

Use of Anticoagulants Remains a Significant Threat to Timely Hip Fracture Surgery

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Abstract

Introduction: Hip fracture remains the biggest single source of morbidity and mortality in the elderly trauma population, and any intervention focused on quality improvement and system efficiency is beneficial for both patients and clinicians. Two of the variables contributory to improving care and efficiency are time to theater and length of stay, with the overall goal being to improve care as reflected within the achievement of best practice tariff. One of the biggest barriers to optimizing these variables is preinjury anticoagulation. **Method:** Building on our previous work with warfarin in this population, we utilized a regional hip fracture collaborative network collecting prospective data through the National Hip Fracture Database with custom fields pertaining to all agents, including novel oral anticoagulants. **Results:** In all, 1965 hip fracture patients median age 83 years (1639 not anticoagulated) were admitted to the 5 centers over 12 months. Median length of stay was 20.71 days; time to theater 23.09 hours, and the populations (anticoagulated vs control) were evenly matched for injury. Anticoagulated patients were delayed to theater ($P \leq .001$), were inpatients for longer ($P \leq .001$) and gained less best practice tariff ($P \leq .05$). All variables per agent were noted and the impact of each assessed. **Conclusions:** Despite the widespread use of newer anticoagulants, popular due to unmonitored reversal and administration, patients stay longer in hospital and wait longer for surgery than nonanticoagulated patients of the same age and injury. Contemporary perioperative practices impact negatively on the ability to perform timely surgery on hip fracture patients. We propose a guideline specific to the management of anticoagulation in the hip fracture population to aid the optimum preparation of patients for theater, achievement of timely surgery, and potentially reduce length of stay.

Keywords

geriatric trauma, trauma surgery, geriatric medicine, anesthesia, pharmacology, hip, coagulation

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The hip fracture continues to grow in health-care importance. For older patients, it is the commonest serious injury and is the most common reason for them to undergo emergency anesthesia and surgery. With one-third of patients dead within a year of injury, it also represents the most frequent cause of accidental death in the elderly population.¹ It is one of the most expensive and resource-intensive health episodes, associated with a significant cost to health and social services. With 65 000 fractures added each year to the United Kingdom National Hip Fracture Database (NHFD), this injury alone accounts for 1% of the nation's health-care budget or around £1 billion per year to the National Health Service (NHS).¹ A substantial part of this cost is due to length of stay (LOS) with one and a half

million bed days being used each year, equivalent to the continuous occupation of over 4000 beds across the United Kingdom. This situation of significant patient impact and

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Table 1. Table to Show the Demographics for All Patients, the Anticoagulated Patients, and the Nonanticoagulated Patients.

	Combined			Anticoagulated			Nonanticoagulated		
	Age	LOS	TTS	Age	LOS	TTS	Age	LOS	TTS
Total	1965	1965	1935	326	326	319	1639	1639	1616
Mean	82.25	20.71	29.59	82.68	24.57	33.78	82.12	19.94 ^a	28.77 ^b
Median	83.00	14.21	23.09	84.00	16.39	28.35	83.00	14.00	22.57
Max	104.0	149.5	491.5	103.0	135.8	142.9	104.0	149.5	491.58
Min	60.00	2.06	4.30	60.00	2.79	7.90	60.00	2.06	0.30
SD	8.48	18.47	26.40	8.65	21.98	19.70	8.68	17.59	27.46
95% CI	0.37	0.82	1.17	0.94	2.39	2.15	0.40	0.85	1.33

Abbreviations: LOS, length of stay; SD, standard deviation; TTS, time to surgery; 95% CI, 95% confidence interval.

^a $P \leq .001$.

^b $P \leq .001$.

considerable societal cost will only worsen with the predicted global increase in incidence of these injuries.

With such numbers, morbidity, and cost implications, any intervention which improves timely access to care and maximizes resource use in this population deserves considerable attention. We have previously described the benefits of quality improvement measures in the perioperative management of patients with hip fracture on warfarin.^{2,3} Over recent years increasing numbers of patients are being treated with the non-vitamin K antagonist anticoagulants, initially called novel oral anticoagulants, and now increasingly termed direct oral anticoagulants (DOACs). Unlike warfarin, established reversal protocols are not widespread for the DOACs and the challenge of managing them perioperatively is beginning to eclipse that of warfarin management.

