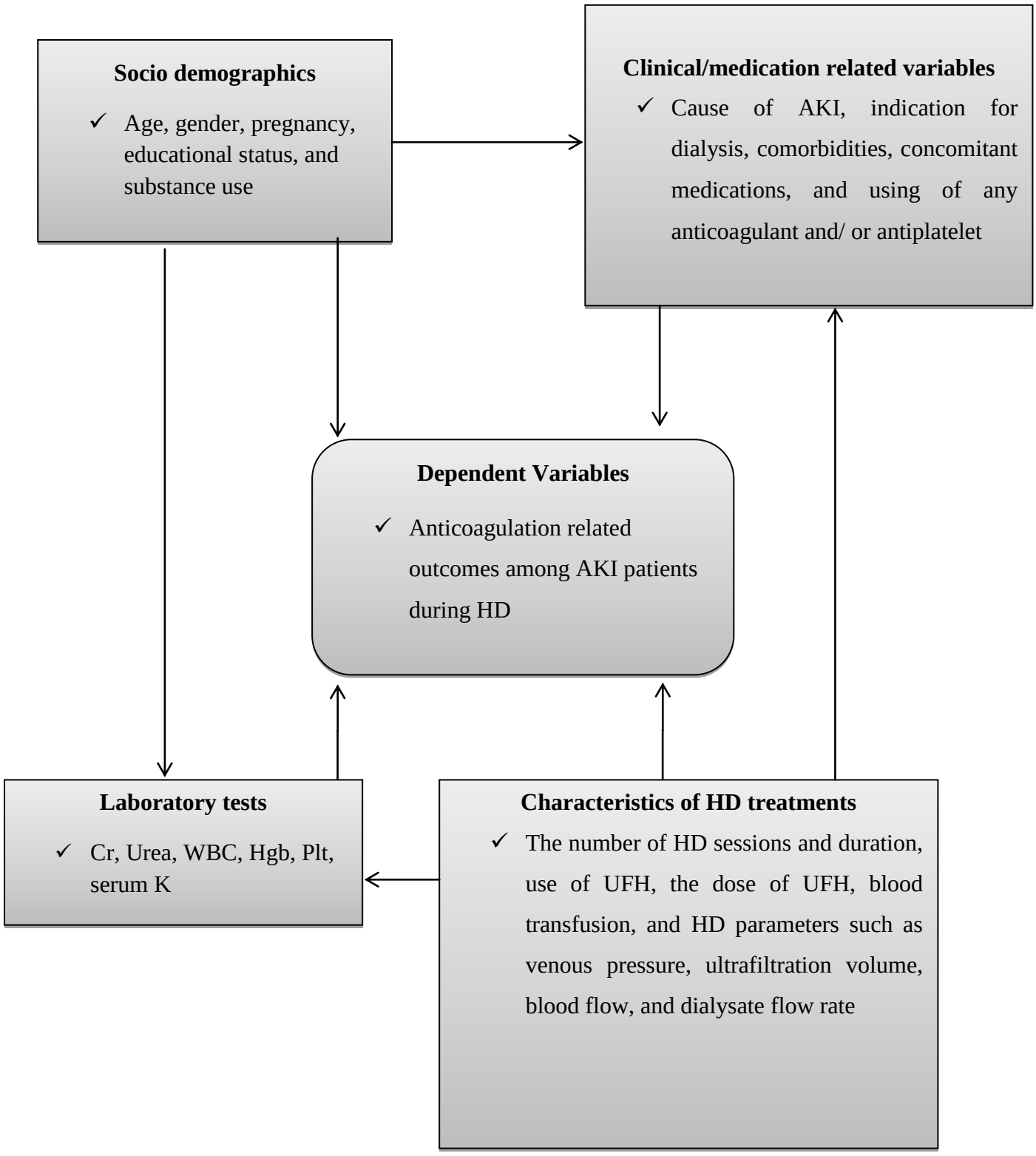

Figure 1: Conceptual Framework

3. Objectives

3.1 General objective

- ✓ To assess anticoagulation outcomes and associated factors among AKI patients during HD at TASH and SPHMMC, Addis Ababa, Ethiopia

3.2 Specific objectives

- ✓ To assess anticoagulation outcomes in HD among AKI patients.
- ✓ To identify factors associated with anticoagulation outcomes in HD among AKI patients at TASH and SPHMMC.

4. Methods

4.1 Study Setting

The study was conducted at the dialysis units of TASH and SPHMMC. Both are the largest teaching tertiary hospitals found in Addis Ababa, Ethiopia, and give care to patients from all corners of the country. They are institutions where advanced comprehensive and clinical services are offered to the entire country, of which HD is one of them. TASH started providing HD in 1980, and the service continued since then even if there where interruptions for some time. Only the acute dialysis service provided by the unit is still in function as the renal clinic renovates the hospital's services. SPHMMC started providing acute dialysis officially in August 2013, and later the unit expanded its capacity and started maintenance dialysis as a bridge to kidney transplantation in early 2015 (Muleta *et al.*, 2020).

Despite the lack of a clear protocol designed specifically for HD patients, anticoagulation was still frequently administered at both hospitals. Although UFH was used during HD, the heparin doses prescribed between the two HD centers varied slightly from one another. At TASH, UFH was ordered using 1 of the 3 approaches: (i) the standard dose, 1 ml (5000 IU) of UFH, was diluted with 4 ml of normal saline (a total of 5 ml). Then 2 ml of an initial bolus was followed by a continuous infusion of 1 ml/hr; (ii) the minimal or half dose of 0.5 ml (2500 IU) of UFH was diluted with 4.5 ml of normal saline (a total of 5 ml). Then 2 ml of an initial bolus was followed by a continuous infusion of 1 ml/hr; (iii) heparin-free, saline flushes of 30 to 50 ml were given every 30 minutes. At SPHMMC, 1 ml of UFH was diluted with 3 ml of normal saline (a total of 4 ml) and a bolus of 1 ml, followed by a continuous infusion of 1 ml/hr.

4.2 Study Design and Period

A prospective, multicenter observational study was conducted for six months starting from October 1st, 2021 to March 31st, 2022 at TASH and SPHMMC, Addis Ababa, Ethiopia.

4.3 Source and Study population

4.3.1 Source Population

All patients with the diagnosis of AKI and who were undergoing HD in Addis Ababa, Ethiopia were the source population.

4.3.2 Study Population

Those patients who fulfilled the inclusion criteria during the study period were the study population.

4.4 Sampling and Sample Size Determination

On average, the dialysis clinics at TASH and SPHMMC serve approximately 15 and 30 AKI patients per month respectively. All patients who met the eligibility criteria were included in the study. Therefore, a total of 175 patients identified during the study period who met the criteria participated in this study. During the study period, 122 of these patients were from SPHMMC and 53 were from TASH.

