

Safety and differences between direct oral anticoagulants and vitamin K antagonists in the risk of post-traumatic intrathoracic bleeding after rib fractures in elderly patients

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Abstract

Closed chest traumas are frequent consequences of falls in the elderly. The presence of concomitant oral anticoagulant therapy can increase the risk of post-traumatic bleeding even in cases of trauma with non-severe dynamics. There is limited information about the differences between vitamin K antagonists and direct oral anticoagulants in the risk of post-traumatic bleeding. To assess differences in the risk of developing intra-thoracic hemorrhages after chest trauma with at least one rib fracture caused by an accidental fall in patients over 75 years of age taking oral anticoagulant

therapy. This study involved data from four emergency departments over two years. All patients on oral anticoagulant therapy and over 75 years of age who reported a closed thoracic trauma with at least one rib fracture were retrospectively evaluated. Patients were divided into two study groups according to their anticoagulant therapy. Of the 342 patients included in the study, 38.9% (133/342) were treated with direct oral anticoagulants and 61.1% (209/342) were treated with vitamin K antagonist. A total of 7% (24/342) of patients presented intrathoracic bleeding, while 5% (17/342) required surgery or died as a result of the trauma. Post-traumatic intrathoracic bleeding occurred in 4.5% (6/133) of patients receiving direct oral anticoagulants and 8.6% (18/209) of patients receiving vitamin K antagonist. Logistic regression analysis, revealed no difference in the risk of intrathoracic haemorrhages between the two studied groups. Direct oral anticoagulants therapy presents a risk of post-traumatic intrathoracic haemorrhage comparable to that of vitamin K antagonist therapy.

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Introduction

Falls in the elderly population (>75 years) are a frequent cause of access to the Emergency Department (ED).¹ Although falls are usually characterized by a non-severe dynamic, the complexity and fragility of the elderly population can lead to serious consequences, even for minor trauma. Closed thoracic trauma is a particularly common consequence of falls in the elderly.^{1,2}

Between 15% and 20% of all accesses to a trauma ED are related to a chest trauma. The majority of these chest traumas are minor blunt traumas, and most of these patients are discharged after being admitted and evaluated in the ED.¹⁻³ Rib fractures occur in more than 20% of blunt chest trauma cases.⁴ In most cases, patients need only one analgesic therapy or a relatively short observation period, but in a non-negligible percentage of cases, rib fractures may result in mild to moderate post-traumatic intrathoracic bleeding and, rarely, in massive haemothorax.⁴⁻⁶ A massive haemothorax is a life-threatening condition that requires rapid surgery and has been associated with elevated morbidity and mortality.^{6,7}

In addition to the dynamics, severity and mechanism of trauma, some pre-existing conditions may facilitate the development of post-traumatic bleeding.⁷⁻⁹ Among these pre-existing conditions, taking anticoagulants prior to the injury could be a risk factor for the development of Intrathoracic Hemorrhage (ITH) in chest trauma with rib fractures.^{6,7} Although some studies have reported that pre-injury anticoagulant leads to increased morbidity and mortality in trauma patients, the risk of post-traumatic ITH in anticoagulated patients

with rib fractures remains unclear.⁸⁻¹² Oral Anticoagulant Therapy (OAT) is currently considered the gold standard for thromboembolic risk conditions.^{13,14} In recent years, there has been an exponential increase in the use of OAT in the elderly population, and more than 10% of the US population aged >80 years are treated with oral anticoagulants.¹⁵ For decades, vitamin K antagonists (VKAs) were commonly used for anticoagulation therapy. More recently, new drugs have been introduced, including Direct Oral Anticoagulants (DOACs), which offer a predefined dosage and do not require continuous monitoring of the therapeutic range via the International Normalised Ratio (INR). Although the effectiveness of DOACs in preventing thrombotic risk has been confirmed as non-inferior to that of VKAs, there is still limited information available about their safety profile for bleeding, especially after trauma.¹⁶ Generating a better definition of the risk of hemorrhage related to DOACs, even in the apparently less severe traumas observed daily in older patients in the ED, is important, given the rapid increase in their use. The aim of our study was therefore to determine the impact of both VKAs and DOACs on the development of complications in elderly patients with blunt thoracic trauma.

