Abstract

Background

Patients who sustain a hip fracture whilst taking direct oral anticoagulants (DOACs) experience delays to surgery, which can increase morbidity and mortality. Achievement of the prompt surgery aspect of the National Hip Fracture Database (NHFD) best practice tariff stipulates surgery within 36 hours, which these patients often fail to meet.

Patients and methods

Our protocol for expedited hip fracture surgery in patients taking DOACs was implemented. We compared surgery within 36 hours (primary outcome) and peri-operative blood transfusions, 30-day mortality, wound leakage, return to theatre and length of hospital stay (secondary outcomes) with standard care of 80 matched non-anticoagulated controls.

Results

Median times to theatre were 26.0 hours (IQR 16.2 hours) in DOAC patients and 22.4 hours (IQR 16.9 hours) in controls: bootstrapped 95% CI for the difference (-0.935, 7.52). Bias-corrected related samples bootstrapped t-testing revealed no evidence for a group difference on the primary outcome (p=0.133) or any secondary outcome, including post-operative transfusions ($\chi^2_{(1)}$=0.533; p=0.465, 95% CI for the difference -18.3% to 8.37%); death within 30 days ($\chi^2_{(1)}$=0.667; p=0.414, 95% CI for the difference -3.48% to 8.48%); wound leakage ($\chi^2_{(1)}$=0.571; p=0.450, 95% CI -1.79% to 0.792%); return to theatre ($\chi^2_{(1)}$=0.00; p=1.00), or median length of hospital stay (p=0.678, bias-corrected bootstrapped 95% CI for the difference -4.47 to 6.68).

Discussion

Our protocol is simple, does not require plasma DOAC level testing and can be used to achieve the NHFD recommendation of surgery within 36 hours without increasing peri-operative transfusions, wound leakage, return to theatre, length of stay or mortality.

Key words: hip fracture, direct oral anticoagulant, factor Xa inhibitor

Introduction

The National Hip Fracture Database (NHFD) Annual Report highlighted that 10% of all hip fracture patients experience a delay to prompt surgery due to their concurrent anticoagulant medication [1]. With comparatively reduced side effects and fewer drug interactions coupled with efficacy without routine drug plasma level monitoring, unsurprisingly direct oral anticoagulant (DOAC) prescriptions now outnumber those of warfarin and are increasing annually [2]. The NHFD report highlighted that 19% of trauma units do not have a perioperative management pathway for patients taking a DOAC [1].