4.5 Inclusion and Exclusion Criteria

4.5.1 Inclusion Criteria

- ✓ AKI patients who were on HD at least once during the study period.
- ✓ Patients who provided informed consent for participation in the study.

4.5.2 Exclusion Criteria

- ✓ Chronic kidney disease (CKD) patients on maintenance dialysis.
- ✓ Those who were unable to provide informed consent or have significant cognitive impairments that preclude their ability to understand the study process.

4.6 Study Variables

4.6.1 Dependent Variables

- ✓ Anticoagulation outcomes among AKI patients during HD

4.6.2 Independent Variables

- ❖ **Socio-demographic variables**
- ✓ Age, sex, pregnancy, educational status, weight and substance use
- ❖ **Clinical/medication-related variables**
- ✓ Cause of AKI, indication for dialysis, comorbidities, concomitant medications, and any concurrent anticoagulant and/ or antiplatelet.
- ❖ **Laboratory findings**
- ✓ Including SCr, urea, white blood cell count, hemoglobin, platelet count, serum potassium.
- ❖ **Characteristics of HD treatments**
- ✓ The number of HD sessions and duration, use of UFH, the dose of UFH, blood transfusion, HD parameters such as venous pressure, ultrafiltration volume, blood flow, and dialysate flow rate.

4.7 Data Collection procedure and management

4.7.1 Data Collection Instruments and Techniques

A data abstraction format that has four sections, was developed by reviewing relevant literatures that address the objectives of the study to capture the demographic characteristics as well as clinical variables of patients in order to assess the anticoagulation related outcomes (Chan *et al.*, 2009; Cronin and Reilly, 2010; Ross, 2011; Herrero-Calvo *et al.*, 2012; Mhatre V. Ho, Ji-Ann Lee, 2012; Shibiru *et al.*, 2013; Krummel *et al.*, 2014). We conducted pre-testing and made all essential adjustments to the data collection tool.

The first section of the data collection instrument was designed to capture details about the socio-demographic characteristics of the patients. Subsequently, the second section evaluated the clinical features of the patients. Within this section, inquiries were made regarding the cause of AKI, the indication for HD, the patient's concurrent medical conditions, any co-administered medications, and the current usage of anticoagulants and/or antiplatelet drugs.

The third section of the data collection instrument focused on documenting necessary laboratory findings during both at admission and discharge. Lastly, the fourth section was specifically designed to capture detailed information about each HD session. The data collectors prospectively documented various parameters related to HD, including venous pressure, ultrafiltration volume, blood flow, dialysate flow, and the approach concerning the use of UFH during each HD sessions. Additionally, incidents of clotting or bleeding during the entire dialysis process were recorded along with the corresponding interventions taken to manage these occurrences (Annex III).

4.7.2 Data Quality assurance

To assure the quality of the data, three BSc. nurses and one B.Pharm pharmacist were recruited as data collectors and were trained to have a similar understanding and interpretation of the instrument, briefing the aim of the study and maintaining the core ethical principles throughout the data collection period. The principal investigator closely monitored each activity to ensure comprehensive data collection. Any unclear terms were clarified, and necessary corrections were made during the pre-test phase before commencing the main study.

4.8 Outcome measurement/ study outcome

Assess anticoagulation outcomes and associated factors in AKI patients on HD at TASH and SPHMMC, Addis Ababa, Ethiopia. Specific outcomes measured: Extracorporeal circuit clotting and bleeding.

4.9 Data Analysis

The data completeness was verified before entering it into the SPSS version 26 for a thorough analysis. Descriptive statistics, including mean, percentage, and standard deviation (SD), were then used to summarize the data succinctly. A multinomial logistic regression was employed to identify predictive factors for anticoagulation-related outcomes in AKI patients undergoing HD, incorporating all potentially relevant variables into the model. A P-value < 0.05 was considered the threshold for declaring statistically significant associations.

4.10 Ethical Considerations

Ethical clearance was secured from Addis Ababa University, School of Pharmacy, the Ethical Review committee with reference number ERB/SOP/257/13/2021, and the Institutional Review Board of SPHMMC with reference number PM25/386. Also, permission was obtained from the dialysis units of both TASH and SPHMMC to conduct the study. Study participants provided consent before participating, and their confidentiality was maintained by avoiding the recording of identifying information, such as patient names.

4.11 Operational definition

- ✓ **Anticoagulation outcomes:** is defined as the occurrence of any circuit clotting or bleeding during HD, whether with the use of UFH as an anticoagulant for dialysis or in a heparin-free approach.

5. Results

5.1 Socio-demographic characteristics of study participants

Out of 175 patients included in the study; almost half (50.9%) were males with a mean age of 40±17.8 years and four female were pregnant. The average length of hospital stay was 14.2 days, with a range of 2–40 days. Among the 175 patients, 66.9% paid out-of-pocket for the dialysis, and 2.3% were involved in all smoking, drinking alcohol, and chewing khat (Table 1).

Table 1: **Socio-demographic characteristics of AKI patients who undergo HD (n=175)**

Variable	**Category**	**n (%)**
Age (years),mean ± SD		40±17.8
Sex	Male	89 (50.9)
	Female	86 (49.1)
Marital status	Single	55 (31.4)
	Married	103 (58.9)
	Widowed	10 (5.7)
	Divorced	7 (4)
Pregnancy	Pregnant	4 (4.7)
	Not pregnant	71 (82.5)
	Postpartum	11 (12.8)
Education	Unable to read and write	23 (13.1)
	Primary education	42 (24)
	Secondary education	63 (36)
	Diploma and above	47 (26.9)
Weight (Kg)		61±13.9
Method of payment	Out of pocket	117 (66.9)
	Insurance	58 (33.1)
Substance use	Smoking	7 (4)
	Chewing Khat	9 (5.1)
	Alcohol	26 (14.9)
	Smoking + Khat + Alcohol	4 (2.3)

5.2 Clinical characteristics

The average length of hospital stay was 14.2 days, with a range of 2–40 days. The three most common causes of AKI were acute tubular necrosis (29%), nephritic syndrome (24%), and sepsis (22.9%). Pregnancy-related causes also include preeclampsia/eclampsia (5.1%) and HELLP (Hemolysis, Elevated Liver enzymes and Low Platelets) syndrome (4.6%). The major indication for dialysis was uremic signs and symptoms (70.3%), followed by fluid overload (50.3%). Common underlying comorbidities identified were hypertension (55.4%) and anemia (49.7%), and 13.1% of AKI were superimposed on CKD. UFH 7500 IU twice per day (48%) was the most widely used anticoagulant regimen in the studied population, followed by 5000 IU twice a day (14.3%) to prevent deep venous thrombosis (Table 2).

