Enoxaparin vs Continuous Heparin for Periprocedural Bridging in Patients With Atrial Fibrillation and Advanced Chronic Kidney Disease

Chandler David Schexnayder, PharmD, BCPS; Christine Aguilar, PharmD, BCPS; and Kathleen Morneau, PharmD, BCPS

Bridging with enoxaparin rather than heparin has the potential to reduce the length of hospital stay, incidence of nosocomial infections, and cost of hospitalization.

Chandler Schexnayder is a Home-Based Primary Care Clinical Pharmacy Specialist, and **Christine Aguilar** is an Inpatient Surgery Clinical Pharmacy Specialist, both at the Michael E. DeBakey VA Medical Center in Houston, Texas. **Kathleen Morneau** is a Clinical Pharmacy Specialist in the Medical Intensive Care Unit and Antimicrobial Stewardship at the Audie L. Murphy Veterans Hospital in San Antonio, Texas. **Correspondence:** Chandler Schexnayder (chandler.schexnayder@va.gov)

There has been a long-standing controversy in the use of parenteral anticoagulation for perioperative bridging in patients with atrial fibrillation (AF) pursuing elective surgery.[1] The decision to bridge is dependent on the patient's risk of thromboembolic complications and susceptibility to bleed.[1] The BRIDGE trial showed noninferiority in rate of stroke and embolism events between low molecular weight heparins (LMWHs) and no perioperative bridging.[2] However, according to the American College of Chest Physicians (CHEST) 2012 guidelines, patients in the BRIDGE trial would be deemed low risk for thromboembolic events displayed by a mean $CHADS_2$ (congestive heart failure [CHF], hypertension, age, diabetes mellitus, and stroke/transient ischemic attack) score of 2.3. Also, the BRIDGE study and many others excluded patients with advanced forms of chronic kidney disease (CKD).[2,3]

Similar to patients with AF, patients with advanced CKD (ACKD, stage 4 and 5 CKD) have an increased risk of stroke and venous thromboembolism (VTE).[4,5] Patients with AF and ACKD have not been adequately studied for perioperative anticoagulation bridging outcomes. Although unfractionated heparin (UFH) is preferred over LMWH in ACKD patients, enoxaparin can be used in this population.[1,6] Enoxaparin 1 mg/kg once daily is approved by the US Food and Drug Administration (FDA) for use in patients with severe renal insufficiency defined as creatinine clearance (CrCl) < 30 mL/min. This dosage adjustment is subsequent to studies with enoxaparin 1 mg/kg twice daily that showed a significant increase in major and minor bleeding in severe renal-insufficient patients with CrCl < 30 mL/min vs patients with CrCl > 30 mL/min.[7] When comparing the myocardial infarction (MI) outcomes of severe renal-insufficient patients in the ExTRACT-TIMI 25 trial, enoxaparin 1 mg/kg once daily had no significant difference in nonfatal major bleeding vs UFH.[8] In patients without renal impairment (no documentation of kidney disease), bridging therapy with LMWH was completed more than UFH in < 24 hours of hospital stay and with similar rates of VTEs and major bleeding.[9] In addition to its ability to be administered outpatient, enoxaparin has a more predictable pharmacokinetic profile, allowing for less monitoring and a lower incidence of heparin-induced thrombocytopenia (HIT) vs that of UFH.[6]

The Michael E. DeBakey Veteran Affairs Medical Center (MEDVAMC) in Houston, Texas, is one of the largest US Department of Veterans Affairs (VA) hospitals in the US, managing > 150,000 veterans in Southeast Texas and other southern states. As a referral center for traveling patients, it is crucial that MEDVAMC decrease hospital length of stay (LOS) to increase space for incoming patients. Reducing LOS also reduces costs and may have a correlation with decreasing the incidence of nosocomial infections. Because of its significance to this facility, hospital LOS is an appropriate primary outcome for this study.

To our knowledge, bridging outcomes between LMWH and UFH in patients with AF and ACKD have never been studied. We hypothesized that using enoxaparin instead of heparin for periprocedural management would result in decreased hospital LOS, leading to a lower economic burden and lower incidence of nosocomial infections with no significant differences in major and minor bleeding and thromboembolic complications.[10]

METHODS

This study was a single-center, retrospective chart review of adult patients from January 2008 to September 2017. The review was conducted at MEDVAMC and was approved by the research and development committee and by the Baylor College of Medicine Institutional Review Board. Formal consent was not required.

