Time to achieving therapeutic international normalized ratio increases hospital length of stay after heart valve replacement surgery

Christopher J. Arendt, PharmD, [a,1] Joon Hwa Hong, MD, PhD, [b,c,1] Richard C. Daly, MD, [b] Christopher Scott, MS, [d] Ramila A. Mehta, MS, [d] Kent Bailey, PhD, [d] Jyotishman Pathak, PhD, [d] and Naveen L. Pereira, MD [e] *Rochester, MN and Seoul, Republic of Korea*

Background Achieving a therapeutic international normalized ratio (INR) before hospital discharge is an important inpatient goal for patients undergoing mechanical cardiac valve replacement (MCVR). The use of clinical algorithms has reduced the time to achieve therapeutic INR (TTI) with warfarin therapy. Whether TTI prolongs length of stay (LOS) is unknown.

Methods Patients who underwent MCVR over a consecutive 42-month period were included. Clinical data were obtained from the Society of Thoracic Surgeons Adult Cardiac Surgery database and electronic medical records. Therapeutic INR was defined as per standard guidelines. Warfarin dose was prescribed using an inpatient pharmacy-managed algorithm and computer-based dosing tool. International normalized ratio trajectory, procedural needs, and drug interactions were included in warfarin dose determination.

Results There were 708 patients who underwent MCVR, of which 159 were excluded for reasons that would preclude or interrupt warfarin use. Among the remainder of 549 patients, the average LOS was 6.4 days and mean TTI was 3.5 days. Landmark analysis showed that subjects in hospital on day 4 (n = 542) who achieved therapeutic INR were more likely to be discharged by day 6 compared with those who did not achieve therapeutic INR (75% vs 59%, $P < .001$). Multivariable proportional hazards regression with TTI as a time-dependent effect showed a strong association with discharge ($P = .0096$, hazard ratio 1.3) after adjustment for other significant clinical covariates.

Conclusions Time to achieve therapeutic INR is an independent predictor of LOS in patients requiring anticoagulation with warfarin after MCVR surgery. Alternative dosing and anticoagulation strategies will need to be adopted to reduce LOS in these patients. (Am Heart J 2017;187:70-7.)

Mechanical valve replacement surgery can be complicated by valve-related thromboembolism, with a 24% incidence in the first year and an incidence between the second and fourth years of 15%, decreasing thereafter.[1,2] Thrombi can be detected as early as 9 days by transesophageal echocardiography after mechanical valve replacement, and it is usually these early thrombi that are associated with greater morbidity and thromboembolic complications.[3] In one study involving 2,982 patients who underwent mechanical aortic valve replacement (AVR), transient ischemic attacks occurred in 42 patients, permanent strokes in 42 patients, and peripheral thromboembolic events in 15 patients before discharge.[4] To minimize thromboembolic complications, initiating anticoagulation therapy with warfarin immediately after mechanical cardiac valve replacement surgery is standard practice at most medical centers. The warfarin dosage is titrated based on international normalized ratio (INR) levels[5,6] using warfarin dosing algorithms, with a goal of reaching therapeutic INR targets before hospital discharge.

Current inpatient algorithms for warfarin dosing adjust for multiple clinical variables. However, despite this protocol-driven approach, clinical experience suggests that time to therapeutic INR (TTI) can vary widely, potentially protracting hospital length of stay (LOS). However, there has been no study performed examining

From the [a]Department of Pharmacy, Mayo Clinic, Rochester, MN, [b]Department of Cardiovascular Surgery, Mayo Clinic, Rochester, MN, [c]Department of Thoracic and Cardiovascular Surgery, Heart Research Institute, Chung-Ang University College of Medicine, Seoul, Republic of Korea, [d]Division of Biomedical Statistics and Informatics, Mayo Clinic, Rochester, MN, and [e]Department of Cardiovascular Diseases, Department of Molecular Pharmacology and Experimental Therapeutics, Mayo Clinic, Rochester, MN.
[1]Both authors contributed equally to this work.
Submitted October 4, 2016; accepted February 8, 2017.
Reprint requests: Naveen L. Pereira, MD, Department of Cardiovascular Diseases, Department of Molecular Pharmacology and Experimental Therapeutics, Mayo Clinic, 200 First St SW, Rochester, MN 55905.
E-mail: pereira.naveen@mayo.edu
0002-8703

