CLINICAL RESEARCH STUDY

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Association of Reversal of Anticoagulation Preoperatively on 30-Day Mortality and Outcomes for Hip Fracture Surgery

Michael S. Yoo, MD,[a] Shiyun Zhu, MPH,[b] Sheng-fang Jiang, MS,[b] Helen L. Hammer, MD,[a] Wesley J. McBride, MD,[a] Caitlin M. McCarthy, MD,[a] Cheryl E. Green, MD,[c] Martin P. Ananias, MD[a]

[a]Department of Hospital Medicine, Kaiser Permanente, Santa Rosa, Calif; [b]Division of Research, Kaiser Permanente, Oakland, Calif; [c]Department of Family Medicine, Sutter Santa Rosa Regional Hospital, Santa Rosa, Calif.

ABSTRACT

BACKGROUND: Hip fracture is common in the elderly, many of whom are on anticoagulation. However, data are limited on outcomes with anticoagulation reversal in patients undergoing hip fracture surgery.

METHODS: Adults ≥60 years old on oral anticoagulation who underwent hip fracture surgery at 21 hospitals in Northern California from 2006 to 2016 were identified through electronic databases. Outcomes were compared among patients treated and untreated with anticoagulation reversal preoperatively.

RESULTS: Of 1984 patients on oral anticoagulation who underwent hip fracture surgery, 1943 (97.9%) were on warfarin and 41 (2.1%) were on direct oral anticoagulants. Reversal agents were administered to 1635 (82.4%). Compared to a watch-and-wait strategy, patients receiving reversal agents were more likely to be white, male, comorbid, and with higher admission and preoperative international normalized ratios (P <0.001 for all comparisons). No difference for 30-day mortality was detected between reversal vs non-reversal (7.8% vs 6.0%, respectively; hazard ratio [HR], 1.30 [95% confidence interval (CI), 0.82-2.07]). For secondary outcomes, reversal was associated with higher risk of delirium (8.6% vs 4.9%, risk ratio [RR], 1.77 [95% CI, 1.08-2.89]) and increased mean length of stay (6.4 vs 5.8 days, P <0.05). After adjustment, associations were no longer significant for delirium (RR 1.60, 95% CI, 0.97-2.65) or length of stay (mean difference 0.08, 95% CI, -0.55-0.71). No associations were detected between reversal and other secondary outcomes.

CONCLUSION: No significant associations were found between reversal agents and 30-day mortality or other outcomes in patients on oral anticoagulation who underwent hip fracture surgery. Further investigation is needed.

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KEYWORDS: Anticoagulation; Hip fracture; Outcomes; Perioperative medicine; Reversal agents

INTRODUCTION

The effect of anticoagulation reversal on mortality in patients with hip fractures undergoing surgery is unclear. Studies have shown that patients with hip fractures on anticoagulation experience surgical delay and increased hospital length of stay,[1-3] whereas anticoagulation reversal reduces time to surgery.[4-11] Because early hip fracture surgery has been shown to decrease mortality,[12-14] one would hypothesize that early anticoagulation reversal, compared to a "watch-and-wait" strategy, might decrease mortality in this population.

Data on outcomes for anticoagulation reversal in patients with hip fractures are limited,[10,11,15-17] and there is a lack of guidelines on reversal prior to hip fracture surgery.[18] A large-scale study on anticoagulation reversal in patients with hip fractures undergoing surgery—addressing time to

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Requests for reprints should be addressed to Michael S. Yoo, MD, FACP, Kaiser Permanente Santa Rosa Medical Center, 401 Bicentennial Way, Santa Rosa, CA 95403.

E-mail address: michael.s.yoo@kp.org

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surgery, choice of reversal agent, and outcomes such as mortality, readmission, and postoperative complications—is needed to clarify risk and guide clinicians in perioperative management.

This cohort study assessed the association of Reversal of Anticoagulation Preoperatively (RAP) on 30-day mortality and outcomes for hip fracture surgery (the RAP Hip study). The aims were 1) to determine all-cause 30-day mortality for patients on oral anticoagulation who sustained hip fracture followed by surgery, comparing those treated and untreated with anticoagulation reversal, and to 2) examine the secondary outcomes of hospital length of stay and 30-day rates of readmission, delirium, venous thromboembolism, acute myocardial infarction, transient ischemic attack or stroke, major bleeding, and blood transfusion requirement.