Included patients were aged ≥ 18 years with diagnoses of AF or atrial flutter and ACKD as recognized by a glomerular filtration rate (eGFR) of < 30 mL/min/1.73 m^2 as calculated by use of the Modification of Diet in Renal Disease Study (MDRD) equation.[11] Patients must have previously been on warfarin and required temporary interruption of warfarin for an elective procedure. During the interruption of warfarin therapy, a requirement was set for patients to be on periprocedural anticoagulation with subcutaneous (SC) enoxaparin 1 mg/kg daily or continuous IV heparin per MEDVAMC heparin protocol. Patients were excluded if they had experienced major bleeding in the 6 weeks prior to the elective procedure, had current thrombocytopenia (platelet count < 100 × 10^9/L), or had a history of heparin-induced thrombocytopenia (HIT) or a heparin allergy.

This patient population was identified using TheraDoc Clinical Surveillance Software System (Charlotte, NC), which has prebuilt alert reviews for anticoagulation medications, including enoxaparin and heparin. An alert for patients on enoxaparin with serum creatinine (SCr) > 1.5 mg/dL was used to screen patients who met the inclusion criteria. A second alert identified patients on heparin. The VA Computerized Patient Record System (CPRS) was used to collect patient data.

Economic Analysis

An economic analysis was conducted using data from the VA Managerial Cost Accounting Reports. Data on the national average cost per bed day was used for the purpose of extrapolating this information to multiple VA institutions.[12] National average cost per day was determined by dividing the total cost by the number of bed days for the identified treating specialty during the fiscal period of 2018. Average cost per day data included costs for bed day, surgery, radiology services, laboratory tests, pharmacy services, treatment location (ie, intensive care units [ICUs]) and all other costs associated with an inpatient stay. A cost analysis was performed using this average cost per bed day and the mean LOS between enoxaparin and UFH for each treating specialty. The major outcome of the cost analysis was the total cost per average inpatient stay. The national average cost per bed day for each treating specialty was multiplied by the average LOS found for each treating specialty in this study; the sum of all the average costs per inpatient stay for the treating specialties resulted in the total cost per average inpatient stay. Permission to use these data was granted by the Pharmacy and Critical Care Services at MEDVAMC.

Patient Demographics and Characteristics

Data were collected on patient demographics (Table 1). Nosocomial infections, stroke/transient ischemic attack, MI, VTE, major and minor bleeding, and death are defined in Table 2.

The primary outcome of the study was hospital LOS. The study was powered at 90% for $\alpha = .05$, which gives a required study population of 114 (1:1 enrollment ratio) patients to determine a statistically significant difference in hospital stay. This sample size was calculated using the mean hospital LOS (the primary objective) in the REGIMEN registry for LMWH (4.6 days) and UFH (10.3 days).[9] To our knowledge, the incidence of nosocomial infections (a secondary outcome) has not been studied in this patient population; therefore, there was no basis to assess an appropriate sample size to find a difference in this outcome. Furthermore, the goal was to collect as many patients as possible to best assess this variable. Because of an expected

