Received: 5 Apr 2022 | **Accepted:** 11 May 2022
DOI: 10.54005/geneltip.1097997

ORIGINAL ARTICLE

The Effect of Long-Term Antithrombotic Therapies on Perioperative Morbidity and Mortality in Elderly Patients Underwent Hip Fracture Surgery

Kalça Kırığı Cerrahisi Geçiren Yaşlı Hastalarda Uzun Dönem Antitrombotik Tedavilerin Perioperatif Morbidite ve Mortalite Üzerine Etkisi

[1]Güzin Ceran, [2]Ayşe Lafçı, [2]İsmail Aytaç, [3]Gazi Akkurt, [2]Nermin Göğüş, [2]Derya Gökçınar

[1]Kırşehir Training and Research Hospital, Department of Anesthesiology and Reanimation, Kırşehir/Turkey
[2]Ankara City Hospital, Department of Anesthesiology and Reanimation Ankara/Turkey
[3]Etlik Zübeyde Hanım Gynecology Hospital, Department of Anesthesiology and Reanimation, Ankara/Turkey

Correspondence

Ayşe Lafçı, Ankara City Hospital, Department of Anesthesiology and Reanimation Ankara/Turkey

E-Mail: ayselafci971@gmail.com

How to cite ?

Ceran G, Lafçı A, Aytaç İ, Akkurt G, Göğüş N, Gokcinar D. The effect of long-term antithrombotic therapies on perioperative morbidity and mortality in elderly patients undergoing hip fracture surgery . Genel Tıp Derg.2022; 32(3): 229-237

ABSTRACT

Objective: Ischemic complications or massive bleeding are important perioperative complications in elderly patients using antithrombotic drugs. The need for blood product replacement, transfusion-related complications, prolonged stay in hospital and intensive care unit, and high mortality in the perioperative period can be seen. The aim of this study was to investigate the effects of long-term different antithrombotic therapies on morbidity and mortality in elderly patients underwent surgery for hip fracture.
Materials and Methods: This retrospective cohort study included patients aged 65 years and older who underwent surgery for hip fracture between 2015 and 2018. Patients with no antithrombotic treatment (Group NonAT), warfarin (Group Warfarin), novel oral anticoagulants (Group NOACs), and dual antiplatelet therapy (Group DAPT) were compared in terms of major bleeding, deep venous thrombosis (DVT) and pulmonary thromboembolism (PTE) complications, length of hospital stay (LOS), ICU admission, and 30-day mortality.
Results: The study included 668 patients; demographic data in Group NonAT(n=442), Group Warfarin (n=59), Group NOACs (n=30) and Group DAPT (n=137) were similar. Major bleeding and red blood cell transfusion did not differ statistically between all groups (p>0.05). The preoperative and postoperative hemoglobin (Hb) values of the patients were not statistically different between the groups (p>0.05). Mortality, only there was statistically significantly higher in the dual antiplatelet group than as the nonuser group (p<0.05). In terms of survival, multivariate analysis showed no difference between the groups (p>0.05). However survival was statistically significantly different (p<0.05) in terms of the PTE and admission to ICU. Kaplan-Meier survival analysis showed that patients in the group NonAT have longer survival period than patients in the group warfarin, group NOACs, and group DAPT.
Conclusion: In this study, we found that the effects of antithrombotic drug classes (warfarin, new oral anticoagulants or dual antiplatelet therapy) on mortality were not different. Mortality rate was higher only in the dual antiplatelet group than in the no drug group. It is important to discontinue these drugs at the timing according to their half-lives and elimination times. Effective bridging therapy should be applied in the perioperative period. Thus, the risk of major bleeding or complications of DVT and PTE can be avoided. New bridging strategies should be researched in patients using antiplatelets.

Keywords: Dual antiplatelets; elderly patient; hip fracture; novel oral anticoagulants; warfarin.

ÖZ

Amaç: Antitrombotik ilaç kullanan yaşlı hastalarda, iskemik komplikasyonlar veya massif kanama önemli perioperatif komplikasyonlardır. Kan ürünü replasmanı ihtiyacı, transfüzyona bağlı komplikasyonlar, hastanede ve yoğun bakım ünitesinde (YBÜ) kalış süresinin uzaması ve perioperatif dönemde yüksek mortalite görülebilmektedir. Bu çalışmanın amacı, kalça kırığı nedeniyle ameliya tedilen yaşlı hastalarda uzun surely farklı antitrombotik tedavilerin morbidite ve mortalite üzerine etkilerini araştırmaktır.
Gereç ve Yöntem: Bu retrospektif kohort çalışmasına 2015 ve 2018 yılları arasında kalça kırığı nedeniyle ameliyat edilen 65 yaş ve üstü hastalar dahil edilmiştir. Antitrombotik tedavi almayan hastalar (GrupNonAT), varfarin (Grup Warfarin), yeni oral antikoagülanlar (GrupNOAC'ler) veya ikili antiplatelet tedavi (Grup DAPT) alan hasta grupları major kanama, derin ven trombozu (DVT) ve pulmoner tromboembolizm (PTE) komplikasyonları, hastanede kalış süresi (HKS), yoğun bakım ünitesine yatış ve 30 günlük mortalite açısından karşılaştırıldı.
Bulgular: Çalışmaya 668 hasta dahil edildi; GrupNonAT(n=442), Grup Warfarin (n=59), Grup NOACs (n=30) veGrup DAPT(n=137) hasta demografik verileri benzerdi. Majör kanama ve kırmızı kan hücresi transfüzyonu açısından tüm gruplar arasında istatistiksel olarak fark yoktu (p>0.05). Hastaların ameliyat öncesi ve sonrası hemoglobin (Hb) değerleri gruplar arasında istatistiksel olarak farklı değildi (p>0.05). Ölüm oranı, sadece ikili antiplatelet grubunda, hiç ilaç kullanmayan gruba gore istatistiksel olarak anlamlı derecede yüksekti (p<0.05).Sağkalım açısından multivariate analysis gruplar arasında fark göstermedi (p>0.05).Ancak sağkalım, PTE ve YBÜ'ye yatış açısından istatistiksel olarak anlamlı farklılık gösterdi (p<0.05). Kaplan-Meier yaşam analizi, NonAT grubundaki hastaların varfarin, grup NOACs veya Grup DAPT'deki hastalardan daha uzun hayatta kalma sürelerine sahip olduğunu gösterdi.
Sonuç: Bu çalışmada, antitrombotik ilaç sınıflarının (varfarin, yeni oral antikoagülanlar veya ikili antiplatelet tedavi) mortalite üzerindeki etkilerinin farklı olmadığını bulduk. Ölüm oranı, sadece ikili antiplatelet grubunda, hiç ilaç kullanmayan gruba gore daha yüksekti. Bu ilaçların yarılanma ömürlerine ve eliminasyon sürelerine gore preoperative kesilmesi önemlidir. Perioperatif dönemde etkin köprüleme tedavisi uygulanmalıdır. Böylece major kanama veya DVT ve PTE komplikasyonları riskinden kaçınılabilir. Antiplatelet kullanan hastalarda yeni köprüleme stratejileri araştırılmalıdır.