There are currently no dedicated guidelines specifically for managing hip fracture patients on these drugs. We present the first multicenter assessment of the impact of DOACs on key domains of hip fracture care and propose the first dedicated DOAC hip fracture perioperative pathway.

Patients and Methods

Five hospitals in the North of England participated in this study (James Cook University Hospital Middlesbrough, York Hospital, Queen Elizabeth Hospital Gateshead, University Hospital North Durham, and Sunderland Royal Hospital) as part of the Northern Hip Fracture Collaborative. Consecutive hip fracture admissions older than 60 years of age between January 1, 2016 and December 31, 2016 were included in an analysis of a prospectively created database designed to comply with the requirements of the NHFD. As with previous studies,^{2,3} additional fields (anticoagulation agent and indication) were added to the mandatorily collected and locally collated core data set of the NHFD. Patients on anticoagulation therapy constituted the main study group, the remainder forming the control group. Several data points were collated, with particular emphasis placed on LOS, time to surgery (TTS), and accrual of best practice tariff (BPT), alongside standard demographics and indications. Statistical analysis (Microsoft Excel, 2016) was

performed utilizing χ^2 tests for categorical variables due to the sample size and independent samples t test for the normally distributed parametric data points.

Results

In all, 1965 patients were admitted to the 5 centers over the 12-month study period (1639 control). Thirty patients were treated nonoperatively (23 control).

The median age was 83 years, similar for both groups. Median LOS for all of the patients was 20.71 days, significantly longer for the anticoagulated patients (19.94 vs 24.57; $P \leq .001$). Overall TTS was 23.09 hours again demonstrating a delay in the anticoagulated population (22.57 vs 28.35; $P \leq .001$; Table 1).

Fracture type and procedure performed were similar for both groups. Best practice tariff accrual was significantly different between the 2 groups—a higher percentage of patients in the anticoagulated group missed BPT due to time to theater compared to the nonanticoagulated patients ($P < .05$; Table 2).

For the anticoagulated patients, cardiac arrhythmia is the commonest reason for administration of an anticoagulant (Table 3). The most commonly prescribed agent in this population is still warfarin. Dabigatran had the longest delay to theater, and both dabigatran and apixaban had the broadest spread of LOS (Table 4).

Discussion

Optimizing perioperative management of hip fracture patients has significant benefits for patients, carers, and health-care systems. This injury population is unique in that it undergoes surveillance at national level and is subject to target-driven tariff payments. No other trauma population is monitored to this extent, or its optimum care rewarded in such numbers.¹

The culture of quality entwined within hip fracture management has driven the research, industry innovation, and quality improvement agenda, all with positive effect on patient care. Similarly, reducing LOS, reducing costs, and improving overall efficiency in hip fracture care has considerable advantage to

Table 2. Fracture, Operation Performed, BPT Outcome, and the BPT Missed Due to Theater Time.

Combined	Combined		Anticoagulated		Nonanticoagulated	
	Frequency	%	Frequency	%	Frequency	%
Fracture type						
Intracapsular	1207	61.42	198	60.74	1010	61.62
Extracapsular	758	38.57	128	39.26	629	38.37
Operation						
THR	165	8.40	17	5.25	148	9.03
Hemiarthroplasty	916	46.62	172	53.09	744	45.39
SHS	594	30.23	80	24.69	514	31.36
Cannulated screws	24	1.22	0	0.00	24	1.46
Cephalomedullary nail	234	11.91	48	14.81	186	11.35
No operation	30	1.5	7	2.15	23	1.40
Total	1965		326		1639	
Operative domain affecting BPT accrual						
Achieved BPT time to surgery	469	61.95	30	20.97	152	34.7 ^a
Failed BPT time to surgery	258	34.08	113	79.03	286	65.3
Total	757		143		438	

Abbreviations: BPT, best practice tariff; THR, total hip replacement; SHS, sliding hip screw.

^aP ≤ .05.

Table 3. Indication for Anticoagulant Prescription.

Anticoagulant Indication	Frequency	%
Arrhythmia	185	56.8
Previous stroke	69	21.2
Thromboembolic event	33	10.1
Ischemic heart disease	27	8.3
Metal heart valve	6	1.8
Other	6	1.8
Total	326	100

Table 4. Anticoagulant Prescribed, Time to Surgery, BPT Accrual, and Length of Stay.