TABLE 1 Baseline Characteristics

Characteristics	Enoxaparin (n = 14)	UFH (n = 36)	*P* Value
Age, y (SD)	73.6 (8.9)	70.4 (9.8)	.31
Actual body weight, kg (SD)	90.9 (17.4)	98.2 (27.6)	.36
Body mass index, (SD)	29.8 (6.0)	30.9 (8.0)	.66
Male, No. (%)	13 (92.9)	26 (100.0)	--
Race, No. (%) White Black Hispanic	 7 (50.0) 5 (35.7) 2 (14.3)	 18 (50) 14 (38.9) 4 (11.1)	-- -- -- --
Type 2 diabetes mellitus, No. (%)	13 (92.9)	26 (72.2)	.15
Chronic kidney disease, No. (%) Stage 4 Stage 5	 11 (78.6) 3 (21.4)	 18 (50.0) 18 (50.0)	.11 .11
Hemodialysis, No. (%)	3 (21.4)	18 (50.0)	.11
Congestive heart failure, No. (%)	11 (78.6)	29 (80.6)	.99
Hypertension, No. (%)	14 (100.0)	36 (100)	.99
Stroke/TIA, No. (%)	3 (21.4)	5 (13.9)	.67
Myocardial infarction, No. (%)	7 (50.0)	12 (33.3)	.34
Vascular disease, No. (%)	8 (57.1)	21 (58.3)	.99
Coronary artery disease, No. (%)	7 (50.0)	23 (63.9)	.52
Cirrhosis, No. (%)	1 (7.1)	2 (5.6)	.99
Surgical history, No. (%)	14 (100.0)	30 (83.3)	.17
Heart valve, No. (%)	3 (21.4)	5 (13.9)	.67
Medications with bleeding risk, No. (%)	8 (57.1)	19 (52.8)	.99
Triple therapy	2 (14.3)	3 (8.3)	.61
$CHADS_{2,}$ (SD)	3.8 1(.2)	3.4 (1.0)	.23
CHA_2DS_2VASc (SD)	5.0 (0.9)	4.7 (1.3)	.46
HAS-BLED (SD)	4.3 (1.1)	4.0 (0.9)	.40
Charlson Comorbidity Index (SD)	8.1 (1.8)	7.6 (1.9)	.35
Revised Cardiac Risk Index (SD)	2.7 (1.0)	2.9 (1.0)	.48
eGFR, mL/min/1.73 m^2 (SD)	22.6 (7.8)	16.8 (8.2)	.03[a]
Creatinine clearance, mL/min (SD)	24.9 (9.6)	20.1 (10.3)	.14
Serum creatinine, mg/dL (SD)	3.6 (2.3)	5.1 (3.1)	.09
Hemoglobin A_{1c}, % (SD)	7.2 (2.3)	6.9 (1.8)	.54
International normalized ratio (SD)	1.7 (0.9)	2.1 (0.8)	.14
White blood cell (SD)	8.0 (2.1)	9.2 (4.1)	.31
Hemoglobin, g/dL (SD)	10.4 (1.2)	10.5 (1.8)	.95
Hematocrit (SD)	31.7 (3.5)	31.7 (5.5)	.99
Platelets, 10^9/L (SD)	181.3 (67.2)	171.2 (64.7)	.65

[a]Statistically significant.

Abbreviations: $CHADS_2$, congestive heart failure, hypertension, age, diabetes, and stroke/TIA; CHA_2DS_2-VASc, cardiac failure or dysfunction, hypertension, age 65-74 years (1 point) or ≥ 75 years (9 points), diabetes mellitus, and stroke/TIA or thromboembolism (2 points), vascular disease, and sex category (female); eGFR, estimated glomerular filtration rate; HAS-BLED, Hypertension, abnormal renal and liver function, stroke, bleeding, labile INR, elderly, drugs or alcohol; TIA, transient ischemic attack; UFH, unfractionated heparin.

TABLE 2 Definitions of Procedures and Events[9,18-20]

Types of Procedures	Definition
Major surgery	Duration > 45 min and orthopedic, cardiothoracic, vascular, or general surgical procedures
Minor surgery	All other procedures, including but not limited to dental procedures, gastrointestinal scopes, and obstetrics and gynecology procedures
Nosocomial	Diagnosis of the respective infection documented in the patients' chart along with documented microorganism > 48 h of hospitalization and ≤ 30 days postprocedure
Major bleed	Decrease in hemoglobin (Hgb) of ≥ 3 g/dL, red blood cell transfusion of > 2 units, need for invasive intervention, or bleeding at a critical anatomic site (intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, pericardial, or intramuscular)
Minor bleed	Clinically overt bleeding that does not meet the criteria of major bleeding: reduction in Hgb of > 2 to < 3 g/dL, gross hematuria (not associated with trauma), gastrointestinal hemorrhage, subconjunctival hemorrhage, hemoptysis, hematoma > 5 cm or leading to prolonged hospitalization, interruption of drug for at least 24 hours, or uncontrolled bleeding requiring protamine sulfate administration
Venous thromboembolism	Documented deep vein thrombosis or pulmonary embolism confirmed by Doppler studies, perfusion scan, spiral computed tomography (CT) or magnetic resonance imaging (MRI) ≤ 30 d postprocedure
Myocardial infarction	Documented myocardial infarction ≤ 30 days postprocedure
Stroke or transient ischemic attack	Documented stroke confirmed by CT or MRI or documented TIA ≤ 30 days postprocedure
Death	Documentation of death ≤ 30 days postprocedure

high exclusion rate, 504 patients were reviewed to target a sample size of 120 patients. Due to the single-center nature of this review, the secondary outcomes of thromboembolic complications and major and minor bleeding were expected to be underpowered.