CLINICAL SIGNIFICANCE

- Hip fracture is common in the elderly, many of whom are on anticoagulation, but data are limited on outcomes with anticoagulation reversal in patients undergoing hip fracture surgery.
- No association was found between anticoagulation reversal and 30-day mortality or other clinical outcomes in patients on oral anticoagulation who underwent hip fracture surgery.
- Clinically significant differences in patients selected to receive reversal agents were observed.

METHODS

Study Design

The RAP Hip study is a multicenter retrospective cohort study at Kaiser Permanente Northern California (KPNC) of elderly patients on oral anticoagulation who sustained hip fracture and underwent surgery. KPNC is an integrated health care system with a diverse, community-based population of >4 million members. The study was approved by the KPNC Institutional Review Board with waiver of consent. Variables of interest were collected from KPNC electronic databases. Data on direct oral anticoagulant use were adjudicated by clinicians.

Patients

Study patients were included if they 1) experienced hip fracture and underwent hip fracture surgery within 30 days of diagnosis from 1/1/2006 through 12/31/2016; 2) were KPNC members of age ≥60 years on index date, defined as the date of hip fracture diagnosis; 3) were on active oral anticoagulation (warfarin or direct oral anticoagulants) prior to the time of diagnosis. Patients were excluded if they suffered multiple traumatic injuries, pathological or periprosthetic fractures, distal or femoral shaft fractures; if they had liver failure or underlying coagulopathy; if they died prior to surgery or did not undergo surgery during their index visit; if they had <3 months of continuous membership with KPNC prior to presentation. Patients on warfarin were identified through KPNC electronic databases, and those who had an international normalized ratio (INR) <1.7 (a threshold considered safe for hip fracture surgery[17]) within 48 hours of initial presentation were excluded from this study. All patients on direct oral anticoagulants were adjudicated through clinician chart review.

Exposures

The presence of anticoagulation reversal agents administered preoperatively included vitamin K, prothrombin complex concentrate, fresh frozen plasma, and idarucizumab.

Outcomes

The primary endpoint was 30-day all-cause mortality. Secondary outcomes included hospital length of stay and 30-day rates of all-cause readmission (only if readmitted within KPNC), delirium (diagnosed during index hospitalization), venous thromboembolism, acute myocardial infarction, transient ischemic attack or stroke, major bleeding (defined as an absolute hemoglobin drop of ≥3 g/dL from day of surgery until up to 30 days postoperatively), and blood transfusion requirement. Measures were based on all-cause utilization that occurred in KPNC facilities. Patients were followed from the index date until death, end of KPNC membership, or time 30 days after index date, whichever came first.

Demographic and Clinical Variables

Demographic variables included age, sex, and race/ethnicity. Clinical variables included 1-year look back of Charlson Comorbidity Index[19] for each patient, time to surgery (categorized as ≤24, ≤36, ≤48, <120, and ≥120 hours), type of procedure (fixation vs replacement), antiplatelet medications (specifically, aspirin and/or clopidogrel, the main medications used within KPNC) within 30 days prior to surgery, platelet count (at admission and prior to surgery), oral anticoagulant type (warfarin or direct oral anticoagulant), INR at 3 time points (on admission; before surgery, ie, INR most proximate to start of surgery; and at discharge, ie, last INR obtained), and choice and administration of reversal agent (vitamin K, prothrombin complex concentrate, fresh frozen plasma, and idarucizumab).

Statistical Analysis

Descriptive statistics were used to define characteristics of the cohort overall and by patients treated versus untreated with reversal agents. Differences in characteristics were assessed by t test for continuous variables and χ^2 test for categorical variables. For the primary outcome, 30-day mortality rates were calculated and compared using Kaplan-Meier curve. Results were stratified by time to surgery (≤24, 25-36, 37-48, 49-119, ≥120 hours). Cox

proportional hazard regression was used to determine the association between potential risk factors and mortality, and variables with P value <0.2 in bivariate associations were included in the adjusted model. Hazard ratios (HRs) with 95% confidence intervals (95% CI) were reported. For secondary outcomes, 30-day rates for each outcome were calculated and a log-binomial model was used to estimate the relative risk (RR) for associations between the main exposure and the outcome. We chose to calculate RR over odds ratio (OR) because OR tends to overestimate, whereas RR provides less biased estimates for cohort studies. Only those demonstrating significant binary associations were included in the adjusted analysis, controlling for covariates that were significantly associated with 30-day mortality. Length of stay was modeled using linear regression and the mean difference between reversal vs no reversal, with 95% CI reported. All data extraction and analyses were performed using SAS, version 9.3 (SAS Institute Inc, Cary, NC).

