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ORIGINAL ARTICLE

Preoperative antithrombotic therapy and risk of blood transfusion and mortality following hip fracture surgery: a Danish nationwide cohort study

C. Daugaard[1] · A.B. Pedersen[1] · N.R. Kristensen[1] · S.P. Johnsen[1,2]

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Abstract

Summary Hip fracture surgery is associated with high risk of bleeding and mortality. The patients often have cardiovascular comorbidity, which requires antithrombotic treatment. This study found that preoperative use of oral anticoagulants was not associated with transfusion or mortality following hip fracture surgery, whereas increased risk may exist for antiplatelet drugs.

Introduction Hip fracture surgery is associated with high bleeding risk and mortality; however, data on operative outcomes of hip fracture patients admitted while on antithrombotic therapy is sparse. We examined if preoperative antithrombotic treatment was associated with increased use of blood transfusion and 30-day mortality following hip fracture surgery.

Methods Using data from the Danish Multidisciplinary Hip Fracture Registry, we identified 74,791 hip fracture surgery patients aged ≥ 65 years during 2005–2016. Exposure was treatment with non-vitamin K antagonist oral anticoagulant (NOAC), vitamin K antagonists (VKA), or antiplatelet drugs at admission for hip fracture. Outcome was blood transfusion within 7 days postsurgery and death within 30 days.

Results A 45.3% of patients received blood transfusion and 10.6% died. Current NOAC use was associated with slightly increased risk of transfusion (adjusted relative risk (aRR) 1.07, 95% confidence interval (CI) 1.01–1.14), but similar mortality risk (adjusted hazard ratio (aHR) 0.88, 95% CI 0.75–1.03) compared with non-users. The pattern remained when restricting to patients with short surgical delay (< 24 h). VKA users did not have increased risk of transfusion or mortality. The risks of transfusion (aRR 1.15 95% CI 1.12–1.18) and 30-day mortality (aHR 1.18 95% CI 1.14–1.23) were increased among antiplatelet users compared with non-users.

Conclusions In an observational setting, neither preoperative NOAC nor VKA treatments were associated with increased risk of 30-day postoperative mortality among hip fracture patients. NOAC was associated with slightly increased risk of transfusion. Preoperative use of antiplatelet drugs was associated with increased risk of transfusion and mortality.

Keywords Anticoagulants · Bleeding · Cohort study · Hip fractures · Platelet inhibitor

Introduction

Hip fracture is a common trauma among elderly people and a frequent cause of hospitalization and death [1]. Hip fracture patients often have cardiovascular comorbidity which requires treatment with antithrombotic drugs [2, 3]. The use of antithrombotic therapy has increased, and currently, more than 40% of patients admitted with hip fracture are on antithrombotic therapy [4]. This may have clinical implications for surgery and subsequent care. Ongoing antithrombotic treatment at the time of hip fracture represents a difficult clinical dilemma. The question is whether surgery should be delayed for drug effects to diminish or if it is preferable to proceed with immediate surgery to facilitate early mobilization and hereby

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✉ C. Daugaard
cecilie.daugaard@gmail.com

[1] Department of Clinical Medicine, Department of Clinical Epidemiology, Aarhus University Hospital, Olof Palmes Alle 43-45, 8200 Aarhus N, Denmark

[2] Danish Center for Clinical Health Services Research, Department of Clinical Medicine, Aalborg University Hospital, Aalborg University, Mølleparkvej 10, 9000 Aalborg, Denmark

reduce the risk of postoperative complications. On one hand, hip fracture surgery remains associated with a substantial risk of adverse outcomes, including perioperative bleeding and an overall 30-day mortality risk of approximately 10% [5]. Performing acute major surgery in a fragile group of patients with ongoing antithrombotic therapy may therefore not be an attractive approach. However, delaying surgery may is also be problematic. It is generally shown that delayed surgery is associated with an increase in mortality [6–9], but this excess mortality may be rooted in medical conditions causing the delay rather than the actual delay itself [10].

Data on perioperative outcomes of hip fracture patients admitted while on antithrombotic therapy including the newer non-vitamin K antagonist oral anticoagulants (NOACs) is sparse. Accordingly, we aimed to examine the association between pre-admission prescription of NOACs, vitamin K antagonists (VKA), and antiplatelets in hip fracture patients with the rate of red blood cell (RBC) transfusion within 7 days and mortality within 30 days. We hypothesized that antithrombotic treatment at time of admission would be associated with a higher risk of blood transfusion and death among hip fracture patients.