Anahtar kelimeler: Dual antiplateletler; kalçakırığı; varfarin; yaşlı hasta; yeni oral antikoagülanlar.

Introduction

Hip fracture in elderly patients is a health problem with high morbidity and mortality. Studies have found that mortality in hip fractures within 30 days is 5-13% and 1-year mortality is 22-30% (1). The incidence of coronary artery disease, heart failure, atrial fibrillation and stroke increases significantly in elderly patients. Cardio-cerebrovascular system diseases such as stroke and cardiac diseases cause morbidity and mortality (2,3). In order to prevent the development of thrombosis and embolism, many patients use warfarin (vitamin K antagonist), antiplatelet drugs (acetylsalicylic acid, clopidogrel, prasugrel, ticagrelor), or novel oral anticoagulant drugs (dabigatran, rivaroxaban, apixaban, edoxaban, betrixaban) known as antithrombotic drugs (4). In patients using antithrombotic drugs, ischemic complications or perioperative massive bleeding, the need for blood product replacement, complications related to transfusion, prolonged hospitalisation and intensive care unit stay, and high mortality can be seen in the perioperative period. Preoperative discontinuation and bridging treatment of patients using antithrombotic drugs should be evaluated individually for each patient.

In this study, the morbidity and mortality rates of elderly patients who underwent surgery for hip fracture, patients who did not receive antithrombotic therapy, and patients who used antithrombotic drugs for at least one year before surgery were investigated. Thus, it was aimed to predict complications that may occur in the perioperative period, to determine the necessary preoperative preparation and what should be considered to be able to reduce mortality in these patients.

Materials-Methods

Study Design and Setting

A retrospective, single-center cohort study was conducted between June 1, 2015 and June 1, 2018. The study patients included were those aged ≥65 years who underwent surgery for hip fracture in the orthopedic clinic of a tertiary hospital.

Data Collection

Data of age, gender, American Society of Anesthesiologists (ASA) score, anesthesia technique, comorbidities, modified Charlson Comorbidity Index (mCCI), major bleeding (the need for ≥2 units of red blood cell (RBC) or a drop of ≥2g/dL in postoperative hemoglobin value compared to the preoperative hemoglobin value) (5), red blood cell transfusion, preoperative and postoperative hemoglobin (Hb) values, deep venous thrombosis (DVT) and pulmonary thromboembolism (PTE) complications, length of hospital stay (LOS), ICU admission, and 30-day mortality. The scores of mCCI were calculated for each patient were retrieved from the patient files (6).

Perioperative management of antithrombotic therapy

In patients had antithrombotic drugs, antithrombotic therapy was discontinued before surgery and bridging with low molecular weight heparin was started. Antithrombotic therapy discontinuation and initiation times were adjusted according to the half-life of each drug and the hepatic and renal functions of the patients. As soon as patients arrive in the emergency room the antithrombotic drugs were discontinued and surgery was delayed for 3-5 times the half-life of drugs.

Inclusion Criteria

The patients included were those aged ≥65 years who underwent surgery for hip fracture in the orthopedic clinic of a tertiary hospital between June 1, 2015 and June 1, 2018.

Exclusion Criteria

Patients who underwent early surgery without waiting for the half-life of antithrombotic drugs were excluded from the study, as it was considered to affect the amount of bleeding and anesthesia method.

Data Analysis

The patients were divided into four groups as those with no antithrombotic treatment (Group NonAT), and patients taking warfarin (Group Warfarin), novel oral anticoagulants (Group NOACs), and dual antiplatelet therapy (Group DAPT). The groups were compared and statistically significant differences were investigated.

Data analysis was performed using IBM SPSS 25.0 software (IBM Corpn., Armonk, NY, USA). While evaluating the study data, in addition to descriptive statistical methods (frequency, percentage, mean, standard deviation, median, min-max, IQR), the Chi-Square ($\chi 2$) test was used to compare qualitative data. Pairwise comparisons were made. The conformity of the data to normal distribution was evaluated using the Kolmogorov-Smirnow test, skewness-kurtosis, and graphical methods (histogram, Q-Q Plot, Stem and Leaf, Boxplot). In the evaluation of the quantitative data showing normal distribution, the Independent Samples t-test was applied and One-Way Anova, and the Paired Samples t-test were used to compare repeated measures. The Mann-Whitney U test and the Kruskal-Wallis test were used for comparisons between groups of data that did not show normal distribution. In cases where there was a difference in multiple comparisons, the post-hoc Tukey HSD test was used to find the source of the difference. Binary Logistic Regression test was used to determine risk ratios, Kaplan-Meier, Log Rank and Cox Regression tests were used for survival and survival analysis. The level of statistical significance was accepted as p=0.05.