RESULTS

Patient Population

Between 1/1/2006 and 12/31/2016, we identified 1984 eligible patients. Figure 1 details the inclusions/exclusions of the cohort. Of 1984 patients, 1635 (82.4%) were given

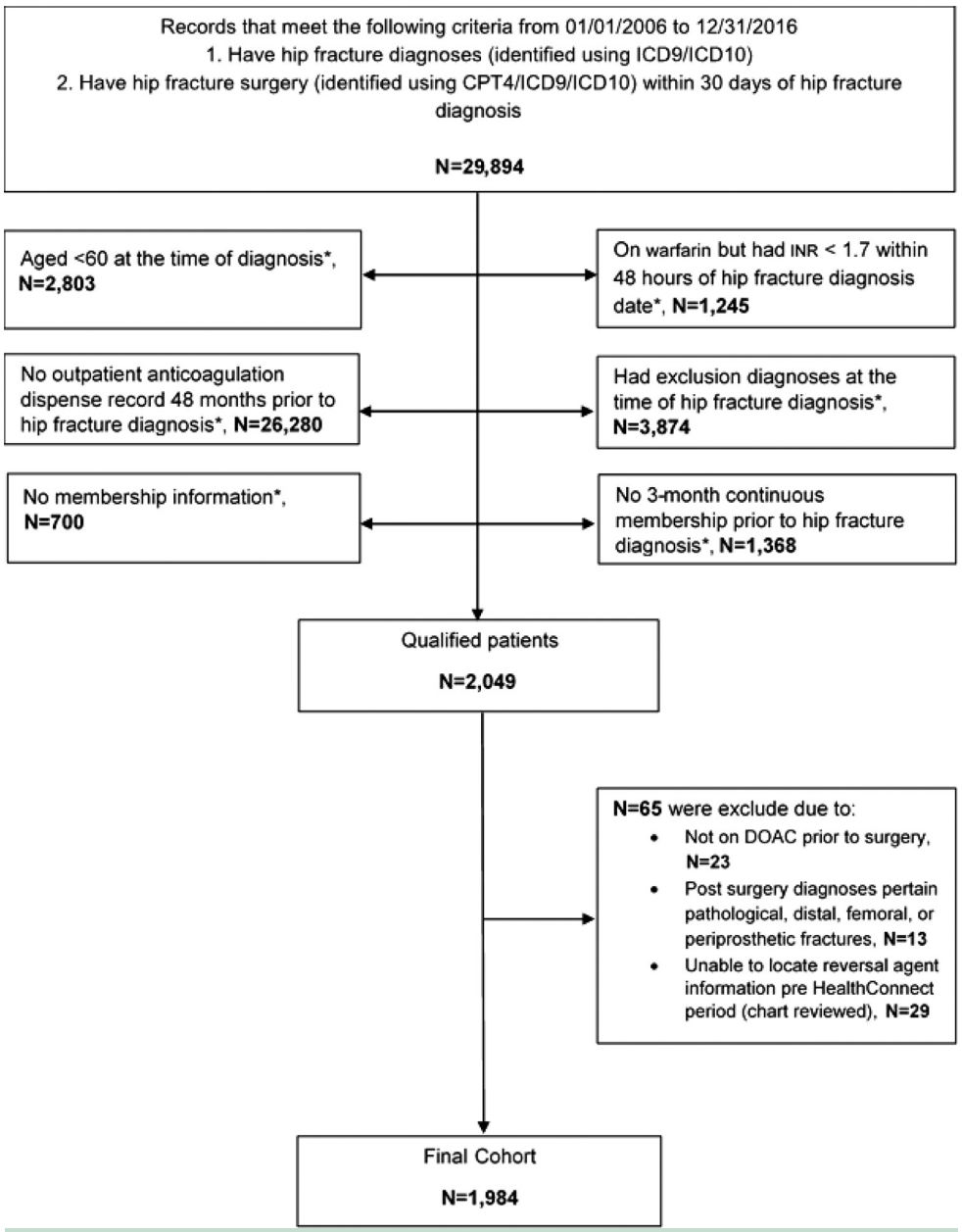

Figure 1 Flow of patients through the RAP Hip study.
*Exclusion criteria are not mutually exclusive

Table 1 Demographic and Clinical Characteristics Among Patients on Anticoagulation Who Underwent Hip Fracture Surgery, 2006-2016

