Management of major bleeding in patients treated with direct oral anticoagulants: from experience to standardized protocols

Sara Mascia,[1] Anna Maria Ferrari,[2] Nicola Macarone Palmieri,[3] Elisa Romagnoli,[4] Chiara Catena,[5] Serena Scarabottini,[5] Francesca Mori,[5] Lucio Brugioni[4]

[1]Emergency Medicine specialist; [2]Emergency Department, AUSL of Reggio Emilia; [3]Emergency Room, Arcispedale Santa Maria Nuova, Reggio Emilia; [4]Internal Medicine and Critical Area Unit, Policlinico di Modena; [5]Emergency Medicine, University of Modena and Reggio Emilia, Italy

ABSTRACT

Evaluation of clinical-laboratory-therapeutic management and related clinical outcomes (thrombotic-hemorrhagic complications) of patients undergoing treatment with direct oral anticoagulants (DOACs) during major bleeding. This is a two-year observational retrospective study. 27 cases of major bleeding in patients undergoing a therapy with DOACs presented to the Emergency Department of Arcispedale Santa Maria Nuova (Reggio Emilia Hospital). 16 cases (59%) underwent reversal of anticoagulation treatment: 19% using specific reversal therapy (idarucizumab) and 81% using non-specific agents [4-factor prothrombin complex concentrate (4F-PCC)]. Routine laboratory data were available for all the cases, but only for some patients it was possible to obtain the plasma dosage of the oral anticoagulant. Laboratory data confirm rapid correction of activated partial thromboplastin time within one hour from the reversal of anticoagulation with idarucizumab. The absence of correlation between standard blood tests and plasma drug dosage in patients treated with factor Xa Inhibitors was confirmed too. The management of major bleeding during treatment with DOACs using reversal therapy (idarucizumab) and non-specific reversal agent (4F-PCC) showed minimal thrombotic (0.3%) and hemorrhagic (0.3%) complications at 90 days; no events occurred after 6 months.

Introduction

Warfarin has been the only drug for the prevention and the treatment of diseases associated with thromboembolic risk for almost half a century. Multiple limits of this therapy led to the development of direct oral anticoagulants (DOACs), approved thanks to wide clinical randomized trials showing clearly the non-inferiority of DOACs in terms of reduction of both thromboembolic risk and major bleedings.[1,2] The first published randomized controlled trials (RCTs) compared DOACs with vitamin K antagonists in patients with non-valvular atrial fibrillation - ARISTOTLE[3] for apixaban; RE-LY trial[4] for dabigatran; ROCKET-AF[5] for rivaroxaban and ENGAGE AF-TIMI 48[6] for edoxaban -, then RCTs were published about venous thromboembolism.

Main concerns in prescribing DOACs are related to the management of active major bleeding in the Emergency Department (ED) and to still persistent difficulties in laboratory monitoring in urgency settings.[7,8]

To monitor anticoagulant therapy with DOACs, traditional laboratory tests (PT and aPTT) present numerous limits and scarce accuracy; providing only qualitative evaluations of the concentration of the drug and quantitative tests for DOACs plasma level [diluted thrombin time (dTT) and ecarin clotting assay for dabigatran and measurement of anti-FXa activity for rivaroxaban, apixaban and edoxaban] are available only in some laboratory.

In case of major bleeding, in our reality, the ther-

Correspondence: Lucio Brugioni, Internal Medicine and Critical Area Unit, Policlinico di Modena, via del pozzo 71, 41121 Modena, Italy.
Tel.: +39.059.4225491. E-mail: luciob2362@gmail.com

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apeutic choice for reversal of anticoagulant activity are specific antidotes (at the time of the study they were available only for dabigatran) or the 4-factor prothrombin complex concentrate (4F-PCC) for other DOACs. There are different formulations of prothrombin concentrates: PCC with 3 factors (II, IX, X; UMAN COMPLEX®/PROTROMPLEX®), with 4 factors containing factor VII in addition to protein S and C (CONFIDEX®, PRONATIV®), the recombinant active factor VII (rFVIIa) and the activated prothrombin complex with 4 factors (aPCC, FEIBA®).