The final analysis compared the enoxaparin arm with the UFH arm. Univariate differences between the treatment groups were compared using the Fisher exact test for categorical variables. Demographic data and other continuous variables were analyzed by an unpaired *t* test to compare means between the 2 arms. Outcomes and characteristics were deemed statistically significant when α (*P* value) was < .05. All *P* values reported were 2-tailed with a 95% CI. No statistical analysis was performed for the cost differences (based on LOS per treating specialty) in the 2 treatment arms. Statistical analyses were completed by utilizing GraphPad Software (San Diego, CA).

RESULTS

In total, 50 patients were analyzed in the study. There were 36 patients bridged with IV UFH at a concentration of 25,000 U/250 mL with an initial infusion rate of 12 U/kg/h. For the other arm, 14 patients were anticoagulated with renally dosed enoxaparin 1 mg/kg/d with an average daily dose of 89.3 mg; the mean actual body weight in this group was 90.9 mg (correlates with enoxaparin daily dose). Physicians of the primary team decided which parenteral anticoagulant to use. The difference in mean duration of inpatient parental anticoagulation between both groups was not statistically significant: enoxaparin at 7.1 days and UFH at 9.6 days (*P* = .19). Patients in the enoxaparin arm were off warfarin therapy for an average of 6.0 days vs 7.5 days for the UFH group (*P* = .29). The duration of outpatient anticoagulation with enoxaparin was not analyzed in this study.

Patient and Procedure Characteristics

All patients had AF or atrial flutter with 86% of patients (n = 43) having a $CHADS_2$ > 2 and 48% (n = 29) having a CHA_2DS_2VASc > 4. Overall, the mean age was 71.3 years with similarities in ethnicity distribution. Patients had multiple comorbidities as shown by a mean Charlson Comorbidity Index (CCI) of 7.7 and an increased risk of bleeding as evidenced by 98% (n = 48) of patients having a HAS-BLED score of ≥ 3. A greater percentage of patients bridged with enoxaparin had DM, history of stroke and MI, and a heart valve, whereas UFH patients were more likely to be in stage 5 CKD (eGFR < 15 mL/min/1.73m^2) with a significantly lower mean eGFR

TABLE 3 Procedure Characteristics

Procedures	Enoxaparin (n = 14)	UFH (n = 36)	*P* Value
Length of procedure, h (SD)	0.93 (0.50)	1.29 (1.46)	.38
Length of procedure ≥ 45 min, No. (%)	9 (64.3)	20 (55.5)	.75
Major surgery, No. (%)	5 (35.7)	14 (38.9)	.99
Minor surgery, No. (%)	9 (64.3)	22 (61.1)	.99
Cardiothoracic, No. (%)	6 (42.9)	13 (36.1)	.75
Vascular, No. (%)	3 (21.4)	13 (36.1)	.50
General, No. (%)	1 (7.1)	2 (5.6)	.99
Gastrointestinal scopes, No. (%)	3 (21.4)	4 (11.1)	.38
Urologic, No. (%)	1 (7.1)	1 (2.8)	.49
Otolaryngologic, No. (%)	0 (0.0)	2 (5.6)	.99
Dermatologic, No. (%)	0 (0.0)	1 (2.8)	.99

(16.76 vs 22.64, *P* = .03). Furthermore, there were more patients on hemodialysis in the UFH (50%) arm vs enoxaparin (21%) arm and a lower mean CrCl with UFH (20.1 mL/min) compared with enoxaparin (24.9 mL/min); however, the differences in hemodialysis and mean CrCl were not statistically significant. There were no patients on peritoneal dialysis in this review.