Materials and Methods

Setting

A retrospective observational study was conducted between January 1st 2017 and December 31st 2018. The EDs of 4 hospitals participated: Ospedale Civile Maggiore di Verona (Italy, 90,000 patients per year), Policlinico Universitario di Verona (Italy, 40,000 patients per year), Fracastoro di San Bonifacio Hospital (Italy, 50,000 patients per year), and Franz Tappeiner Hospital in Merano (Italy, 70,000 patients per year).

This retrospective study was conducted in accordance with local legislation and the Declaration of Helsinki. As this was a retrospective study, no specific authorization was required; only a declaration to the individual committees was made.

Patients

All patients aged 75 years or more who were receiving OAT and reported at least one rib fracture due to a blunt chest trauma during the ED evaluation during the study period were considered.

The following procedure was used to identify the study sample: all patients subjected to a chest wall radiological study [X-rays or Computed Tomography (CT)] were extracted from the different ED databases using individual extraction software (FirstAid for the Ospedale Civile Maggiore di Verona, the Policlinico Universitario di Verona and the Ospedale Fracastoro di San Bonifacio and QlickView for the Ospedale di Merano). A group of emergency physicians manually re-evaluated all of the electronic records of the extracted patients, selecting those: i) with at least one rib fracture resulting from a closed thoracic trauma that led to an ED evaluation of the patient; ii) being treated with OAT; iii) aged 75 years or more; and iv) who experienced chest trauma within 48 hours of the ED evaluation.

The identified patients were divided into two groups according to the type of OAT they received: patients treated with VKAs and patients treated with DOACs. Finally, all patients with an ineffective OAT, defined as a last dose of DOACs more than 24 hours before the trauma or, for patients with VKA, an inadequate anticoagulant effect, defined as an international normalized ratio (INR) <1.5, were excluded. Patients with a dynamic trauma related to a car accident, a penetrating chest trauma, severe changes in con-

sciousness (Glasgow Coma Scale <13), hemodynamic instability or the need for mechanical life support immediately upon ED arrival were excluded from the study.

Data collection, variables, and outcomes

The demographic, anamnestic and clinical characteristics of the patients were input into a specific pre-designed database during the manual re-evaluation of the patients' charts. The independent variables considered as possible confounding factors were defined a priori, according to current studies.⁶⁻¹⁰ These included patient age, injury mechanism, number of rib fractures, baseline haemorrhagic risk (HAS-BLED score), chronic therapy (included the use of antiplatelet agents) and the presence of concomitant lesions.

The primary outcome of the study was the presence or development of post-traumatic ITH within 48 hours of chest trauma. All available radiological procedures were re-evaluated using IMPAX software by two radiologists with more than 15 years of experience to assess the presence of an ITH.⁷ In cases for which any doubt arose, a third radiologist with more than 20 years of experience confirmed or excluded the presence of hemorrhage. The secondary outcome of the study was the combination of the need for surgery and trauma-related death. Survival data were obtained directly from the registry office.

Statistical analysis

Continuous variables were expressed as median and Interquartile Ranges (IQRs) and categorical variables were reported as numbers and percentages of total events.

The two groups of patients (DOACs vs VKAs) were analysed to assess possible imbalances in baseline, anamnestic and clinical characteristics. Where appropriate, the use of balancing analyses was considered to balance the two treatment groups and to achieve a homogeneous cohort of patients for prognostic evaluation.

Severe post-traumatic bleeding is reported as a number of events and a percentage of the total. Comparisons between variables and study outcomes were performed using Fisher's exact test, a Chi-square test or a Mann-Whitney U test, as appropriate.

A logistic regression analysis, adjusted for all of the variables that were found to be statistically significant in the previous univariate analysis, was performed to verify the differences in ITH between the two groups of patients. All analyses were considered statistically significant if the p-value was <0.05. Statistical analyses were conducted with STATA 14.0 (StataCorp, College Station, Texas, USA).

Results

Over the 2-years period of our study, 2184 patients with rib fractures were evaluated in the participating EDs. We enrolled in our study 342 patients who were least 75 years old and were receiving concomitant OAT. Of the 342 patients, 38.9% (133/342) were treated with DOACs and 61.1% (209/342) were treated with VKAs.