Table 2: **Clinical Characteristics of AKI patients who undergo HD (n=175)**

Variables	**Category**	**n (%)**
		Yes
Length of hospitalization (days), mean ± SD		14.2 ± 9.9
Cause of AKI	Acute tubular necrosis	49 (28)
	Nephritic syndrome	42 (24)
	Sepsis	40 (22.9)
	Interstitial nephritis	25 (14.3)
	Shock	19 (10.9)
	Severe dehydration	17 (9.7)
	Poison	17 (9.7)
	Urinary tract obstruction	11 (6.3)
	Lupus nephritis	9 (5.1)
	Preeclampsia/Eclampsia	9 (5.1)
	Nephrotoxic drugs	8 (4.6)
	HELLP syndrome	8 (4.6)
	Acute Glomerulonephritis	7 (4)
	Post-kidney transplant rejection	6 (3.4)
	Hemorrhage	5 (2.9)
	Rhabdomyolysis	3 (1.7)
	Others*	4 (2.3)

Dialysis indication	Uremic signs and symptoms	123 (70.3)
	Fluid overload	88 (50.3)
	Hyperkalemia	79 (45.1)
	Metabolic Acidosis	66 (37.7)
Comorbidity	Hypertension	97 (55.4)
	Anemia	87 (49.7)
	GI ulceration	29 (16.6)
	Chronic Kidney Disease	23 (13.1)
	Congestive heart disease	22 (12.6)
	Type 2 Diabetes	22 (12.6)
	HIV	11 (6.3)
	Pulmonary tuberculosis	9 (5.1)
	Stroke	6 (3.4)
	Deep vein thrombosis	5 (2.9)
	Hepatitis B virus	5 (2.9)
	Pulmonary embolism	3 (1.7)
	Coronary arterial disease	1 (0.6)
	Atrial fibrillation	1 (0.6)
	Others**	41 (23.4)
Concurrent anticoagulant and/or antiplatelet		124 (70.9)
	UFH 7500 IU SC Bid	84 (48)
	UFH 5000 IU SC Bid	25 (14.3)
	Aspirin 81mg PO Daily	20 (11.4)
	Warfarin 5mg PO Daily	8 (4.6)
	UFH 17500 IU SC Bid	5 (2.9)
	Enoxaparin 40mg SC Bid	3 (1.7)
	Clopidogrel 75mg PO Daily	2 (1.1)
	UFH 2500 IU SC BID	1 (0.6)
Concomitant drugs use		166 (94.9)

** (malaria, kidney trauma, cardio-renal syndrome, acute fatty liver of pregnancy)*
*** (prostate cancer, BPH, epilepsy, leukemia, gout arthritis, cerebral malaria)*
IU: international unit; SC: Subcutaneous; BID: twice a day; PO: by mouth (orally).

5.3 Laboratory findings

Low hemoglobin had been shown at both admission and discharge. The average SCr level at admission was 8.3 ± 3.4, with a drop of 3 mg/dl at discharge. Table 3 summarizes the values for selected laboratory parameters.

Table 3: **Selected Laboratory Values of AKI patients who undergo HD (n=175)**

Variables	**Mean ± SD**	
	Admission	**Discharge**
Hemoglobin (g/dl)	10.3 ± 7.6	10.3 ± 6.4
WBC count (10^3/ml)	11.1 ± 5.6	9.8 ± 4.9
Platelet count (10^3/ml)	235.9 ± 140.1	268.3 ± 131
SCr (mg/dl)	8.3 ± 3.4	5.3 ± 3.1
Urea (mg/dl)	137.5 ± 80.3	82.1 ± 63.4
Serum potassium (mEq/L)	5.3 ± 1.1	4.4 ± 0.8

5.4 Characteristics of HD sessions

Between October 2021 to March 2022, 1010 HD sessions were performed in 175 patients. The mean number of dialysis session of patients was 5.8 ± 3.8, with a maximum of 15 and a minimum of 1, and the average duration of one session was 3.1 ± 0.6 hours. Patients received HD treatments 3 times per week, and catheters were used as vascular access to all study patients. Blood products were transfused in 99 (9.8%) of sessions. UFH anticoagulation of the circuit was prescribed in 626 sessions (62%), with an average dose of 1 mL (5000 IU). Out of the 626 sessions where UFH was used, the infusion termination time was 60 minutes before the time off in 546 sessions (87.2%). The mean recorded pressure in the venous chamber and dialysis blood flow rate were 125 ± 39.3 mmHg and 227.2 ± 22.8ml/min, respectively.

Of the 175 patients, extracorporeal circuit clotting occurred in 34 patients in 39 (3.9%) sessions, and 27 patients in 29 (2.9%) sessions experienced bleeding. HD circuit clotting resulted in the discarding of the bloodline and the early termination of the dialysis in 17 sessions. Additionally, nursing interventions i.e. the use of UFH and a normal saline flush were required in 10 and 5 sessions, respectively, to prevent abrupt HD treatment interruptions

due to circuit clotting. Some of the measures taken when bleeding occurred included holding UFH at the time, and for the next session/s (n = 14 sessions), blood transfusion (n = 2 sessions), and applying pressure at catheter insertion site in 6 sessions (Table 4).

Table 4: **Characteristics of HD sessions included in the study (N=1010)**

Variables		**mean ± SD**
Total number of HD sessions (N=1010)		5.8 ± 3.8
HD duration (in hour)		3.1 ± 0.6
Venous chamber pressure (mmHg)		125 ± 39.3
Ultrafiltration volume (ml)		885 ± 650.9
Blood flow rate (ml/min)		227.2 ± 22.8
Dialysate flow rate (ml/min)		481 ± 46.6
Total UFH dose (ml)*		1 ± 0.2
	Category	**n (%)**
UFH infusion stopped		
	Before 30 minutes	70 (11.3)
	Before 60 minutes	546 (87.2)
	Before 120 minutes	8 (1.3)
	At the end of dialysis	1 (0.2)
Blood transfusion during HD		99 (9.8)
Using UFH during HD		626 (62)
Circuit clotting (34 patients, 19.4%)		39 (3.9)
Measures taken when circuit clotting occurs	Discard the blood line and HD terminated early	17 (1.7)
	Additional UFH given	10 (1)
	Continued HD by using normal saline flush	5 (0.5)
	Return the blood and HD terminated early	2 (0.2)
	Manipulate the access and continued HD	3 (0.3)
	Use UFH intermittently for the next sessions	2 (0.2)

