Original article

Crit Care Shock (2020) 23:221-231

Does preinjury anticoagulant or antiplatelet medication increase the need for blood transfusions in patients aged older than 65 years with traumatic brain injury?

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Abstract

***Background*: Anticoagulant or antiplatelet medications are commonly prescribed in older adults, increasing bleeding tendency and affecting traumatic brain injury (TBI)-related morbidity and mortality.**

***Objectives*: This study aimed to determine the effects of preinjury anticoagulant or antiplatelet medication on blood transfusions and outcomes in patients aged >65 years with TBI.**

***Methods*: We retrospectively reviewed records of patients with TBI without other injuries admitted to our hospital between January 2016 and June 2019. We compared the number of blood transfusions administered and outcomes between patients who were receiving anticoagulant/antiplatelet medication and those who were not.**

***Results*: Overall, 82 patients (66% male) with an average±standard deviation age of 76.6±7.29 years were enrolled. Thirty-one patients were receiving anticoagulants or antiplatelets and 51 were not. There were no differences in age, medical history, Injury Severity Score, and Glasgow Coma Scale score between the groups. International normalized ratios of patients who were on warfarin were significantly higher than those of patients who were not (p<0.05). Analysis of covariance demonstrated that patients who were receiving medications needed more plasma transfusions than did those who were not (p<0.05). The incidence of complications was 64.5% and 37.3% in patients who were and were not receiving medication, respectively (p<0.05). Multivariate regression analysis showed that patients who were receiving medications bled 5.62 times more than did those who were not (95% confidence interval: 1.52~20.70).**

***Conclusions*: Bleeding incidence and plasma transfusion requirements are increased by preinjury anticoagulant or antiplatelet medication in patients aged >65 years with TBI.**

Key words: Bleeding, head trauma, medication, old age, outcome.

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Introduction

Population aging is a global phenomenon, and in the Republic of Korea, 14.9% of the population is over 65 years old. (1) Advances in medicine and social environments have led to a more active older adult population, resulting in increased risks of trauma such as falls and road traffic accidents. (2) When sustaining trauma, older adults are more susceptible to injury and death in view of underlying disease and impaired physiology such as an aging cardiovascular system and a compromised immune system. (3)

In the older adult population, traumatic brain injury (TBI) is one of the leading causes of death or irreversible damage, and rates of TBI are on the rise. (4) In the United States, more than 80,000 older adult patients with TBI visit the emergency department each year. (5) Furthermore, financial loss is common in trauma patients, and overall treatment costs are reported to be higher in older patients than in younger patients. (6) In patients with TBI, in addition to treating the primary damage of head trauma, the prevention of secondary damage, which results from hypotension, hypoxemia, and anemia, is crucial. (7) Although the degree of secondary damage depends on the primary damage, brain edema and hemorrhage are additional key factors. (8) In order to minimize secondary damage, initial resuscitation and transfusion are important in the management of patients with TBI. A 2017 study reported higher survival rates in patients with TBI who received early plasma transfusion than in those who did not. (9) Older patients are more likely to be on anticoagulant or antiplatelet therapy due to underlying diseases, making early transfusion and intensive care even more critical. (10,11)

Several studies have reported the effects of anticoagulant or antiplatelet medications on mortality rates and outcomes related to head trauma. (12-14) Although one study reported that platelet transfusions do not affect treatment outcomes in patients receiving antiplatelet drugs, (15) others reported that blood transfusions are a risk factor of mortality. (16) In view of these contradictory findings, further research on the relationship between preinjury medication and transfusion is warranted. The aim of this study was to determine the effects of preinjury anticoagulant or antiplatelet medication on blood transfusions and outcomes in older adult patients with TBI who were admitted to the intensive care unit (ICU).

Materials and methods

Patients and data

Between January 2016 and June 2019, a total of 5736 trauma patients were admitted to our hospital. Among these, 1326 patients were admitted to the ICU, 466 of whom were over 65 years old. Medical records were extracted from the Korean Trauma Data Base (KTDB) and were retrospectively reviewed for the following data: blood tests, imaging studies, transfusions, rates of complications, and prescriptions of anticoagulant or antiplatelet medication. These medications included aspirin, clopidogrel, warfarin, and non-vitamin K antagonist oral anticoagulant. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Institutional Review Board of the Chungbuk National University Hospital (approval number: 2019-10-002)); the need for informed consent was waived by the Institutional Review Board owing to the retrospective nature of the study.