In addition, 7% (24/342) of the patients enrolled in the study presented an ITH, while 5% (17/342) of patients required a surgical intervention or died as a result of the bleeding.

The demographic, anamnestic and clinical characteristics of the patients on OAT, divided into the two treatment groups, are listed in Table 1. No difference in baseline characteristics of patients was found between patients treated with DOACs and VKAs. Only one previous cerebral ischaemic event was more strongly represented in the group treated with DOACs (Table 1).

We found that 4.5% of patients receiving DOACs (6/133) developed ITH after rib fractures, compared to 8.6% (18/209) of patients receiving VKAs ($p=0.193$). Moreover, 4.5% of patients receiving DOAC (6/133) required surgery or died compared to 4.3% (9/209) of patients receiving VKAs ($p=0.988$).

Table 2 shows the univariate analysis between the characteristics recorded upon entry into the ED and the presence of an ITH following rib fractures.

Factors associated with the occurrence of ITH were age ($p=0.045$), chronic heart failure ($p=0.046$), chronic renal failure ($p=0.012$), the number of rib fractures ($p<0.001$), a high Injury Severity Score (ISS) value ($p<0.001$) and dangerous trauma dynamics ($p<0.001$). Logistic regression analysis, adjusted for age,

chronic heart and renal failure, the number of broken ribs, severity of trauma (ISS score) and trauma dynamics, showed no difference in the risk of ITH occurrence between the two groups (DOACs vs VKA).

If we consider only patients with fewer than three fractured ribs ($n=204$), only 2.4% (5/204) developed an ITH. All five of these patients were being treated with VKAs ($p=0.062$); none of the patients receiving DOACs and who had fewer than three fractured ribs developed post-traumatic ITH. Among patients with three or more fractured ribs ($n=138$), 12.8% (6/47) of patients being treated with DOACs and 14.3% (13/91) of patients treated with VKAs presented a post-traumatic ITH ($p=0.807$).

Among the entire sample, 15.5% of the patients (53/342)

Table 1. Clinical, anamnestic and demographic characteristics of patients enrolled in the study, grouped according to their oral anti-coagulation therapy.

Variables	Global	DOACs	VKAs	p
Patients, n (%)	342	133 (38.9)	209 (61.1)	
Age, median (IQR)	84 (79-89)	83 (77-89)	84 (79-89)	0.267
Reason for anticoagulation				0.712
Atrial fibrillation	309 (90.4)	119 (89.5)	190 (90.9)	
Pulmonary embolism	33 (9.6)	14 (10.5)	19 (9.1)	
Previous clinical history, n (%)				
Ischemic heart disease	67 (19.6)	26 (19.5)	41 (19.6)	1.000
Hypertension	297 (86.8)	117 (88.0)	180 (86.1)	0.743
Chronic heart failure	59 (17.3)	25 (18.8)	34 (16.3)	0.560
Chronic obstructive pulmonary disease	19 (5.6)	6 (4.5)	13 (6.2)	0.631
Pacemaker	36 (10.6)	14 (10.6)	22 (10.5)	1.000
Active cancer	27 (7.9)	8 (6.0)	19 (9.1)	0.411
Chronic liver disease	10 (2.9)	2 (1.5)	8 (3.2)	0.327
Stroke	33 (9.6)	24 (18.0)	9 (4.3)	<0.001
Kidney disease	39 (11.4)	12 (9.0)	27 (12.9)	0.299
Diabetes	63 (18.4)	24 (18.0)	39 (18.7)	1.000
Dangerous dynamics	38 (11.1)	15 (11.3)	23 (11.0)	1.000
Number of broken ribs, mediana (IQR)	2 (1-3)	2 (1-3)	2 (1-3)	0.262
Injury Severity Score, mediana (IQR)	4 (1-5)	4 (1-5)	4 (1-5)	0.724
Patient outcome				0.370
Discharged at home	197 (57.6)	81 (60.9)	116 (55.5)	
Hospitalized	145 (42.4)	52 (39.1)	93 (44.5)	

Table 2. Univariate analysis of clinical, demographic and anamnestic characteristics divided into patients who have or have not reported intrathoracic hemorrhage.