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the impact of TTI on LOS after mechanical cardiac valve replacement. Length of stay plays an important role in determining the cost of treating patients after elective surgery, and hospitals have a significant economic incentive to expedite discharge of patients especially in the era of capitated reimbursements.[7]

There are many factors that contribute to prolonged LOS after cardiac surgery, and some of these include prolonged intensive care unit (ICU) stay, postoperative atrial fibrillation, congestive heart failure, and age. Whether TTI is a determinant in prolonging LOS in patients undergoing mechanical cardiac valve replacement and who receive warfarin is unknown. Although patient-related risk factors may not necessarily be modifiable, algorithms can be designed and used to safely but effectively prescribe warfarin in the postoperative setting to minimize LOS if TTI indeed plays an important role in prolonging LOS. Such an intervention could result in significant cost savings. In this study, we reviewed and analyzed data from electronic medical records and the Society of Thoracic Surgeons Adult Cardiac Surgery Database to investigate whether TTI is an independent predictor for increased hospital LOS after mechanical cardiac valve replacement surgery.

Methods

Patients

Consecutive patients who underwent either mechanical aortic (AVR) or mitral valve replacement (MVR) or both at Mayo Clinic, Rochester, MN, were included. Warfarin dose was prescribed using an inpatient pharmacy-managed algorithm and computer-based dosing tool for all patients in the analysis as described in detail below. Patients who were on warfarin before surgery or patients who could not continue the algorithm-based warfarin therapy for clinical reasons were excluded from the analysis. Blood samples for INR were taken every morning, collected in 3.2% sodium citrate and evaluated using the STA-R Evolution (Stago, Parsippany, NJ) fully automated electromechanical viscosity detection system using RecombiPlasTin 2G reagents (Instrumentation Laboratory, Milan, Italy). Therapeutic INR was defined as per standard guidelines to a target[8-12] INR 2.0 or greater but less than 4 (goal INR 2.5) in patients with AVR, and target INR 2.5 or greater but less than 4 (goal INR 3.0) in patients with MVR.[5] Definition of therapeutic INR in patients with both AVR and MVR was the same as that of MVR. No extramural funding was used to support this work.

The initial warfarin dose was according to expected patient response adjusted for sensitivity and risk factors[13] but not exceeding 5 mg daily per the algorithm. Loading doses were avoided due to risks associated with initial excessive suppression of coagulation factor activity (factors VII and IX, proteins S and C), and hemorrhagic complications.[14] Very high-sensitivity risk factors included profound liver dysfunction[15] or malnutrition as indicated by a baseline INR value 1.7 or greater. High-sensitivity risk factors were identified as hepatic disease[15] or hepatic malignancy, hepatic congestion secondary to right heart failure (post-cardiac valve surgery),[16,17] acute heart failure, age 80 years or greater,[18] concomitant strong medication potentiators of warfarin, serum albumin <2.5, baseline INR 1.4-1.6, actual body weight <50 kg,[13] poor nutritional state, or malabsorptive states. Moderate-sensitivity risk factors were defined as age 70-79 years,[18] acute hyperthyroidism,[19] serum albumin 2.6 to 3, heart failure diagnosis,[17] (stable) concomitant medications that lower warfarin potentiation effects: (1-3 medications in lower potentiator risk account for 1 risk factor, >3 medications in lower potentiator risk list count for 2 risk factors).