Blood tests and transfusions

Patients' initial blood loss and general condition at 24 h post-treatment were determined by blood tests, including red blood cell count and coagulation function; these were carried out on admission at the trauma center and repeated 24 h later. Coagulation function was determined using the prothrombin time, international normalized ratio (INR), and activated partial thromboplastin time (aPTT). Patients' data were reviewed for transfusion records, including the administration of individual component transfusions (e.g., red blood cells, plasma, platelets) within 4 h upon arrival and for the following 20 h, and for total transfusions within 24 h from arrival.

Definitions and complications

Injury severity was determined using the Injury Severity Score (ISS), and consciousness level was determined using the Glasgow Coma Scale (GCS) score. As for complications, an increase in intracranial hemorrhage was defined when the radiologist reported worsening of hemorrhage on follow-up brain computed tomography scans, and neurosurgeons determined a deterioration in the patient's condition requiring further treatment. Pneumonia was defined by the presence of clinical symptoms including cough, sputum-positive imaging studies on plain X-ray or computed tomography scans, and growth of pathogens on culture requiring antibiotic treatment. Acute renal failure was defined by the presence of a low urine output (<0.5 ml/kg/h for more than 6 h), and a 50-100% increase in serum creatinine levels when compared to baseline levels. (17) Infection was defined by the presence of redness or warmth on the injury site or surgical site, along with positive growth of pathogens on culture. The mortality rate was calculated by death or survival at discharge.

Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics v. 23.0 (IBM Co., Armonk, NY, USA). The Kolmogorov-Smirnov test was used to confirm normal distribution of variables. Statistical analyses were performed using the chi-squared test, independent t-test, nonparametric test, and analysis of covariance. And the odds ratio was expressed by multivariable logistic regression. The variables of multivariate logistic regression were determined by univariate regression. Two-tailed p values of less than 0.05 were considered reflective of statistical significance.

Results

A total of 82 patients (54 males and 28 females; average±standard deviation age: 76.6±7.29 years) with head trauma were included in this study (**Figure 1**). Demographics are shown in **Table 1**. Past medical history included hypertension (44 patients) and diabetes (23 patients). The most frequent mechanism of injury was a slip (20 patients), followed by a fall (16 patients), and motorcycle and motor vehicle accidents (10 patients each). The average ISS and GCS scores were 19.05 and 9.82, respectively. Amongst the 82 included patients, 31 patients with an average age of 78.1 years were on anticoagulant or antiplatelet medication (medication group). The non-medication group had a lower average age (75.6 years), although this was not statistically significant. Notably, relative to the non-medication group, the medication group suffered from more previous medical conditions, as noted in their past medical history, such as diabetes, cardiovascular disease, and cerebrovascular disease, but this was not statistically significant. The ISS and GCS scores were better in the medication group, but again, this was not statistically significant.

There were no differences in red blood cell count upon arrival and at 24 h after arrival between the two groups. Upon arrival, the INR and aPTT were higher in the medication group ($p<0.05$) than in the non-medication group; however, at 24 h after arrival, the INR and aPTT were not different between the groups (**Table 2**). The INR of patients who were on warfarin was significantly higher than the INR of any other subgroup (**Figure 2**). The medication group received more component transfusions than did the non-medication group, but this was not statistically significant (**Table 2**). To verify the effect of patients who were receiving medications on blood transfusions, the influence of ISS was controlled and an analysis of covariance (ANCOVA) was conducted. As a result, the total fresh frozen plasma (FFP) showed statistically significant difference according to the preinjury medications ($F=4.012$, $p<0.05$) (**Table 3**).

Total mortality was 29.3% (24 patients), and 44 patients underwent surgery. Among the 63 patients who were on mechanical ventilation, 10 patients had a tracheostomy inserted for prolonged ventilation. Pneumonia was the most frequent complication (21 cases), followed by bleeding (15 cases). In total, there were 39 cases of complications. The medication group demonstrated a higher mortality rate, longer length of ICU stay, and longer duration on mechanical ventilation, but these results were not statistically significant. However, an increase in hemorrhage occurred significantly more frequently in the medication vs non-medication group, resulting in a significantly higher overall complication rate in the medication vs non-medication group (**Table 4**). Multivariate regression analysis including age, ISS, and GCS score showed that the risk of bleeding was 5.62 times higher in the medication group than in the non-medication group (**Table 4**).