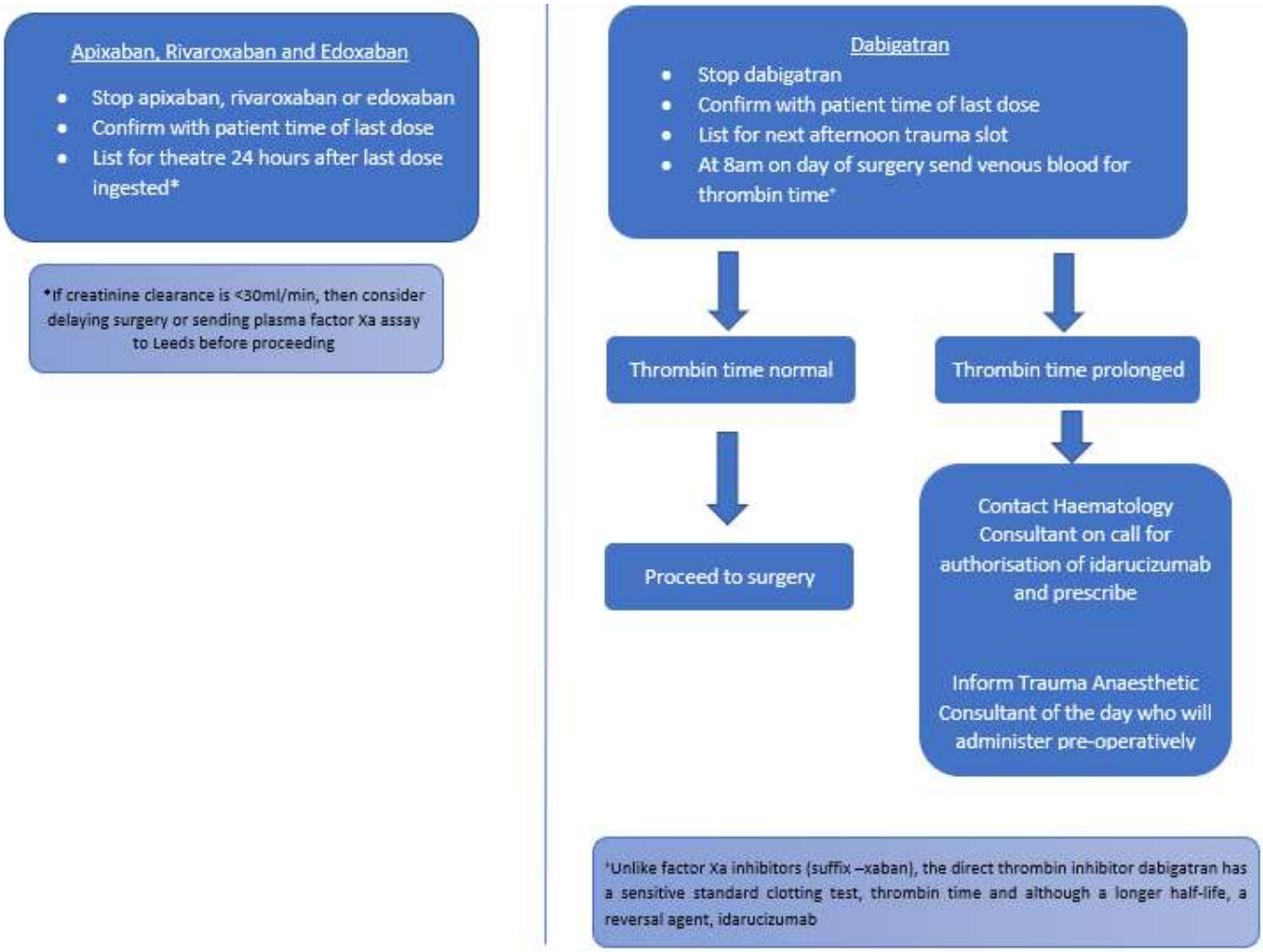
Delays to surgery for hip fracture patients increases mortality and morbidity by leaving patients bed-bound and at risk of pathologies of recumbency such as pressure ulcers, atelectasis, urinary tract infections and venous thromboembolism (VTE). NICE guidance recommends performing surgery for hip fracture on the day or day after admission [3]. Indeed, an element of the UK's NHFD Best Practice Tariff (BPT) for hip fracture care is prompt surgery within 36 hours.

In recent years as DOAC prescriptions increased, but without evidence for the safe timing of hip fracture surgery in patients taking a DOAC (FNOF-DOAC), several studies demonstrated delays to surgery in these individuals and the resulting harm. In 2018 Rutenberg et al. demonstrated delays to theatre in FNOF-DOACs and increased pressure ulceration, a known complication of surgical delay [4]. In 2019 Bruckbauer et al. showed FNOF-DOACs were delayed to theatre almost three times longer than non-anticoagulated cohorts [5]. In 2018, Schermann et al. established increased one year mortality: 26.7% versus 16.1%, in people taking a DOAC (n=60) versus non-anticoagulated controls [6]. In 2018 Taranu et al. again demonstrated delays to theatre associated with increased length of stay and reductions in attainment of Best Practice Tariff [7].