Similar to the nomogram model of warfarin dosing by Kovacs et al,[20] a fixed warfarin dose was used for the first 2 days and subsequent dose adjustment was made according to a change in INR values. Initial dose was started based on sensitivity risk factors. For individuals with 1 very high-sensitivity risk factor, a warfarin dose of 1 mg was administered on days 1 and 2. For persons with 1 high-sensitivity risk factor, 3 mg warfarin on days 1 and 2 was initiated; however, if the person has 2 or more high-sensitivity risk factors, a lower dose of 2 mg on days 1 and 2 was started. For persons with 2 or more moderate-sensitivity risk factors, 3 mg was initiated on days 1 and 2, and for those with only 1 moderate-sensitivity risk factor or no risk factors, the initial warfarin dose was 5 mg on days 1 and 2. By the third day of warfarin therapy, dose adjustments of 10% to 50% were made in response to INR results. If at any time the INR increased by more than 1.2 on any single day, an overshoot avoidance protocol was initiated, using low-dose oral phytonadione 0.25 mg given once,[21] and holding that days warfarin dose, with a resumption of warfarin the following day at a reduced dose. Daily INR laboratory results, clinical evaluation of potential interacting medications, nutrition and drug elimination considerations, and INR trajectory, along with computer nomogram–generated dose adjustment recommendations, allowed the pharmacist to adjust the warfarin dose in response to multiple variables each day. Intravenous unfractionated heparin originally initiated 12 to 24 hours after surgery according to thromboembolic risk and early bleeding and dosed to achieve and activated partial thromboplastin time 1.5 to 2 times the norm using a heparin nomogram system was stopped once the INR achieved the target goal. Concomitant aspirin therapy was continued according to comorbid risk factors and standard guidelines.

Statistical analysis

The descriptive characteristics of patients at the time of surgery were summarized using mean and SD for continuous variables and number and percentage for categorical variables. To investigate the timing of achieving INR target goals, Cox proportional hazards

regression was used. In this analysis, the event of interest was considered to be time to discharge from the hospital and models were started on the day of surgery. Characteristics occurring after surgery, namely, atrial fibrillation and time of starting warfarin, were entered as time-dependent variables in the Cox model. Time to therapeutic INR was also considered as a time-dependent effect and was the primary variable of interest. Results of these analyses are summarized with hazard ratios (HRs) and associated 95% CIs. A secondary analysis considering time of warfarin initiation as the starting time was also evaluated and showed similar results (data not shown).

To illustrate the time-dependent effect of achieving therapeutic INR, a Landmark analysis was used. In this analysis, patients were classified based on whether they had achieved therapeutic INR on or before day 4. Kaplan-Meier methods were then used to illustrate the probability of discharge starting at day 4 and tested with the log-rank test. For all analyses, a 2-sided P value <.05 was considered to be statistically significant. SAS version 9.3 (Cary, NC) was used for all analyses.

The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the manuscript, and its final contents.

Results

Among a total of 708 patients who underwent mechanical cardiac valve replacement surgery, 159 patients were excluded. These patients were excluded a priori because they were not administered warfarin therapy on a regular schedule during their hospital admission for the following reasons: in-hospital death, infection, acute renal failure, new-onset advanced heart block, cardiac tamponade, reoperations, neurologic complications, cardiac arrest, and multisystem failure. These factors in of itself would prolong hospital stay and would confound the interpretation of the TTI. After these exclusions, a total of 549 patients were included in the analysis.

Baseline demographics

General preoperative characteristics of the 549 patients who were included in the study are described in Table I. The average patient age was 55.5 years (11.3 years), the majority (62%) was male and 95% were white. There were significant comorbidities shared by the population, 88% had COPD and 61% had hypertension, 15% of patients had diabetes, nearly one-third were obese (BMI> 32), 21% had a history of arrhythmias and 17% had CHF. There were approximately equal proportion of patients who were NYHA Functional Class I-II and Class III-IV. Almost 25% of the patient population had undergone prior cardiac surgeries (predominantly coronary artery bypass).

Table I. General preoperative patient characteristics

Variable	All patients (n = 549)
Age (y)	55.56 (11.33)
Male/female, n (%)	341/208 (62/38)
Race, n (%)	
American Indian	2 (0)
Asian	5 (1)
African American	5 (1)
Hawaiian	1 (0)
White	510 (95)
Other	12 (2)
Body mass index	30.07 (6.48)
<20 kg/m^2, n (%)	9 (2)
>32 kg/m^2, n (%)	165 (30)
Diabetes, n (%)	83 (15)
Dialysis, n (%)	13 (2)
Arrhythmia, n (%)	116 (21)
Hypertension, n (%)	333 (61)
CHF, n (%)	92 (17)
COPD, n (%)	484 (88)
Stroke, n (%)	38 (51)
Cardiogenic shock, n (%)	3 (1)
Resuscitation, n (%)	1 (0)
Infectious endocarditis, n (%)	49 (9)
Peripheral vascular disease, n (%)	20 (4)
NYHA class, n (%)	
I-II	288 (52)
III-IV	260 (48)
Use of inotrope, n (%)	2 (0)
Use of IABP, n (%)	16 (3)
Previous cardiac surgeries, n (%)	142 (26)