Bleeding (27 patients, 15.4%)		29 (2.9)
	Bleeding from nose	15 (1.5)
	Catheter site bleeding	6 (0.6)
	Vaginal bleeding	4 (0.4)
	Others**	4 (0.4)
Measures taken when bleeding occurs	Hold UFH at the time, and for the next session/s	14 (1.4)
	Blood transfused	2 (0.2)
	Applied pressure at catheter insertion site	6 (0.6)
	Use UFH intermittently for the next sessions	2 (0.2)
	Return the blood and HD terminated early	1 (0.1)
	No measure taken	4 (0.4)

***1ml=5000 IU*
*** bleeding form rectum, bloody vomiting, subcutaneous hematoma, bleeding form bullet penetrating injury site*

5.5 Predictive factors associated with anticoagulation outcomes during HD

To determine predictors of anticoagulation outcomes during HD (clotting and bleeding risks); a multinomial logistic regression analysis was used. Based on the model comparing participants who had HD circuit clotting with those not having of any clotting/bleeding, as the total number of HD sessions increased, the probability of circuit clotting occurrence increased (AOR=1.932, 95% CI, 1.227-3.043, p= 0.004). Whereas, higher blood flow rate was associated with lower HD circuit clotting risks (AOR=0.868, 95% CI, 0.812-0.928, p< 0.001) (Table 5).

The model comparing study participants with bleeding event to those not having of any clotting/bleeding showed that bleeding was more likely to occur in participants who had longer hospitalization (AOR=1.247, 95% CI, 1.053-1.478, p= 0.010), and elevated SCr at admission (AOR=1.886, 95% CI, 1.285-2.769, p= 0.001). While, the rate of bleeding in patients who had no uremic signs and symptoms was lower (AOR=0.092, 95% CI, 0.009-0.955, p= 0.004) than those having it. Likewise, patients who did not receive prophylactic or

therapeutic anticoagulant and/or antiplatelet drug were less likely to develop bleeding (AOR=0.017, 95% CI, 0.001-0.446, p= 0.014) compared to those taking these drugs (Table 5).

Table 5: Multinomial logistic regression of predictive factors associated with anticoagulation outcomes during HD

Variables	Outcomes		
	Clotting	**Bleeding**	**P-value**
	AOR (95% CI)	**AOR (95% CI)**	
Total no of HD sessions	1.932 (1.227-3.043)[a]	1.068 (0.713-1.601)	0.004*
Blood flow rate (ml/min)	0.868 (0.812-0.928)[a]	1.026 (0.974-1.081)	<0.001*
Length of hospitalization (days)	0.946 (0.843-1.06)	1.247 (1.053-1.478)[a]	0.010*
SCr (mg/dl) at admission	0.911 (0.699-1.189)	1.886 (1.285-2.769)[a]	0.001*
Uremic signs and symptoms			
Yes	1	1	
No	0.532 (0.079-3.57)	0.092 (0.009-0.955)[a]	0.04*
Using of anticoagulant and/or antiplatelet drug			
Yes	1	1	
No	1.156 (0.168-7.936)	0.017 (0.001-0.446)[a]	0.014*

Reference Variable: No clotting/bleeding

**Variables that showed a significant association, P < 0.05*

[a]Variable category with P <0.05

6. Discussion

As the first prospective study in the Ethiopian context on anticoagulation among AKI on patients on HD, the study gives insight into extracorporeal circuit clotting or bleeding occurrences and predictive factors associated with these complications. In this study, 1010 HD sessions performed on 175 patients were prospectively followed. Clotting and bleeding data were expressed as the percentage of both participants and sessions. Circuit clotting occurred in 3.9% of HD sessions (19.4% patients), and bleeding in 2.9% sessions (15.4% patients).

Similar result was reported from the United States of America (USA) that evaluated clotting of the HD circuit in general care patients and then in critically ill patients. The overall rate of extracorporeal circuit clotting was 5.2% of all sessions (Safadi *et al.*, 2017). Circuit clotting occurred in 2.4% of HD sessions with heparin, according to a retrospective study comparing two intra-dialytic heparin protocols: "routine heparin-use" during HD (routine heparin prime/bolus dose) and heparin-free HD (saline prime, heparin avoidance). However, heparin-free HD was associated with a higher rate of HD circuit clotting (9.1%) (Liang, 2016). On the contrary some other studies have reported a higher rate of circuit clotting during HD. A study done in Brazil showed that filter clotting occurred in 19 patients (25.3%) and in 29 sessions (14.9%) (Albino, Balbi and Ponce, 2014). The study evaluated and compared intra- and post-dialysis complications in critically ill AKI patients undergoing extended daily dialysis sessions of different durations (6 versus 10 hours) and this could be the explanation for higher rate of HD filter clotting events and many critically ill patients develop hemostatic abnormalities in addition to the longer dialysis duration.

Additionally, a retrospective cohort study conducted in Belgium found that circuit coagulation was reported in 17.5% of all sessions. This higher rate of clotting events could be attributed to the absence of systemic anticoagulation (François *et al.*, 2014). Moreover, the study conducted a retrospective analysis of HD sessions in ICU patients, which could be an additional factor contributing to clotting occurrences. Patients admitted to the ICU and requiring dialysis for AKI often present a systemic inflammatory state (Aleksandrova, Reĭ and Pervakova, 2007), known to be associated with the activation of coagulation pathways (Franchini, Veneri and Lippi, 2007).

Lower clotting of the hemodialyzer circuit incidence was reported in a retrospective study done in USA (1 % of the 400 HD treatments) (Sahota and Rodby, 2014). It might be attributed to the operational definition of clotting used in the study. The researchers defined clotting as complete clotting that required replacement of the blood tubing and dialyzer to complete the treatment. The higher blood flow rate (378±46 mL/min), and the more aggressive normal saline flushing of the circuit that employed in this protocol could be also the explanation for lower rate of clotting. Moreover, there might be under reporting of clots due to the retrospective study design in which existing data was extracted from chart reviews. Another study from Spain found that 1.9% of patients developed clotting which is lower than our finding (19.4% of patients) (Herrero-Calvo *et al.*, 2012) with higher mean blood pump flow (346±47 ml/min) given a higher risk of coagulation from a lower pump flow.

In the current study, 15.4 % of patients developed bleeding, and this finding was higher than a study conducted in Spain (4.4%) (Herrero-Calvo *et al.*, 2012). This variation might be due to the difference in the study design and setting even though the study reported that oral anticoagulants were given to 18.4% of patients which by itself is thought to increase the risk of bleeding occurrence. But in the Spain study, each patient was asked to report any bleeding or thrombotic complications that arose in the previous week of the data collection time only.