	Treatment (N = 1635) Mean (SD) or N (%)	No Treatment (N = 349) Mean (SD) or N (%)	*P* Value
Demographic			
Age (years)	82.5 (7.2)	81.2 (7.6)	<0.05
Female sex	986 (60.3)	247 (70.8)	<0.001
Race			<0.001
Hispanic	85 (5.2)	22 (6.3)	
Non-Hispanic white	1460 (89.3)	287 (82.2)	
Non-Hispanic black	42 (2.6)	14 (4.0)	
Non-Hispanic asian	39 (2.4)	25 (7.2)	
Non-Hispanic other	9 (0.6)	1 (0.3)	
Clinical			
Anticoagulants			<0.001
Warfarin	1631 (99.8)	312 (89.4)	
DOAC	4 (0.2)	37 (10.6)	
Procedure*			0.08
Fixation	941 (59.2)	183 (53.8)	
Replacement	650 (40.9)	157 (46.2)	
INR			
At admission	2.6 (0.9)	2.0 (0.8)	<0.001
Prior to surgery	2.0 (0.8)	1.8 (0.7)	<0.001
At discharge†	1.7 (0.6)	1.9 (0.7)	<0.001
Platelet Count			
At admission	207.7 (81.7)	209.8 (88.9)	0.05
Prior to surgery	180.9 (74.7)	193.8 (92.1)	<0.001
Time to surgery (hours)	47.1 (28.1)	37.0 (42.5)	<0.05
Charlson Comorbidity Index			<0.001
None	557 (34.1)	104 (29.8)	
1-2	354 (21.7)	111 (31.8)	
≥3	724 (44.3)	134 (38.4)	

DOAC = direct oral anticoagulant; INR = international normalized ratio; SD = standard deviation.

*Unable to differentiate N=53 patient procedures by ICD codes.

†N = 71 patients who died during hospitalization; therefore, their discharge INR values were not collected.

reversal agents prior to surgery and 349 patients (17.6%) received no reversal. Baseline characteristics are seen in Table 1. Overall, most patients were on warfarin compared to direct oral anticoagulants (97.9% vs 2.1%). Patients who received reversal agents were significantly different from those who underwent a "watch-and-wait strategy" in several aspects. They were more likely to be white and male, have a greater proportion of comorbid conditions examined, have higher INR at admission and prior to surgery, and lower INR at discharge (P <0.001 for all comparisons). Patients who received reversal also had longer average time to surgery (47.1 hours vs 37.0 hours, P <0.05). Only 71 patients in the cohort (3.6%) were found to be taking at least 1 of 2 prespecified antiplatelet agents (aspirin and/or clopidogrel) in addition to anticoagulation prior to surgery.

Table 2 HR and aHR for 30-Day Mortality Between Patients Receiving Reversal Agents and Patients Not Receiving Reversal Agents, Stratified by Time to Surgery, 2006-2016.

	Reversal vs No Reversal	
	HR (95% CI)	aHR (95% CI)*
Time to surgery (hours)		
≤24	2.14 (0.81, 5.67)	1.30 (0.44, 3.82)
25-36	0.91 (0.28, 3.02)	0.81 (0.24, 2.79)
37-48	0.63 (0.22, 1.81)	0.48 (0.16, 1.44)
49-119	1.13 (0.48, 2.66)	1.09 (0.46, 2.58)
≥120	1.14 (0.23, 5.63)	0.86 (0.16, 4.60)

aHR = adjusted hazard ratio; CI = confidence interval; HR = hazard ratio; INR = international normalized ratio.

*Model adjusted for age, sex, race/ethnicity, admission INR, and Charlson Comorbidity Index.

Primary Outcome

For 30-day mortality, 127 of 1635 (7.8%) patients died in the reversal agent group compared to 21 of 349 patients (6.0%) not receiving reversal. Among those who died, 47.2% died during hospitalization in the reversal group vs 42.9% in the nonreversal group. No significant association was detected between anticoagulation reversal and 30-day mortality for both bivariate (HR 1.30, 95% CI, 0.82-2.07) and multivariable analysis (HR 1.00, 95% CI, 0.62-1.60).

Thirty-day mortality risk stratified by time to surgery appears in Table 2. No association was detected between anticoagulation reversal and 30-day mortality when using an adjusted model stratified by time to surgery at each specified time interval.