Methods

Setting

We performed a nationwide population-based cohort study including all patients who underwent hip fracture surgery during 2005–2016. All Danish residents are assigned a unique ten-digit personal identification number at birth or immigration, enabling unambiguous individual-level linkage between Danish registers [11].

Study population

We used the Danish Multidisciplinary Hip Fracture Registry (DMHFR) to identify all first-time hip fracture patients aged 65 or older treated surgically between 1 January 2005 and 31 December 2016. The DMHFR is a nationwide clinical quality database containing information on all patients with either a primary or secondary inpatient diagnosis of femoral neck, pertrochanteric, or subtrochanteric fractures undergoing surgery including insertion of a primary hip replacement or open reduction and internal fixation in Denmark since 2003. Reporting to the database is mandatory for all Danish orthopedic departments [12, 13] and includes detailed pre-, per-, and postoperative data. No patients were excluded, and the total cohort included 71,791 patients.

Exposure

Medicine data was obtained from The Danish National Health Service Prescription Database which holds individual-level data on all prescription drugs sold by all community and hospital-based outpatient pharmacies in Denmark since 2004 [14]. Data on the following antithrombotic drugs were obtained: NOAC (Anatomical Therapeutic Chemical (ATC) code: B01AE07, B01AF01, B01AF02, B01AF03), VKA (ATC code: B01AA), and antiplatelets including acetylsalicylic acid (ATC code: B01AC, N02BA01, N02BA51). Patients were categorized into non-users (no redemption of prescribed antithrombotics in the year prior to surgery), former users (redemption of one prescription 91–365 days prior to hip fracture surgery) and current users (at least one prescription ≤ 90 days prior to hip fracture surgery) for each class of antithrombotic drugs.

Outcome

The outcomes were RBC transfusion within 7 days after hip fracture surgery and all-cause 30-day mortality. Information on all allogenic RBC transfusion was obtained from the Danish Transfusion Database (DTDB). Patients were classified as having received either none or one or more RBC units. The 7-day window was chosen to capture transfusions related to surgery rather than other factors such as comorbidity. The DTDB is a nationwide clinical quality database collecting data on the use of blood products in Denmark since 2000. It contains individual level information on types and numbers of blood components administered, date of blood transfusion, and clinical biochemical data.

Information on all-cause mortality (30-days postsurgery) was obtained from the Danish Civil Registration System. This national registry has maintained records on vital status, migration, and residence for the entire Danish population since 1968 [11].

Covariates

From DMHFR, we obtained information on a range of prespecified covariates: sex, age, body mass index (BMI), type of hip fracture (femoral neck or pertrochanteric and subtrochanteric fractures), type of surgery (osteosynthesis, or total- and hemi-hip arthroplasty), surgery delay (< 24 h, 25–36, and > 36 h), and surgery year. Following BMI (weight in kilograms (kg) divided by the square of height in meters (m)) categories were applied: underweight (BMI was < 18.5 kg/m^2), normal weight (BMI was 18.5–24.9 kg/m^2), overweight (BMI was 25–29.9 kg/m^2), and obese (BMI was ≥ 30 kg/m^2).

Surgery delay was defined as the time period from hip fracture admission to surgical procedure. For each patient, we extracted information on diagnosis in relation to

hospitalization and outpatient visits through a period of 10 years prior to hip fracture and calculated a Charlson comorbidity index (CCI) score for each patient using all ICD-10 discharge diagnoses available from The Danish National Patient Registry [15, 16]. In addition, we extracted information on diagnosis of atrial fibrillation or flutter (ICD-10 diagnosis code I48). From the Danish National Health Service Prescription Database, we collected information on all redeemed prescriptions for non-steroidal anti-inflammatory drugs (NSAIDs), antidepressants (selective serotonin reuptake inhibitors (SSRIs)), corticosteroids, statins, and antibiotics in the year prior to hip fracture surgery. ATC-codes are provided in Online Resource 1.

Statistics

We computed the cumulative incidence with 95% confidence intervals (CIs) of RBC transfusion within 7 days of surgery according to antithrombotic use considering death as competing risk. In the complete case analyses, we excluded patients with missing data on BMI and surgery delay. Then, using a log-binomial model, we estimated relative risks (RRs) for RBC transfusion and corresponding 95% CIs, both crude and adjusted for age, sex, BMI, CCI, type of fracture, surgery delay, year of surgery, and other prescription medicine using non-user patients as reference. We did not adjust for type of surgery, as this variable was considered to be colinear with type of fracture. Since hospital-related factors including the surgeon behavior and the decision-making process may affect the need for transfusion, we adjusted for a cluster effect by departments.