In the present study, it was observed that anticoagulation was achieved with UFH or sometimes saline flushes of 30 to 50ml given every 30min if UFH was contraindicated. There were three strategies regarding UFH order for HD in our study settings and each patient was dialyzed with any of these anticoagulation methods. The first one is the standard dosing regimen of UFH consisted of a bolus of 1250–2000 U, followed by a continuous infusion of 1000–1250 U/h. The second was minimal/half dose method with 625–1000 bolus dose and 500–625 infusion rate. Heparin-free dialysis was also the third method used in patients who were actively bleeding or were at an increased risk of bleeding.

Since it has a short half-life and a long history in medicine, UFH has become the most popular anticoagulant used for HD,(Cronin and Reilly, 2010) but the dose administered varies widely. In this study, the mean total dose of UFH during HD was 5000±1000 units, and infusion of heparin was stopped 1 hour prior to the end of dialysis in most (87.2%) of the sessions to minimize the risk of bleeding from the access site after withdrawal of the access needles.

In the present study, extracorporeal circuit clotting was assessed using visual inspection and noted by the nurses. It is characterized by extremely dark blood or black striations in the tube and sudden rise in pressure readings. They only recorded clotting as being present or absent without grading it in line with several studies done elsewhere (Herrero-Calvo *et al.*, 2012; Albino, Balbi and Ponce, 2014; Liang, 2016). On the contrary, some other study had reported the degree of clotting by classifying it into mild/slight, moderate, and severe (Murea *et al.*, 2018).

HD is often done three times a week for three to four hours each session; however, the length of these sessions varies from patient to patient. One intradialysis consequence, circuit clotting, includes treatment interruption and patient blood loss, which may exacerbate the haemodynamic instability (Albino, Balbi and Ponce, 2014). In 1.7% of all sessions with clotting, the dialysis was stopped early without the possibility to retransfuse blood from the extracorporeal circuit; hence, the blood line was discarded. However, in 0.2% of the sessions, the dialysis was terminated early by returning the blood.

According to a study from Belgium, clotting reduced the length of time spent receiving dialysis in 15.2% of sessions, and it completely blocked the circuit and prevented retransfusion in 4.2% of sessions, which is greater than our findings (François *et al.*, 2014). These variations might be due to the difference in the dialysis protocol. In contrast to ours, the study combined a citrate-enriched dialysate with a heparin-coated dialyzer with no systemic UFH. Similarly, a study done in USA by comparing two intra-dialytic heparin protocols reported that in heparin-free HD protocol, circuit clotting resulted in a change of the extracorporeal circuit in 7.3% of sessions. Whereas, this was required in only 0.8% of HD sessions with heparin use, and early termination of HD (1.6%) was almost similar with this study (Liang, 2016). Bleeding was also another important encountered intradialysis complication which might require adjusting the dose of UFH (1.6% of all sessions with bleeding), or blood transfusion (0.2%). Another study revealed that patient weight, clotting of the circuit, and bleeding of the vascular access after disconnection were the most often employed techniques for changing the dosage (Herrero-Calvo *et al.*, 2012).

Identifying predictors of anticoagulation related outcomes during HD in AKI patients is important. Identifying and preventing patients at risk for such complications can heighten

practitioner awareness of HD related clotting and bleeding. Similar to some other studies (François *et al.*, 2014; Sahota and Rodby, 2014; Liang, 2016; Safadi *et al.*, 2017); blood flow rate showed a statistically significant association with the occurrence of circuit clotting. In this study, lower delivered blood flow rates were associated with higher circuit clotting rates. Additionally, as the total number of HD sessions increased, the probability of circuit clotting occurrence increased unlike a study done in Belgium (François *et al.*, 2014). The difference could be due to variations in their research methodology and the inclusion of study participants with varying levels of clotting risk.

Patients who did not receive prophylactic or therapeutic anticoagulant and/or antiplatelet drug were less likely to develop bleeding compared to those taking these drugs. Similarly, a study from Spain found that bleeding complications were more frequent in patients with oral anticoagulants (Herrero-Calvo *et al.*, 2012). In line with previous studies, age and sex were not associated with bleeding events (Herrero-Calvo *et al.*, 2012; Liang, 2016).

7. Strength and Limitation

7.1 Strength

- ✓ The prospective nature of the study allows the collection of data in the context of actual setting, which increases the quality of data and minimizes bias.
- ✓ Conducted a multicenter study, which allowed for diverse population coverage, and increased generalizability.
- ✓ Used as a foundation to carry out further studies on this topic.

7.2 Limitation

- ✓ The study recruited participants over a 6-month period, but the event being studied is infrequent. Consequently, the sample size was small, making it challenging to extrapolate the findings to the broader population.
- ✓ The HD nurses' visual inspection alone was used to record the data about the filter clotting, and this can be subjective and prone to individual interpretation. So, clotting rate might be underestimated if it can't be examined visually.
- ✓ The bleeding reported was only at the time of the dialysis session. So, this may not provide a comprehensive picture of the bleeding risk associated with the dialysis procedure.
- ✓ The study did not exclude patients with co-morbidities (such as deep vein thrombosis, active malignancy, severe heart failure, or severe liver disease). These conditions can impact anticoagulation outcomes and may confound the interpretation of results.

8. Conclusion and Recommendation

8.1 Conclusion

In conclusion, a comparable number of circuit clotting was found when compared to other studies. However, this requires careful attention as it resulted in treatment interruptions and blood loss. Blood flow rate and the number of HD sessions were significantly associated with the occurrence of circuit clotting. Additionally, the study revealed a notable incidence of bleeding during HD, with most cases being minor. Study participants who received prophylactic or therapeutic anticoagulants and/or antiplatelet drugs were more likely to develop bleeding compared to those not taking these drugs.

8.2 Recommendations

The following recommendations were provided in light of the study findings:

- ✓ Develop a comprehensive written guidelines specifically addressing anticoagulation during HD. This guideline should clearly outline when anticoagulation is necessary during HD, dosing protocols, and monitoring parameters including strategies for managing bleeding complications.
- ✓ It is advisable to employ a structured scoring system for assessing filter clotting, focusing on various laboratory values. This approach is particularly relevant for patients who have previously encountered clotting during their dialysis sessions.
- ✓ Clinicians should give special attention to AKI patients undergoing HD who are concurrently using prophylactic or therapeutic anticoagulant and antiplatelet drugs and carefully weigh the benefits and risks of using these medications. Also, consider alternative strategies to manage clotting risk during HD in patients already on anticoagulants or antiplatelet therapy.
- ✓ Furthermore, conducting a follow-up study that focuses specifically on the bleeding risk associated with dialysis sessions, including a more comprehensive assessment of bleeding risk, such as monitoring patients for bleeding events outside of the dialysis session, could also be considered.

9. References

Albino, B. B., Balbi, A. L. and Ponce, D. (2014) 'Dialysis complications in AKI patients treated with extended daily dialysis: Is the duration of therapy important?', *BioMed Research International*, 2014. doi: 10.1155/2014/153626.

