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RESEARCH ARTICLE

Adherence to protocols for the use of reversal agents in patients treated with direct oral anticoagulants

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ABSTRACT

Objectives: This study aimed to evaluate the adherence to protocols for the use of reversal agents in direct oral anticoagulant (DOAC) users in Dutch hospitals.

Methods: A retrospective cohort study was conducted in seven hospitals in the Netherlands. Treatment protocols for bleeding and (urgent) procedures in patients on DOAC were collected from each hospital. All patient data on the use of reversal agents were retrospectively collected from September 2021 to April 2022 and compared to the protocols. The degree of per-protocol adherence (compliance score) was categorized into four levels as follows: poor (<45%), moderate (45–79%), high (80–89%), and full (> 90%) adherence rates.

Results: A total of 290 patients were included in our study. In patients with bleeding under DOAC, the protocol adherence for prothrombin complex concentrate (PCC) was "moderate" (61%). In the remaining cases (39%), non-adherence was mainly caused by underdosing (68%), overdosing (12%), and a lack of indication (14%). Furthermore, idarucizumab was administered for bleeding with "full" adherence (96%). For andexanet alfa, adherence to the hospital bleeding protocol was "moderate" (67%), with a lack of indication being the only reason for non-adherence. In case of reversal for an urgent procedure, the protocol adherence for PCC was "low" (45%), with underdosing, a lack of indication, and missing lab data being the main reasons for non-adherence. Missing lab data on dabigatran plasma concentration before reversal was the main reason for "low" adherence (26%) in idarucizumab. The adherence for andexanet alfa was also "low" (0%).

Conclusion: In case of reversal for bleeding under DOAC, overall adherence to the protocol was "moderate"; however, in patients needing an urgent procedure, it was "low." The major reasons for non-adherence were underdosing, off-label use, and a lack of specific lab testing. The results of this study can assist in improving the implementation of hospital protocols.

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DOAC; bleeding; intervention; adherence; protocol; reversal

Introduction

As with all antithrombotic agents, patients using direct oral anticoagulants (DOAC) are at risk of bleeding complications. For various mild and moderate bleeding events, DOAC withdrawal and a "wait and support" policy are sufficient. The bleeding event will eventually be resolved without further complications. In case of planned procedures with an increased risk of complications due to extensive bleeding, DOAC therapy may be interrupted before the procedure to consider the DOAC type, the risk of bleeding during the procedure, and renal function. In patients with life-threatening bleeding or in need of an urgent procedure, an immediate reversal of anticoagulation is required[1]. Together with other medical treatment options, reversal agents such as prothrombin complex concentrate (PCC; registered for vitamin K antagonist and recommended for Xa inhibitor bleeding reversal), idarucizumab (registered for life-threatening bleeding and urgent procedures under dabigatran), and andexanet alfa (registered only for life-threatening bleeding under rivaroxaban and apixaban) are currently available to treat this group of patients. Considering the specific indications and the fact that some agents reverse only dabigatran (idarucizumab) or the anti-Xa DOACs (andexanet alfa), these agents

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need to be incorporated into local, regional, or national anticoagulation reversal protocols and guidelines.

After the implementation of the anticoagulation reversal protocol, it is essential to monitor its compliance with the (local) protocol, in clinical practice. This is of particular importance because several studies assessed associations between survival and adherence to protocols that may imply a cause-and-effect relationship[2–6]. Furthermore, all DOAC reversal agents are expensive, with specific antidotes (idarucizumab and andexanet alfa) being more expensive than non-specific factor concentrates (PCC). An online survey reported that 66% of the hospitals that had not added andexanet alfa to their formulary mentioned costs as a reason[7].

In our previous studies, we provided an overview of the content of protocols for the management of DOAC-related bleeding and perioperative protocols in patients treated with DOAC in the Netherlands[8,9]. We concluded that protocols are often incomplete and show a high degree of variation.

In this study, we evaluated the use of DOAC-reversal agents in seven Dutch hospitals and in particular, their protocol adherence.

Methods

Study design

A retrospective cohort study was conducted in seven hospitals in the Netherlands. Data were collected from the electronic patient records (EPR; Chipsoft, Epic and Nexus) of these seven hospitals (two academic, three teaching, and two general). Treatment protocols for bleeding and urgent procedures, in patients on DOAC, were collected from all hospitals.

Patient population

All patients that received 4 F-PCC (Beriplex or Cofact), andexanet alfa (Ondexxya), or idarucizumab (Praxbind) as the first-line treatment of DOAC because of bleeding or urgent surgery between January 2016 and April 2022 were included. Subsequently, the indication of the reversal agent in relation to DOAC use was tested against the local protocol. Patients who had not used DOACs (apixaban, rivaroxaban, edoxaban, or dabigatran) before the start of reversal agent treatment were excluded. Patients who objected to the use of their data for medical research were also excluded.