“Time to theatre” for FNOF-DOACs is controversial. A balance is needed between expediting surgery to improve outcomes while allowing enough time for sufficient renal elimination of the drug, which theoretically reduces the risk of bleeding with regards to vertebral canal haematoma following spinal anaesthesia and haemorrhage and wound dehiscence from the surgery itself. Further adding to the controversy around surgical timing is many hospitals lack the technology “in house” to process DOAC plasma level assays. However, this is often a moot point as there is currently a lack of evidence defining a safe DOAC plasma level to proceed with urgent hip fracture surgery.

Therefore, to create a protocol to standardise prompt care for FNOF-DOACs, we designed a pharmacokinetic pathway based on two-times the elimination half-life of each DOAC, a concept highlighted by The European Society of Anaesthesiology [8]. The pathway was approved by the Medicines Management Committee as a Trust protocol and instituted into clinical use (Figure 1).

Figure 1: pre-operative direct oral anticoagulant reversal for fractured neck of femur surgery



We hypothesised that our protocol would expedite prompt surgery to meet the NHFD 36-hour target but not increase peri-operative morbidity and mortality. A retrospective control-matched audit assessed time to theatre for FNOF-DOACs treated by our pathway and whether expedited surgery had any impact on peri-operative blood transfusions, wound leakage, return to theatre, length of stay or mortality.

Patients and Methods

Patient selection

Data was retrospectively collected over a 2 year period by identifying all hip fracture admissions taking DOACs; the factor Xa inhibitors apixaban, rivaroxaban, edoxaban, and the direct thrombin inhibitor dabigatran. Some patients were also concurrently taking the antiplatelet agents clopidogrel and aspirin.

All FNOF-DOACs listed as receiving operative management on the Bluespier Theatre Management System (Clanwilliam Group, UK) were included in the study. For each FNOF-DOAC, age at time of surgery, sex, American Society of Anaesthesiologists (ASA) grade and surgery type was recorded using data retrieved from Bluespier.

Matching with non-anticoagulated controls

Using Bluespier, each FNOF-DOAC was individually matched by age, sex, ASA and surgery type to a control who also sustained a fractured neck of femur during a similar time period. The Electronic Patient Record (EPR) (Cerner, USA) for each matched control was scrutinised to ensure that controls were not taking any anticoagulant or antiplatelet agents at the time of sustaining hip fracture. If so, they were rejected and the FNOF-DOAC re-matched.

Data collection

Time to theatre was calculated as the difference between the documented ED admission time (or referral for in-patient falls) on the EPR to anaesthetic start on Bluespier for each individual. Type of anaesthetic was identified by analysing each anaesthetic record and was defined as general anaesthesia +/- peripheral nerve block and/or spinal anaesthesia +/- peripheral nerve block. From transfusion prescriptions and fated red cell unit records, each patient was classified as receiving pre-operative (defined as those occurring before anaesthesia induction) and/or post-operative (administered after anaesthesia induction) or no blood transfusion.

Post-operative wound complications were assessed by scrutinising all post-operative EPR documentation. To exclude definition interpretation bias, the Trust's Fractured Neck of Femur Orthopaedic Clinical Lead reviewed all data entries. A wound complication was defined as any of: a persistent wound leak in the 24-hour post-operative period, strikethrough on the post-operative dressing requiring dressing change, evidence of swab-proven infection, suspected infection on clinical examination, a wound that required a return to theatre for any cause. Each patient was categorised as either having or not having a post-operative wound complication.

All in-patients who returned to theatre due to wound complications were identified by a second Bluespier theatre encounter following hip fracture fixation, and by the presence of an operation note confirming such. Length of hospital stay for each patient was calculated from EPR data; date of ED arrival (or referral for in-patient falls) to date of discharge from the Trust. Mortality data was provided by the Trust's Health Informatics Service, and patients classified as deceased or surviving 30 days post-surgery.

Statistical analysis

A sample size calculation determined that a sample of 73 pairs of subjects achieves 80.0% power at a significance level of 0.050 to reject the null hypothesis of equal times to theatre (the primary outcome), conservatively anticipating a small effect size, and using a two-sided paired t-test.