Effectiveness of clotting factors concentrates has been described in patients undergoing therapy with AVK with major bleeding.[9-11]

However, their effectiveness in bleeding associated with DOACs has not been proven by large randomized controlled studies.[12-16] Anyway, the use of 4F-PCC is the therapeutic nonspecific strategy more widely used to revert the activity of the direct inhibitors of FXa[12,18-21] while there is even less certainty about the aPCC usage.[22,23]

The best strategy remains the use of specific antidotes, allowing an optimal management of those patients who present to the ED with major bleeding or requiring emergency surgery or procedure. Idarucizumab has been approved and it is already in use for reversal dabigatran activity, while the antidote for direct inhibitors of FXa (andexanet alpha) has been approved by FDA and EMA has granted a conditional authorization.

The studies that analyzed the efficacy and safety of these antidotes are: REVERSE AD (dabigatran-idarucizumab), ANNEXA-A and ANNEXA-R (andexanet-inhibitor FXa).

The aim of our study is to observe retrospectively how in our reality (Emergency Department of Arcispedale Santa Maria Nuova, Reggio Emilia) major bleedings in course of DOACs were managed. We collected data about the chosen strategy of reversal, coagulation assay, plasma levels used and clinical outcome of patients.

Materials and Methods

In this retrospective single-center study we enrolled a cohort of 27 consecutive patients who presented in a two-year period (March 2016-March 2018) at the ED of Santa Maria Nuova Hospital in Reggio Emilia with a major hemorrhage (defined according to ISTH classification[24]) during treatment with direct oral anticoagulants.

Numerous data were collected for each patient and inserted into a database, including the following: i) previous ischemic and/or hemorrhagic events; ii) type of DOACs, dosage and time elapsed since the last intake, indication for anticoagulant treatment: atrial fibrillation (AF) associated or not with previous stroke, recent or previous diagnosis of venous thromboembolism (VTE) and duration of treatment (if undertaken during the previous 3 months); iii) data about the admission to the emergency room: color code assigned in triage; hemodynamic and/or neurological state of the patient on arrival; iv) plasma level of the drug, when available, and coagulation assay at 0-1-12 h (PT and aPTT for dabigatran; PT for rivaroxaban, apixaban and edoxaban); v) dosage and type of drug chosen for the reversal of anticoagulation activity and the time elapsed between the access to ED and its administration; vi) clinical outcomes: intrahospital death, ischemic and/or hemorrhagic events during follow-up (at 30-90 days and at 6 months detected by computerized patient archive).

All the data were used for subsequent simple statistical analysis.

Results

Of the 27 patients enrolled, 4 were treated with dabigatran, 10 with rivaroxaban, 12 with apixaban and only one with edoxaban. Among them, 19 were on anticoagulant therapy in primary prevention for non-valvular atrial fibrillation, while 3 were in secondary prevention for AF. The remaining 5 patients in the study were on anticoagulant treatment following VTE.

In the study group, 4 patients (15%) had started anticoagulant therapy less than 3 months before the major hemorrhagic event.

In ED 52% (n=14) of patients showed gastro-intestinal bleeding and 48% (n=13) intracranial bleeding (Table 1). Among the latter, in 6 cases bleeding was due to post-traumatic events (1 case of subarachnoid hemorrhage and 5 subdural hemorrhages); the other 7 patients developed spontaneous events (4 deep-thalamus localization hemorrhages/base nuclei and 3 lobe hemorrhages).

Table 2 shows data that we have collected.

Table 1. Number and site of major bleeding.

Type of drug	Number of major bleeding	Bleeding site ICH	GI
Dabigatran	4	3	1
Rivaroxaban	10	2	8
Apixaban	12	8	4
Edoxaban	1	1	
Total	27	13	14

ICH, intracerebral hemorrhage; GI, gastrointestinal.

Patients treated with reversal of anticoagulation activity

Sixteen patients (59%) were treated with reversal of anticoagulant activity.

For three patients receiving dabigatran, idarucizumab 5 g was administered intravenously as two-bolus doses of 2.5 g no more than 15 min apart. Two cases had intracranial bleeding and one had digestive bleeding. All patients had taken the last dose less than 7 h before the hemorrhagic event. Only for one patient DOACs plasma concentration was performed at time 0 and at 12-h intervals for control (which confirmed dTT normalization). In all 3 cases, routine laboratory tests showed normal renal function; aPTT at time 0 was prolonged with subsequent normalization in all cases within one hour after administration of the specific antidote. The mean time between presentation to the ED and administration of idarucizumab was 85 min.