Power analysis was performed using G*Power 3.1.9.4 statistical package program. With the group sizes of Group NonAT=442, Group Warfarin=59, Group

NOACs=30, and Group DAPT=137, the results showed p=0.05, effect Size (f)=0.15, and power=92%.

Results

Characteristics of the Patient Groups

The study included 668 patients; 442 in Group NonAT, 59 in Group Warfarin, 30 in Group NOACs, and 137 in Group DAPT. Gender and age were not statistically different between the groups. ASA and anesthesia method were statistically different between Group NonAT and the other groups ($p<0.05$). Patients in Groups warfarin, NOACs and DAPT had higher ASA scores and more general anesthesia procedures. Comorbidities and mCCI were statistically significantly lower in Group NonAT, but there was no statistically significant difference between Group warfarin, NOACs and DAPT. (Table 1)

Comparisons of Major Bleeding, RBC Transfusion and Hb values

Major bleeding and red blood cell transfusion did not differ statistically between all groups. ($p>0.05$) (Table 2) The preoperative and postoperative Hb values of the patients were not statistically different between the groups ($p>0.05$). (Table 3)

LOS and Outcomes

The rates of DVT and PTE were not different between all the groups. The ICU admission ($p <0.001$) and length of hospital stay ($p <0.001$) were statistically different between Group NonAT and the other groups ($p<0.05$). The ICU admission rate was lower (16.7%) in Group NonAT patients, and there was no difference between the other groups. The mortality rate was statistically significantly different between Group NonAT and only Group DAPT ($p<0.05$); the mortality rate was highest (8.8%) in Group DAPT. (Table 4)

Comparison of Outcomes of Alive and Deceased Patients

It was found that patients who died were older, had higher ASA and mCCI values, higher rates of using dual antiplatelet, higher rates of PTE, and higher rates of stay at the ICU than alive. (Table 5)

To find risk factors associated with mortality logistic regression analysis was performed. Variables, with difference between alive and deceased patients in pairwise comparisons; Age, ASA, mCCI, antithrombotic used, PTE and ICU admission variables were included in the model and Backward Stepwise method was used in the analysis, and the model was terminated in the third step. In this model, approximately 59% of the dependent variable (Survival-Mortality) could be explained (Nagelkerke R2 = 0.589). According to this model, a statistically significant relationship was found between survival-mortality status and age, NonAT versus DAPT, PTE and admission ICU ($p<0.05$). Those who are older are approximately 1.2 times more likely to die than those who are not, those who use dual antiplatelet are approximately 6.2 times more likely than those who do not use antithrombotic drugs, those with PTE are approximately 146 times more frequent than those without, and those who are admitted in ICU are approximately 12 times more likely to die than those who do not. (Table 6)

Multivariate Analysis of Survival in Patients

There was no statistically significant difference between the antithrombotics used ($p>0.05$), while there was a statistically significant difference ($p<0.05$) between PTE, admitted to ICU and anesthesia types in terms of survival. (Table 7) Kaplan Meier survival curve according to antithrombotic drug use is shown in Figure 1.

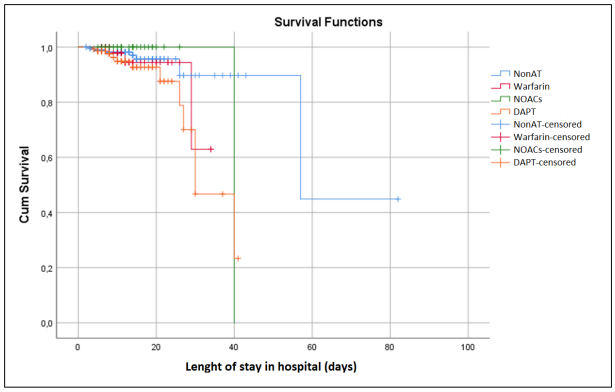

Figure 1. Kaplan-Meier curve shows that patients in the no antithrombotic treatment group (NonAT) have longer survival duration than patients in the warfarin group (Warfarin), novel oral anticoagulants group (NOACs), or dual antiplatelet therapy group (DAPT).

Cox Regression Analysis

Variables with difference between survival-mortality conditions in pairwise comparisons; Age, ASA, MCKI, Antithrombotic used, PTE and admitted to ICU variables were included in the model and the Backward Stepwise method was used in the analysis. According to this model, a statistically significant relationship was found between survival-mortality status and PTE ($p<0.05$). Those with PTE present an approximately 55 times higher risk of periodic death than those without. (Table 8) Kaplan-Meier curve shows comparison hazard function between patients without PTE vs patients with PTE. (Figure 2)

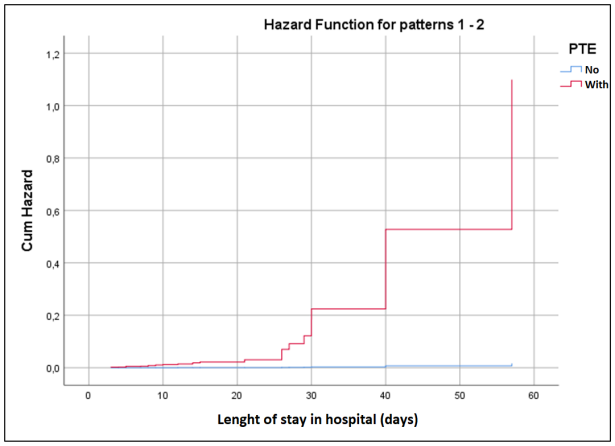

Figure 2. Kaplan-Meier curve shows comparison hazard function between patients without pulmonary thromboembolism (PTE) vs patients with PTE.