The sample was summarised descriptively; by patient episode type (FNOF-DOAC or control; i.e. non-anticoagulated) and as a full cohort. Matching effectiveness was assessed by comparison of summary values on matching variables. The need for further statistical control was assessed by a comparative analysis of summary statistics on non-matched variables.

The primary outcome was patient time to theatre: assessing differences in times to theatre in FNOF-DOAC patients (treated according to the pathway in figure 1) and control patients (non-anticoagulated patients receiving standard care), using bias-corrected bootstrapped related samples (matched pairs) t-testing. Secondary outcomes included: proportions of patients experiencing peri-operative blood transfusions, length of hospital stay (in days), wound leakage, return to theatre and 30-day mortality. All secondary outcomes were compared using McNemar's test for the difference between two proportions conducted on matched data, except length of hospital stay, for which groups were compared using bootstrapped paired samples t-testing. Main inferential testing was conducted in the context of test of superiority: subsidiary testing assessed non-inferiority of the pathway using a pre-specified margin of 15%.

Results

Descriptive & exploratory analysis

Data was collected on 171 procedures from 168 patients, including three patients who had fractured both hips during the 2-year data collection period. Clustering of data due to within-patient commonalities from these patients was judged to be negligible and was disregarded. Eight patients were excluded from the study due to: conservative management (5 patients); post-operative complications unrelated to the surgery necessitating a large transfusion (one patient); and FNOF-DOAC who could not be matched to control patients (two patients). Hence 160 patient episodes were included in the analysis, yielding 80 matched pairs (FNOF-DOAC–control); achieving adequate study power. Of the 80 people taking DOACs, 50 were taking apixaban (including one with additional aspirin and four with additional clopidogrel); 27 were taking rivaroxaban (including one with additional clopidogrel); one was taking edoxaban and two were taking dabigatran.

Patient episodes were matched exactly on sex, surgery type and ASA grade in all pairs. Near-exact matching was achieved on patient age, with mean ages of 83.5 years (SD 9.31 years) in the control group and 83.2 years (SD 10.3 years) in the FNOF-DOAC group. Exact age matches (in years) were created on 50 pairs. 22 pairs were matched to within 1 year of age. Eight pairs were matched to between 1 and 10 years of age.

Sample characteristics of matched categorical variables for included patients are summarised in Table 1 with outcomes summarised in Table 2. Summary statistics quoted are frequency and percentage unless otherwise indicated. Missing values were recorded for one control patient on time to anaesthesia and length of stay. These values were not imputed, and complete case analyses were conducted for analyses involving these variables.

Table 1: summary of patient characteristics on matched categorical variables (exact matching achieved on all tabulated variables)

Variable	**All patients (*n*=160) (Control patients *n*=80;**

	FNOF-DOAC patients *n*=80)
Sex	
Male	48 (30.0%)
Female	112 (70.0%)
Surgery type	
Cannulated hip screw	6 (3.75%)
Dynamic hip screw	34 (21.25%)
Gamma nail	32 (20.0%)
Hemiarthroplasty	88 (55.0%)
ASA grade	
2	8 (5.0%)
3	94 (58.75%)
4	58 (36.25%)

Table 2: summary of patient outcomes

Variable	**Control patients (*n*=80)**	**FNOF-DOAC patients (*n*=80)**	**All patients (*n*=160)**
Time (in hours) to theatre (median (IQR))	22.4 (16.9)[1]	26.0 (16.2)	23.3 (17.6)
Time to theatre within 36 hours target			
Target met	61 (76.25%)	62 (77.5%)	123 (76.9%)
Target not met	19 (23.75%)	18 (22.5%)	37 (23.1%)
Length (in days) of hospital stay (median (IQR))	17.1 (18.2)[1]	18.1 (14.9)	18.0 (16.2)
Pre-operative transfusion			