Aleksandrova, I. V., Reĭ, S. I. and Pervakova, E. I. (2007) 'Acute renal failure in critically ill patients', *Anesteziologiia i reanimatologiia*, 294(4), pp. 72–76.

Bellomo, R. *et al.* (2004) 'Acute renal failure - definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group.', *Critical care (London, England)*, 8(4), pp. 1–9. doi: 10.1186/cc2872.

Carrier, M. *et al.* (2008) 'Increased mortality in hemodialysis patients having specific antibodies to the platelet factor 4-heparin complex', *Kidney International*, 73(2), pp. 213–219.

Chan, K. E. *et al.* (2009) 'Anticoagulant and antiplatelet usage associates with mortality among hemodialysis patients', *Journal of the American Society of Nephrology*, 20(4), pp. 872–881. doi: 10.1681/ASN.2008080824.

Chawla, L. S. *et al.* (2011) 'The severity of acute kidney injury predicts progression to chronic kidney disease', *Kidney International*, 79(12), pp. 1361–1369. doi: 10.1038/ki.2011.42.

Chong, B. H. (1988) 'Heparin-induced thrombocytopenia', *Blood Reviews*, 2(2), pp. 108–114. doi: 10.1016/0268-960X(88)90032-X.

Chuang, Y. J. *et al.* (2001) 'Heparin enhances the specificity of antithrombin for thrombin and factor Xa independent of the reactive center loop sequence. Evidence for an exosite determinant of factor Xa specificity in heparin-activated antithrombin', *Journal of Biological Chemistry*, 276(18), pp. 14961–14971. doi: 10.1074/jbc.M011550200.

Cronin, R. E. and Reilly, R. F. (2010) 'Unfractionated Heparin for Hemodialysis: Still the Best Option', *Seminars in Dialysis*, 23(5), pp. 510–515. doi: 10.1111/j.1525-139X.2010.00770.x.

Daugirdas, J. T., Blake, P. G. and Ing, T. S. (2014) *Handbook of dialysis: Fifth edition*, *Handbook of Dialysis: Fifth Edition*.

Davenport, A. (2008) 'Heparin-induced thrombocytopenia during renal replacement therapy in the intensive care unit.', *Critical care (London, England)*, 12(3), pp. 1–2. doi: 10.1186/cc6914.

Davenport, A. (2009) 'Review article: Low-molecular-weight heparin as an alternative anticoagulant to unfractionated heparin for routine outpatient haemodialysis treatments', *Nephrology*, 14(5), pp. 455–461. doi: 10.1111/j.1440-1797.2009.01135.x.

Del, R. *et al.* (2019) 'Vitrectomy in Diabetic Patients with Chronic Kidney Disease and Diabetic Retinopathy', (November 2020).

Dirkes, S. and Wonnacott, R. (2016) 'Continuous Renal Replacement Therapy and Anticoagulation: What Are the Options?', *American Association of Critical-Care Nurses*, 36(2), pp. 1–12. doi: 10.1093/0199270023.003.0001.

Edes, T. E. and Ettayapuram, V. (1985) 'Heparin-Induced Hyperkalemia', *Archives of internal medicine*, 145(6), pp. 1070–1072.

European Best Practice Guidelines Expert Group on Hemodialysis, E. R. A. (2002) 'Section V. Chronic intermittent haemodialysis and prevention of clotting in the extracorporal system.', *Nephrol Dial Transplant*, 17, pp. 63–71. doi: 10.1093/ndt/17.suppl_7.63.

Fischer, K. G. (2007) 'Essentials of anticoagulation in hemodialysis', *Hemodialysis International*, 11(2), pp. 178–189. doi: 10.1111/j.1542-4758.2007.00166.x.

Flanigan, M. J. *et al.* (1996) 'Regional hemodialysis anticoagulation: Hypertonic tri-sodium citrate or anticoagulant citrate dextrose-A', *American Journal of Kidney Diseases*, 27(4), pp. 519–524. doi: 10.1016/S0272-6386(96)90162-6.

Franchini, M., Veneri, D. and Lippi, G. (2007) 'Inflammation and hemostasis: A bidirectional interaction', *Clinical Laboratory*, 53(1–2), pp. 63–67.

François, K. *et al.* (2014) 'Avoidance of systemic anticoagulation during intermittent haemodialysis with heparin-grafted polyacrilonitrile membrane and citrate-enriched dialysate: A retrospective cohort study', *BMC Nephrology*, 15(1), pp. 1–7. doi: 10.1186/1471-2369-15-104.

Hattersley, P. G. *et al.* (1983) 'Adjusting heparin infusion rates from the initial response to activated coagulation time', *Drug Intelligence and Clinical Pharmacy*, 17(9), pp. 632–634. doi: 10.1177/106002808301700904.

Herrero-Calvo, J. A. *et al.* (2012) 'Spanish study of anticoagulation in haemodialysis', *Revista Nefrología*, 32(2), pp. 153–159. doi: 10.3265/Nefrologia.pre2011.Nov.11106.

Hewitt, S. M., Dear, J. and Star, R. A. (2004) 'Discovery of protein biomarkers for renal diseases', *Journal of the American Society of Nephrology*, 15(7), pp. 1677–1689. doi: 10.1097/01.ASN.0000129114.92265.32.

Himmelfarb, J. and Ikizler, T. A. (2007) 'Acute kidney injury: Changing lexicography, definitions, and epidemiology', *Kidney International*, 71(10), pp. 971–976.

Hoffman, M. M. and Monroe, D. M. (2005) 'Rethinking the coagulation cascade.', *Current hematology reports*, 4(5), pp. 391–396. doi: 10.2491/jjsth.16.70.

Holden, R. M. *et al.* (2008) 'Major bleeding in hemodialysis patients', *Clinical Journal of the American Society of Nephrology*, 3(1), pp. 105–110. doi: 10.2215/CJN.01810407.

Hoste, E. A. J. *et al.* (2015) 'Epidemiology of acute kidney injury in critically ill patients: the multinational AKI-EPI study', *Intensive Care Medicine*, 41(8), pp. 1411–1423. doi: 10.1007/s00134-015-3934-7.

Hoste, E. A. J. and Kellum, J. A. (2006) 'Acute kidney injury: epidemiology and diagnostic criteria', *Curr Opin Crit Care*, 12(6), pp. 531–7. doi: 10.1007/978-1-4471-5547-8_5.

Janssen MJ, Deegens JK, Kapinga TH, Beukhof JR, Huijgens PC, van Loenen AC, van der M. J. (1996) 'Citrate compared to low molecular weight heparin anticoagulation in chronic hemodialysis patients', *Kidney Int*, 49(3), pp. 806–13.