Five patients undergoing therapy with rivaroxaban were all treated with a 4F-PCC. Two of them had intracranial bleeding and three of them had major gastrointestinal bleeding. Both patients with cerebral hemorrhage had taken the last dose between 13 and 16 hours earlier: the dosage of 25 IU/kg 4F-PCC was chosen. In blood tests renal function was normal, plasma FXa activity showed different plasma concentrations (for one patient 20 ng/mL and for another >200 ng/mL) compared to a qualitative coagulation test (PT) that was normal in both cases. The remaining three patients with a gastro-intestinal hemorrhage had taken the last dose of the drug within the previous 3 hours. They were all treated with doses of 4F-PCC ranging between 25 and 37.5 IU/kg. Laboratory tests showed conflicting pictures: in two patients PT was prolonged and for one of them the anti-FXa activity was >300 ng/mL; in the third patient, PT was normal and the plasma concentration of the drug was 20 ng/mL.

In the eight patients treated with apixaban therapy, the anticoagulation activity was reverted with 4F-PCC (Pronativ®) using doses between 25 and 50 IU/kg: all of them presented cerebral bleeding (post traumatic in three cases). Five cases had taken the last dose of the drug less than 5 h earlier, the remaining 3 between 13 and 17 h earlier. All had normal renal function. In patients who had taken the drug between 13 and 17 h before the hemorrhage, laboratory tests showed plasma concentrations of apixaban between 80 and 180 ng/mL with a normal PT in 100% of patients; in patients who had taken the dose earlier, the plasma dose of the drug was >200 ng/mL. The average time between ED access and reversal therapy was 64 minutes.

All patients with gastrointestinal bleeding received endoscopic treatment beyond 24 h after arrival at ED.

Patients not treated with reversal of anticoagulation activity

Eleven patients have not undergone reversal therapy: 10 had gastrointestinal hemorrhage (all treated with FXa inhibitors) and 1 had cerebral hemorrhage.

The case of intracranial bleeding was the only one among patients on dabigatran treatment not to be managed by administration of the specific antidote. This choice derived from the finding of a minimal blood quota in the tomographic scan (two spontaneous intracranial hemorrhagic petechiae). The last intake of the drug was 14 h earlier in this patient; the coagulation pattern of the biohumoral tests was altered (aPTT>2), dTT was not performed.

Among the five patients receiving rivaroxaban: 3 patients had eGFR >60 mL/min and two <35 mL/min (calculated with Cockcroft-Gault formula). The drug was taken more than 24 h earlier and all were hemodynamically stable. Laboratory tests showed discrepancies: in two cases PT was prolonged but in one of them the plasma concentration of the drug was <30 ng/mL; in the other three cases, PT was normal but only for one patient the plasma concentration of the drug was assessed, which was 60 ng/mL. Four of these patients were treated endoscopically within 3 h from the arrival to the ED.

All patients receiving apixaban had normal renal function and altered blood coagulation with PT prolongation. The plasma drug concentration was only required in two patients and for both patients it was >160 ng/mL. Two had taken the drug less than 4 h before and the other two between 11 and 13 hours before. Of them, one patient died within one hour from the arrival in the emergency room for hemor-

Table 2. Types of treatment.

Type of drug (number of bleeding)	Specific reversal agents	Non-specific reversal agents
Dabigatran (4)	3	/
Rivaroxaban (10)	/	5
Apixaban (12)	/	8
Edoxaban (1)	/	/

rhagic shock; the others presented hemodynamically stable.

The only patient on edoxaban did not undergo re-coagulation, because clinical stability at the onset and the last dose of DOACs had been taken more than 24 h earlier.

Only one of the patients with intracranial bleeding required neurosurgery approach: he presented an acute subdural hemorrhage and was treated with clotting factors concentrates (4F-PCC).

Clinical outcomes

Four deaths (15% of the total) occurred within 72 hours most likely in relation to the severity of the clinical condition at the onset: they were all hemodynamically unstable, treated with direct factor Xa inhibitors and received reversal therapy with clotting factors concentrates (4F-PCC).