Table 1. Comparisons of the patient characteristics between groups

		Group NonAT (n=442)	Group Warfarin (n=59)	Group NOACs (n=30)	Group DAPT (n=137)	P-value	Difference	
Sex	Female	305 (69.0%)	44 (74.6%)	18 (60.0%)	81 (59.1%)		0.077[a]	--
	Male	137 (31.0%)	15 (25.4%)	12 (40.0%)	56 (40.9%)			
Age (Years)		79.2 ± 8.2	79.5 ± 8.2	82.2 ± 6.4	79.6 ± 7.1		0.244[b]	--
	<75	146 (33.0%)	17 (28.8%)	5 (16.7%)	33 (24.1%)		0.129 [a]	--
	75-84	162 (36.7%)	26 (44.1%)	11 (36.7%)	62 (45.3%)			
	≥85	134 (30.3%)	16 (27.1%)	14 (46.7%)	42 (30.7%)			
ASA	II	131 (29.6%)	7 (11.9%)	1 (3.3%)	13 (9.5%)		<0.001[a]	1 vs. 2-3-4
	III	248 (56.1%)	34 (57.6%)	21 (70.0%)	82 (59.9%)			
	IV	63 (14.3%)	18 (30.5%)	8 (26.7%)	42 (30.7%)			
Anesthesia Technique	General	85 (19.2%)	16 (27.1%)	9 (30.0%)	48 (35.0%)		<0.001[a]	1vs. 2-3-4
	Spinal	320 (72.4%)	32 (54.2%)	18 (60.0%)	73 (53.3%)			
	Peripheral Block	37 (8.4%)	11 (18.6%)	3 (10.0%)	16 (11.7%)			
Comorbidity	No	116 (26.2%)	--	--	--		<0.001[a]	1 vs 2-3-4
	Yes	326 (73.8%)	59 (100.0%)	30 (100.0%)	137 (100.0%)			
	Cardiac disease.	122 (27.6%)	23 (39.0%)	13 (43.3%)	47 (34.3%)			
	Respiratory disease.	16 (3.6%)	--	--	--			
	Cardiac disease. + Metabolic disease.	83 (18.8%)	14 (23.7%)	6 (20.0%)	27 (19.7%)			
	Cardiac disease. + Neurological disease.	45 (10.2%)	11 (18.6%)	2 (6.7%)	22 (16.1%)			
	Cardiac disease. + Renal failure.	35 (7.9%)	3 (5.1%)	5 (16.7%)	12 (8.8%)			
	Cardiac disease. + Neurological disease +Metabolic disease	10 (2.3%)	7 (11.9%)	2 (6.7%)	22 (16.1%)			
	Cardiac disease. + Metabolic disease. + Renal failure.	15 (3.4%)	1 (1.7%)	2 (6.7%)	7 (5.1%)			
mCCI	≤4	150 (33.9%)	6 (10.2%)	1 (3.3%)	4 (2.9%)		<0.001[a]	1 vs 2-3-4
	5 - 8	268 (60.6%)	48 (81.4%)	26 (86.7%)	100 (73.0%)			
	≥9	24 (5.4%)	5 (8.5%)	3 (10.0%)	33 (24.1%)			

1:Group NonAT; 2: Group Warfarin; 3: Group NOACs; 4: Group DAPT

[a]: Chi-Square Test (n / %); [b]: One-WayAnova (Mean ± SD)

mCCI: Modified Charlson Comorbidity Index

Table 2. Comparisons of major bleeding and red blood cell transfusion

		Group NonAT (n=442)	Group Warfarin (n=59)	Group NOACs (n=30)	Group DAPT (n=137)	P-value
Major Bleeding	No	81 (18.3%)	7 (11.9%)	3 (10.0%)	29 (21.2%)	0.287 [a]
	Yes	361 (81.7%)	52 (88.1%)	27 (90.0%)	108 (78.8%)	
RBC transfusion	No	117 (26.5%)	13 (22.0%)	4 (13.3%)	41 (29.9%)	0.251 [a]
	Yes	325 (73.5%)	46 (78.0%)	26 (86.7%)	96 (70.1%)	

RBC: Red Blood Cell;[a]: Chi-Square Test (n / %)

Table 3. Comparisons of preoperative and postoperative Hb values

	Group NonAT (n=442)	Group Warfarin (n=59)	Group NOACs (n=30)	Group DAPT (n=137)	P-value
Preoperative Hb	12.4 ± 1.7	12.0 ± 1.6	12.4 ± 1.8	12.0 ± 1.8	0.133 [a]
<10g/dL	29 (6.6%)	3 (5.1%)	3 (10.0%)	14 (10.2%)	0.420 [b]
≥10g/dL	413 (93.4%)	56 (94.9%)	27 (90.0%)	123 (89.8%)	
Postoperative Hb	9.9 ± 0.9	9.8 ± 0.9	10.1 ± 0.7	9.9 ± 0.9	0.389 [a]
<10g/dL	246 (55.7%)	36 (61.0%)	14 (46.7%)	78 (56.9%)	0.630 [b]
≥10g/dL	196 (44.3%)	23 (39.0%)	16 (53.3%)	59 (43.1%)	
P-value[c]	<0.001	<0.001	<0.001	<0.001	

a: One-Way Anova (Mean ± SD); b:Chi-Square Test (n / %); c: Paired Samples t Test

Table 4. Comparison of complications, ICU admission, length of hospital stay and mortality

