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The publisher's version is available at:

DOI: 10.1007/s11739-025-04078-z

When citing, please refer to the published version.

Oral anticoagulants-related bleeding: what happens in the Emergency Room?

The Galeno study.

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Abstract

There are no real-world data on the modalities and outcomes of managing major or life-threatening bleeding related to oral anticoagulants in the emergency room (ER).

The primary endpoint of this prospective observational study was to evaluate the therapeutic regimen ER physicians started to manage bleeding and 30-day mortality. The secondary endpoint was to evaluate the appropriateness of DOACs prescription and hospital admissions. Data were collected using RedCap. Patient's general characteristics, laboratory test results, therapy started in the ER to manage bleeding, patient transfer to another hospital department or discharge home, and 30-day mortality were recorded.

A total of 526 consecutive patients were enrolled, 67% treated with DOACs and 33% with VKAs. Reversal of oral anticoagulants was successfully performed in a minority of patients, while in a percentage ranging from 30.5% for dabigatran to 60.2% for VKAs, patients did not receive any treatment, even if necessary. Thirty-day mortality was 11% and 17% for patients treated with DOACs and VKAs, respectively. Major bleeding conferred a higher risk of death (OR = 2.95, 1.42-6.16). Compared with VKAs, DOACs therapy reduced the risk of death by 57% (OR = 0.43, 0.26-0.72). Excessive doses were administered to 10.8%, 13%, 18%, and 19% of patients treated with rivaroxaban, edoxaban, apixaban, and dabigatran, respectively. In these patients, major bleeding occurred in a percentage ranging from 66.7% to 94.7% depending on the drug administered. Overall, 25.8% of patients, treated primarily with DOACs, were discharged. The management of oral anticoagulant-related major or life-threatening bleeding in the ER appears poor.

Keywords: anticoagulants, antidotes, Emergency Service, hemorrhage, inappropriate prescribing.

Introduction

For decades, vitamin K antagonists (VKAs) have been the gold standard for the treatment of thromboembolic events, until the introduction of direct-acting oral anticoagulants (DOACs) in 2010 [1]. This new therapy quickly spread worldwide, increasing and surpassing the number of patients treated with warfarin. Although DOACs have revolutionized anticoagulation management, bleeding events remain a trouble [2]. Randomized clinical trials and observational studies have shown that DOACs, in comparison with VKAs, have a superior or similar efficacy and safety with an overall rate of bleeding of approximately 2-3% [3].

The Emergency Room (ER) often represents the first and decisive medical intervention in oral anticoagulated patients with major or life-threatening bleeding. In the United States, a comprehensive study of drugs requiring medical monitoring for adverse events showed that warfarin and DOACs contribute approximately 15.5%, mostly in the elderly. [4]. Contrary to expectations, the more widespread use of DOACs has been accompanied by an increase in the number of ER admissions for active bleeding, 1 in 15 elderly treated with warfarin and 1 in 23 elderly treated with DOACs, with a percentage of hospitalized patients of approximately 50% in comparison with 45.7% of patients treated with warfarin [5].

In 2023 a group of European Experts published a consensus paper [6] to provide clinicians with a systematic approach for the management of major bleeding in the ER to improve the care of anticoagulated patients, who are often complex with multiple comorbidities or who sometimes are admitted to the ER because of post-traumatic hemorrhage.

To our knowledge, the literature lacks real-life data reporting the modalities and outcomes of managing oral anticoagulant-related bleeding in the ER. We therefore planned a prospective observational study called GALENO (oral anticoaGulAnts-related bleeding in the EmergeNcy ROom) to assess what can happen in an ER when faced with bleeding due to oral anticoagulants.

The primary endpoint of the GALENO study is to evaluate the therapeutic regimen used by ER physicians to manage bleeding related to either VKAs or DOACs therapy and 30-day mortality in these patients. The secondary endpoint is to determine the appropriateness of DOACs prescriptions and the percentage of hospital admissions.