Discussion

Anticoagulation and antiplatelet medications including aspirin, clopidogrel, and warfarin are used to treat various cardiovascular and cerebrovascular diseases, commonly seen in older adults. (11) Despite their advantages, these medications come with an increased risk of bleeding, which can be fatal in cases of trauma with hemorrhage. Thus, proper examination and monitoring of coagulation function and bleeding are important, and many studies utilize the INR when testing coagulation function. (18-20) In their study, Fredric, et al (21) reported higher INRs in patients who were on warfarin than in those who were not, and higher INRs in patients receiving therapeutic doses of warfarin than in those receiving non-therapeutic doses. Other studies also revealed higher INRs in patients on warfarin than other groups. (22,23) The present study likewise demonstrated higher initial INRs in patients who were on warfarin prior to injury (average levels higher than 2.0) than in patients who were on other medications or no medication, with statistical significance. However, when comparing INR levels between patients on anticoagulation or antiplatelet medications and those on no medication, the average INRs of both groups were lower than 1.5, with no statistically significant difference. These numbers are lower than those reported in other studies, (22,23) and this is probably due to the limited number of patients who were receiving warfarin in this study. Further studies involving more patients will yield more accurate results.

With regard to the amount of transfusions required, we demonstrated a difference in the initial INRs, which was dependent on medication, but no differences in the amount of plasma transfused. However, the medication group and higher ISSs required more plasma transfusions. This result is similar to the findings of other studies showing that more transfusions were required in patients with higher ISSs and in those who were receiving anticoagulation or antiplatelet medications. (24,25) However, these studies presented findings related to increased requirements of total transfusion and massive transfusion, whilst the present study demonstrated increased requirements of plasma only. For this reason, further studies with larger population samples are required.

This study demonstrated high complication rates related to preinjury medication, along with a high frequency of blood loss cases. Several studies have reported that patients on warfarin are more susceptible to bleeding than are patients on non-vitamin K antagonist oral anticoagulant, (12,26) while one study revealed more bleeding episodes in patients on clopidogrel than in patients on warfarin. (19) Due to these diverse results related to complications and their dependence on medications, further studies are warranted. Nevertheless, these studies, along with the present study, do share a common finding, i.e., preinjury anticoagulant or antiplatelet medications result in an increase in initial intracranial hemorrhage or an increased chance of delayed hemorrhage.

The present study did not reveal significant differences in the length of ICU stay, duration of mechanical ventilation, and mortality rates according to medication usage. Similar to the present study, several prior studies reported no difference in patient outcomes depending on anticoagulant or antiplatelet medication usage. (27-29) In contrast, some studies reported poorer outcomes and higher mortality rates in patients on anticoagulant or antiplatelet medications than those who did not take them. (13,22,26) Other studies reported higher mortality rates in patients on warfarin, and no differences in mortality or length of ICU stay between in patients on antiplatelet medications and those not. (12,30) Since our study included only five patients on warfarin, further studies involving more patients will yield better comparisons between each medication.

This study had several limitations. First, this was a retrospective study conducted in a single institution, with a small sample size of less than 100 patients. This limited the authors' confidence in the results and their ability to understand how the outcomes were dependent on the type of medication. Further studies involving more cases are warranted to clarify any differences in outcomes that are dependent on medications. In addition, if a multicenter study was conducted with other trauma centers, the results could have been further enhanced. Second, this study was not performed under the randomization of a sample because of its retrospective design. Third, initial resuscitations varied due to different medical personnel for each patient. Since doctors' decisions differed from each other with regard to transfusion prescriptions, some patients might have received too few transfusions whilst others might have received too many. We expect more accurate results if we apply a standardized protocol for initial resuscitation, especially with transfusion. Finally, this study was limited to major trauma patients who were treated in the ICU, and thus does not represent the whole population of patients with TBI. Strength of our study was the accuracy of the extracted data from the Korean Trauma Data Base (KTDB)-registered trauma patients in the collection of data points for review and analysis.