Jarraya, F. *et al.* (2010) 'Regional citrate anticoagulation for hemodialysis: a safe and efficient method.', *Saudi journal of kidney diseases and transplantation : an official publication of the Saudi Center for Organ Transplantation, Saudi Arabia*, 21(3), pp. 533–534.

Kawamura, M. *et al.* (1998) 'Incidence, outcome, and risk factors of cerebrovascular events in patients undergoing maintenance hemodialysis', *American Journal of Kidney Diseases*, 31(6), pp. 991–996. doi: 10.1053/ajkd.1998.v31.pm9631844.

Kellum, J. A. *et al.* (2012) 'Kidney disease: Improving global outcomes (KDIGO) acute kidney injury work group. KDIGO clinical practice guideline for acute kidney injury', *Kidney International Supplements*, 2(1), pp. 1–138. doi: 10.1038/kisup.2012.1.

Kessler, M., Moureau, F. and Nguyen, P. (2015) 'Anticoagulation in Chronic Hemodialysis: Progress Toward an Optimal Approach', *Seminars in Dialysis*, 28(5), pp. 474–489. doi: 10.1111/sdi.12380.

Krummel, T. *et al.* (2014) 'Haemodialysis in patients treated with oral anticoagulant : should we heparinize ?', 29(4), pp. 906–913. doi: 10.1093/ndt/gft522.

Liang, E. (2016) 'Outcomes Associated with a Heparin-Free Hemodialysis Protocol and Review of the Literature', *Journal of Clinical Nephrology and Renal Care*, 2(1), pp. 1–6. doi: 10.23937/2572-3286.1510010.

Lim, W., Cook, D. J. and Crowther, M. A. (2004) 'Safety and efficacy of low molecular weight heparins for hemodialysis in patients with end-stage renal failure: A meta-analysis of randomized trials', *Journal of the American Society of Nephrology*, 15(12), pp. 3192–3206. doi: 10.1097/01.ASN.0000145014.80714.35.

Liyanage, T. *et al.* (2015) 'Worldwide access to treatment for end-stage kidney disease: A systematic review', *The Lancet*, 385(9981), pp. 1975–1982. doi: 10.1016/S0140-6736(14)61601-9.

Lohr, W. and Schwab, J. (1991) 'Minimizing hemorrhagic complications in dialysis patients', *J Am Soc Nephrol*, 2(5), pp. 961–75.

Mehta, R. L. *et al.* (2001) 'A randomized clinical trial of continuous versus intermittent dialysis for acute renal failure', *Kidney International*, 60(3), pp. 1154–1163. doi: 10.1046/j.1523-1755.2001.0600031154.x.

Mehta, R. L. *et al.* (2007) 'Acute kidney injury network: Report of an initiative to improve outcomes in acute kidney injury', *Critical Care*, 11(2), pp. 1–8. doi: 10.1186/cc5713.

Mhatre V. Ho, Ji-Ann Lee, and K. C. M. (2012) 'Use and Safety of Unfractionated Heparin for Anticoagulation During Maintenance Hemodialysis', *Am J Kidney Dis*, 23(1), pp. 1–7. doi: 10.1038/jid.2014.371.

Muleta, M. B. *et al.* (2020) 'Original Article Milestones of Renal Replacement Therapy in

Ethiopia', *Ethiopian Medical Journal*, Supplement(January), pp. 5–13.

Murea, M. *et al.* (2018) 'Efficacy and safety of low-dose heparin in hemodialysis', *Hemodialysis International*, 22(1), pp. 74–81. doi: 10.1111/hdi.12563.

Mureebe, L. *et al.* (2004) 'Heparin-associated antiplatelet antibodies increase morbidity and mortality in hemodialysis patients', *Surgery*, 136(4), pp. 848–853. doi: 10.1016/j.surg.2004.07.004.

Østerud, B. and Bjørklid, E. (2006) 'Sources of Tissue Factor', *Seminars in Thrombosis and Hemostasis*, 32(01), pp. 011–023.

Peña De La Vega, L. *et al.* (2005) 'Association of heparin-dependent antibodies and adverse outcomes in hemodialysis patients: A population-based study', *Mayo Clinic Proceedings*, 80(8), pp. 995–1000. doi: 10.4065/80.8.995.

Ridel, C. *et al.* (2005) 'Regional citrate anticoagulation during hemodialysis: A simplified procedure using duocart biofiltration', *Blood Purification*, 23(6), pp. 473–480. doi: 10.1159/000089652.

Ross, S. (2011) 'Anticoagulation in Intermittent Hemodialysis: Pathways, Protocols, and Pitfalls', *Veterinary Clinics of North America - Small Animal Practice*, 41(1), pp. 163–175. doi: 10.1016/j.cvsm.2010.12.001.

Royal Liverpool and Broadgreen University Hospitals NHS Trust (2015) *Protocol for anticoagulation of extracorporeal circuits during kidney replacement therapy or plasma exchange*.

Safadi, S. *et al.* (2017) 'Prospective Study of Routine Heparin Avoidance Hemodialysis in a Tertiary Acute Care Inpatient Practice', *Kidney International Reports*, 2(4), pp. 695–704. doi: 10.1016/j.ekir.2017.03.003.

Sahota, S. and Rodby, R. (2014) 'Inpatient hemodialysis without anticoagulation in adults', *Clinical Kidney Journal*, 7(6), pp. 1–5. doi: 10.1093/ckj/sfu114.

Sanders, P. W., Taylor, H. and Curtis, J. J. (1985) 'Hemodialysis Without Anticoagulation', *American Journal of Kidney Diseases*, 5(1), pp. 32–35.

Schrader, J. *et al.* (1988) 'Comparison of low molecular weight heparin to standard heparin in hemodialysis/hemofiltration', *Kidney International*, 33(4), pp. 890–896. doi: 10.1038/ki.1988.81.

Schwab, S. J. *et al.* (1987) 'Hemodialysis without anticoagulation. One-year prospective trial in hospitalized patients at risk for bleeding', *The American Journal of Medicine*, 83(3), pp. 405–410. doi: 10.1016/0002-9343(87)90748-0.

Seliger, S. L. *et al.* (2003) 'Elevated risk of stroke among patients with end-stage renal disease', *Kidney International*, 64(2), pp. 603–609. doi: 10.1046/j.1523-1755.2003.00101.x.

Shibiru, T. *et al.* (2013) 'Survival patterns of patients on maintenance hemodialysis for end stage renal disease in Ethiopia : summary of 91 cases', *BMC nephrology*, 14(1–6).

Shrewsbury and Telford NHS (2017) ‘Guidelines for administration of Anticoagulation for patients receiving haemodialysis’.