Design of the study

The GALENO study is a phase IV, regional, multicenter, unsponsored, prospective observational study. It was designed to evaluate patients on oral anticoagulant therapy who were bleeding and required access to the ER of one of the five largest Sardinian hospitals in the north, center, and south of the island. The study was approved by the Independent Ethics Committee of the Azienda Ospedaliero-Universitaria (AOU) of Cagliari and Sassari (Prot. NP/2019/4031) and by the Ethics Committee of the Azienda per la Tutela della Salute (ATS) of Sardinia (Prot. 156/2019/C.E.).

Unfortunately, the beginning of the SARS-CoV-2 pandemic overlapped with the start of the study, January 2020, so data were collected mainly in the AOU of Cagliari, which included 503 patients. A total of 23 patients (4.4%) came from the ER of Sassari (n=8), Nuoro (n=10), Oristano (n=1), and Azienda Ospedaliera Brotzu, Cagliari (n=4). The pandemic has created significant inconvenience and difficulties in the emergency rooms of all hospitals, so after an initial participation in the study, colleagues no longer entered patients into the eCRF. In the AOU of Cagliari this was possible because our group of the Departmental Unit of Haemostasis and Thrombosis gave great help to colleagues in the emergency room in entering the data. The study ended in December 2022.

Patients and Methods

Patients

Five hundred and twenty-six consecutive patients on VKAs or DOACs therapy, admitted to the ER of the Sardinian hospitals for a bleeding episode, were included in the study.

The predefined exclusion criteria were: patients younger than 18 years of age, patients treated with heparins (calcium heparin, low molecular weight heparin, fondaparinux), either as a single drug or in combination with VKAs and DOACs, patients treated with antiplatelet drugs alone and those who did not give their informed consent to participate.

The study protocol did not provide specific guidance for the diagnosis and treatment of major or clinically relevant non-major bleeding; therefore, patients were managed according to the protocols used by emergency physicians in their daily clinical practice.

All patients or their caregivers gave informed consent to participate in the study.

Methods

Data were collected via RedCap, an electronic Case Report Form (eCRF) made freely available by the Arianna Foundation, a non-profit organization based in Bologna, created with the aim of

improving knowledge on antithrombotic therapies and promoting scientific research. Access to RedCap was allowed to researchers through a personal account, while patient anonymity was guaranteed through identification with a progressive entry number automatically generated by the system. For each patient, the eCRF allowed the collection of general characteristics (age, gender, body weight, indication and type of oral anticoagulant, prescribers of VKAs or DOACs, concomitant use of other drugs); laboratory test results [hemoglobin (Hb) values, platelet count, liver and renal function, prothrombin time (PT), activated partial thromboplastin time (aPTT), dilute thrombin time (dTT), and anti-activated factor X (a-FXa) activity for each DOAC]; therapy started in the ER to address the hemorrhage (supportive therapy with packed red blood cells and/or plasma, reversal agent or antidotes for VKAs and DOACs, antifibrinolytic agents and invasive procedures), transfer of the patient to another hospital department or discharge home, and 30-day in-hospital mortality. The severity of bleeding events was assessed according to ISTH criteria [7, 8]. Liver function was assessed by performing alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ -glutamyl transferase (γ -GT) and cholinesterase (Che) while renal function was assessed by creatinine or glomerular filtration rate (GFR) calculated according to the CKD-EPI formula [9]. The management of major bleeding was evaluated according to the European Expert consensus criteria [6] that suggests targeting anticoagulant therapy when the time since last dosage is short or the drug excretion is impaired because of renal insufficiency. It is noteworthy that the short half-life of DOACs comes from studies in healthy volunteers, while data from the German RADOA registry have demonstrated a prolongation of their half-life in emergency patients up to 20 hours [10]. So, we considered time since last dosage ≤ 6 hours or GFR < 30 ml/min.

The appropriateness of DOAC prescription was assessed by applying drug-specific dose reduction criteria [11]. Finally, 30-day mortality, defined as in-hospital death from all causes within 30 days, was ascertained by consulting the discharge sheet of the medical record. Patients who were discharged and might have died at home or elsewhere within the 30-day window were not considered.