Conclusion

Despite several limitations, this study demonstrated that preinjury anticoagulant or antiplatelet medication increases the bleeding risk and plasma transfusion requirements in older adult patients with TBI. Future studies involving more cases will further enhance our results.

Declarations

Author contributions

SH Kim: Acquisition of data, analysis and interpretation of the data, and drafting of the manuscript; YH Sul: Study conception and design, acquisition of data, and critical revision of the manuscript; JY Lee: Acquisition of data; JB Ye: Acquisition of data; JS Lee: Acquisition of data; HR Kim: Acquisition of data, SY Yoon: Acquisition of data; JS Kim: critical revision of the manuscript; MS Ahn: Critical revision of the manuscript. All authors reviewed and approved the final submitted manuscript.

Funding

This study was supported by a research grant from the Chungbuk National University in 2019.

Conflicts of interest

There is no conflict of interest to disclose.

Informed consent

The need for informed consent was waived by the Institutional Review Board owing to the retrospective nature of the study.

Ethical approval

This study was approved by the Institutional Review Board of the Chungbuk National University Hospital (approval number: 2019-10-002).

Table 1. Demographics and clinical data of included patients

	Total patients (n=82)	No anticoagulation or antiplatelet (n=51)	Anticoagulation or antiplatelet (n=31)	p value
Average age, years (SD)	76.6 (7.29)	75.62 (6.68)	78.12 (8.07)	0.13
Sex, n (%)				0.63
Male	54 (65.9%)	35 (68.6%)	19 (61.3%)	
Female	28 (34.1%)	16 (31.4%)	12 (38.7%)	
Past medical history, n (%)				
HTN	44 (53.7%)	27 (52.9%)	17 (54.8%)	0.86
DM	23 (28.0%)	17 (33.3%)	6 (19.4%)	0.21
Cardiovascular disease	9 (11.0%)	3 (5.9%)	6 (19.4%)	0.07
Cerebrovascular disease	2 (2.4%)	0 (0.0%)	2 (6.5%)	0.14
Other	33 (40.2%)	18 (35.3%)	15 (48.4%)	0.25
Mechanism of injury, n (%)				0.38
Fall	16 (19.5%)	10 (19.6%)	6 (19.4%)	
Slip	20 (24.4%)	10 (19.6%)	10 (32.3%)	
Motorcycle	10 (12.2%)	9 (17.6%)	1 (3.2%)	
Motor vehicle	10 (12.2%)	5 (9.8%)	5 (16.1%)	
Bicycle	5 (6.1%)	4 (7.8%)	1 (3.2%)	
Pedestrian traffic accident	10 (12.2%)	7 (13.7%)	3 (9.7%)	
Other	11 (13.4%)	6 (11.8%)	5 (16.1%)	
GCS score	9.82	9.61	10.16	0.60
Average ISS (SD)	19.05 (7.56)	19.67 (7.68)	18.03 (7.38)	0.34

Legend: SD=standard deviation; HTN=hypertension; DM=diabetes mellitus; GCS=Glasgow Coma Scale; ISS=Injury Severity Score.

Table 2. Laboratory data and transfusion stratified by preinjury medication

	No anticoagulation or antiplatelets	Anticoagulation or antiplatelets	p value
Laboratory data*			
Initial INR	1.10 (0.18)	1.41 (0.86)	0.03
Initial aPTT	30.49 (13.52)	35.76 (22.65)	0.19
Initial Hb	12.13 (2.40)	12.71 (1.73)	0.21
INR at 24 h	1.21 (0.23)	1.31 (0.34)	0.18
aPTT at 24 h	33.57 (11.37)	34.49 (11.47)	0.72
Hb at 24 h	10.89 (1.82)	11.34 (1.55)	0.25
Transfusion, number of units*			
Within 4 h of arrival			
RCC	0.47	0.71	0.49
FFP	0.25	0.65	0.20
PC	0.16	0.26	0.72
Within 24 h after the initial 4 h			
RCC	0.84	0.87	0.94
FFP	0.90	1.35	0.38
PC	2.00	2.52	0.62
Within 24 h of arrival			
Total RCC	1.31	1.58	0.65
Total FFP	1.16	2.00	0.21
Total PC	2.16	2.77	0.60

Legend: INR=international normalized ratio; aPTT=activated partial thromboplastin time; Hb=hemoglobin; RCC=red cell concentration; FFP=fresh frozen plasma; PC=platelet concentration. *Data are presented as the average (standard deviation).