The risk of death within 30 days was analyzed using a Cox proportional hazard regression model. We estimated hazard ratios (HRs) and corresponding 95% CI for 30-day mortality, both crude and adjusted for the same covariates as in log-binominal model, comparing current and former users of NOAC with non-users of NOAC. We did not adjust for transfusion as this variable was more likely to be an intermediate step rather than a confounder in the association between antithrombotic therapy and postoperative mortality. Similarly, HRs were calculated for users of VKA and antiplatelets. The assumption of proportional hazards was evaluated by visual inspection of plots.

In addition, all analyses were stratified by surgical delay to investigate whether the risk associated with antithrombotic therapy differed among patients according to time to surgery. Also, we made analyses restricted to patients diagnosed with atrial fibrillation or atrial flutter.

We assumed the data on BMI and surgery delay to be missing at random. Thus, we repeated all analyses using multiple imputation method. This method creates several plausible imputed datasets and thereafter combines the results based on information from available data [17]. In order to impute the data on BMI and surgery delay, we used all available information from the patients presented in Table 1 and Online Resource 2 (age, sex, BMI, CCI, type of fracture, type of surgery, surgery delay, year of surgery, other prescription medicine, and outcome data) and generated five imputed datasets. The presented adjusted RRs and HRs were calculated as the geometric mean of the RRs or HRs of the five datasets, with the corresponding CIs corrected for between- and within-imputation variation [18].

All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA). The study was approved by the Danish Data Protection Agency (Record no. 1-16-02-467-15). According to Danish law, registry-based studies do not require ethical approval.

Results

Patient characteristics

Among the 74,791 first time hip fracture patients, 29,792 patients (39.8%) were on antithrombotic therapy at admission; 1.4% were current users of NOAC, 5.6% were current users of VKA, and 32.9% were current users of antiplatelet drugs. Users of any antithrombotics were more likely to be male, to receive statin treatment, and had more comorbid conditions (Table 1 and Online Resource 2). Compared to non-users, current users of anticoagulant drugs (NOAC and VKA) experienced more often surgery delay, while current users of antiplatelets did not experience excess time to surgery. Apart from BMI (20.8% missing) and surgery delay (0.2% missing), data were complete for all variables.

Risk of RBC transfusion

Among all hip fracture patients, 45.3% received RBC transfusion within 7 days postsurgery (Table 2).

The adjusted RR of RBC transfusion was 1.07 (95% CI 1.01–1.14) for current users compared to non-users of NOAC. Among patients undergoing surgery within 24 h after hip fracture, the adjusted RR of RBC transfusion was 1.14 (95% CI 1.02–1.27) for current NOAC users compared with non-users (Table 3).

Treatment with VKA was not associated with increased risk of RBC transfusion, since the adjusted RR among current compared to non-VKA users was 1.00 (95% CI 0.95–1.05). For patients who underwent surgery within 24 h after hip fracture, the adjusted RR of RBC transfusion was also 1.00 (95% CI 0.94–1.07).

The analysis restricted to hip fracture patients with atrial fibrillation or flutter confirmed the findings of no increased risk of transfusion among current users of NOAC and VKA (Table 6).

Table 1 Patient characteristics and surgery-related factors of all hip fracture patients according to antithrombotic treatment