Procedure Characteristics

The average Revised Cardiac Risk Index (RCRI) score was about 3, indicating that these patients were at a Class IV risk (11%) of having a perioperative cardiac event (Table 3). Nineteen patients (38%) elected for a major surgery with all but 1 of the surgeries (major or minor) being invasive. The average length of surgery was 1.2 hours, and patients were more likely to undergo cardiothoracic procedures (38%). There were 2 out of 14 (14%) patients on enoxaparin who were able to have surgery as an outpatient; whereas this did not occur in patients on UFH. The procedures completed for these patients were a colostomy (minor surgery) and arteriovenous graft repair (major surgery). There were no statistically significant differences regarding types of procedures between the 2 arms.

Outcomes

The primary outcome of this study, hospital LOS, differed significantly in the enoxaparin arm vs UFH: 10.2 days vs 17.5 days, *P* = .04 (Table 4). The time-to-discharge from initiation of parenteral anticoagulation was significantly reduced with enoxaparin (7.1 days) compared with UFH (11.9 days); *P* = .04. Although also reduced in the enoxaparin arm, ICU LOS did not show statistical significance (1.1 days vs 4.0 days, *P* = .09).

About 36% (n = 18) of patients in this study acquired an infection during hospitalization for elective surgery. The most common microorganism and site of infection were *Enterococcus* species and urinary tract, respectively (Table 5). Nearly half (44%, n = 16) of the patients in the UFH group had a nosocomial infection vs 14% (n = 2) of enoxaparin-bridged patients with a difference approaching significance; *P* = .056. Both patients in the enoxaparin group had the urinary tract as the primary source of infection; 1 of these patients had a urologic procedure.

Major bleeding occurred in 7% (n = 1) of enoxaparin patients vs 22% (n = 8) in the UFH arm, but this was not found to be statistically significant (*P* = .41). Minor bleeding was similar between enoxaparin and UFH arms (14% vs 19%, *P* = .99). Regarding thromboembolic complications, the enoxaparin group (0%) had a numerical reduction compared to UFH (11%) with VTE (n = 4) being the only occurrence of the composite outcome (*P* = .57). There were 4 deaths within 30 days posthospitalization—all were from the UFH group (*P* = .57). Due to the small sample size of this study, these outcomes (bleeding and thrombotic events) were not powered to detect a statistically significant difference.

Economic Analysis

The average cost differences (Table 6) of hospitalization between enoxaparin and UFH were calculated using the average LOS per treating specialty multiplied by the national average cost of the MCO for an inpatient bed day in 2018.[12] The treating specialty with the longest average LOS in the enoxaparin arm was thoracic (4.7 days). The UFH arm also had a large LOS (average days) for the thoracic specialty (6.4 days); however, the vascular specialty (6.7 days) had the longest average LOS in this group. Due to a mean LOS of 10.2 days in the enoxaparin arm, which was further stratified by treating spe-

cialty, the total cost per average inpatient stay was calculated as $51,710. On the other hand, patients in the UFH arm had a total cost per average inpatient stay of $92,848.

Monitoring

Anti-factor Xa levels for LMWH monitoring were not analyzed in this study due to a lack of values collected; only 1 patient had an anti-factor Xa level checked during this time frame. Infusion rates of UFH were adjusted based on aPTT levels collected per MEDVAMC inpatient anticoagulation protocol. The average percentage of aPTT in therapeutic range was 46.3% and the mean time-to-therapeutic range (SD) was about 2.4 (1.3) days. Due to this study's retrospective nature, there were inconsistencies with availability of documentation of UFH infusion rates. For this reason, these values were not analyzed further.

DISCUSSION

In 2017, the American College of Cardiology published the Periprocedural Anticoagulation Expert Consensus Pathway, which recommends for patients with AF at low risk (CHA_2DS_2VASc 1-4) of thromboembolism to not be bridged (unless patient had a prior VTE or stroke/TIA).[13] Nearly half the patients in this study, were classified as moderate-to-high thrombotic risk as evidenced by a $CHA_2DS_2VASc > 4$ with a mean score of 4.8. Due to this study's retrospective design from 2008 to 2017, many of the clinicians may have referenced the 2008 CHEST antithrombotic guidelines when making the decision to bridge patients; these guidelines and the previous MEDVAMC anticoagulation protocol recommend bridging patients with AF with $CHADS_2 > 2$ (moderate-to-high thrombotic risk) in which all but 1 of the patients in this study met criteria.[1,14] In contrast to the landmark BRIDGE trial, the mean $CHADS_2$ score in this study was 3.6; this is an indication that our patient population was of individuals at an increased risk of stroke and embolism.