Secondary Outcomes

The secondary outcomes included hospital length of stay and 30-day rates of delirium, acute myocardial infarction, transient ischemic attack or stroke, venous thromboembolism, major bleeding, blood transfusion requirement, and readmission. Compared to the nonreversal group, patients in the reversal group were found to have longer mean length of stay (6.4 vs 5.8 days, β 0.61, 95% CI, 0.01-1.21) and were more likely to develop postoperative delirium (8.6% vs 4.9%, RR 1.77, 95% CI, 1.08-2.89) (Table 3). However, the association of treatment with reversal agents was no longer significant for either length of stay or delirium after adjustment. No associations were detected between anticoagulation reversal and 30-day rates of acute myocardial infarction, transient ischemic attack/stroke, venous thromboembolism, major bleeding, transfusion requirement, or readmission.

The 71 patients in our cohort on antiplatelet therapy were assessed for association with major bleeding. Overall, 17.7% of patients on concomitant anticoagulation and antiplatelet medications had major bleeding 30 days postoperatively, compared to 21.9% of patients on anticoagulation alone. The results were not significant (P = 0.41).

Table 3 Primary and Secondary Outcomes From Surgery Until 30-Day Follow-Up, 2006-2016

Primary Outcome	Reversal (N = 1635)	No Reversal (N = 349)	Reversal vs No Reversal	
	N (%)	N (%)	HR (95% CI)	aHR (95% CI)
30-day mortality*	127 (7.8)	21 (6.0)	1.30 (0.82,2.07)	1.00 (0.62,1.60)
Secondary Outcomes	N (%) or mean (SD)	N (%) or mean (SD)	RR or β (95% CI)	aRR or β (95% CI)
Blood transfusion†	429 (33.3)	90 (37.5)	0.83 (0.74, 1.06)	
Delirium†	141 (8.6)	17 (4.9)	1.77 (1.08,2.89)	1.60 (0.97,2.65)
Acute myocardial infarction†	32 (2.0)	7 (2.0)	0.98 (0.43,2.19)	
TIA/Stroke†	105 (6.4)	19 (5.4)	1.18 (0.73,1.90)	
Venous thromboembolism†	105 (6.4)	13 (3.7)	1.72 (0.98,3.03)	
Major bleeding†	335 (20.7)	76 (24.0)	0.86 (0.69,1.07)	
All-cause readmission†	264 (16.8)	44 (12.9)	1.30 (0.96,1.75)	
Hospital length of stay‡	6.4 (0.1)	5.8 (0.3)	0.61 (0.01,1.21)	0.08 (-0.55,0.71)

aHR = adjusted hazard ratio; aRR = adjusted relative risk; CI = confidence interval; HR = hazard ratio; INR = international normalized ratio; RR = relative risk; SD = standard deviation; TIA = transient ischemic attack.

*Estimated using Cox proportional Hazard Model. Model adjusted for age, sex, race/ethnicity, admission INR, and Charlson Comorbidity Index.

†Estimated using Log-binomial model. Only outcomes with significant bivariate associations were further adjusted for age, sex, race/ethnicity, admission INR, and Charlson Comorbidity Index.

‡Estimated using Linear Regression Model. Model adjusted for age, sex, race/ethnicity, admission INR, and Charlson Comorbidity Index.

Post Hoc Exploratory Analyses

After the completion of our data collection and analysis, a study published findings that among adults undergoing hip fracture surgery, increased wait time was associated with greater 30-day mortality risk and other complications, with a 24-h wait time potentially representing a threshold defining higher risk.[12] In our cohort of patients on anticoagulation who underwent hip fracture surgery, we recategorized time to surgery based on a 24-h point and used it as a covariate in our statistical model. Compared to patients who underwent surgery within 24 hours, patients with longer wait time had a significantly higher 30-day risk of mortality (HR 1.59, 95% CI, 1.04-2.53). However, the effect of time to surgery was no longer significant after adjustment (HR 1.32, 95% CI, 0.84-2.04).

Because of observed differences by treatment, we then used a propensity score method with inverse probability treatment weighting to balance the treated and untreated groups based on age, admission INR, sex, and Charlson Comorbidity Index. Anticoagulation reversal was not associated with 30-day mortality (HR 0.82, 95% CI, 0.66-1.02) but was associated with higher likelihood of developing postoperative delirium (RR 2.18, 95% CI, 1.67-2.84) and a slightly shorter length of stay compared to no reversal, 6.3 vs 7.1 days (β -0.81, 95% CI, -1.30-[-0.32]) (data not shown).