	All patients	Users of NOACs[a]			Users of VKAs[b]			Users of antiplatelets		
		Non-users	Former	Current	Non-users	Former	Current	Non-users	Former	Current
	N (%)	*N* (%)	*N* (%)	*N* (%)	*N* (%)	*N* (%)	*N* (%)	*N* (%)	*N* (%)	*N* (%)
Total	74,791	73,507	221	1063	68,948	1681	4162	43,245	6979	24,567
	(100.0)	(98.3)	(0.3)	(1.4)	(92.2)	(2.2)	(5.6)	(57.8)	(9.3)	(32.8)
Age										
65–74	14,411	14,221	38	152	13,533	231	647	9575	1158	3678
	(19.3)	(19.3)	(17.2)	(14.3)	(19.6)	(13.7)	(15.5)	(22.1)	(16.6)	(15.0)
75–84	28,750	28,266	94	390	26,157	730	1863	16,455	2752	9543
	(38.4)	(38.5)	(42.5)	(36.7)	(37.9)	(43.4)	(44.8)	(38.1)	(39.4)	(38.8)
85+	31,630	31,020	89	521	29,258	720	1652	17,215	3069	11,346
	(42.3)	(42.2)	(40.3)	(49.0)	(42.4)	(42.8)	(39.7)	(39.8)	(44.0)	(46.2)
Sex										
Female	53,359	52,522	142	695	49,784	1062	2513	31,815	4735	16,809
	(71.3)	(71.5)	(64.3)	(65.4)	(72.2)	(63.2)	(60.4)	(73.6)	(67.8)	(68.4)
Male	21,432	20,985	79	368	19,164	619	1649	11,430	2244	7758
	(28.7)	(28.5)	(35.7)	(34.6)	(27.8)	(36.8)	(39.6)	(26.4)	(32.2)	(31.6)
CCI score[c]										
0	30,111	29,846	44	221	28,775	339	997	22,189	1958	5964
	(40.3)	(40.6)	(19.9)	(20.8)	(41.7)	(20.2)	(24.0)	(51.3)	(28.1)	(24.3)
1–2	30,251	29,638	105	508	27,619	746	1886	15,218	3045	11,988
	(40.4)	(40.3)	(47.5)	(47.8)	(40.1)	(44.4)	(45.3)	(35.2)	(43.6)	(48.8)
3 ≤	1442	14,023	72	334	12,554	596	1279	5838	1976	6615
	(19.3)	(19.1)	(32.6)	(31.4)	(18.2)	(35.5)	(30.7)	(13.5)	(28.3)	(26.9)
BMI[d]										
No data	15,552	15,315	45	192	14,440	347	765	8863	1417	5272
	(20.8)	(20.8)	(20.4)	(18.1)	(20.9)	(20.6)	(18.4)	(20.5)	(20.3)	(21.5)
Underweight	6455	6360	12	83	6113	123	219	3984	589	1882
	(8.6)	(8.7)	(5.4)	(7.8)	(8.9)	(7.3)	(5.3)	(9.2)	(8.4)	(7.7)
Normal	33,987	33,408	95	484	31,484	739	1764	19,965	3156	10,866
	(45.4)	(45.4)	(43.0)	(45.5)	(45.7)	(44.0)	(42.4)	(46.2)	(45.2)	(44.2)
Overweight	14,691	14,409	50	232	13,300	358	1033	8178	1403	5110
	(19.6)	(19.6)	(22.6)	(21.8)	(19.3)	(21.3)	(24.8)	(18.9)	(20.1)	(20.8)
Obese	4106	4015	19	72	3611	114	381	2255	414	1437
	(5.5)	(5.5)	(8.6)	(6.8)	(5.2)	(6.8)	(9.2)	(5.2)	(5.9)	(5.8)
Type of fracture										
Femoral neck	39,605	38,935	111	559	36,485	916	2204	23,062	3628	12,915
	(53.0)	(53.0)	(50.2)	(52.6)	(52.9)	(54.5)	(53.0)	(53.3)	(52.0)	(52.6)
Per- or sub-trochanteric	35,186	34,572	110	504	32,463	765	1958	20,183	3351	11,652
	(47.0)	(47.0)	(49.8)	(47.4)	47.1)	(45.5)	(47.0)	(46.7)	(48.0)	(47.4)
Surgery delay (hours)										
No data	171	171	0	0	154	5	12	106	19	46
	(0.2)	(0.2)	(0.0)	(0.0)	(0.2)	(0.3)	(0.3)	(0.2)	(0.3)	(0.2)
< 24	45,027	44,438	120	469	42,694	763	1570	26,132	4065	14,830
	(60.2)	(60.5)	(54.3)	(44.1)	(61.9)	(45.4)	(37.7)	(60.4)	(58.2)	(60.4)
24–36	13,654	13,430	38	186	12,453	315	886	7788	1282	4584
	(18.3)	(18.3)	(17.2)	(17.5)	(18.1)	(18.7)	(21.3)	(18.0)	(18.4)	(18.7)
> 36	15,939	15,468	63	408	13,647	598	1694	9219	1613	5107
	(21.3)	(21.0)	(28.5)	(38.4)	(19.8)	(35.6)	(40.7)	(21.3)	(23.1)	(20.8)

Underweight if BMI < 18.5 kg/m2, normal weight if BMI 18.5–24.9 kg/m2, overweight if BMI 25–29.9 kg/m2, and obese if BMI ≥ 30 kg/m2

[a] *NOACs* non-vitamin K antagonist oral anticoagulants

[b] *VKAs* vitamin K antagonists

[c] *CCI score* Charlson comorbidity index score

[d] *BMI* body mass index

The adjusted RR for RBC transfusion was 1.15 (95% CI 1.12–1.18) for antiplatelet users and 1.13 (95% CI 1.10–1.16) for former antiplatelet users compared to non-users. Among patients who experienced > 36 h surgery-delay, the adjusted RR among users of antiplatelets compared to non-users was 1.08 (95% CI 1.04–1.11).