Variables	No presence of ITH	Presence of ITH	p
Patients, n (%)	318 (93.0)	24 (7.0)	
Age, median (IQR)	84 (79-89)	81 (76-86)	0.045
Anticoagulation, n (%)			0.193
DOACs	127 (39.9)	6 (25.0)	
VKAs	191 (60.1)	18 (75.0)	
Previous clinical history, n (%)			
Ischemic heart disease	63 (19.8)	4 (16.7)	1.000
Hypertension	277 (87.1)	20 (83.3)	0.538
Chronic heart failure	51 (16.0)	8 (33.3)	0.046
Active cancer	25 (7.9)	2 (8.3)	1.000
Chronic liver disease	9 (2.8)	1 (4.2)	1.000
Diabetes	58 (18.2)	5 (20.8)	0.785
Chronic kidney failure	32 (10.1)	7 (29.2)	0.012
Chronic obstructive pulmonary disease	18 (5.7)	1 (4.2)	1.000
Number of broken ribs, median (IQR)	2 (1-3)	4 (3-5)	<0.001
Injury Severity Score, median (IQR)	3 (1-5)	9 (6-13)	<0.001
Dangerous dynamics, n (%)	26 (8.2)	12 (50.0)	<0.001
HAS-BLED score, median (IQR)	2 (2-2)	2 (2-3)	0.603

received a radiological examination only upon arrival in the ED, while the remaining 84.5% (289/342) receiving another radiological control examination within the next 72 hours. A total of 2.6% (9/342) of the patients showed an immediate post-traumatic ITH. Of these, 8 were being treated with VKAs, while 1 patient was being treated with DOACs ($p=0.077$). In addition, 5.3% (15/280) of the patients who underwent radiological control examination within 72 hours of the previous examination showed delayed bleeding. Of these, 5 patients were receiving DOACs and 10 patients were receiving VKAs ($p=0.788$).

Discussion

In this study, performed on a cohort of 342 patients over 75 years of age receiving OAT and evaluated in the ED for closed chest trauma with at least one rib fracture, patients taking DOACs presented a comparable risk of post-traumatic ITH to patients taking VKAs. In addition, in cases of minor trauma (<3 rib fractures), no ITHs were observed in patients receiving DOACs.⁷

The elderly population is known to have a greater risk of trauma than younger individuals.¹³ Elderly patients' falls frequently lead to visits to the ED and, though they generally have non-severe dynamics, they can lead to insidious traumatic conditions.¹⁻³

In cases with the same severity and dynamics of the trauma, elderly patients have a risk of death twice as high as that of patients under 65 years of age.³ The risk of death over the age of 65 is estimated to increase by 6.8% each year due to the known fragility of the elderly, the high number of comorbidities and the chronic therapies commonly received by this population.^{2,3} Taking an OAT pre-trauma is a factor that promotes both immediate and delayed post-traumatic hemorrhage and can also cause serious hemorrhagic conditions even in non-severe trauma (minor head trauma, chest trauma, hip fracture).^{17,18} OAT can certainly cause problems in elderly and frail patients.¹⁹ The safety profile of DOACs is not as well defined as that of the older VKAs.^{17,18} Without clear indications, currently, it seems necessary to maintain a high level of caution for every elderly patient with even minor trauma receiving OAT.¹⁹ To our knowledge, this is the first study that, in addition to analysing the risk of ITH in patients receiving OAT, analyses the differences in risk between VKAs and DOACs in cases of chest trauma with minor dynamics.

A previous study found that 7% of elderly patients receiving OAT presented a post-traumatic hemorrhagic complication, a statistic that can be compared with rates in other areas of minor trauma, such as mild traumatic brain injury, in which post-traumatic bleeding occurs in between 3% and 10% of cases.¹⁷⁻²⁰

This study was designed to focus attention on elderly patients treated with OAT who present in the ED mainly due to a chest trauma caused by an apparently non-severe dynamic injury (accidental fall, direct trauma). Along with mild traumatic brain injury, chest trauma appears to be a frequent consequence of falls in the elderly, and although the risk of complications does not appear high for either of these conditions, concomitant OAT complicates their management.