Table 3. Analysis of covariance (ANCOVA) of transfusions

		Sum of squares	df	Mean square	F	P
Total RCC†	ISS	60.473	1	60.473	10.163**	<0.01
	Pre-injury medication	3.940	1	3.940	0.662	0.42
Total FFP†	ISS	96.574	1	96.574	17.412***	<0.001
	Pre-injury medication	22.250	1	22.250	4.012*	<0.05
Total PC†	ISS	48.122	1	48.122	1.812	0.18
	Pre-injury medication	11.741	1	11.741	0.442	0.51

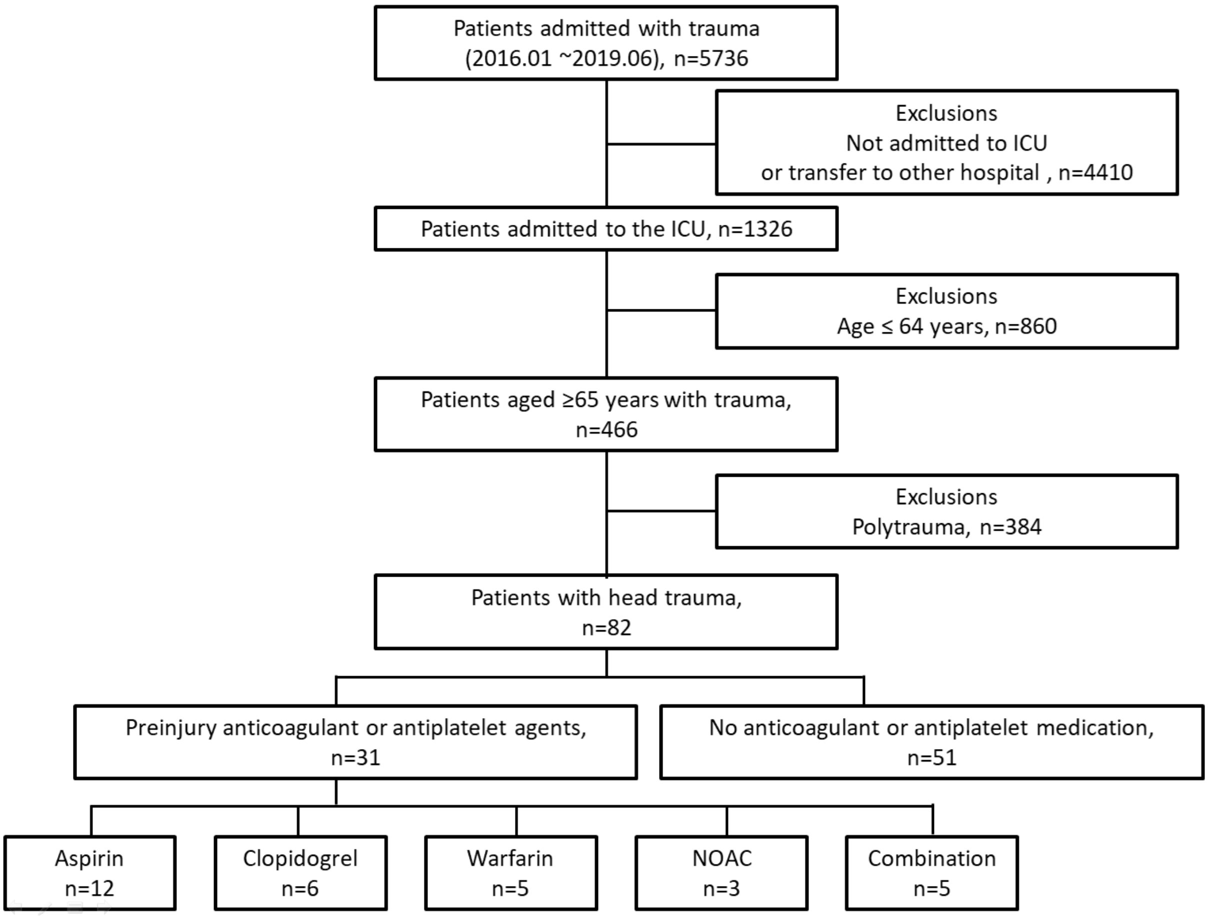
Legend: RCC=red cell concentration; FFP=fresh frozen plasma; PC=platelet concentration; ISS=Injury Severity Score.
†Transfusion within 24 h of arrival; *p<0.05; **p<0.01; ***p<0.001.