Variables are described as numbers (percentage) or value (SD).
Abbreviations: *CHF*, Congestive heart failure; *COPD*, chronic obstructive pulmonary disease; *NYHA*, New York Heart Association; *IABP*, intra-aortic balloon pump.

Surgical and post-operative data

The surgical and post-operative data are summarized in Table II. Among the 549 included patients, 68% underwent AVR, 22% of patients underwent MVR and 10% of patients underwent both AVR and MVR. Of those who had mitral valve surgery, 30% were replacements, while 1% was annuloplasty only, and 2% reconstruction with or without annuloplasty. Of the AVR group which constituted the majority of valves 53% were replacements, while 17% were aortic root reconstruction with valve conduits, 8% were replacements including ascending graft. 27% of AVR and MVR surgeries involved concomitant bypass surgery. As to infectious complications, 1% of patients had pneumonia, while 9% of patients had infectious endocarditis post-op, and 4% had a prolonged ventilation time (defined as >4 hours). 22% (119) of patients had atrial fibrillation post-op. The total ICU hours per patient were 33.73 (31.83).

Warfarin initiation

Of the 594 included patients, 443 (81%) were started on warfarin by day 1 from surgery, 537 (97.81%) were started on warfarin by 2 days after surgery. 83% of patients achieved their first therapeutic INR in hospital,

Table II. Surgical and postoperative data

Variable	All patients (n = 549)
Type of surgery, n (%)	
AVR only	373 (68)
MVR only	120 (22)
AVR and MVR	56 (10)
LOS (d)	6.37 (2.65)
Reached stable therapeutic INR, n (%)	301 (55)
Time to stable therapeutic INR	2.61 (2.67)
Reached first therapeutic INR, n (%)	457 (83)
Time to first therapeutic INR	3.45 (2.29)
Total ICU hours	33.73 (31.83)
% INRs out of range (hospital) ≤1.5	54.95 (19.08)
% INRs out of range (hospital) ≥4.0	1.99 (5.82)
Mitral valve replacement, n (%)	
None	368 (67)
Annuloplasty only	5 (1)
Replacement	165 (30)
Reconstruction with annuloplasty	7 (1)
Reconstruction without annuloplasty	4 (1)
Multiple valve surgery, n (%)	
No	118 (21)
Replacement	290 (53)
Repair/Reconstruction	2 (0)
Root reconstruction with valve conduit	94 (17)
Replacement + ascending graft	45 (8)
Concomitant bypass surgery (AO aneurysm), n (%)	147 (27)
Pneumonia, n (%)	5 (1)
Prolonged ventilation, n (%)	24 (4)
Atrial fibrillation, n (%)	119 (22)

Abbreviations: *AVR*, Aortic valve replacement; Stable therapeutic *INR*, therapeutic INR values in 2 consecutive days.

and 55% had a stable (at least 2 measurements within acceptable range) therapeutic INR before discharge (Table II). Of all INR measurements acquired in hospital, 55% of measurements were ≤1.5, whereas only 2% had INR ≥ 4. The average hospital LOS was 6.4 days (2.65) days and mean TTI was 3.5 days. The distribution of the LOS of the patient cohort is outlined in Figure 1.