Statistical analysis

Continuous variables were expressed as median and range or mean and standard deviation on the basis of their distribution. Categorical variables were expressed as absolute numbers and percentages. Fisher exact test and the logistic regression stepwise model were also used.

P values < 0.05 were considered statistically significant. Medcalc software (version 17.7.2, Ostend, Belgium) was used for data processing.

Results

Between January 2020 and December 2022, a total of 526 consecutive patients, 354 (67%) on DOACs and 172 (33%) on VKAs therapy, required access to the ER of Sardinian hospitals for a bleeding event and were included in the study. It was not possible to calculate the rate of admissions for oral anticoagulant-related bleeding in the Sardinian ER given the small number of patients supplied by the other hospitals. In the ER of the AOU of Cagliari, the incidence is approximately 0.65% per year (a mean of 175/27000 total accesses per year), although affected by the reduced number of admissions in general, due to the SARS-CoV-2 pandemic. General characteristics of the patients are reported in Table 1.

Overall, 494 (93.9%) unprovoked and 32 (6.1%) post-traumatic bleeds were recorded. Gastrointestinal bleeding (270, 51%), epistaxis (86, 16.3%), and cerebral haemorrhage (30, 5.7%) were the most frequent adverse events recorded. Major, clinically relevant non-major (CRNM), and minor bleeding were 372 (70.7%), 139 (26.5%), and 15 (2.8%), respectively. No difference between VKAs and DOACs was found in the evaluation of the two groups of patients in relation to the site of bleeding, except gastrointestinal (Table 2). In particular, the risk of bleeding from the lower gastrointestinal tract is significantly reduced in patients treated with VKAs compared to patients treated with DOACs (OR=0.36, 0.17-0.78). No differences were found when upper and upper and low gastrointestinal tracts were considered.

Appropriateness of DOAC prescription

In a percentage between 11% and 19% the administered dose of DOACs was too high for patients who met the dose reduction criteria as recommended by FDA and EMA. In these patients, major bleeding occurred in a percentage range between 66.7% and 94.7%. Compared to patients on standard doses, only patients treated with excessive dosage of apixaban showed in increased rate of major bleeding. Detailed data regarding the appropriateness of DOAC prescription are reported in Table 3.

Treatment of major bleeding in the Emergency Room

Supportive therapy with packed red blood cells was required in more than fifty percent of patients. Oral anticoagulant reversal was administered in a minority of patients, while in a percentage ranging from 30.5% for dabigatran to 60.2% for VKAs, patients did not receive any treatment, even if necessary. INR values and DOACs plasma concentration were never checked at the end of treatment to verify whether the clotting potential of these patients had been restored. The therapeutic regimen used in the ER to counteract major hemorrhages is detailed in Table 4. Overall, 135 patients (25.8%) were discharged home, of which 39 (28.9%) were treated with VKAs. The remaining 388 patients were transferred to other departments, mainly Internal Medicine (57%), Gastroenterology (13.6%), and Haemostasis and Thrombosis Unit (10.3%). No data are available for 3 patients.

Mortality at 30 days

Data were available for 521 patients, in 5 it was not possible to evaluate the outcome of the bleeding event at 30 days because the patients had been transferred to other hospitals.

A total of 68 patients (13%) died in hospital within 30 days from the bleeding event, median age was 84 ± 8 years, 51.5% (35/68) were female and the indication for treatment with oral anticoagulants was venous thromboembolism (n=5), acute coronary syndrome (n=3) and atrial fibrillation (n=60). A total of 39 patients (39/354, 11%) were treated with a DOAC (10 apixaban, 5 dabigatran, 17 edoxaban and 7 rivaroxaban), while VKAs had been prescribed to the other 29 patients (29/171, 17%) (10 warfarin, 18 acenocoumarol and 1 phenprocoumon). The median duration of hospitalization was 7.5 (1-30) days. Major bleeding events were 59 (87%) of which 31 were gastrointestinal bleeding and 9 cerebral hemorrhages. Ninety-six percent of hemorrhages were unprovoked. Antiplatelet drugs (aspirin, clopidogrel, or ticlopidine) were chronically taken by 7 patients (10%). There was no difference in 30-days in-hospital mortality between ER-treated and untreated patients with DOACs or VKAs therapy reversal (DOACs: treated 26.6% vs untreated 23%, $p=0.74$; VKAs: treated 43% vs untreated 34%, $p=0.55$).