		NonAT (n=442)	Warfarin (n=59)	NOACs (n=30)	DAPT (n=137)	P-value	Difference
DVT	No	439 (99.3%)	59 (100.0%)	30 (100.0%)	137 (100.0%)	0.673[a]	
	Yes	3 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		
PTE	No	432 (97.7%)	55 (93.2%)	30 (100.0%)	132 (96.4%)	0.168[a]	
	Yes	10 (2.3%)	4 (6.8%)	0 (0.0%)	5 (3.6%)		
ICU Admission	No	368 (83.3%)	42 (71.2%)	19 (63.3%)	94 (68.6%)	<0.001[a]	1 vs 2-3-4
	Yes	74 (16.7%)	17 (28.8%)	11 (36.7%)	43 (31.4%)		
Length of Hospital stay (days)		9.0 (7.0 – 13.0)	11.0 (9.0 – 14.0)	12.0 (8.8 – 17.3)	9.0 (7.0 – 14.5)	<0.001[b]	1 vs 2-3
Discharge		431 (97.5%)	56 (94.9%)	29 (96.7%)	125 (91.2%)	0.013[a]	1 vs 4
Exitus		11 (2.5%)	3 (5.1%)	1 (3.3%)	12 (8.8%)		

DVT: Deep vein thrombosis; PTE: Pulmonary thromboembolism; ICU: Intensive care unit
1: Group NonAT; 2: Group Warfarin; 3: Group NOACs; 4: Group DAPT
a: Chi-Square Test (n / %); b: Mann-Whitney U Test (Median/IQR)

Table 5. Comparison of outcomes of alive and deceased patients

		Outcomes		P-value
		Alive (n=641)	Deceased (n=27)	
Anticoagulant	NonAT	431 (%67.2)	11 (%40.7)	0.013 [a]
	Warfarin	56 (%8.7)	3 (%11.1)	
	NOACs	29 (%4.5)	1 (%3.7)	
	DAPT	125 (%19.5)	12 (%44.4)	
Major bleeding	No	113 (%17.6)	7 (%25.9)	0.303 [a]
	Yes	528 (%82.4)	20 (%74.1)	
RBC transfusion	No	167 (%26.1)	8 (%29.6)	0.849 [a]
	Yes	474 (%73.9)	19 (%70.4)	
RBC transfusion number		2.4 ± 1.6	2.8 ± 2.1	0.301 [b]
Preoperative Hb		12.3 ± 1.7	11.8 ± 1.8	0.105 [b]
	<10	45 (%7.0)	4 (%14.8)	0.128 [a]
	≥10	596 (%93.0)	23 (%85.2)	
Postoperative Hb		9.9 ± 0.9	9.8 ± 1.4	0.862 [b]
	<10	358 (%55.9)	16 (%59.3)	0.897 [a]
	≥10	283 (%44.1)	11 (%40.7)	
	P-value	<0.001 [c]	<0.001 [c]	
DVT	No	638 (%99.5)	27 (%100.0)	1.000 [a]
	Yes	3 (%0.5)	0 (%0.0)	
PTE	No	636 (%99.2)	13 (%48.1)	<0.001 [a]
	Yes	5 (%0.8)	14 (%51.9)	
ICU Admission	No	519 (%81.0)	4 (%14.8)	<0.001 [a]
	Yes	122 (%19.0)	23 (%85.2)	
Length of ICU stay (days)		3.0 (2.0 – 7.0)	7.0 (2.0 – 17.0)	0.076 [d]
Length of hospitals (days)		9.0 (7.0 – 13.0)	12.0 (5.0 – 27.0)	0.161 [d]

[a]: Chi-Square Test (n / %), [b]: Independent Samples t Test (Mean ± SD), [c]: Paired Samples t Test (Mean ± SD), [d]: Mann-Whitney U Test (Median/IQR),
DVT: Deep vein thrombosis; PTE: Pulmonary thromboembolism; ICU: Intensive care unit

Table 6. Logistic regression analysis of risk factors associated with mortality

Risk factor	β	Odds	95% CI	Wald	P-value*
Age	0.162	1.176	1.056 – 1.310	8.734	0.003
NonAT versus DAPT	1.831	6.243	1.897 – 20.546	9.079	0.003
PTE (Yes)	4.988	146.713	28.763 – 748.348	36.008	<0.001
ICU Admission (Yes)	2.474	11.871	3.329 – 42.322	14.551	<0.001

*: Binary Logistic Regression Test; Nagelkerke R^2 = 0.589; Hosmer and Lemeshow Test = 0.985; NoAT: No antithrombotic treatment; DAPT: Dual antiplatelet therapy

Table 7. Multivariate analysis of survival in patients who underwent surgery for hip fracture

		Mean			Median			P-value[1]	P-value[2]	P-value[3]
		Survival time estimation (days)	SE	95% CI	Survival time estimation (days)	SE	95% CI			
Overall		50.6	6.4	38.1 - 63.1	57.0	11.3	34.8 - 79.2			
Gender	Female	36.9	1.5	34.0 - 39.8	40.0	5.2	29.8 - 50.2	0.736	0.576	0.536
	Male	55.5	8.8	38.2 - 72.8	57.0	20.7	16.4 - 97.6			
Anticoagulant	NonAT	64.4	8.4	47.9 - 80.8	57.0	22.0	13.8 - 100.2			
	Warfarin	31.1	1.5	28.1 - 34.1	0.0	0.0	0.0 - 0.0	0.087	0.528	0.328
	NOACs	40.0	0.0	40.0 - 40.0	40.0	0.0	0.0 - 0.0			
	DAPT	32.3	2.1	28.2 - 36.5	30.0	4.4	21.4 - 38.6			
PTE	No	53.6	6.9	40.1 - 67.1	57.0	12.8	31.9 - 82.1	<0.001	<0.001	<0.001
	Yes	13.1	2.3	8.6 - 17.5	9.0	1.3	6.5 - 11.5			
Admission to ICU	No	38.7	0.1	38.5 - 39.0	0.0	0.0	0.0 - 0.0	<0.001	<0.001	<0.001
	Yes	46.0	5.9	34.4 - 57.5	40.0	7.0	26.2 - 53.8			
Anesthesia Technique	Genel	35.4	2.2	31.2 - 39.6	40.0	0.0	0.0 - 0.0			
	Spinal	59.0	7.9	43.5 - 74.4	57.0	19.4	18.9 - 95.1	0.049	0.598	0.321
	Nerve block	30.2	5.0	20.5 - 39.9	26.0	8.5	9.3 - 42.7			