Finally, we noted fewer patients in 2006 and 2007 compared to subsequent years. As our electronic health record system was not implemented across all KPNC hospitals until 2009, we performed sensitivity analyses of the primary and secondary outcomes by limiting the cohort to the years 2009 through 2016 (eTables 1-3 in the Supplemental Appendix, available online). Patients administered reversal agents were more likely to develop venous thromboembolism within 30 days compared with patients who had not received reversal agents in our sensitivity analyses (eTable 2). Results were otherwise consistent in the protocol analyses and all other sensitivity analyses.

DISCUSSION

To our knowledge, this is the first large cohort study examining the association between reversal agents and outcomes in patients on anticoagulation undergoing hip fracture surgery. We did not find significant associations between anticoagulation reversal and 30-day mortality, nor most other 30-day clinical outcomes. Although no significant associations were detected, it should be noted that the reversal agent group had longer length of stay and higher rates of mortality, readmission, delirium, transient ischemic attack and stroke, venous thromboembolism, and transfusion requirement. This observation may be explained in part because patients receiving reversal were slightly older and had a greater proportion of comorbid conditions examined, higher admission INR, and longer average time to surgery. In fact, after balancing the groups using propensity score analysis, we found that anticoagulation reversal was associated with shorter length of stay (albeit clinically insignificant) and higher likelihood for delirium.

A previous study of an elderly population found no differences in adverse outcomes between individuals taking warfarin prior to hip fracture surgery (most of whom had received reversal agents) and those not taking warfarin, suggesting that anticoagulation reversal may facilitate earlier surgery without increasing complications.[15] Although we did not detect an association between anticoagulation reversal and 30-day mortality, further investigation is needed to study the possibility of adverse outcomes associated with preoperative reversal agent administration.

Direct oral anticoagulants have become the standard of care for anticoagulation therapy in patients with atrial

fibrillation and venous thromboembolism. However, direct oral anticoagulants were only recently introduced into clinical practice at the end of 2010[20] and not introduced at KPNC until 2012. Dabigatran, a direct thrombin inhibitor, was the main direct oral anticoagulant in use at KPNC during our study period (34 patients in the study were on dabigatran) and only 7 patients (0.4%) in our cohort were on oral factor Xa inhibitors. Overall, 41 patients (2.1%) in our cohort were on direct oral anticoagulants, and we additionally evaluated idarucizumab as a reversal agent for dabigatran, administered to 4 patients. The number of patients on direct oral anticoagulants in our study is so small as to not be clinically meaningful at this time. Studies to date on patients with hip fractures taking direct oral anticoagulants are limited, and larger studies are needed to investigate the association of reversal on outcomes in patients taking this class of medications. Although the number of patients treated with direct oral anticoagulants has increased significantly, the lack of specific reversal agents for these medications until recent years and their associated cost are potential barriers for their use.[21] Thus, we can still anticipate that many patients will continue to present on vitamin K antagonists who experience hip fracture.

Consistent with findings in a previous study that described 24-h wait time for hip fracture surgery as a threshold for higher risk,[12] post hoc analysis in our cohort showed that patients on anticoagulation who underwent hip fracture surgery within 24 hours had significantly lower mortality risk than those whose surgery was delayed beyond that cutoff point. However, the association was no longer significant after adjustment. Interestingly, although not significant, point estimates when stratifying time to surgery indicate lower mortality in the reversal group if surgery occurred between 25 and 48 hours. Our findings suggest that patients in the reversal group who had early surgery (ie, $\leq$24 h) may differ from those whose surgery was delayed post 24 hours.