Table 2 Cumulative incidence and relative risk (RR) with 95% confidence interval (95% CI) for red blood cell transfusion within 7 days after surgery according to antithrombotic therapy

	Transfusion (%)	Complete case method		Multiple imputation method[a]
		Crude RR (95% CI)	Adjusted[b] RR (95% CI)	Adjusted[b] RR (95% CI)
NOAC[c]				
Non-users	45.4 (45.05–45.7)	Reference	Reference	Reference
Former users	40.7 (34.2–47.1)	0.90 (0.79–1.02)	1.00 (0.85–1.18)	0.99 (0.86–1.15)
Current users	43.0 (40.0–45.9)	0.95 (0.87–1.03)	1.07 (1.00–1.14)	1.07 (1.01–1.14)
Vitamin K antagonists				
Non-users	45.4 (45.0–45.7)	Reference	Reference	Reference
Former users	45.7 (43.3–48.1)	1.01 (0.95–1.07)	0.95 (0.90–1.01)	0.97 (0.91–1.03)
Current users	44.5 (43.0–46.0)	0.98 (0.94–1.03)	0.99 (0.95–1.04)	1.00 (0.95–1.05)
Antiplatelets				
Non-users	41.0 (40.6–41.5)	Reference	Reference	Reference
Former users	49.1 (48.0–50.3)	1.20 (1.16–1.23)	1.13 (1.10–1.17)	1.13 (1.10–1.16)
Current users	51.8 (51.2–52.4)	1.26 (1.23–1.30)	1.16 (1.12–1.20)	1.15 (1.12–1.18)

[a] To impute the data, we used all available information from the patients presented in Table 1 and Online Resource 2

[b] Adjustments were made for age, sex, body mass index, Charlson comorbidity index score, type of fracture, surgery delay, year of surgery, and other prescription medication (non-steroidal anti-inflammatory drugs (NSAIDs), selective serotonin reuptake inhibitors (SSRIs), corticosteroids, statins and antibiotics)

[c] *NOAC* non-vitamin K antagonist oral anticoagulant

Table 3 Adjusted relative risk (RR) with 95% confidence interval (95% CI) for red blood cell transfusion within 7 days after surgery according to antithrombotic therapy. Results stratified by surgery delay

	Surgery delay		
	< 24 h	24–36 h	> 36 h
NOAC[a]			
Non-users	Reference	Reference	Reference
Former users	0.98 (0.78–1.24)	1.36 (0.93–1.97)	0.72 (0.38–1.37)
Current users	1.14 (1.02–1.27)	1.03 (0.92–1.16)	0.96 (0.87–1.06)
Vitamin K antagonists			
Non-users	Reference	Reference	Reference
Former users	0.96 (0.87–1.05)	1.00 (0.88–1.13)	0.92 (0.85–1.01)
Current users	1.00 (0.94–1.07)	0.96 (0.89–1.04)	0.97 (0.92–1.04)
Antiplatelets			
Non-users	Reference	Reference	Reference
Former users	1.12 (1.08–1.16)	1.10 (1.03–1.18)	1.13 (1.09–1.18)
Current users	1.16 (1.12–1.20)	1.15 (1.10–1.20)	1.08 (1.04–1.11)

Adjustments were made for age, sex, body mass index, Charlson comorbidity index score, type of fracture, surgery delay, year of surgery and other prescription medication (non-steroidal anti-inflammatory drugs (NSAIDs), selective serotonin reuptake inhibitors (SSRIs), corticosteroids, statins and antibiotics)

Results shown for multiple imputation model. To impute the data, we used all available information from the patients presented in Table 1 and Online Resource 2

[a] *NOAC* non-vitamin K antagonist oral anticoagulant

Mortality risk

At 30 days after hip fracture surgery, 10.6% of all patients had died. Mortality within 30 days of surgery was 11.3% for patients dispensed NOAC, 10.8% for those dispensed VKA, and 12.7% for those dispensed antiplatelets.