Medication	Frequency (%)	Median Time to Surgery (hours)	BPT Missed	
			Due to Theater Time (%)	Median Length of Stay (d)
Warfarin	140 (42.9)	28.34	52 (37.1)	16.71
Rivaroxaban	46 (14.1)	35.09	22 (47.8)	17
Clopidogrel	89 (27.3)	21.65	22 (24.7)	15.43
Dipyridamole	5 (1.5)	22.88	2 (40.0)	15.23
Dabigatran	10 (3.1)	48.28	7 (70.0)	13.49
Apixaban	33 (10.1)	36.7	16 (48.5)	20.45
Other	3	14.77	0	20.2
Total	326			

Abbreviation: BPT, best practice tariff.

health-care systems. When these factors are put in the context of a growing elderly population, the value of exploring any variable that impacts on timely hip fracture management is evident. We have previously demonstrated the continuing impact of warfarin on timely hip fracture care and have introduced a pathway to reduce time to theater. With the increasing use of DOACs, we

sought to assess the continuing impact and similarly produce a hip fracture-specific protocol to include these agents.

The adoption of DOACs as an alternative to warfarin has been driven by cost-effectiveness (reduced requirement for monitoring, rapid therapeutic onset, and reduced complications) and ease of use by patients (predictable pharmacokinetics and fewer drug and dietary interactions). We have demonstrated that there remains significant, anticoagulant attributable, delays to surgery, and increased hospital stay in this population. There are numerous confounding variables that can impact on outcome, but we have shown that anticoagulated patients stay longer in hospital and wait longer for surgery than nonanticoagulated patients of the same age and injury and have accounted specifically for other reasons for delay. Anticoagulated patients less frequently achieve the BPT uplift payment available in England for meeting the 7 BPT process measures, particularly in relation to the operative domain.

The challenge of optimizing perioperative anticoagulation care is not new, and delayed surgery due to warfarin prescription and, more recently, antiplatelet agents are well recognized. The latter group, introduced to impede platelet aggregation and therefore impair clot formation, initially resulted in considerable delays to theater due to fears of excessive bleeding. This was especially true in the case of clopidogrel, but ultimately, following careful introduction of protocol-driven early surgery, these fears were shown to be unfounded.⁴ Now, patients anticoagulated with clopidogrel proceed to theater without delay. Patients on warfarin proceed to theater with a controlled international normalized ratio (INR) driven by early vitamin K prescription and timely INR sampling. The same cannot be said of the DOACs. There is considerable variation in practice both within and between units and among individual surgeons and anesthetists. There are considerable gains to be made in standardizing perioperative care of the DOAC hip fracture