Factors influencing LOS

Multivariable Cox proportional hazards regression was used to investigate the effects of age, type of valve surgery, total hours in the ICU, time-dependent effects of postoperative atrial fibrillation, time of initiating warfarin therapy, and TTI (Table III). Time to therapeutic INR was independently associated with LOS. There was a 28% higher probability of leaving the hospital with a therapeutic INR than without a therapeutic INR (HR 1.28 [1.06-1.65], $P = .01$). Each decade of age was also associated with an 8% (HR 0.92 [0.85-0.99], $P = .03$) reduction in probability of discharge. For each 5 additional hours of ICU stay, there was a 7% reduction in probability of discharge (HR 0.93 [0.92-0.95], $P = <0.001$). Patients were 36% more likely to be discharged (HR 1.36 [1.13-1.64], $P = .001$) if they underwent AVR only as compared with MVR ± AVR. Postoperative atrial fibrillation did not significantly extend length of hospitalization in our group (HR 0.85 [0.69-1.05], $P = .12$). Further analyses in the subset of subjects without atrial fibrillation showed a more significant association of TTI and LOS with a 40% higher probability of leaving the hospital with a therapeutic INR than without a therapeutic INR (HR 1.4 [1.12-1.69], $P = .002$).

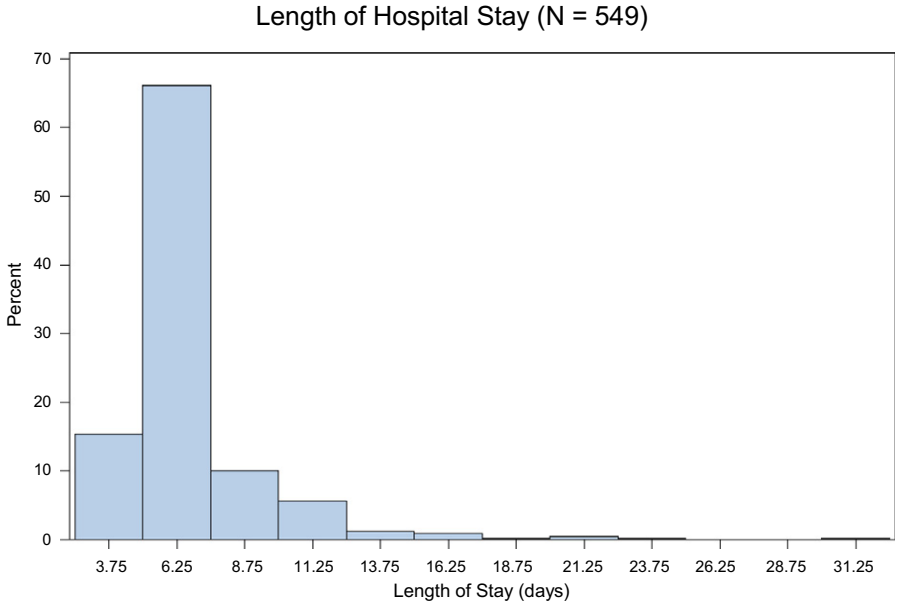
Landmark analysis was used to illustrate the effect of achieving therapeutic INR on LOS. We demonstrate that those achieving therapeutic INR on or before day 4 after surgery (n = 542) were more likely to be discharged by day 6 compared with those who did not achieve therapeutic INR (75% vs 59%, $P < .001$) (Figure 2). Sensitivity analysis using a model with date of warfarin as a starting point and including covariates such as age, type of valve replacement, and time spent in the ICU showed that TTI continued to remain an independent predictor of LOS (Table IV).

Discussion

This is the first study that provides evidence that TTI is an important independent predictor of prolonged length of hospital stay after heart valve replacement surgery with mechanical prosthesis. Prolonged hospitalization after cardiac surgery is associated with increased cost, complication, and risk. Factors that have been reported to prolong hospitalization after cardiac valve surgery are age, sex, comorbidities (chronic obstructive pulmonary disease, diabetes, atrial fibrillation, congestive heart failure), blood transfusions, and prolonged ICU LOS.[22,23] Because these factors also may be related indirectly to therapeutic warfarin dose and TTI, it has been difficult to demonstrate until now whether delay in achieving therapeutic INR in itself is independently related to prolonged hospital stay.