No transfusion required	72 (90.0%)	74 (92.5%)	146 (91.3%)
Transfusion required	8 (10.0%)	6 (7.5%)	14 (8.8%)
Post-operative transfusion			
No transfusion required	34 (42.5%)	38 (47.5%)	72 (45.0%)
Transfusion required	46 (57.5%)	42 (52.5%)	88 (55.0%)
Nerve block administration			
Not performed	10 (12.5%)	14 (17.5%)	24 (15.0%)
Performed	70 (87.5%)	66 (82.5%)	136 (85.0%)
Type of anaesthetic			
GA	33 (41.25%)	23 (28.75%)	56 (35.0%)
Spinal	47 (58.75%)	55 (68.75%)	102 (63.75%)
GA and spinal	0 (0.0%)	2 (2.5%)	1 (1.25%)
Return to theatre			
Patient not returned to theatre	79 (98.75%)	79 (98.75%)	158 (98.75%)
Patient returned to theatre	1 (1.25%)	1 (1.25%)	2 (1.25%)
Wound status			
No wound leakage	57 (71.25%)	61 (76.25%)	118 (73.75%)
Wound leakage	23 (28.75%)	19 (23.75%)	42 (26.25%)
Mortality			
Patient survived	77 (96.25%)	75 (93.75%)	152 (95.0%)
Patient death	3 (3.75%)	5 (6.25%)	8 (5.0%)

[1]*n*=79

Table 2 revealed no substantive imbalances on any non-matching variables.

Inspection of data distributions of numerical outcomes (time to theatre and length of hospital stay) revealed right-skewed data, with skewness stronger in the control group in both cases, and small numbers of outliers (Figures 2, 3). These were investigated on an individual basis and checked for validity. Histograms of time to theatre distributions (Figure 2) also revealed

that modal times to theatre were 20-25 hours for control patients and 15-20 hours for FNOF-DOAC patients, with similar number in each group with times in excess of 36 hours (indicated with a dotted line on the figures). Histograms of length of stay distributions (Figure 3) revealed that modal lengths of hospital stays were 5-10 days for control patients and 15-20 days for FNOF-DOAC patients; however, a larger number of control patients had excessively long lengths of stay. No evidence for violation of distributional assumptions was revealed for either variable.

Figure 2: distribution of times to theatre (hours): control group and FNOF-DOAC group patients (showing 36-hour reference)