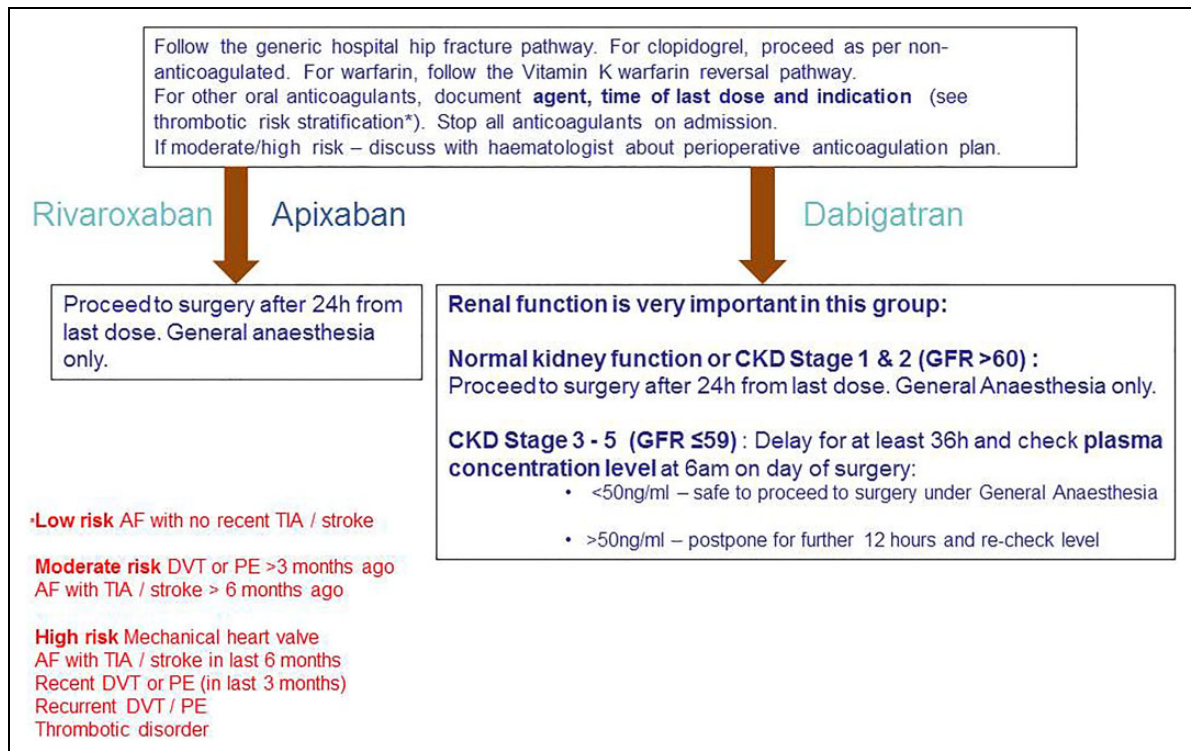


Figure 1. Hip fracture anticoagulant protocol.

population by implementing an evidence-based protocol that prevents unnecessary delays to theater. We have evaluated the existing evidence base incorporating the DOAC agents and have produced the first dedicated protocol for this group (Figure 1).

In order to derive this, we performed a detailed literature search through EBSCO database and OvidSP using Boolean operators (AND and OR) and using the following search terms: neck of femur, hip fracture, proximal femur oral anticoagulants, nonvitamin K anticoagulants, thrombin inhibitors, factor Xa inhibitors, antifactor Xa, dabigatran, rivaroxaban, apixaban, edoxaban, bleeding, and hemorrhage. Twenty-three articles were identified and then filtered by reading the title and abstract. One article (case report) was then considered for full-text reading.

OvidSP search resulted in 568 selected studies which were reduced to 510 articles following removal of duplicates. Only 3 articles were considered for full-text reading after being filtered by title and abstract. Further hand search was performed by reading the references of previously selected studies.

Ciurus et al advise that emergency surgery should be performed at least 12 hours (preferably 24 hours) after the last dose in a review of all agents including both elective and emergency procedures in all specialities.⁵ These recommendations however are too broad and vague to meaningfully guide subspecialist urgent surgery. Sie et al report on behalf of a French working group on perioperative hemostasis and recommend performing urgent surgery after at least 1 or 2 elimination half-lives of the anticoagulant which would mean

that surgery could proceed between 24 and 36 hours from the last dose for all 3 agents (apixaban, rivaroxaban, and dabigatran) and certainly comfortably within this time for agents other than dabigatran.⁶

It is difficult to precisely quantify the presence of DOACs, but it seems that for dabigatran a plasma concentration of >400 ng/mL poses a major hemorrhagic risk.⁷ If the level is between 200 and 400 ng/mL, surgery should be delayed for 24 hours whereas a level between 30 and 200 ng/mL requires postponing for 12 hours. Dundon et al are in consensus with these findings, suggesting that surgery can safely proceed if rivaroxaban or dabigatran level is <30 ng/mL but their results could only be considered as recommendations due to lack of evidence-based data in patients undergoing orthopedic procedures.⁸ Makris et al report on the findings of a guideline writing group on behalf of the British Committee for Standards in Haematology regarding the management of bleeding in patients on antithrombotic agents. Although recommending the use of dialysis to reduce the plasma concentration of these agents including particularly dabigatran, their review of the evidence up until 2011 did not provide any practical management options in the hip fracture (urgent but not bleeding nor emergency surgery) population.⁹

Keeling et al published an updated set of guidelines on behalf of the British Committee for Standards in Haematology addressing perioperative management of anticoagulation and antiplatelet therapy.¹⁰ As with other guidelines, there is evidence for elective practice and emergency surgery and for dealing with patients admitted with hemorrhage on these

agents. It is less clear as to how to proceed with surgery in the hip fracture population, and no robust evidence is provided for such injury profiles in which time is critical, but emergency surgery does not need to be performed. Keeling et al do state in their recommendations that a normal thrombin time can be interpreted as indicating that there is a minimal circulating concentration of dabigatran.