Table 4. Odds ratio of outcomes by preinjury anticoagulation or antiplatelet agent use

	Unadjusted OR (95% CI)	p value	Model 1† adjusted OR (95% CI)	p value	Model 2†† adjusted OR (95% CI)	p value
Mortality	1.26 (0.47~3.32)	0.80	1.70 (0.53~5.43)	0.37	1.68 (0.57~4.95)	0.34
Operation	1.33 (0.54~3.27)	0.64	1.27 (0.47~3.40)	0.63	0.98 (0.66~1.47)	0.95
Complications	3.06* (1.20~7.76)	0.02	2.96* (1.05~3.38)	0.04	3.25* (1.26~8.36)	0.02
- Increase in hemorrhage	6.46*** (1.83~22.75)	<0.001	5.62** (1.52~20.70)	<0.01	6.50*** (1.83~23.06)	<0.001
- Pneumonia	1.33 (0.48~3.65)	0.61	1.01 (0.36~3.58)	0.87	1.45 (0.52~4.07)	0.48
- Pleural effusion	0.39 (0.04~3.67)	0.64	0.33 (0.03~3.50)	0.35	0.45 (0.05~4.31)	0.48
- Infection	1.71 (0.32~9.07)	0.66	1.73 (0.32~9.50)	0.52	1.74 (0.33~9.33)	0.51
- Acute renal failure	1.69 (0.23~12.65)	0.63	0.90 (0.10~8.37)	0.93	1.70 (0.22~12.87)	0.61
- Two or more complications	1.21 (0.35~4.20)	0.75	1.02 (0.26~4.02)	0.97	1.36 (0.38~4.85)	0.63

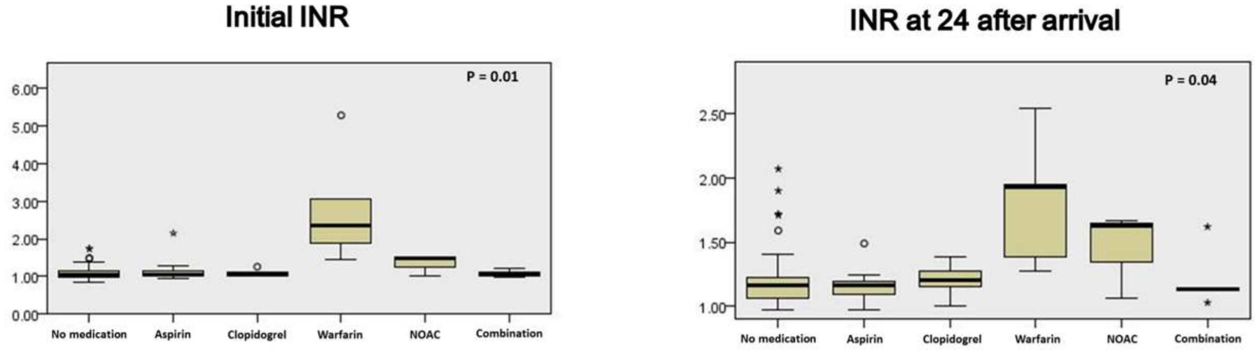
Legend: OR=odds ratio; CI=confidence interval.
*p<0.05; **p<0.01; ***p<0.001.
†Model 1: Multivariable logistic regression analysis including Injury Severity Score, age, and Glasgow Coma Scale score.
††Model 2: Multivariable logistic regression analysis including the Injury Severity Score.

Figure 1. Flowchart describing the study population and patient selection algorithm



Legend: ICU=intensive care unit; NOAC=non-vitamin K antagonist oral anticoagulant.

Figure 2. Comparison of initial average INR levels and average INR levels measured after 24 h



Legend: INR=international normalized ratio; NOAC=non-vitamin K antagonist oral anticoagulant.

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