The adjusted HR of death within 30 days was 0.88 (95% CI 0.75–1.03) for current users of NOAC compared to non-users (Table 4). For patients who experienced > 36 h surgery delay, the adjusted HR for 30-day mortality was 0.70 (95% CI 0.54–0.91) for NOAC users compared to non-users (Table 5). Among patients with atrial fibrillation or atrial flutter, the adjusted HR for 30-day mortality was 0.59 (95% CI 0.48–0.73) for NOAC users compared with non-users (Table 6).

Users of VKA had an adjusted HR of 30-day mortality of 0.91 (95% CI 0.82–1.01) compared to non-users. When patients underwent surgery within 24 h after hip fracture, current users of VKA did not have an excess 30-day mortality, as the adjusted HR was 1.04 (95% CI 0.91–1.18) for VKA users compared to non-users. For patients with atrial fibrillation or atrial flutter, the adjusted HR for 30-days mortality was 0.65 (95% CI 0.56–0.76) for VKA users compared with non-users.

Antiplatelet users had increased risk of 30-day mortality, with an adjusted HR of 1.18 (95% CI 1.14–1.23) compared to non-users. The increased mortality was consistent when stratifying for time to surgery. For antiplatelet users compared to

Table 4 Hazard ratio (HR) with 95% confidence interval (95% CI) for 30-day mortality according to antithrombotic therapy

	Death (%)	Complete case method		Multiple imputation method[a]
		Crude HR (95% CI)	Adjusted[b] HR (95% CI)	Adjusted[b] HR (95% CI)
NOAC[c]				
Non-users	10.5	Reference	Reference	Reference
Former users	10.9	1.03 (0.80–1.33)	0.84 (0.58–1.21)	0.88 (0.69–1.13)
Current users	11.3	1.07 (0.90–1.29)	0.90 (0.73–1.11)	0.88 (0.75–1.03)
Vitamin K antagonists				
Non-users	10.5	Reference	Reference	Reference
Former users	14.1	1.38 (1.22–1.57)	1.08 (0.91–1.27)	1.10 (0.96–1.24)
Current users	10.8	1.04 (0.93–1.15)	0.96 (0.83–1.10)	0.91 (0.82–1.01)
Antiplatelets				
Non-users	9.2	Reference	Reference	Reference
Former users	11.8	1.31 (1.20–1.43)	1.10 (0.99–1.21)	1.09 (1.00–1.17)
Current users	12.7	1.42 (1.36–1.47)	1.21 (1.15–1.28)	1.18 (1.14–1.23)

[a] To impute the data, we used all available information from the patients presented in Table 1 and Online Resource 2

[b] Adjustments were made for age, sex, body mass index, Charlson comorbidity index score, type of fracture, surgery delay, year of surgery, and other prescription medication (non-steroidal anti-inflammatory drugs (NSAIDs), selective serotonin reuptake inhibitors (SSRIs), corticosteroids, statins and antibiotics)

[c] *NOAC* non-vitamin K antagonist oral anticoagulant

Table 5 Adjusted hazard ratio (HR) with 95% confidence interval (95% CI) for 30-day mortality according to antithrombotic therapy. Results stratified by surgery delay

	Surgery delay		
	< 24 h	24–36 h	> 36 h
NOAC[a]			
Non-users	Reference	Reference	Reference
Former users	1.23 (0.89–1.69)	0.21 (0.03–1.61)	0.79 (0.36–1.73)
Current users	1.08 (0.83–1.39)	0.95 (0.69–1.30)	0.70 (0.54–0.91)
Vitamin K antagonists			
Non-users	Reference	Reference	Reference
Former users	1.12 (0.93–1.34)	1.29 (0.92–1.80)	1.14 (0.92–1.42)
Current users	1.04 (0.91–1.18)	1.10 (0.90–1.34)	0.87 (0.74–1.03)
Antiplatelets			
Non-users	Reference	Reference	Reference
Former users	1.11 (0.99–1.23)	1.18 (1.05–1.34)	1.07 (0.91–1.27)
Current users	1.20 (1.13–1.27)	1.36 (1.25–1.49)	1.11 (0.98–1.25)

Adjustments were made for age, sex, body mass index, Charlson comorbidity index score, type of fracture, surgery delay, year of surgery, and other prescription medication (non-steroidal anti-inflammatory drugs (NSAIDs), selective serotonin reuptake inhibitors (SSRIs), corticosteroids, statins and antibiotics)

Results shown for multiple imputation model. To impute the data, we used all available information from the patients presented in Table 1 and Online Resource 2

[a] *NOAC* non-vitamin K antagonist oral anticoagulant

non-users, the adjusted HR was 1.02 (95% CI 0.94–1.10) among patients with atrial fibrillation or atrial flutter.