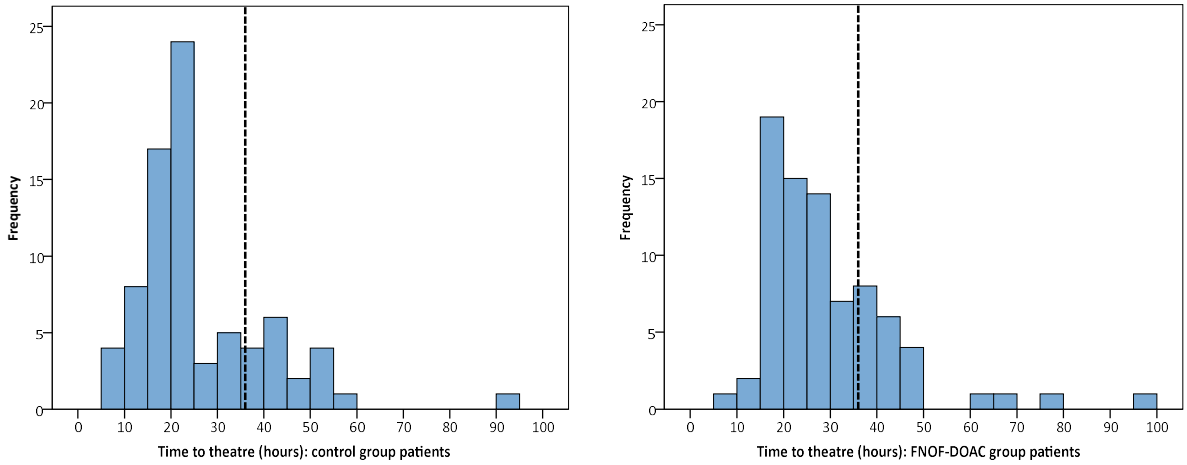
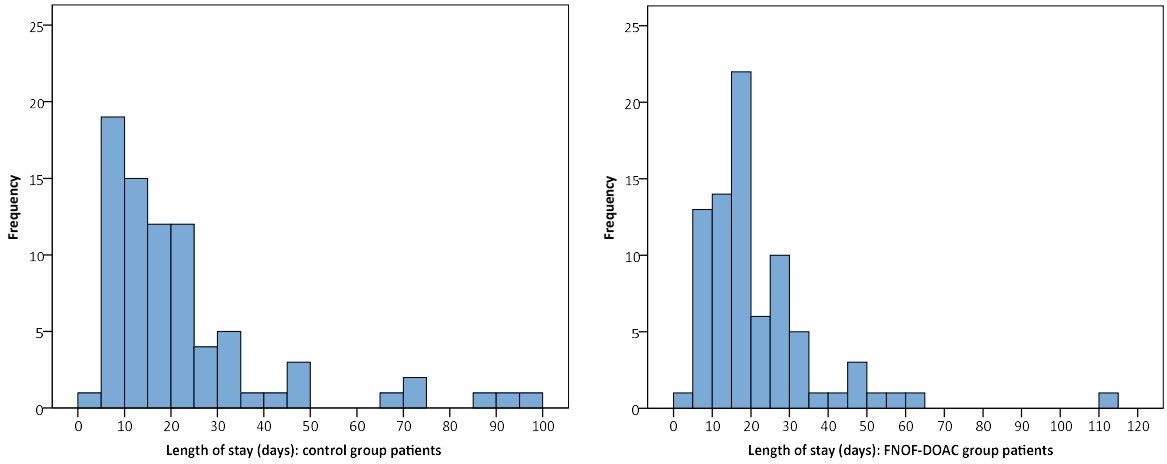


Figure 3: distribution of length of hospital stay (days): control group and FNOF-DOAC group patients



Median times to theatre were 26.0 hours (IQR 16.2 hours) in the FNOF-DOAC group; and 22.4 hours (IQR 16.9 hours) in controls. Mean times to theatre were 29.5 hours (SD 15.0 hours) in the FNOF-DOAC group; and 26.2 hours (14.5 hours) in controls. A bootstrapped 95% CI for this difference was given by (-0.935, 7.52). A bias-corrected related samples t-test using bootstrapping revealed no evidence for a difference between groups (p=0.133).

McNemar's test for matched proportions revealed no evidence for a difference between groups with respect to any of the categorical secondary outcomes including: proportion of patients requiring post-operative transfusion ($\chi^2_{(1)}$=0.533, p=0.465, 95% CI for the difference in population proportions -18.3% to 8.37%); 30-day mortality ($\chi^2_{(1)}$=0.667, p=0.414, 95% CI for the difference in population proportions -3.48% to 8.48%); wound leakage ($\chi^2_{(1)}$=0.571, p=0.450, 95% CI for the difference in population proportions -1.79% to 0.792%); and return to theatre ($\chi^2_{(1)}$=0.00, p=1.00). A bias-corrected related samples t-test using bootstrapping revealed no evidence for a difference in length of hospital stay between groups (p=0.678, bootstrapped 95% CI -4.47 to 6.68).

Hence no evidence was revealed for superiority of the control group receiving standard care with respect to any measured outcome; and evidence was revealed for non-inferiority of the FNOF-DOAC pathway at the 15% margin; again with respect to any measured outcome.