Modern mechanical cardiac valve prostheses provide excellent hemodynamic profiles and have excellent long-term results.[24,25] A major drawback of using mechanical prostheses is the need for systemic anticoagulation and thromboembolic potential.[1] To prevent thromboembolic complications, patients with mechanical valves require lifelong anticoagulation therapy, and warfarin is the most commonly recommended oral anticoagulant with a high level of evidence supporting its use despite the advent of newer anticoagulation drugs.[26,27] However, during the early postoperative period, it is difficult to achieve stable warfarin dosing and risk of thromboembolism or bleeding complications is particularly high.[28,29] Hemostasis after surgery is complicated by transfusion exposure, liver hypoperfusion, exposure to the bypass circuit, hypocalcemia, hypothermia, acidemia, inflammation, endothelial cell activation, and reduced plasma proteins.[30] Enhanced sensitivity to warfarin after cardiac valve surgery has been

Figure 1



Distribution of the LOS in patients undergoing cardiac mechanical valve replacement (n = 549).

Table III. Therapeutic INR model with time-dependent modeling of atrial fibrillation and warfarin initiation

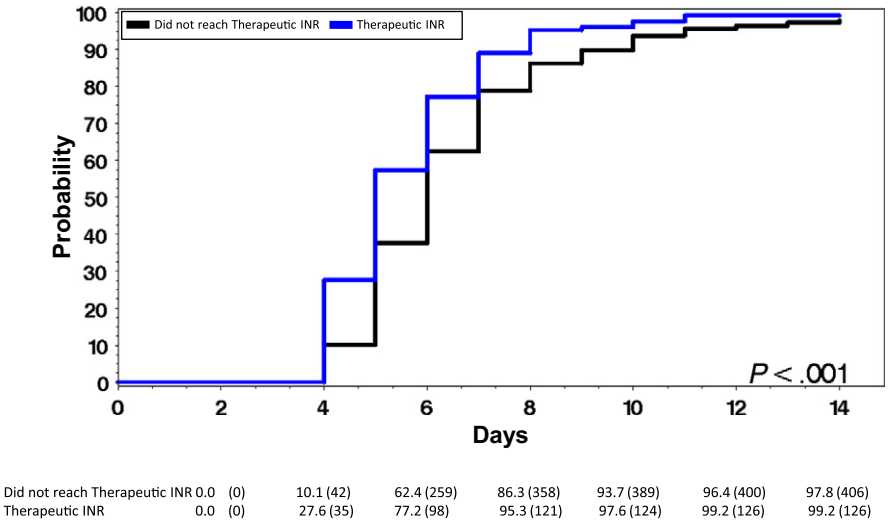
Parameter	ChiSq	ProbChiSq	HR	HR Lower CI	HR Upper CI
Age	4.7043	.0301	0.992	0.984	0.999
AVR only	10.4748	.0012	1.361	1.129	1.640
Total ICU hours	55.8679	<.0001	0.986	0.982	0.990
AFIB postsurgery (time dependent)	2.3807	.1228	0.848	0.688	1.045
Starting warfarin (time dependent)	0.0022	.9630	NA		
Achieve therapeutic INR (time dependent)	6.7041	.0096	1.279	1.062	1.541

demonstrated, necessitating consideration for conservative warfarin dosing postoperatively.[31] In our population of 95% white valve recipients, the expected higher dose requirements due to genetic variability potentially could have contributed to a longer LOS due to the time needed to escalate the dose and achieve a therapeutic INR.[32]

Moreover, because of warfarin's narrow therapeutic index, individual pharmacokinetic and pharmacodynamic variation, and interaction with food and other drugs, a delay in achieving therapeutic range of INR occurs frequently in patients who start anticoagulation therapy with warfarin. This delay might be one of the factors that prolongs hospital stay after mechanical cardiac valve replacement surgery, and such delays in hospital dismissal raise concerns regarding delays in patient rehabilitation, increased incidence of nosocomial infections, unnecessary hospital resource utilization, higher costs, and increased in-hospital mortality.[33] Known risk factors contributing to an increased LOS observed in other populations and our study included age, complexity of surgery, time in the ICU, and atrial fibrillation. Atrial fibrillation after cardiac surgery increases LOS by as much as 5 days; however, we did not observe this association in our cohort of patients, although atrial fibrillation was present in 22% of participants.[34]

Warfarin's anticoagulant effect relies on interference with production of hepatic vitamin K–dependent coagulation factors (II, VII, IX, X), as well as interference with anticoagulants protein S and C synthesis. The biological elimination half-life between the clotting factors is variable, and determines the extent of anticoagulation effect of warfarin and is reflected in the INR. It therefore takes 4 to 5 days for antithrombotic effects of warfarin to take effect after drug initiation.[35,36] The reason we selected day 4 as our time point for Landmark analysis is because it correlates with the usual onset of the

Figure 2



Landmark analysis of probability of discharge by therapeutic INR after day 4.