Discussion

This study found that current NOAC users had a slightly increased risk of RBC transfusion, whereas current VKA users had similar risk of RBC transfusion as non-users. We found no evidence of increased 30-day mortality among hip fracture patients who are current NOAC or VKA users compared to non-users. However, among hip fracture patients admitted on antiplatelets, we found a 15% relative increase in RBC transfusion risk and 18% relative increase in mortality compared with non-users. An early surgery within 24 h was associated with an increased risk of transfusion but had no association with mortality among NOAC users.

To our knowledge, this is the first nationwide study on the impact of long-term preoperative antithrombotic treatment including NOAC on bleeding measured with transfusion and mortality among hip fracture patients. However, in accordance with our findings among patients with atrial-fibrillation or flutter, a recent population-based study by Ge et al. reported no association between use of oral anticoagulants and bleeding or 30-day mortality among patients with atrial fibrillation undergoing urgent major non-cardiac surgery including hip fracture surgery [19]. Small-scale studies support our findings of no difference in transfusion or 30-day mortality among hip

Table 6 Results restricted to hip fracture patients with atrial fibrillation or flutter. Adjusted relative risk for red blood cell transfusion within 7 days after surgery and adjusted hazard ratio for 30-day mortality according to antithrombotic therapy

	Adjusted relative risk (RR) with 95% confidence interval (95% CI) for red blood cell transfusion within7 days after surgery	Adjusted hazard ratio (HR) with 95% confidence interval (95% CI) for 30-day mortality
NOAC[a]		
Non-users	Reference	Reference
Former users	0.88 (0.75–1.03)	0.59 (0.43–0.82)
Current users	0.97 (0.90–1.04)	0.59 (0.48–0.73)
Vitamin K antagonists		
Non-users	Reference	Reference
Former users	0.93 (0.87–1.00)	0.82 (0.69–0.98)
Current users	0.92 (0.87–0.97)	0.65 (0.56–0.76)
Antiplatelets		
Non-users	Reference	Reference
Former users	1.08 (1.03–1.15)	0.95 (0.81–1.13)
Current users	1.16 (1.12–1.20)	1.02 (0.94–1.10)

Adjustments were made for age, sex, body mass index, Charlson comorbidity index score, type of fracture, surgery delay, year of surgery, and other prescription medication (non-steroidal anti-inflammatory drugs (NSAIDs), selective serotonin reuptake inhibitors (SSRIs), corticosteroids, statins and antibiotics). Results shown for multiple imputation model. To impute the data, we used all available information from the patients presented in Table 1 and Online Resource 2

[a] *NOAC* non-vitamin K antagonist oral anticoagulant

fracture patients in general who were users of warfarin compared to non-users [20, 21]. In contrast, a recent register-based cohort study conducted in the UK including 2036 hip fracture patients found an increase in 1-year mortality among patients admitted on warfarin compared to non-users [22]. In our study, antiplatelet users consisted of patients treated with either platelet aggregation inhibitors or acetylsalicylic acid. A recent meta-analysis also showed preoperative clopidogrel treatment to be associated with a small increase in transfusion risk among hip fracture patients [23]. In additional agreement with our findings, small-scale studies indicate an increase in blood transfusion risk and 1-year mortality among hip fracture patients treated with acetylsalicylic acid [24–26].

When undergoing early surgical intervention to enable early mobilization and reduce mortality, hip fracture patients on antithrombotic therapy may experience prolonged bleeding time secondary to the drug pharmacokinetics. However, the increased risk of bleeding must be balanced by the potential benefits of early surgery. Guidelines recommend that antithrombotics are discontinued prior to invasive procedures; however, recommendation becomes difficult when patients undergo non-planned urgent hip fracture surgery. In this study, we found that twice as many current users of NOAC or VKA experienced surgery delay > 36 h compared to non-users. However, despite early surgery, the RBC transfusion and 30-day mortality risks were similar between anticoagulated (VKA and NOAC) and non-anticoagulated patients. This suggests that even early hip fracture surgery may be safe among anticoagulated patients. Surprisingly, we also found that patients on NOAC had a lower mortality risk compared to non-users of NOAC when surgery was delayed > 36 h. The lower mortality may potentially be due to enhanced attention and more intensive perioperative observation of NOAC patients awaiting surgery.