During the follow-up, 19 patients (70%) resumed anticoagulant therapy, all with direct oral anticoagulants.

Only one case of thrombotic complication (recurrent femoral-popliteal deep vein thrombosis) has been reported at 90 days: this patient was previously treated with apixaban for VTE and received 4F-PCC for a subependymal cerebral hemorrhage, furthermore, after the acute event, the patient did not restart any anticoagulant therapy.

At 90 days only one hemorrhagic complication developed too: one case of minor hemorrhage (rectal bleeding) was observed in a patient treated with rivaroxaban for AF.

Thrombotic or hemorrhagic complications at 6 months have not been registered in any case,

Conclusions

Data collected reveal the great variability in the management of major bleeding during DOACs in an emergency department.

The effectiveness and safety of treatment with idarucizumab is already known and confirmed in our study.

Generally, routine coagulation test (PT and aPTT) does not provide an accurate assessment of DOACs anticoagulant effect. For dabigatran, aPTT may provide a qualitative assessment of dabigatran activity while aPTT and also PT cannot be used for any meaningful evaluation of FXa inhibitory effect. In particular, they should not play any role in guiding the treatment of major bleeding and the possible administration of reversal. In our study the use of idarucizumab allowed the correction of both dTT at 12 h and the aPTT within one hour.

The decision to administer reversal agents was mainly guided by the type of hemorrhage, patient clinical condition and time from last drug intake (for drugs with well-known elimination half-life): all intracranial hemorrhages, being considered major hemorrhages, have been treated, while some cases of gastrointestinal hemorrhage have been treated without reversal because causal and also operative therapy could be applied.

In the emergency setting of a major bleeding, it would be desirable to perform the quantification of DOACs plasma levels but these tests are not yet widely available, not low-cost and reference ranges for peak and through levels are not standardized, although complex technology (most routine coagulometers are capable of measuring DOACs plasma levels within <30 min) is not required. Management protocols shared with laboratory are necessary in order to implement the use of such data that could really guide the management of the patient with major bleeding during DOACs. In particular, if plasma level has not been confirmed, the administration of 4F-PCCs and specific antidotes (drugs with high-cost and with thrombotic high-risk) is not indicated.

In our study, the timing of endoscopic examination in patients with gastrointestinal hemorrhage was very variable (within 3 h or more than 24 h): the possibility for DOACs to predict the expected time of normalization of plasma levels based on renal function allows to safely delay the endoscopic examination; the correct timing shall be always agreed with the reference specialist, according to the patient clinical status.

Thrombotic and/or hemorrhagic events were minimal at 90 days (0.3%) and these were absent at 6 months, underlying the effectiveness of the treatment of major bleeding if it is performed according to available scientific evidence. In addition, these data demonstrate the need for short-term evaluation for the timing of anticoagulation reinitiation.

Therefore, in all emergency departments it is necessary to create and to follow standardized multidisciplinary protocols based on scientific evidence available for the management of major bleeding during treatment with DOACs.

Although this is a small observational retrospective study carried out on a limited number of patients, our work emphasizes the great variability in the management of such emergency and the absolute necessity to follow shared standardized protocols. In this regard, in case of a major hemorrhage in a patient on DOACs treatment, our study further supports the adoption of the practical indications reported by HERA Guidelines 2018[25] and ACC consensus 2017,[26] which first require a classification of hemorrhagic events to consequently apply the specific treatment (Figure 1; Tables 3 and 4).