SE: Standard error; CI: Confidence interval; P1: Log Rank; P2: Breslow; P3: Tarone-Ware

Table 8. Proportional hazards regression analysis to identify risk factors associated with survival and mortality

Risk factor	β	Hazard-ratio	95% CI	Wald	P value*
Age	0.063	1.065	1.0 - 1.1	3.326	0.068
NonAT				8.429	0.058
Warfarin	-1.323	0.266	0.1 - 1.3	2.737	0.098
NOACs	0.373	1.452	0.2 - 11.9	0.121	0.728
DAPT	0.716	2.045	0.9 - 4.8	2.667	0.102
PTE	4.010	55.127	19.4 - 156.8	56.532	<0.001

*: Cox regression analysis

Discussion

In the current study, there was no difference in survival between the groups of warfarin, novel oral anticoagulants, or dual antiplatelet therapy. However only Group DAPT had a statistically significant higher mortality rate than Group NonAT (8.8%, 2.5%, respectively). In contrast, mortality in patients using Warfarin and NOACs was not statistically different from those using no antithrombotic drugs. Preoperative drug discontinuation and postponing surgery may have increased mortality in patients receiving DAPT. One of the most important problems is significant hypercoagulability after fracture surgery. Wilson et al. showed by thrombelastography that hypercoagulability occured despite the use of low-molecular weight heparin after fracture surgery (7). Low-molecular weight heparin may be insufficient to prevent coagulative events. In another study it has been reported that thrombotic events start in the preoperative period (8). Bridging with intravenous glycoprotein IIb/IIIa inhibitors (eptifibatide, tirofiban) with a short half-life has been suggested for these patients in recent years (9, 10).

In patients who have undergone hip or femur fracture surgery, studies about the effects of antithrombotic drugs on mortality have reported controversial results. Leer-Salvesen et al. observed no difference in mortality between patients using NOACs and non-users in their study (11). Schuetze et al. also detected no significant difference in mortality in a study comparing NOACs, antiplatelet, and VKA users (12). Vinogradova et al. compared VKA and NOACs and reported higher mortality with NOACs (13). Collinge et al. reported no difference in mortality between users of antiplatelet therapy and VKA (14). Feely et al. compared patients using clopidogrel and non-users and found no difference in terms of bleeding the complications and mortality (15).Lin et al. showed that patients undergoing emergency surgery for hip fracture had a similar one-year mortality rate for those taking antiplatelets compared with those not taking medication (16). Lopez et al. in a prospective observational study, compared two group of patients who received antiplatelet treatment versus received oral anticoagulant treatment. They showed 2-years mortality rate was higher in patients received oral anticoagulant treatment (17).

Yang et al. analyzed 24 studies involving 5423 patients in their recently published metaanalysis. They found that antiplatelet therapy was associated with a decrease in Hb values in hip fracture patients who underwent early surgery (< 5 days) (p<0.001). Antiplatelet therapy was found to be associated with an increase in the number of transfusions (p=0.03). On the other hand, early surgery shortened the length of hospital stay (p<0.001) and decreased mortality (p=0.006). Yang et al. suggested that early surgery is safer in hip fracture patients receiving antiplatelets. They showed that early surgery led to a higher risk of bleeding and an increased need for blood product transfusions. They

have suggested that delaying surgery to restore platelet function is unnecessary, and that early surgery will reduce mortality and hospital stay (18). In our study, unlike theirs, the preoperative waiting time changed differently according to the half-life and elimination of each antithrombotic drug. It may be beneficial to administer anticoagulation reversal agents without waiting for drug elimination. Yoo et al. administered reversal agents of anticoagulation (vitamin K, prothrombin complex concentrate, fresh frozen plasma, and idarucizumab) to patients who underwent hip fracture surgery preoperatively. They found no difference for 30-day mortality between reversal versus non-reversal (19).

Collinge et al. reported that the use of antithrombotic drugs in hip fracture surgeries did not increase bleeding (14). In our study, perioperative major bleeding was not statistically different between the drug-using and non-medicated patient groups ($p>0.05$).

Yoon et al. retrospectively compared patients who received and did not receive red blood cell transfusion in hip fracture surgeries and accepted the target Hb value as >10 g/dl preoperatively and >8 g/dl postoperatively (20). In a meta-analysis evaluating 5780 patients by Simon et al., restrictive red blood cell transfusion has been found to be associated with increased mortality and cardiac morbidity in elderly patients undergoing surgery (21). In our study, the preoperative Hb value was >10 g/dl in 90% of the patients in all the groups, and the postoperative Hb value was >10 g/dl in 40-50% of the patients. Despite the recommendations regarding the target Hb value, in practice, red blood cell transfusion is performed in some patients, even above the target hemoglobin value, in cases with anemia symptoms such as headache and dizziness. Red blood cell replacement was performed in >70% of the patients in all our study groups.

Leer-Salvesen et al. compared patients using NOACs and non-users and they found no difference in the length of hospital stay (11). In contrast, Collinge et al. reported that patients using antiplatelet drugs had longer hospital stay compared to non-users (14). In our study, Group NonAT had a significantly lower rate of ICU admission and shorter length of hospital stay ($p<0.05$). This difference between studies may be related to patient comorbidities, because the proportion of patients in the ASA III and above risk group was 80% in the study of NOACs users by Leer-Salvesen et al. and 95% in the current study patient groups. This indicates that our study patients had more comorbid factors, which resulted in higher rates of ICU admission and longer hospital stay. Menzies et al. studied the impact of comorbidities on the perioperative outcome of hip fractures in geriatric patients. They studied 1077 patients aged 60 years and older who had surgery for a proximal femur fracture. They found that the average CCI score was 3.06. Frailty and comorbidity were high risk factors for adverse perioperative outcomes (22). Roche et al. showed that the 30-day mortality was 9.6% in their study of 2448 elderly patients who underwent hip fracture surgery. They found that having 3 or more comorbid diseases was the most important risk factor for 30-day mortality (23).