Srisawat, N. *et al.* (2010) ‘Cost of acute renal replacement therapy in the intensive care unit: Results from The Beginning and Ending Supportive Therapy for the Kidney (BEST Kidney) Study’, *Critical Care*, 14(2), pp. 1–10. doi: 10.1186/cc8933.

Tolwani, A. J. and Wille, K. M. (2009) ‘Anticoagulation for continuous renal replacement therapy’, *Seminars in Dialysis*, 22(2), pp. 141–145. doi: 10.1111/j.1525-139X.2008.00545.x.

Warkentin, T. E. *et al.* (1995) ‘Heparin-Induced Thrombocytopenia in Patients Treated with Low-Molecular-Weight Heparin or Unfractionated Heparin’, *New England Journal of Medicine*, 332(20), pp. 1330–1336. doi: 10.1056/nejm199505183322003.

Wasse, H. *et al.* (2003) ‘Risk factors for upper gastrointestinal bleeding among end-stage renal disease patients’, *Kidney International*, 64(4), pp. 1455–1461. doi: 10.1046/j.1523-1755.2003.00225.x.

Yang, J. Y. *et al.* (2012) ‘Trends in acute nonvariceal upper gastrointestinal bleeding in dialysis patients’, *Journal of the American Society of Nephrology*, 23(3), pp. 495–506. doi: 10.1681/ASN.2011070658.

10. Annex

10.1 Annex I: Information Sheet

Dear participant, Good Morning/Afternoon

Introduction

My name is Hanan Muzeyin (BPharm). I am a member of the study that is carried out at Tikur Anbessa Specialized Hospital, and St. Paul's Hospital Millennium Medical College among Acute kidney injury patients who underwent hemodialysis Addis Ababa, Ethiopia, entitled “Anticoagulation Outcomes and Associated Factors among Acute Kidney Injury Patients during Hemodialysis at Two Selected Hospitals in Addis Ababa, Ethiopia: A Prospective Study”. The main purpose of this study is to assess anticoagulation outcomes and associated factors among AKI patients who undergo HD at Tikur Anbessa Specialized Hospital and St. Paul's Hospital Millennium Medical College, Addis Ababa, Ethiopia.

Thank you so much in advance.

10.2 Annex II: Informed Consent Form

Everything from your information and records would be completely confidential to the research and the data are stored without your name and only used for the purpose of this study. None of this would affect the care you receive from renal clinics of both TASH and SPHMMC, but will help in future planning for the hospital. No identifying names or characteristics will go into my report, so you may share your thoughts openly. Additionally, taking part in this study is completely voluntary. It is your choice whether to participate or not. You may skip any questions that you do not want to answer. Please ask me to stop as we go through the information and I will take time to explain. I would be grateful if you could sign the attached form to say you have no objections to our accessing any records and interviewing you. Would you be willing to assist me?

If the interviewee responds "Yes", Please proceed and let him/her to sign or replies "No" gratitude him/her and quit the interview. If you have any questions concerning the study, please call Hanan Muzeyin + 251 91 227 5828.

_____ _____

Signature of respondent Signature of interviewer

Date: _____ (Day/month/year)

Principal Investigator: Hanan Muzeyin

Addis Ababa University, CHS, School of Pharmacy, Department of Pharmacology and Clinical Pharmacy

Email: hanuaymu@gmail.com

10.3 Annex III: Data Collection Instrument

Section I. Socio-demographic characteristics

Age(in years)____				
Length of hospitalization (days) ____				
Sex	I. Male		II. Female	
Marital status	I. Single	II. Married	III. Widowed	IV. Divorced
If female	I. Pregnant		II. Non-Pregnant	III. Postpartum
Educational status	I. Unable to read and write	II. Primary education	III. Secondary education	IV. Diploma and above
Weight (Kg)_____				
Method of payment	I. Free		III. Out of pocket payment	
Substance use	I. Nothing	II. Smoking	III. Chewing Khat	IV. Alcohol

Section II. Medical, medication and laboratory data

1. Cause of AKI
    a. Acute tubular necrosis
    b. Severe dehydration
    c. Poison
    d. Nephritic syndrome
    e. Interstitial nephritis
    f. Urinary tract obstruction
    g. Sepsis
    h. Shock
    i. Nephrotoxic drugs
    j. Other (please specify_____)
2. Indication for Dialysis
    I. Fluid overload
    II. Uremic signs and symptoms
    III. Hyperkalemia
    IV. Metabolic Acidosis

3. Co-morbid medical conditions
    I. Atrial fibrillation
    II. Coronary arterial disease
    III. Myocardial infarction
    IV. Stroke
    V. Hypertension
    VI. Congestive heart disease
    VII. Gastrointestinal ulceration
    VIII. CKD
    IX. Venous thrombosis
    X. Pulmonary embolism
    XI. Others, (please specify) _____
4. Anti-platelet and/or anticoagulant treatment for another indication

Method of anticoagulation	**Dose/Frequency/Route**
No anticoagulation or anti-platelet	
Warfarin	
UFH	
LMWH	
Rivaroxaban	
Aspirin	
Clopidogrel	
Others (please specify)	

5. Is there any other concomitant medications? Yes❑ No❑

Section III. Selected Laboratory Values during Admission (before starting HD) AND Discharge

1. CBC
    a. Hgb (g/dl) _____; _____
    b. WBC (10^3 /ul) _____; _____
    c. Platelet (10^3 /ul) _____; _____
2. Serum Creatinine (mg/dl) _____; _____
3. Urea (mg/dl) _____; _____
4. Serum electrolyte
    a. K (mEq/L) _____; _____

Section IV. HD related data and anticoagulants for HD procedures

1. How many sessions underwent _____
2. Frequency of dialysis per week
   I. Once II. Twice III. Three times
3. Vascular access
   I. Fistula II. Catheter III. Graft _____
4. Anticoagulation methods using: Yes ☐; No ☐
5. Which method: UFH ☐; LMWH ☐; Other (specify) _____
6. If used other method, specify the dose_____
7. Number of dialysis sessions, duration per session and blood transfusion

Date	**Session**	**Duration**	**Blood transfusion** (During HD)	
			Yes	No

8. Dosing of unfractionated heparin (UFH) during HD

Session	**UFH**				**NS (ml)**
	Dose (IU/ml)	Bolus dose	Infusion rate	When was the infusion stopped	

9. Occurrences of thrombosis and/or bleeding complications

Type of complication (bleeding or clotting)	**Measures taken**	**Session**
1.		
2.		
3.		
4.		
5.		
6.		
7.		
8.		
9.		
10.		

10. HD parameters

Session	**Venous pressure (mmHg)**	**UF Volume (ml)**	**Blood flow (ml/min)**	**Dialysate flow (ml/min)**	**UFH (Perprotocol, minimal, free…etc)**