In addition to thromboembolic complications, patients in the current study also were at increased risk of clinically relevant bleeding with a mean HAS-BLED score of 4.1 and nearly all patients having a score > 3. The complexity of the veteran population also was displayed by this study's mean CCI (7.7) and RCRI (3.0) indicating a 0% estimated 10-year survival and a 11% increase in having a perioperative cardiac event, respectively. A mean CCI of 7.7 is associated with a 13.3 relative risk of death within 6 years postoperation.[15] All patients had a diagnosis of hypertension, and > 75% had this diagnosis complicated by DM. In addition, this patient population was of those with extensive cardiovascular disease or increased risk, which makes for a clinically relevant application of patients who would require periprocedural bridging.

Another positive aspect of this study is that all the baseline characteristics, apart from renal function, were similar between arms, helping to strengthen the ability to adequately compare the 2 bridging modalities. Our assumption for the reasoning that more stage 5 CKD and dialysis patients were anticoagulated with UFH vs enoxaparin is a result of concern for an increased risk of bleeding with a medication that is renally cleared 30% less in CrCl < 30 mL/min.[16] Although, enoxaparin 1 mg/kg/d is FDA approved as a therapeutic anticoagulant option, clinicians at MEDVAMC likely had reservations about its use in end-stage

TABLE 4 Outcomes

	Enoxaparin (n = 14)	UFH (n = 36)	95% CI	*P* Value
Hospital LOS, d (SD)	10.2 (7.6)	17.5 (11.9)	-14.2 to -0.4	.04[a]
ICU LOS, d (SD)	1.1 (2.8)	4.0 (6.0)	-6.3 to 0.5	.09
Anticoagulation time-to-discharge, d (SD)	7.1 (5.9)	11.9 (7.5)	-9.3 to -0.3	.04[a]
Nosocomial infections, No. (%)	2 (14.3)	16 (44.4)	-0.6 to -0.0	.06
Major bleeding, No. (%)	5 (35.7)	14 (38.9)	-0.4 to 0.1	.41
Minor bleeding, No. (%)	9 (64.3)	22 (61.1)	-0.3 to 0.2	.99
Thromboembolic events, No. (%)	0 (0.0)	4 (11.1)	-0.3 to 0.1	.57
VTE , No. (%)	0 (0.0)	4 (11.1)	-0.3 to 0.1	.57
Stroke/TIA, No. (%)	0 (0.0)	0 (0.0)	—	.99
Myocardial infarction, No. (%)	0 (0.0)	0 (0.0)	—	.99
Death, No. (%)	0 (0.0)	1 (2.8)	-0.3 to 0.1	.49

Abbreviations: ICU, intensive care unit; LOS, length of stay; TIA, transient ischemic attack; UFH, unfractionated heparin; VTE, venous thromboembolism.
[a]Statistical significance.

TABLE 5 Infection Characteristics

Infection Sources	Enoxaparin, No. (%) (n = 14)	UFH, No. (%) (n = 36)
Blood	0 (0)	3 (8.3)
Urinary	2 (14.3)	7 (19.4)
Respiratory	0 (0)	6 (16.7)
Abdominal	0 (0)	3 (8.3)
Surgical site	0 (0)	3 (8.3)
Microorganisms		
Staphylococcus sp	0 (0)	4 (11.1)
Streptococcus sp	0 (0)	1 (2.8)
Enterococcus sp	1 (7.1)	6 (16.7)
Escherichia coli	0 (0.0)	3 (8.3)
Klebsiella sp	1 (7.1)	1 (2.8)
Citrobacter sp	0 (0)	1 (2.8)
Moraxella sp	0 (0)	1 (2.8)
Proteus sp	0 (0)	1 (2.8)
Stenotrophomonas sp	0 (0)	1 (2.8)
Clostridium difficile	0 (0)	1 (2.8)
Other bacteria	0 (0)	1 (2.8)
Candida sp	0 (0)	3 (8.3)

Abbreviations: sp, species; UFH, unfractionated heparin.

CKD patients. Unlike many studies, including the BRIDGE trial, patients with ACKD were not excluded from this trial, and the outcomes with enoxaparin are available for interpretation.