Usually, fixation or arthroplasty is used in the treatment of hip fractures. Displaced femoral neck fractures are most often treated with arthroplasty. Non-displaced or minimally displaced fractures are treated with cancellous screw fixation or sliding hip screw. Intertrochanteric fractures are treated with sliding hip screw or intramedullary nail fixation (24). Görmeli et al. retrospectively reviewed 143 patients who had undergone intertrochanteric femoral fracture surgery. They performed proximal femoral nail surgery in 68 patients and bipolar hemiarthroplasty in 75 patients. Intraoperative blood loss and mortality rates were statistically significantly higher in the bipolar hemiarthroplasty surgery group ($p<0.005$). They recommended the proximal femoral nail for the treatment of intertrochanteric femoral fractures (25).

It is controversial which anesthesia method to apply in elderly hip fracture patients. No difference was found in terms of morbidity and mortality in the comparison of general anesthesia and neuraxial anesthesia in hip fracture surgery in elderly patients (26-30). The results of this study demonstrated that patients in Groups warfarin, NOACs and DAPT had higher ASA scores and more general anesthesia procedures. Most of the patients using antithrombotic drugs in the current study were in the ASA III and higher risk group. Regional anesthesia (spinal anesthesia, peripheral blocks) methods are often preferred in elderly patients with hip fractures due to comorbidities related to the respiratory system. However, it is known that spinal anesthesia can cause spinal or epidural hematoma in patients with impaired coagulation parameters. Ueoka et al. reported that general anesthesia was preferred more in patients receiving anticoagulant and antiplatelet treatment in hip fracture surgeries (31). In a study by Leer-Salvesen et al., general anesthesia was preferred more in patients using NOACs (11). The rate of general anesthesia in the our study was 19.2% in Group NonAT, 27.1% in Group Warfarin, 30% in Group NOACs, and 35% in Group DAPT. The fact that general anesthesia was significantly higher in patients using drugs ($p<0.05$) was considered to be associated with the effect of the antithrombotic drugs used by the patient on the anesthesia preference. In this study, the rate of preoperative long-term use of any thromboprophylactic drug was approximately 35%. In a study by Collinge et al., it was reported that of 1036 patients who underwent hip fracture surgery, 40% were using antithrombotic drugs for any comorbidies (14). This demonstrates the importance of maintaining a good balance between the risk of thromboembolism and the risk of serious bleeding in both surgery and anesthesia practice. Cha et al. found elevated charlson comorbidity index in patients treated with VKA and NOAC (32). Lange et al. reported that the incidence of VTE is high and

the complication rate is high due to the low quality of antithrombotic treatment in multimorbid patients with a high mCCI index, who use multiple drugs, and especially those who use antiplatelet therapy (33).In our study, the patients with the highest risk for mCKI which determines the surgical risk, and mortality were the patients receiving antiplatelet treatment.

There may be some possible limitations to this study. The number of patients in the NOAC group was very small (n=30). Autopsy was not carried out to investigate pulmonary embolism or bleeding in patients who died. Data on the types of surgery was not collected.

Conclusion

In conclusion, in our study, there was no difference in survival between the groups of warfarin, novel oral anticoagulants, or dual antiplatelet therapy. Only Group DAPT had a statistically significant higher mortality rate than Group NonAT. In contrast, mortality in patients using Warfarin and NOACs was not statistically different from those using no antithrombotic drugs. The drugs used did not increase major bleeding. There is a need for further studies with larger numbers of patients to be able to determine the causes of death of these patients. If the presence of hypercoagulation and ischemic complications after discontinuation of drug therapy in long-term dual antiplatelet therapy can be demonstrated, new bridging treatment protocols can be established.

Ethics Committee Approval: Approval for this study was obtained from the Local Ethics Committee of ANTRH. (Date: 20.09.2018, Decision no: E-2156).

Conflict of Interest: None declared.

Financial Disclosure: The authors declared that this study has received no financial support.

References

1.de Jong L, van Rijckevorsel V, Klem TMAL, Kuijper M, Roukema GR. Prospective cohort protocol examining the perioperative indicators for complications and early mortality following hip fracture surgery in the frail patient. BMJ Open. 2020:29;10:e038988.

2.Bohm E, Loucks L, Wittmeier K, Lix LM, Oppenheimer L. Reduced time to surgery improves mortality and length of stay following hipfracture: results from an intervention study in a Canadian health authority. Canadian Journal of Surgery 2015;58:257.

3.Omsland TK, Emaus N, Tell GS, et al. Mortality following the first hip fracture in Norwegian women and men (1999–2008). A NOREPOS study. Bone 2014;63:81-6.

4.Moon JY, Nagaraju D, Franchi F, Rollini F, Angiolillo DJ. The role of oral anticoagulant therapy in patients with acute coronary syndrome. Therapeutic Advances in Hematology. 2017:353-66.

5.The European Agency for the Evaluation of Medicinal Products. Guideline on clinical investigation of medicinal products for prophylaxis of high intra- and post-operative venous thromboembolic risk. CPMP/EWP/707/98 Rev. 1.2007. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/05/WC500143764.pdf. Accessed 30 June 2015.

6.Quach LH, Jayamaha S, Whitehouse SL, et al. Comparison of the Charlson Comorbidity Index with the ASA score for predicting 12-month mortality in acute hip fracture. Injury. 2020;51:1004-10.

7.Wilson D, Cooke EA, McNally MA, et al. Changes in coagulability as measured by thrombelastography following surgery for proximal femoral fracture. Injury. 2001;32:765-70.