Our results also suggest that even when hip fracture surgery was delayed more than 36 h, and drug effects may have diminished, both the risk of RBC transfusion and 30-day mortality remained higher for patients on antiplatelet drugs. Thus, delaying surgery among hip fracture patients on antiplatelet therapy did not appear to be associated with better perioperative outcomes.

Antithrombotic therapy is commonly used to prevent cardiovascular events in patients with atrial fibrillation and flutter. Thus, the finding of excess 30-day mortality among patients on antiplatelet therapy may be caused by confounding by indication. Accordingly, Ge et al. suggested atrial fibrillation to be an independent predictor of perioperative mortality in urgent non-cardiac surgery which was not mediated by oral anticoagulant therapy [19]. In our analysis restricted to patients with atrial fibrillation or atrial flutter, we found no association between antiplatelet drug use and 30-day mortality risk. Hence, underlying atrial fibrillation or atrial flutter appeared to be a potential effect modifier in the association between use of antiplatelet drugs and postoperative outcome, either directly or as a proxy marker of other cardiovascular illnesses. In addition, the excess mortality among patients on antiplatelets drug may be mediated by transfusion, as antiplatelet users had increased risk of RBC transfusion. Studies indicate that transfusion may have fatal outcome [27–29]; however, a recent Cochrane meta-analysis showed the same mortality risk when hip fracture patients were treated with restrictive or liberal transfusion policy [30]. As our mortality outcome was 30-day mortality by all causes, this study cannot verify or exclude the possibility of complications to transfusion as contributors to mortality. In conclusion, further research should focus on the mechanisms linking antiplatelets with an adverse postoperative outcome in hip fracture patients.

Strengths and limitations

This study was based on unselected prospectively collected data from nationwide DMHFR with high validity [12]. Data on blood transfusions was directly drawn from the blood bank

systems in which registration of all blood products is mandatory according to Danish law [31]. The Danish National Patient Registry provides full coverage of hospitals and ensures complete follow-up [32].

However, limitations of this study should be noted. As antithrombotic drug exposure was defined by drug redemption at general pharmacies, we were unable to ascertain drug indication, compliance, and treatment adherence. Additionally, we did not capture medication administered during hospitalization including bridging therapy, perioperative pharmacological venous thromboembolism prophylaxis, and reversal agents. We could not ascertain the date of antithrombotic discontinuation prior to surgery. In addition, although we adjusted for several covariates, there is always the risk of unmeasured confounding. Furthermore, we lacked information on the severity of comorbid diseases included in the CCI score, which may have introduced residual confounding. We used multiple imputation to handle missing data on BMI and surgery delay. Due to prospective registration of patient data, any lack of reporting to the DMHFR is probably independent of both BMI level and time to surgery.

In this article, we use RBC transfusion within the first week of a hip fracture as a surrogate for perioperative blood loss. The time frame of 7 days supports this premise, but information about potential active bleeding or anemia is missing.

Although this study contributes to the debate regarding safety among hip fracture patients treated with antithrombotic drugs, further work is required to form a future clinical practice particularly for hip fracture patients admitted on newer NOAC treatment. Also, we found preoperative antiplatelet drugs to be associated with increased risk of blood transfusion and mortality, why clinicians should ensure this group of patients receives an appropriate level of care. However, further studies are needed to understand the nature of these associations.

Conclusions

Hip fracture patients preoperatively treated with NOAC can safely be operated as there is only slightly increased risk of RBC transfusion but not of 30-day mortality. Users of VKA preoperatively had similar risk of RBC transfusion and mortality as VKA non-users. Preoperative use of antiplatelet drugs among hip fracture patients was associated with significantly increased risk of RBC transfusion and 30-day all-cause mortality. However, delaying hip fracture surgery among patients on antiplatelet therapy did not significantly improve the survival, while immediate surgery may still be considered the best treatment strategy.

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Compliance with ethical standards

This article does not contain any studies with human participants or animals performed by any of the authors. The study was approved by the Danish Data Protection Agency (record no. 1-16-02-467-15), and no patient consent was needed as detail has been removed from the case description to ensure anonymity. According to the Danish law, registry-based studies do not require ethical approval.

Conflicts of interest Cecilie Daugaard, Alma B. Pedersen, and Nickolaj R. Kristensen declare that they have no conflict of interest. Søren P. Johnsen has, outside the submitted work, received speaker honorarium from BMS and Pfizer; participated in board meetings for BMS, Pfizer, and Bayer; and received previous research funding from BMS and Pfizer.

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