The stepwise logistic model showed that major bleeding confers a higher risk of death (OR=2.95, 1.42-6.16), while, compared to VKAs, treatment with DOAC reduces the risk of death by 57% (OR=0.43, 0.26-0.72). No significant associations were found between mortality and antiplatelet drugs, age, or gender.

Discussion

The Galeno study was designed to obtain real-life data on the ER management of bleeding related to oral anticoagulants, both VKAs and DOACs. In our study, the management of major bleeding due to VKAs was, in general, poor because the guidelines for the reversal were not properly followed. The use of vitamin K IV along with 4-factor PCC administration was, in fact, only seldom used, even if they are able to allow effective hemostasis [12]. In the case of dabigatran, although idarucizumab is a well-established antidote [13], it was used to reverse therapy only in 8% of patients. Factor Xa inhibitors also have a specific antidote, which is Andexanet α . It was licensed for use in patients treated with rivaroxaban and apixaban. Andexanet- α was never used in our ER since it is a very expensive drug which is not reimbursed by the regional health department, at least in our country, but is entirely charged to the single hospital. Nevertheless, only 16.5% of the patients treated with direct factor Xa inhibitors received PCCs. It is worth noting that while INR was always requested to the laboratory, dilute thrombin time and anti-FXa activity were never performed at the time of admission of patients to the ER, although these tests were available in our laboratory. Reversal of DOACs therapy was performed without knowing the drug concentrations and without verifying that the reversal had been performed effectively. This poor behavior is in contrast with what is recommended in case of major bleeding due to the use of DOACs [14,15]. In-hospital 30-day mortality from any cause was 13%. This percentage is quite high compared to that reported in randomized clinical trials on atrial fibrillation: 3.64% for dabigatran, 7.26% for edoxaban, and 3.52% for apixaban. As expected, major bleeding generally conferred a threefold increased risk of death, while no significant associations were found between mortality and antiplatelet drugs, age, or sex. Compared with VKAs, treatment with DOACs reduced the risk of death by 57%. This result is in line with that of randomized clinical trials, even if the percentage of reduction is higher. The absence of difference in mortality between patients treated and those not treated with a reverse approach deserves a comment. As a matter of fact, although essential, the reverse procedure is probably not the only aspect to be taken into account in reviewing the entire management of bleeding induced by DOACs. The appropriateness of DOACs prescription has been evaluated by several studies. A recent systematic review of the literature found that the appropriateness of DOAC prescription is poor, with a percentage of patients in whom errors were identified equal to 20% (from 4% to 43%) [16]. The results of our study, in line with those reported in this meta-analysis, show, in particular, the percentage of prescription errors based on the type of drug: 24% for apixaban, 19% for dabigatran, 17% for edoxaban, and 12.5% for rivaroxaban. The