8.Song K, Yao Y, Rong Z, et al. The preoperative incidence of deep vein thrombosis (DVT) and its correlation with postoperative DVT in patients undergoing elective surgery for femoral neck fractures. Arch Orthop Trauma Surg. 2016;136:1459-64

9.Karadağ B, Ikitimur B, Öngen Z. Perioperative management in patients receiving newer oral anticoagulant and antiaggregant agents. Turk Kardiyol Dern Ars. 2012;40:548-51.

10.Dargham BB, Baskar A, Tejani I, et al. Intravenous Antiplatelet Therapy Bridging in Patients Undergoing Cardiac or Non-Cardiac Surgery Following Percutaneous Coronary Intervention. Cardiovasc Revasc Med. 2019;20:805-11.

11.Leer-Salvesen S, Dybvik E, Ranhoff AH, et al. Do direct oral anticoagulants (DOACs) cause delayed surgery, longer length of hospital stay, and poorer outcome for hip fracture patients? EurGeriatr Med. 2020;11:563-9.

12.Schuetze K, Eickhoff A, Dehner C, Gebhard F, Richter PH. Impact of oral anticoagulation on proximal femur fractures treated within 24h - A retrospective chart review. Injury. 2019;50:2040-4.

13.Vinogradova Y, Coupland C, Hill T, Hippisley-Cox J. Risks and benefits of direct oral anticoagulants versus warfarin in a real world setting: cohort study in primary care. BMJ. 2018 4;362:k2505.

14.Collinge CA, Kelly KC, Little B, Weaver T, Schuster RD. The effects of clopidogrel (Plavix) and other oral anticoagulants on early hip fracture surgery. J Orthop Trauma 2012;26:568-73.

15.Feely MA, Mabry TM, Lohse CM, Sems SA, Mauck KF. Safety of clopidogrel in hip fracture surgery. Mayo Clin Proc. 2013;88:149-56.

16.Lin SY, Huang HT, Chou SH, et al. The Safety of Continuing Antiplatelet Medication Among Elderly Patients Undergoing Urgent Hip Fracture Surgery. Orthopedics. 2019;42:268-74.

17.López S, da Casa C, Pablos-Hernández C, et al. The impact of antithrombotic therapy on surgical delay and 2-year mortality in older patients with hip fracture: a prospective observational study. EurGeriatr Med. 2020 ;11:555-61.

18.Yang Z, Ni J, Long Z, et al. Is hip fracture surgery safe for patients on antiplatelet drugs and is it necessary to delay surgery? A systematic review and meta-analysis. J Orthop Surg Res. 2020 ;15:105.

19.Yoo MS, Zhu S, Jiang SF, et al. Association of Reversal of Anticoagulation Preoperatively on 30-Day Mortality and Outcomes for Hip Fracture Surgery. Am J Med. 2020;133:969-75.

20.Yoon BH, Ko YS, Jang SH, Ha JK. Feasibility of Hip Fracture Surgery Using a No Transfusion Protocol in Elderly Patients: A Propensity Score-Matched Cohort Study. J Orthop Trauma 2017;31:414-9.

21.Simon GI, Craswell A, Thom O, Fung YL. Outcomes of restrictive versus liberal transfusion strategies in older adults from nine randomised controlled trials: a systematic review and meta-analysis. Lancet Haematol. 2017;4:465-74.

22.Menzies IB, Mendelson DA, Kates SL, Friedman SM. The impact of comorbidity on perioperative outcomes of hip fractures in a geriatric fracture model. Geriatr Orthop Surg Rehabil. 2012;3:129-34.

23.Roche JJ, Wenn RT, Sahota O, Moran CG. Effect of comorbidities and postoperative complications on mortality after hip fracture in elderly people: prospective observational cohort study. BMJ. 2005; 10;331:1374.

24.Lu Y, Uppal HS. Hip Fractures: Relevant Anatomy, Classification, and Biomechanics of Fracture and Fixation. Geriatr Orthop Surg Rehabil. 2019;10:2151459319859139.

25.Görmeli G, Korkmaz MF, Görmeli CA, et al. Comparison of femur intertrochanteric fracture fixation with hemiarthroplasty and proximal femoral nail systems. Ulus Travma Acil Cerrahi Derg. 2015;21:503-8.

26.Valentin N, Lomholt B, Jensen JS, Hejgaard N, Kreiner S. Spinal or general anaesthesia for surgery of the fractured hip? A prospective study of mortality in 578 patients. Br J Anaesth. 1986;58:284-91.

27.Davis FM, Woolner DF, Frampton C, et al. Prospective, multi-centre trial of mortality following general or spinal anaesthesia for hip fracture surgery in the elderly. Br J Anaesth. 1987;59:1080-8.

28.Heidari SM, Soltani H, Hashemi SJ, Talakoub R, Soleimani B. Comparative study of two anesthesia methods according to postoperative complications and one month mortality rate in the

candidates of hip surgery. J Res Med Sci. 2011;16:323-30.

29.Parker MJ, Griffiths R. General versus regional anaesthesia for hip fractures. A pilot randomised controlled trial of 322 patients. Injury. 2015;46:1562-6.

30.Shin S, Kim SH, Park KK, et al. Effects of Anesthesia Techniques on Outcomes after Hip Fracture Surgery in Elderly Patients: A Prospective, Randomized, Controlled Trial. J Clin Med. 2020;9:1605.

31.Ueoka K, Sawaguchi T, Goshima K, et al. The influence of pre-operative antiplatelet and anticoagulant agents on the outcomes in elderly patients undergoing early surgery for hip fracture. J Orthop Sci 2019;24:830-5.

32.Cha YH, Lee YK, Koo KH, Wi C, Lee KH. Difference in Mortality Rate by Type of Anticoagulant in Elderly Patients with Cardiovascular Disease after Hip Fractures. Clin Orthop Surg 2019;11:15-20.

33.Lange N, Méan M, Stalder O, et al. Anticoagulation quality and clinical outcomes in multimorbid elderly patients with acute venous thromboembolism. Thromb Res 2019;177:10-6.