Discussion

This study established with statistical significance (at the 5% level) that using our protocol in Figure 1, patients taking DOACs received their hip fracture surgery as quickly as non-anticoagulated controls receiving standard care. Furthermore, there was no statistically significant difference between peri-operative complications in FNOF-DOACs with respect to blood transfusion, wound leakage, return to theatre, length of stay and 30-day mortality compared to non-anticoagulated controls.

Average (median) time to theatre for patients in the FNOF-DOAC group was 26.0 hours, comfortably within attainment of the NHFD best practice tariff of surgery within 36 hours. In fact, despite FNOF-DOACs having a higher average time to theatre than controls (26.0 versus 22.4 hours), there were actually *fewer* FNOF-DOACs than controls whose times breached the 36-hour limit; overall 62 FNOF-DOACs (77.5%) were taken to theatre within 36 hours compared to 61 controls (76.25%).

Fewer FNOF-DOACs received post-operative transfusions despite *less* pre-operative transfusions compared to controls. Bias was eliminated due to a hip fracture transfusion guideline which was applied to all patients.

After 24 hours, the passage of two half-lives, 75% of the active DOAC has been eliminated. It could be hypothesised that without significant circulating DOAC, the person's inherent pathological high thrombotic tendency, for which they required a DOAC, is reinstated. This may explain why peri-operative haemorrhage was not seen. Furthermore, there is an assumption that a drug's pharmacodynamic ability to *prevent* VTE is commensurate with *causing* bleeding, but this may not be the case. Schermann et al. (2018) demonstrated that DOAC use before hip fracture surgery was not associated with increased perioperative blood loss and similarly point out the lack of firm evidence for the assumption that drug activity is associated with intra-operative bleeding [6]. Of note, no FNOF-DOAC who received spinal anaesthesia or a peripheral nerve block suffered a complication of vertebral canal haematoma or peripheral nerve injury.

National recommendations

When this protocol was developed there was a lack of national guidance on when was considered safe to proceed to surgery. Many clinicians relied on conservative elective guidance which arguably cannot be applied to hip fracture patients who require urgent surgical intervention, and where delays ironically increase, not decrease, their risk profile. Initial data following implementation of our pathway demonstrated an increase from 64.4% of FNOF-

DOACs receiving prompt surgery within 36 hours to 92.3% [9]. The clinical success of our pathway led to endorsement from the Association of Anaesthetists of Great Britain and Ireland, and its incorporation into the much-needed national recommendations in the publication "Guideline for the management of hip fractures 2020" [10]. This study has shown the efficacy of a now nationally endorsed protocol and non-inferiority to standard care of non-anticoagulated hip fracture patients.

Strengths and limitations

Other studies, such as Franklin et al.'s 2018 study also support prompt surgery and demonstrated no significant difference between their FNOF-DOAC and control group in terms of estimated blood loss, transfusion rates, length of stay, post-operative wound complications, reoperation rates and or 30-day survival rates [11]. Leer-Salvesen et al.'s 2020 retrospective study showed a time to theatre for FNOF-DOAC patients of 29 hours versus 26 hours for controls; very similar to our data [12]. They also had a transfusion policy to exclude bias and were not able to find an increase in perioperative blood loss, transfusion rates, bleeding complications or mortality between the two groups and concluded that early surgical intervention appeared to be safe in FNOF-DOAC patients [12].

A further strength of our study was the large sample size, leading to higher power to detect any group differences; and highly effective matching of patient data, leading to minimisation of the potential for confounding bias. By comparison, other studies assessing the effectiveness of DOACs on patient outcomes, did not utilise matching, statistical control or other method to minimise confounding bias, and used smaller DOAC group sizes than in our study [12,13].