dosage taken by these patients was too high because the criteria for its reduction have not been applied. When compared to patients on standard doses, only patients treated with excessive dosage of apixaban, showed an increased rate of major bleeding. The limited number of patients treated with excessive doses of the other DOACs may have influenced the negative results. The dosage of DOACs should be evaluated not only at the time of prescription of the anticoagulant drug, but also during the clinical and laboratory follow-up of these patients. Cerebral and gastrointestinal bleeding were, together with epistaxis, the most frequently observed adverse events at the time of admission to the ER. Overall, gastrointestinal hemorrhages were more frequent in patients treated with DOACs. In particular, the risk of bleeding from the lower gastrointestinal tract was significantly reduced in patients treated with VKAs compared to patients treated with DOACs, confirming the results previously obtained in the studies of Barcellona et al. [17] and Zoppellaro et al. [18]. Colonoscopy, therefore, should be the first endoscopic procedure to be performed in patients receiving DOACs who present with anemia or enterorrhagia. A surprising finding was that no difference was found between VKAs and DOACs in terms of cerebral haemorrhages, even if unprovoked and post-traumatic events were considered separately. A possible explanation is that patients enrolled in the clinical trials randomized to VKAs did not show a good quality of therapy. Patients treated with DOACs, on the contrary, have been carefully followed during those studies in terms of dose prescription and adherence [19]. Since patients admitted to the ER were not selected but represent a real-life condition, more advanced age than that of randomized clinical trials, comorbidities and DOACs inadequate prescription dosage may justify the results obtained. However, it is worth noting that a protective effect of DOACs was evident when referring to in-hospital 30-day mortality. Another surprising finding from this study is that it shows a significant percentage of patients, about 10%, arriving at the ER with epistaxis or minor hemorrhages. It is true that uncontrolled epistaxis can induce severe bleeding and sometimes to a hemorrhagic shock [20], but the question that arises is that these patients did not have a Hemostasis and Thrombosis Center or a specialist to turn to in case of adverse events, showing a significant absence of the Territorial Medicine in the management of problems involving oral anticoagulants. Post-traumatic hemorrhages represented 11% of the bleeding events, a not-so-high percentage considering that the median age of the patients studied was 83 years and that accidental falls are quite frequent in old age. A program for preventing falls in the elderly has recently been published that has been shown to be effective and cost-effective, and may further reduce the incidence of falls in these patients [21].

Strengths and limits

The strength of this study was to obtain a real-life picture of the physicians working in the ERs of our region when faced with hemorrhagic events due to oral anticoagulants. Moreover, this study confers very useful information on how to ameliorate ER performance on the anticoagulant bleeding management. The major limit of this study was the relatively small sample size, but this was due to the pandemic, which has grossly modified the behavior of the health care status everywhere. Another limit is that the findings in this study may not be generalized since they represent predominantly the practice in one large hospital.

Conclusions

Management of major or life-threatening bleeding related to oral anticoagulant use in the ER appears to be lacking. Reversal of oral anticoagulant therapy was performed in a minority of patients and plasma concentrations of DOACs were never monitored either before or after reversal. Major bleeding and VKAs therapy were significantly associated to 30-days in-hospital mortality for any cause.

Acknowledgements: none

Authors' contributions: all authors contributed to the study's conception and design.

Material preparation and data collection were performed by Antonio Bussu, Monica Orrù, Maria Laura Caddeo.

The data analysis and the first draft of the manuscript was carried out by Doris Barcellona and Francesco Marongiu.

All authors commented on previous versions of the manuscript and read and approved the final manuscript.

Funding: The project was performed with no specific financial or material support.

Data availability: data are available on request due to privacy/ethical restrictions.

Declarations

Conflict of interest: all the authors declare that they have no conflicts of interest.

Ethical approval: obtained.

Human and animal rights statements and Informed consent: all participants provided informed consent prior to their participation.

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Table 1. General characteristics of the patients.