We observed clinically significant differences in patients selected to receive anticoagulation reversal. Patients administered reversal agents were more likely to be white and male, have a greater proportion of comorbid conditions examined, and higher INR at admission and prior to surgery. Female patients made up >62% of our cohort but were significantly less likely than male patients to receive treatment. Non-white patients across racial/ethnic groups were significantly less likely than white patients to receive reversal agents. Although higher INR at admission would be expected in the reversal group, no objective guidelines justify treatment differences along gender or racial lines. Without consensus guidelines or extensive data to support reversing anticoagulation, our results suggest a perceived intervention bias[22] exists among providers that reversal may be associated with improved outcomes, and among some providers, an unconscious racial or gender bias contributing to higher intervention on white male patients. Studies have demonstrated a pattern of racial/ethnic disparities across multiple diagnoses such as coronary artery disease, cancer, stroke, kidney disease, and human immunodeficiency virus infection; non-white patients receive interventions far less frequently than white patients.[23] In African Americans, disparities in total knee replacement offer and complication rates result in significant loss of quality-adjusted life years.[24] Gender disparities have been studied; women with non-ST-segment elevation acute coronary syndrome, despite presenting with higher risk characteristics and in-hospital risk, were treated less aggressively than men.[25] Most health care disparities—differences in medical decision making triggered by unconscious biases leading to differences in outcomes among certain populations—result in worse outcomes for those unfairly targeted and improved outcomes for those receiving a beneficial intervention or treatment. In our study, however, the intervention bias led to no significant differences in outcomes. Our study demonstrates the role cohort studies may play in further elucidating the extent of unconscious biases in point-of-care clinical decision making.

This study has several limitations. First, we had fewer patients in 2006-2007 compared to other years (data not shown) because HealthConnect (ie, the electronic medical record system used at KPNC) was not fully implemented across KPNC hospitals until 2009. As a result, reversal agent administration was not as well documented compared to subsequent years. Thus, we performed post hoc sensitivity analyses limiting the cohort to the years of 2009 through 2016. We detected an increased risk of venous thromboembolism with reversal agent administration in this cohort that was not present in our initial analyses, while all other outcomes of sensitivity analyses were consistent. Despite the possibility we may not have achieved sufficient power because of fewer patients in the initial years and concerns regarding data quality during that time period, no study to date has investigated the association of anticoagulation reversal on outcomes to the extent of the RAP Hip study.

Second, significant differences were detected between reversal and nonreversal groups. Differences may be due in part to intervention bias but also secondary to legitimate reasons. For example, higher admission INR would be expected in the reversal group. Although differences were mitigated by statistical methods, further prospective studies are needed to investigate the effect of reversal agents on mortality.

Third, despite inclusion of covariates to adjust for confounders, residual and unmeasured confounding may exist, such as INR variability as a result of underlying medical causes, transfer from referring centers outside of KPNC, concurrent injuries, exacerbations of comorbid conditions, and other unaccounted reasons. We took prespecified measures to counteract the potential effects of confounding, such as exclusion of all patients on warfarin with an INR <1.7, which was the threshold considered safe for hip fracture surgery from a previous study.[17] We predefined multiple variables and applied stringent exclusion criteria to minimize the possibility of confounding in our study.

Fourth, we did not take reversal agent dosage, frequency, route, or timing of administration into account in our analysis. Patients may have received varying or multiple doses/units of vitamin K, prothrombin complex concentrate, or fresh frozen plasma, and these variables were not factored into our analysis. It is unclear if association to the exposure is dose and frequency dependent. The timing of reversal agent administration can be inferred from time to surgery because all patients in the reversal group were administered reversal agents prior to surgery.

Fifth, only a small percentage of patients were found to be taking antiplatelet medications. Although we attempted to identify antiplatelet medications electronically through multiple data sources (outpatient dispense records, medication list history 30 days prior to surgery, and active medication list during the hospital encounter), it is likely that patients taking over-the-counter aspirin were unaccounted for. However, given the limited data and lack of significance for association with major bleeding, aspirin is unlikely to be a confounder.

CONCLUSIONS

Among patients on anticoagulation who underwent hip fracture surgery, no significant association was found between anticoagulation reversal and 30-day mortality or other outcomes. However, clinically significant differences in patients selected to receive reversal agents were observed. Further studies are needed to determine the effect of anticoagulation reversal on outcomes in randomized controlled trials and to investigate provider variation in patient selection for treatment.

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SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amjmed.2020.01.002.

eTable 1 Demographic and Clinical Characteristics Among Patients on Anticoagulation Who Underwent Hip Fracture Surgery, Cohort 2009-2016.