Table IV. Model with date of warfarin as the starting point

Parameter	ChiSq	ProbChiSq	HR	HR Lower CI	HR Upper CI
Age	5.0443	.0247	0.992	0.964	0.999
AVR only	10.4881	.0012	1.359	1.128	1.635
Total ICU hours	48.1024	<.0001	0.988	0.984	0.991
Achieve therapeutic INR (time dependent)	5.0936	.0240	1.239	1.028	1.493

anticoagulation effect of warfarin. Initial dose selection is critical then to achieving the target INR, because underdosing results in further delays to achieving therapeutic INR extending thrombotic risk and overdosing causes excess anticoagulation, another potential contributor to LOS due to development of bleeding complications. Underdosing of warfarin did not occur in our study because the average TTI was 3.45 days, which is approximately the time of onset of warfarin action. Overdosing did not occur in most of the patients in our study because only 2% of measured INRs were ≥4. Similar to other reports in the literature, our in-patient–managed anticoagulation algorithm has been shown to reduce the likelihood of excessively high INRs and TTI. Despite our pharmacy-managed algorithm that includes multiple variables that affect warfarin dosing, TTI was an independent predictor of LOS in these patients.

Many medical centers have adopted clinical dosing algorithms for patients who start warfarin anticoagulation therapy. Two studies evaluated the effectiveness of anticoagulation management services on the inpatient cardiac surgery population and concluded that these provide benefit, with fewer days with INR > 4, resulting in fewer clinically significant postoperative bleeding events, and fewer repeat surgeries for late postoperative bleeding, and up to a 17% decrease in average postsurgical LOS (13.9 vs 11.6 days, $P = .015$).[37,38] The average LOS in our study population was 6.37 (2.65) days, with only 2% of measured INR ≥ 4. The shorter LOS in our study is likely a reflection of excluding patients who developed postoperative complications that would have interrupted warfarin administration.

In-hospital training of patients with INR self-testing and engaging patients and families in warfarin dosing and education has also been proved to improve anticoagulation management.[39] More recently, there have been studies incorporating *CYP2C9* and *VKORC1* genetic variants to guide warfarin dosing.[40-42] COAG with the use of a clinical variable dosing algorithm did not show the benefit of pharmacogenetics in reducing the TTI; however, EU-PACT using fixed dose of warfarin demonstrated that incorporating pharmacogenetic information reduces the TTI. Another important difference was that genotyping results were made available within 2 hours for individuals in the EU-PACT trial, but only 45% of participants had genetic information available to guide dosing on day 1 in the COAG trial. An alternative approach to shorten LOS, given the narrow therapeutic

index of warfarin therapy, could be using bridging therapies with low-molecular-weight heparin or unfractionated heparin subcutaneously. However, this is complicated by the nuances necessary to administer a subcutaneous medication as an outpatient, bleeding risk in certain populations, therapeutic failures in pregnancy, and cost associated with such therapies.[43]

Limitations

This analysis excluded many known variables that impact LOS to account for uninterrupted warfarin therapy, but included other common variables such as atrial fibrillation, complexity of surgery, and time in the ICU. Our results are therefore applicable to a relatively stable group of patients. However, this group also happens to include most patients who undergo mechanical cardiac valve replacement surgery, that is, 78% of our total surgical population. Another limitation with Landmark analysis is the choice of the landmark time point. This too was evaluated, and it was shown that irrespective of the date of warfarin initiation, TTI remained an independent predictor of LOS in this cohort of patients.

Conclusion

In our study, TTI is an important and independent predictor of LOS in patients with cardiac valve replacement surgery with mechanical prosthesis and requiring anticoagulation with warfarin. Further study for improved warfarin dosing strategies to reduce TTI or alternative therapeutic anticoagulation postoperative approaches needs to be conducted to reduce LOS in patients undergoing valve replacement surgery with mechanical prosthesis.

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