Using a very conservative approach and reporting the only specific intervention in the hip fracture population, Byron et al present a case report in which a patient was delayed for 5 days prior to hemiarthroplasty for her hip fracture.¹¹ This case does illustrate the impact of renal function as is well established. The patient had a creatinine clearance of 33 mL/min. Equally, the authors reinforce the use of thrombin time in reflecting dabigatran activity as discussed by Keeling et al.

Although none of the evidence available specifically guides hip fracture care, there are several themes that emerge. Renal function is key, particularly in patients on dabigatran. There is a clear difference between the impact of all of the agents in use and the guidance is not clear or easily interpreted for each agent. The one overriding feature is that renal function clearly plays a predominant role in the safe management of patients on oral anticoagulant medication and thrombin time can be used to guide dabigatran levels in the small subgroup with significant kidney disease, and hence we have incorporated a renal assessment with thrombin evaluation in our protocol.

Having looked at the evidence and recommendations around perioperative care from the hematology standpoint, these issues and our proposed guidance must be seen in the context for evidence surrounding the drive for timely surgery. The most recent authoritative assessment of the ideal time to operate on patients with a fractured hip has been provided by Lewis and Waddell. In a comprehensive overview of guidelines, national registry data, systematic reviews, and randomized studies, the authors provide an excellent synthesis of both sides of the argument around operating time for these patients.¹² The significant heterogeneity of contributory evidence is highlighted and the lack of clarity of what “early surgery” actually constitutes is raised. Nevertheless, some key points are made. Prompt operating enables reduced pain and allows patients to be nursed comfortably and with dignity. Perioperative complications including pressure ulcers are reduced following early surgery, with subsequent reductions in LOS and health-care costs. Equally, operating on those patients physiologically unstable due to an easily correctable medical comorbidity has avoidable consequences. They conclude that a limited delay to surgery is justified in some circumstances, namely to optimize concurrent medical conditions (including long-term anticoagulation), and that the key to avoiding unnecessary delays is early identification of reversible features.

Alongside, the evidence suggesting early surgery for appropriate patients is beneficial; there is the considerable driver of the BPT. Together, these drivers should ensure that hip fracture teams work on behalf of their patients taking oral anticoagulants to safely navigate them toward timely surgery. Along with our previous work on the hip fracture population on warfarin,

we could recommend all units trial the instigation of a similar guide for the safe effective management of the patients on the next generation of anticoagulant drugs.

There are several limitations of this work. The evidence base surrounding DOAC use in hip fractures is absent and while this makes accurate recommendations difficult, it highlights the need for work such as this and for units to optimize practice rather than leave patients delayed for over 48 hours based on nonrelevant evidence. These data are prospectively gathered but subject to all limitations of large registry data fields. Confounding factors are not addressed fully and independent association of any outcome can have an effect. Big numbers can seem counter intuitively to strengthen the argument of clinical outcomes discovered that may have little actual clinical relevance. This is illustrated in our work in that we may be able to demonstrate differences but as to the importance of that outcome on a given patient, that is, less clear. For example, we have not presented mortality statistics as these are not available for the majority of the patients. Once again, while viewed in isolation as a limitation, looking at the review of Lewis and Waddell, the overall evidence regarding outcomes in hip fracture care and true impact on mortality in all patients is yet to be proven. We do know however that for most patients, timely surgery attracts improved outcomes, and equally, the health economic standpoint of decreasing LOS, for example, is increasingly important.

In conclusion, we have demonstrated in a regional study that anticoagulant medications continue to impact negatively on the ability to perform timely surgery on hip fracture patients on these medications. Delays are significant and there is an impact on LOS and BPT accrual. We recommend units adopt a guideline specific to the management of anticoagulation in the hip fracture population and propose a template from which one can be drawn for local use. Although we highlight this situation with a regional analysis, the subject matter would benefit from a national sprint type study to provide more compelling, robust evidence.

Declaration of Conflicting Interests

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