	Treatment (N = 1288) Mean (SD) or N (%)	No Treatment (N = 240) Mean (SD) or N (%)	*P* Value
Demographic			
Age (years)	82.7 (7.3)	80.6 (7.9)	<0.001
Female sex	772 (59.9)	179 (74.6)	<0.001
Race			<0.001
Hispanic	69 (5.4)	20 (8.3)	
Non-Hispanic white	1140 (88.5)	186 (77.5)	
Non-Hispanic black	37 (2.9)	10 (4.2)	
Non-Hispanic Asian	34 (2.6)	24 (10.0)	
Non-Hispanic other	8 (0.6)	0 (0.0)	
Clinical			
Anticoagulants			<0.001
Warfarin	1284 (99.7)	203 (84.6)	
DOAC	4 (0.3)	37 (15.4)	
Procedure*			0.07
Fixation	727 (58.4)	121 (51.9)	
Replacement	517 (41.6)	112 (48.1)	
INR			
At admission	2.6 (0.8)	1.8 (0.7)	<0.001
Prior to surgery	2.0 (0.8)	1.7 (0.7)	<0.001
At discharge†	1.7 (0.6)	1.9 (0.7)	<0.001
Platelet count			
At admission	205.0 (79.4)	202.8 (80.9)	0.7
Prior to surgery	176.8 (70.6)	186.2 (84.2)	<0.05
Time to surgery (hours)	45.6 (26.7)	30.5 (41.5)	<0.001
Charlson Comorbidity Index			<0.001
None	476 (37.0)	78 (32.5)	
1-2	258 (20.0)	72 (30.0)	
≥3	554 (43.0)	90 (37.5)	

DOAC = direct oral anticoagulant; ICD = International Classification of Diseases; INR = international normalized ratio; SD = standard deviation.

*Unable to differentiate N = 53 patient procedures by ICD codes.

†N = 51 patients who died during hospitalization; therefore, their discharge INR values were not collected.

eTable 2 Primary and Secondary Outcomes From Surgery Until 30-Day Follow-Up, Cohort 2009-2016.

	Reversal (N = 1288)	No Reversal (N = 240)	Reversal vs No Reversal	
Primary Outcome	N (%)	N (%)	HR (95% CI)	aHR (95% CI)
30-day mortality*	127 (7.8)	21 (6.0)	1.42 (0.81,2.54)	0.98 (0.53,1.80)
Secondary outcomes	N (%) or mean (SD)	N (%) or mean (SD)	RR or β (95% CI)	aRR or β (95% CI)
Blood transfusion†	429 (33.3)	90 (37.5)	0.83 (0.74, 1.06)	
Delirium†	99 (7.7)	13 (5.4)	1.97 (1.10,3.51)	1.69 (0.93,3.07)
Acute myocardial infarction†			0.60 (0.22,1.61)	
TIA/Stroke†	127 (9.7)	12 (5.0)	1.49 (0.81,2.75)	
Venous thromboembolism†	16 (1.2)	5 (2.1)	2.70 (1.18,6.04)	3.14 (1.34,7.40)
Major bleeding†	88 (6.8)	11 (4.6)	0.89 (0.68,1.17)	
All-cause readmission†	86 (6.7)	6 (2.5)	1.40 (0.97,2.02)	
Hospital length of stay‡	255 (20.0)	47 (22.5)	1.00 (0.41,1.58)	0.61 (-0.02,1.24)

aHR = adjusted hazard ratio; aRR = adjusted relative risk; CI = confidence interval; HR = hazard ratio; INR = international normalized ratio; RR = relative risk; SD = standard deviation; TIA = transient ischemic attack.

*Estimated using Cox proportional Hazard Model. Model adjusted for age, sex, race/ethnicity, admission INR, and Charlson Comorbidity Index.

†Estimated using Log-binomial model. Only outcomes with significant bivariate associations were further adjusted for age, sex, race/ethnicity, admission INR, and Charlson Comorbidity Index.

‡Estimated using Linear Regression Model. Model adjusted for age, sex, race/ethnicity, admission INR, and Charlson Comorbidity Index.

eTable 3 HR and aHR for 30-Day Mortality Between Patients Receiving Reversal Agents And Patients Not Receiving Reversal Agents, Stratified by Time to Surgery, Cohort 2009-2016.

	Reversal vs No Reversal	
	HR (95% CI)	aHR (95% CI)*
Time to surgery (hours)		
≤24	2.44 (0.83, 7.22)	1.33 (0.40, 4.37)
25-36	0.76 (0.18, 3.26)	0.78 (0.17, 3.54)
37-48	0.43 (0.13, 1.43)	0.25 (0.06, 0.98)
49-119	1.18 (0.36, 3.82)	1.03 (0.31, 3.46)
≥120	0.97 (0.09, 10.71)	0.30 (0.00, 29.25)

aHR = adjusted hazard ratio; CI = confidence interval; HR = hazard ratio; INR = international normalized ratio.

*Model adjusted for age, sex, race/ethnicity, admission INR, and Charlson Comorbidity Index