To no surprise, for patients included in this study, enoxaparin use led to shorter hospital LOS, reduced ICU LOS, and a quicker time-to-discharge from initiation. This is credited to the 100% bioavailability of SC enoxaparin in conjunction with its means to be a therapeutic option as an outpatient.[16] Unlike IV UFH, patients requiring bridging can be discharged on SC injections of enoxaparin until a therapeutic INR is maintained with warfarin. The duration of hospital LOS in both arms were longer in this study compared with that of other studies.[9] This may be due to clinicians being more cautious with renal insufficient patients, and the patients included in this study had multiple comorbidities. According to an economic analysis performed by Amorosi and colleagues in 2004, bridging with enoxaparin instead of UFH can save up to $3,733 per patient and reduce bridging costs by 63% to 85% driven primarily by decreased hospital LOS.[10]

Economic Outcome

In our study, we conducted a cost analysis using national VA data that indicated a $41,138 or 44% reduction in total cost per average inpatient stay when bridging 1 patient with enoxaparin vs UFH. The benefit of this cost analysis is that it reflects direct costs at VA institutions nationally; this will allow these data to be useful for practitioners at MEDVAMC and other VA hospitals. Stratifying the costs by treating specialty instead of treatment location minimized skewing of the data as there were some patients with long LOS in the ICU. No patients in the enoxaparin arm were treated in otolaryngology, which may have skewed the data. The data included direct costs for beds as well as costs for multiple services, such as procedures, pharmacy, nursing, laboratory tests, and imaging. Unlike the Amorosi study, our review did not include acquisition costs for enoxaparin syringes and bags of UFH or laboratory costs for aPTT and anti-factor Xa levels in part because of the data source and the difficulty calculating costs over a 10-year span.

Patients in the enoxaparin arm had a trend toward fewer occurrences of hospital-acquired infections than did those in the UFH arm, which we believe is due to a decreased LOS (in both total hospital and ICU days) and fewer blood draws needed for monitoring. This also may be attributed to a longer mean duration of surgery in the UFH arm (1.3 hours) vs enoxaparin (0.9 hours). The percentage of patients with procedures ≥ 45 minutes and the types of procedures between both arms were similar. However, these outcomes were not statistically significant. In addition, elderly males who are hospitalized may require a catheter (due to urinary retention), and catheter-associated urinary tract infection (CAUTI) is one of the highest reported infections in acute care hospitals in the US. This is in line with our patient population and may be a supplementary reason for the increase in infection incidence with UFH. Though, whether

urinary catheters were used in these patients was not evaluated in this study.

Despite being at an increased risk of experiencing a major adverse cardiovascular event (MACE), no patients in either arm had a stroke/TIA or MI within 30 days postprocedure. The only occurrences documented were VTEs, which happened only in 4 patients on UFH. Four people died in this study, solely in the UFH arm. The incidence of thromboembolic complications and death along with major and minor bleeding cannot be deduced as meaningful as this study was underpowered for these outcomes. Despite anti-factor Xa monitoring being recommended in ACKD patients on enoxaparin, this monitoring was not routinely performed in this study. Another limitation was the inability to adequately assess the appropriateness of nurse-adjusted UFH infusion rates largely due to the retrospective nature of this study. The variability of aPTT percentage in therapeutic range and time-to-therapeutic range reported was indicative of the difficulties of monitoring for the safety and efficacy of UFH.

In 1991, Cruickshank and colleagues conducted a study in which a standard nomogram (similar to the MEDVAMC nomogram) for the adjustment of IV heparin was implemented at a single hospital.[17] The success rate (aPTT percentage in therapeutic range) was 59.4% and average time-to-therapeutic range was about 1 day. The success rate (46.3%) and time-to-therapeutic range (2.4 days) in our study were lower and longer, respectively, than was expected. One potential reason for this discrepancy could be the differences in indication as the patients in Cruickshank and colleagues were being treated for VTE, whereas patients in our study had AF or atrial flutter. Also, there were inconsistencies in the availability of documentation of monitoring parameters for heparin due to the study time frame and retrospective design. Patients on UFH who are not within the therapeutic range in a timely manner are at greater risk of MACE and major/minor bleeding. Our study was not powered to detect these findings.