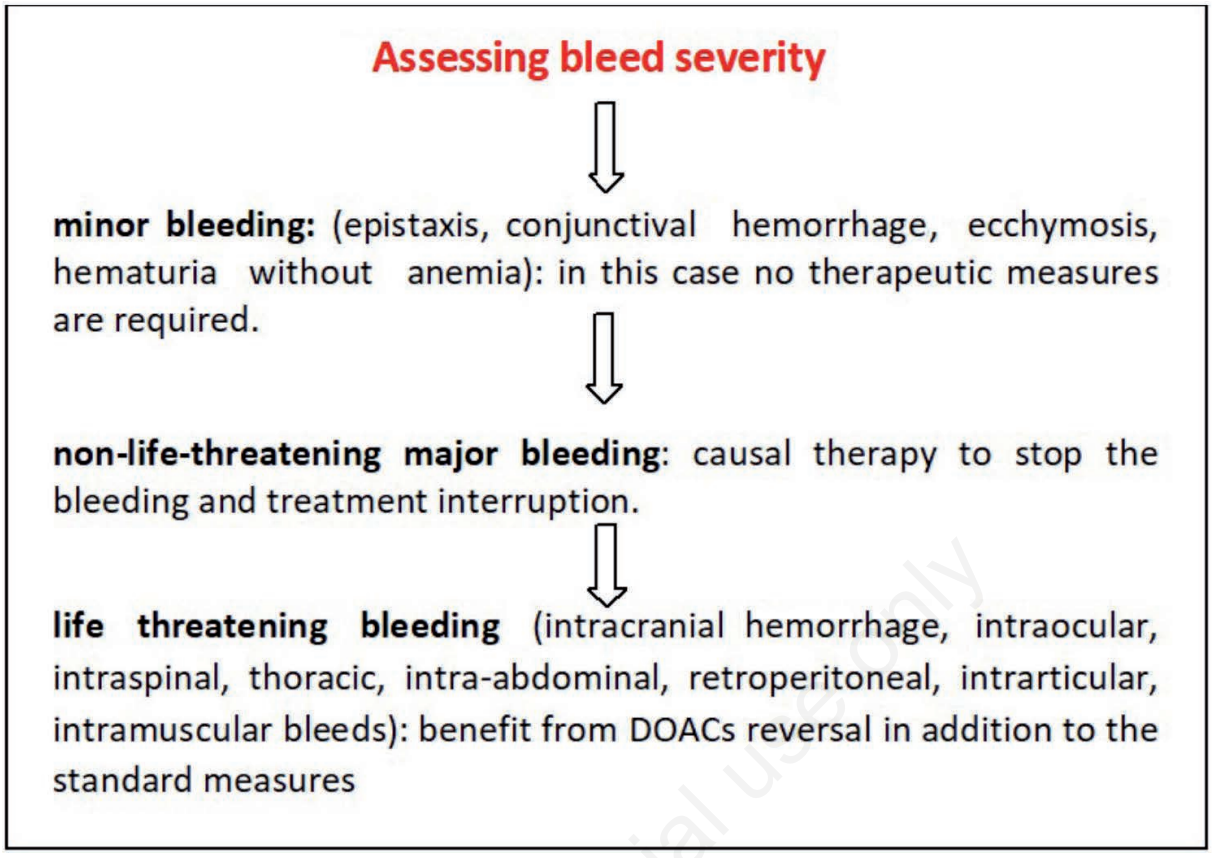

Figure 1. Classification of hemorrhagic events.

Table 3. Management of non-life-threatening major bleeding.

Direct thrombin inhibitors (dabigatran)	FXa inhibitors (apixaban, rivaroxaban, edoxaban)
• Identify the drug, dosing regimen and inquire about last intake • Urgently perform the specific laboratory tests for assessing the anticoagulant activity (diluted thrombin time and ecarin clotting assay for dabigatran; chromogenic anti-Xa assay for FXa inhibitors) • Stop DOACs • Consider the use of tranexamic acid (1 gr i.v. repeated every 6 h if needed) especially in bleeding following trauma • Consider activated charcoal for known recent ingestion (<2 h, only for dabigatran use) • Fluid replacement and maintain diuresis • Execute, when possible, supportive measures for mechanical hemostasis (endoscopic, surgical, interventional radiology, *etc.*)	
• Estimate normalization of plasma levels: i) normal renal function 12-24 h; ii) CrCl </min: 36-48 h • Consider idarucizumab (see below)	• Normalization of plasma levels in 12-24 h

Table 4. Management of life-threatening bleeding.

Direct thrombin inhibitors (dabigatran)	FXa inhibitors (apixaban, rivaroxaban, edoxaban)
• All of the above • Direct reversal with idarucizumab 5 gr i.v. in two boluses of 2.5 gr no more than 15 min apart	• All of the above • 4F-PCC 25-50 UI/kg
• Activated PCC or human recombinant coagulation factor VII can be considered only if 4F-PCC is unavailable • Fresh frozen plasma not as reversal agent	

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