General characteristics	VKAs	DOACs	p
Patients, n (%)	172 (33%)	354 (67%)	<0.0001
Age, median (range)	84 (47-97)	83 (33-103)	0.35
Women, n (%)	87 (50.6%)	174 (49.1%)	0.78
BMI, median (range)	26 (15.4-41.1) ^{1*}	26.7 (15.6-40) ^{2*}	0.19
Atrial fibrillation, n (%)	147 (85.5%)	330 (93.2%)	0.006
Acute coronary syndrome, n (%)	9 (5.2%)	4 (1.1%)	0.01
Venous thromboembolism, n (%)	16 (9.3%)	20 (5.6%)	0.14
Antiplatelet drugs or NSAIDs, n (%)	16 (14.1%) ^{3*}	20 (8.3%) ^{4*}	0.13
Steroids, n (%)	3 (2.6%) ^{3*}	13 (5.4%) ^{4*}	0.28
Insulin or oral hypoglycemics, n (%)	13 (11.5%) ^{3*}	47 (19.6%) ^{4*}	0.07
Anti-hypertensive drugs, n (%)	90 (79.6%) ^{3*}	165 (68.7%) ^{4*}	0.04
Warfarin, n (%)	73 (42.4%)	–	
Acenocoumarol, n (%)	98 (57%)	–	
Phenprocoumon, n (%)	1 (0.6%)	–	
Dabigatran, n (%)	–	47 (8.9%)	
Rivaroxaban, n (%)	–	89 (16.9%)	
Apixaban, n (%)	–	121 (23%)	
Edoxaban, n (%)	–	97 (18.4%)	
Prescribers of oral anticoagulant therapy			
Cardiologists, n (%)	106 (68.8%) ^{5*}	235 (71.2%) ^{6*}	
Haemostasis and Thrombosis Unit, n (%)	36 (23.4%) ^{5*}	69 (20.9%) ^{6*}	
Internal Medicine, n (%)	12 (7.8%) ^{5*}	22 (6.7%) ^{6*}	
Neurology Department, n (%)	0 (0%) ^{5*}	4 (1.2%) ^{6*}	

Legend: ^{1*}data was available from 286 patients; ^{2*} data was available from 125 patients;

^{3*}data was available from 113 patients; ^{4*} data was available from 240 patients;

^{5*}data available for 154 patients; ^{6*}data was available for 330 patients.

Table 2. Sites of bleeding of patients treated with either VKAs or DOACs.

Site of bleeding	VKAs	DOACs	p
Gastrointestinal, n (%)	67 (45.6%)	174 (52.7%)	0.02
Cerebral, n (%)	12 (8.2%)	15 (4.5%)	0.20
Emoftoe/Hemoptysis, n (%)	4 (2.7%)	7 (2.1%)	0.74
Hemothorax, n (%)	0 (0%)	3 (0.9%)	0.55
Hematuria, n (%)	5 (3.4%)	8 (2.4%)	0.55
Metrorrhagia, n (%)	1 (0.7%)	2 (0.6%)	0.99
Retroperitoneal, n (%)	1 (0.7%)	0 (0%)	0.31
Epistaxis, n (%)	25 (17%)	60 (18.2%)	0.80
Muscle hematomas, n (%)	4 (2.7%)	7 (2.1%)	0.74
Soft tissue, n (%)	3 (2.0%)	5 (1.5%)	0.70
Other sites, n (%)	25 (17%)	49 (15%)	0.58

Table 3. Patients treated with too high a dose of DOACs and major bleeding events.

Patients on DOACs	Too high dose n, (%)	Major bleeding n, (%)	Standard dose n, (%)	Major bleeding n, (%)	p
Apixaban, n 106*	19 (18%)	18 (94.7%)	87 (82%)	52 (59.8%)	0.003
Dabigatran, n 47	9 (19%)	7 (77.8%)	38 (81%)	24 (63%)	0.7
Edoxaban, n 85 [#]	11 (13%)	9 (81.9%)	74 (87%)	53 (71.6%)	0.18
Rivaroxaban, n 83 [°]	9 (10.8%)	6 (66.7%)	74 (89.2%)	39 (52.7%)	0.49

Legend: * data were not available in 15 patients, [#] data were not available in 12 patients,

[°] data were not available in 6 patients.

Table 4. Major bleeding management in the ER.

	VKAs	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Patients, n	123	47	121	97	89
Transfused, n (%)	72 (58.5%)	22 (61.1%)	56 (65%)	48 (92.3%)	37 (65%)
Vitamin K + PCCs, n (%)	14 (11.4%)	–	–	–	–
PCCs only, n (%)	2 (1.6%)	–	8 (9.5%)	0 (0%)	4 (7%)
Vitamin K only, n (%)	22 (17.9%)	–	–	–	–
Idarucizumab, n (%)	–	3 (8.3%)	–	–	–
Andexanet- α , n (%)	–	–	0 (0%)	–	0 (0%)
Not treated, n (%)	74 (60.2%)	11 (30.5%)	34 (39.5%)	28 (36.4%)	18 (31.5%)