Limitations of this study were minimised due to a high matching process on key variables, good balance on additional variables and the hip fracture transfusion policy eliminating objective transfusion bias. However, median time to theatre in the FNOF-DOAC group was still 3.6 hours longer compared to the control group (26.0 hours versus 22.4 hours). This was due to the small cohort of 7 patients with exceptionally poor renal function who required an

appropriate delay to theatre to allow DOAC renal excretion. This level of group imbalance is within expectations for study of this size which considered several patient-level and procedural-level factors; nonetheless such individuals for whom excessive length of hospital stay or time to theatre values have been recorded may well be influential data points in that their inclusion may lead to changes in model inferences. However, we had no *a priori* grounds for exclusion of any such people from the study.

Conclusion

The NHFD 2019 annual report highlighted that 19% of all units do not have a protocol to expedite safe hip fracture surgery in people taking a DOAC and recommends that protocols be implemented to prevent delays to prompt surgery. Our protocol is simple, does not require DOAC plasma level testing, can be used to attain the NHFD prompt surgery aspect of best practice tariff and does not increase peri-operative transfusion rates, length of stay, wound leakage, return to theatre or mortality when compared to standard care of matched non-anticoagulated hip fracture patients.

Disclosure of Interests

The authors declare that there is no conflict of interest.

References

1. National Hip Fracture Database Annual Report 2019

   https://www.nhfd.co.uk/files/2019ReportFiles/NHFD_2019_Annual_Report_v101.pdf

2. Mullins B, Akehurst H, Slattery D, Chesser T. Should surgery be delayed in patients taking direct oral anticoagulants who suffer a hip fracture? A retrospective, case-controlled observational study at a UK major trauma centre. *BMJ Open*. 2018;8:e020625.

3. NICE Guidance. Hip fracture: management. 2011. www.nice.org.uk/guidance/cg124

4. Rutenberg TF, Velkes S, Vitenberg M et al. Morbidity and mortality after fragility hip fracture surgery in patients receiving vitamin K antagonists and direct oral anticoagulants. *Thrombosis Research*. 2018. 166: 106-112.

5. Bruckbauer M, Prexl O, Voelckel W et al. Impact of Direct Oral Anticoagulants in Patients With Hip Fractures. *J Orthop Trauma*. 2019; 33(1):e8-e13.

6. Schermann H, Gurel R, Gold A et al. Safety of urgent hip fracture surgery protocol under influence of direct oral anticoagulation medications. *Injury*. 2018. https://doi.org/10.1016/j.injury.2018.10.033

7. Taranu R, Redclift C, Williams P et al. Use of Anticoagulants Remains a Significant Threat to Timely Hip Fracture Surgery. *Geriatric Orthopaedic Surgery &Rehabilitation*. 2018; 9:1-6.

8. Gogarten W, Vandermeulen E, Van Aken et al. Regional anaesthesia and antithrombotic agents: recommendations of the European Society of Anaesthesiology. *European Journal of Anaesthesiology*. 2010; 27(12): 999-1015.

9. National Hip Fracture Database – Charts & Reports https://www.nhfd.co.uk/20/nhfdcharts.nsf/vwCharts/BestPractice?opendocument&org=HUD

10. Griffiths R, Babu S, Dixon P et al. Guideline for the management of hip fractures 2020. *Anaesthesia*. 2020; 76(2):225-237. https://doi.org/10.1111/anae.15291

11. Franklin NA, Ali AH, Hurley RK et al. Outcomes of Early Surgical Intervention in Geriatric Proximal Femur Fractures Among Patients Receiving Direct Oral Anticoagulation. *J Orthop Trauma*. 2018; 32(6): 269-273.

12. Leer-Salvesen S, Dybvik E, Ranhoff AH et al. Do direct oral anticoagulants (DOACs) cause delayed surgery, longer length of hospital stay and poorer outcomes for hip fracture patients? *European Geriatric Medicine*. 2020. https://doi.org/10/1007/s41999-020-00319-w

13. Aziz S, Almeida K, Taylor G. How should we manage hip fracture patients on direct oral anticoagulants? *BMJ Evidence-based Medicine*. 2021; 26(1)