TABLE 6 Total Cost per Average Inpatient Stay

Enoxaparin (n = 14)			
Treating Specialties	**Cost/ Bed Day, $[a]**	**Length of Stay, Mean, d[b]**	**Cost/ Inpatient Stay, $[c]**
Thoracic	5,425	4.7	25,226
Vascular	5,462	1.8	10,050
Gastroenterology	2,871	1.8	5,139
Otolaryngology	5,570	0	0
General	5,281	0.9	4,911
Urology	6,320	1.0	6,383
Total		10.2	51,710
Unfractionated Heparin			
Treating Specialties	**Cost/Bed Day, $[a]**	**Length of Stay, Mean, d[b]**	**Cost/ Inpatient Stay, $[c]**
Thoracic	5,425	6.4	34,829
Vascular	5,462	6.7	36,432
Gastroenterology	2,871	1.4	3,933
Otolaryngology	5,570	1.5	8,188
General	5,281	0.6	2,957
Urology	6,320	1.0	6,510
Total[d]		17.5	92,848

[a]National data from the VA Managerial Cost Accounting Reports retrieved from Michael E. DeBakey VA Medical Center Systems Redesign.
[b]Mean length of stay (days) per treating specialty found in this study.
[c]Average cost/bed day multiplied by average days per treating specialty found in this study.
[d]Total cost per average inpatient stay: the sum of all the average costs per inpatient stay for the treating specialties.

Strengths and Limitations

A significant limitation of this study was its small sample size; the study was not able to meet power for the primary outcome; it is unknown whether our study met power for nosocomial infections. The study also was not a powered review of other adverse events, such as thromboembolic complications, bleeding, and death. The study had an uneven number of patients, which made it more difficult to appropriately compare 2 patient populations; the study also did not include medians for patient characteristics and outcomes.

Due to this study's time frame, the clinical pharmacy services at MEDVAMC were not as robust as they are now, which is the reason the decisions on which anticoagulant to use were primarily physician based. The use of TheraDoc to identify patients posed the risk

of missing patients who may not have had the appropriate laboratory tests performed (ie, SCr). Patients on UFH had a reduced eGFR compared with that of enoxaparin, which may limit our extrapolation of enoxaparin's use in end-stage renal disease. The reduced eGFR and higher number of dialysis patients in the UFH arm may have increased the occurrence of more labile INRs and bleeding outcomes. Patients on hemodialysis typically have more comorbidities and an increased risk of infection due to the frequent use of catheters and needles to access the bloodstream. In addition, the potential differences in catheter use and duration between groups were not identified. If these parameters were studied, the data collected may have helped better explain the reasoning for increased incidence of infection in the UFH arm.

Strengths of this study include a complex patient population with similar characteristics, distribution of ethnicities representative of the US population, patients at moderate-to-high thrombotic risk, the analysis of nosocomial infections, and the exclusion of patients with normal renal function or moderate CKD.

CONCLUSION

To our knowledge, this is the first study to compare periprocedural bridging outcomes and incidence of nosocomial infections in patients with AF and ACKD. This review provides new evidence that in this patient population, enoxaparin is a potential anticoagulant to reduce hospital LOS and hospital-acquired infections. Compared with UFH, bridging with enoxaparin reduced hospital LOS and anticoagulation time-to-discharge by 7 and 5 days, respectively, and decreased the incidence of nosocomial infections by 30%. Using the mean LOS per treating specialty for both arms, bridging 1 patient with AF with enoxaparin vs UFH can potentially lead to an estimated $40,000 (44%) reduction in total cost of hospitalization. Enoxaparin also had no numeric differences in mortality and adverse events (stroke/TIA, MI, VTE) vs that of UFH, but it is important to note that this study was not powered to find a significant difference in these outcomes. Due to the mean eGFR of patients on enoxaparin being 22.6 mL/min/1.73 m^2 and only 1 in 5 having stage 5 CKD, at this time, we do not recommend enoxaparin for periprocedural use in stage 5 CKD or in patients on hemodialysis. Larger studies are needed, including randomized trials, in this patient population to further evaluate these outcomes and assess the use of enoxaparin in patients with ACKD.

Author disclosures

The authors report no actual or potential conflicts of interest with regard to this article.

Disclaimer

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