Previously, the risk of ITH after chest trauma with at least one rib fracture was studied in patients taking antiplatelet therapy and in patients taking antithrombotic therapy.^{12,21} In particular, in the study by Storlarski *et al.*, antithrombotic therapy, comprised of all patients receiving OAT and antiplatelet therapy, did not present a greater risk than that observed in patients who were not receiving any therapy that modified the blood coagulative structure, as deter-

mined by presenting the composite outcome of the study (lung complications, hospitalizations in intensive care, LOS in intensive care and rate of respiratory failure).¹² However, combining anticoagulant and antiplatelet therapy, which are characterized by different indications and actions, did not allow the researchers to deduce precise information about the characteristics of OAT and the risk of adverse events after a chest trauma.^{12,21} The risk of lung complications in patients treated with only with VKAs was found to be 24.2% (33/149).¹²

While it is well established that DOACs are not inferior to VKAs in cardioembolic prevention, possible differences in post-traumatic bleeding risk have not been fully explored. Feeney *et al.* compared the risk of bleeding between patients taking VKAs and those taking DOACs in the case of severe closed trauma (ISS >15), excluding head trauma.²² In a cohort of 114 patients (78 VKAs vs 36 DOACs), patients receiving DOACs presented significantly lower mortality than those in the VKA group (DOACs group 8.3%, VKA group 29.5%, $p=0.015$), as well as a lower number of transfused units per patient ($p=0.001$).²² In contrast, as reported by Dennis *et al.*, who focused on severe chest trauma with more than 3 rib fractures, the current study showed no difference between VKA and DOACs in this subgroup of more severe patients (14.3% vs 12.8%, $p=0.807$).⁷ In cases of thoracic trauma with fewer than 3 ribs fractured, ITH occurred only in patients treated with VKAs. Similar findings have been described in cases of minor head trauma, for which some studies have demonstrated a significant increase in the risk of bleeding in patients taking VKAs compared to those taking DOACs. Spinola *et al.*, whose cohort included 402 patients, observed a higher incidence of intracranial haemorrhage in patients taking VKAs than those taking DOACs (10.2% vs 2.6%, $p<0.01$).^{17,20,23} This was confirmed in the study by Cipriano *et al.* ($n = 206$), in which the risk of ITH was significantly higher for patients treated with VKAs (15.7% vs 4.7%, RR 3.34, 95% CI 1.18–9.46, $p<0.05$). No difference was observed in delayed bleeding after an initial negative CT scan.²⁴ In the current study, no difference was noted in the risk of intrathoracic bleeding 48 hours after the first negative radiological chest examination between patients receiving VKAs and DOACs. It is also confirmed that, in cases of thoracic trauma, although rare, there is a risk of delayed bleeding in patients receiving OAT.

The present study has some limitations, including its retrospective nature. However, the manual reassessment of individual folders, the presence of multiple centers and the radiological reassessment have minimized possible bias. Second, only some of the patients underwent a CT scan. However, in the departments that participated in the study, in cases with non-severe dynamics, conventional chest X-rays were performed and an adequate period of observation was adopted, with an eventual radiological control performed at an appropriate number of hours after the previous examination. Third, in the absence of a precise classification of ITH and due to the retrospective nature of the study, which did not allow the execution of CT scans on all patients, the presence of post-traumatic ITH was defined by the radiological reassessment of the examination results by two radiologists. It was not always possible to differentiate between the different amounts of bleeding and, given the objective of the study, all forms of ITH were globally included. Fourth, it was not possible to reconstruct the doses of DOACs taken; therefore, it was not possible to investigate an association between dose and hemorrhagic risk. The study, however, has eliminated all doubts of an incorrect anticoagulant therapy. Finally, there are no data available on any treatment after hospitalization. However, therapeutic choices were made according to international guidelines and the risk of hemorrhage (the main

result of the study) should not be affected by possible therapeutic interventions.

Conclusions

DOACs contributed to the exponential increase in the use of OAT, especially among those in the elderly population who were previously concerned about some problems related to VKAs. DOAC therapy, which in recent years has proven to be as effective in reducing thromboembolic risk as VKA therapy, has not been associated with a higher risk of intrathoracic bleeding in the elderly population requiring OAT. In addition, despite the preliminary nature of the study, the risk appears to be low in the case of non-severe trauma, allowing for rapid and safe management of these patients in the ED. Future studies will be necessary to confirm these preliminary findings.

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