Ethics

Ethical committees of all participating hospitals reviewed the study protocol before the start of the study and decided that, under Dutch law, a full medical ethical review was not required.

Study procedures and definitions

Minor and major bleeding types were defined according to the International Society on Thrombosis and Haemostasis[10]. The adherence was categorized into four levels, defined by the French Healthcare Authorities as follows: poor (<45%), moderate (45–79%), high (80–89%), and full (>90%)[2]. The conformance of the reversal agent usage with the treatment protocol of the relevant hospital (in terms of indication, reversal agent, dose, type of bleeding, etc.) was examined for each patient. However, no independent reviewers were involved to confirm the reliability of the scoring. The compliance rate for each reversal agent group was calculated as the percentage of the total cases, where reversal agents were applied according to the protocol. Compliance rates (%) for each analyzed reversal agent were used to describe their adherence.

Underdosing and overdosing are defined as the doses given below or above the advised dosages in hospital protocols. A lack of indication is defined as an indication for which the reverse agent was used but not registered. In case of missing lab data, we referred to the blood levels for dabigatran, apixaban, edoxaban, and rivaroxaban before idarucizumab use.

Primary and secondary outcomes

The primary outcome is the overall compliance rate per reversal agent, reported separately for bleeding and urgent procedures. Secondary outcomes are overall compliance rates for bleeding and urgent procedure protocols and the specific aspects of the protocols for which adherence was poor.

Data collection

Data were analyzed according to the research protocol in which the DOAC and reversal agents used (type, dosage, etc.), site of bleeding, type of urgent intervention, bleeding classification (minor or major), concomitant antiplatelet use, and additional prohemostatic agent given were considered.

Data analysis

In the descriptive study, no formal hypothesis testing was performed. Only descriptive statistics were used for reporting primary and secondary outcomes. Categorical variables were presented using frequency counts and percentages and continuous variables as the mean value with standard deviation. Data analysis was performed using MS Office Excel 2019.

Results

Inclusion and baseline characteristics

A total of 290 patients under DOAC were included. Among them, 228 experienced bleeding and 62 underwent an urgent intervention, in which reversal agent(s) were used. The mean ages of the bleeding and urgent-procedure groups were 76 ± 10 years and 73 ± 11 years, respectively. The majority of the patients belonged to the teaching (50–73%) and academic (34–24%) hospitals. The major DOAC usage

Table 1. Baseline characteristics.

	Bleeding ($n = 228$)	Intervention ($n = 62$)
Age (years), mean (SD)	76 (10)	73 (11)
Indication DOAC, no. (%)		
Atrial fibrillation	191 (84)	54 (87)
Venous thromboembolism	15 (6)	7 (11)
Other	1 (1)	0 (0)
Unknown	21 (9)	1 (2)
DOAC type, no. (%)		
Apixaban	77 (34)	13 (20)
Dabigatran	67 (30)	40 (65)
Edoxaban	7 (3)	3 (5)
Rivaroxaban	77 (33)	6 (10)
Concomitant antiplatelet, no. (%)		
Acetylsalicylic Acid	13 (6)	2 (3)
P2Y12 inhibitor	8 (4)	2 (3)
Dual antiplatelet therapy	3 (1)	1 (2)
Type of hospital in which treatment has taken place, no. (%)		
Community	37 (16)	2 (3)
Teaching	114 (50)	45 (73)
Academic	77 (34)	15 (24)

Abbreviations. SD, standard deviation; no., number; DOAC, direct oral anticoagulant; P2Y12 inhibitors, clopidogrel, prasugrel, and ticagrelor.

was for atrial fibrillation, which contributed to 84 and 87% in bleeding and intervention groups, respectively (Table 1).

Bleeding

Detailed information on the use of reversal agents in patients with bleeding is shown in Table 2. In 80% of the cases, the indication for the reversal agent was intracranial or gastrointestinal bleeding. The above-mentioned bleeding cases made up 69% of the major bleeding cases.

PCC

Of the 151 patients treated with PCC, 59 were non-compliant, resulting in "moderate" adherence for PCC (61%). The reasons for non-adherence were underdosing (68%), overdosing (12%), lack of indication (used for minor bleeding over major bleeding) (14%), and others (6%). PCC was administered in a wide range of dosages, with 50 IE/kg being the most prescribed (62%). Tranexamic acid, andexanet alfa, and vitamin K were additional prohemostatic treatments given with PCC

Idarucizumab

Idarucizumab was used in 68 patients, of which, one used apixaban instead of dabigatran. Idarucizumab was used with nearly "full" adherence (96%). Non-adherence in three (4%) cases was caused by underdosing (33%), overdosing (33%), and a lack of indication (used for bleeding under apixaban; 33%). The dosage of this reversal agent ranged from 2.5 to 10 g, with 5 g being the most frequently used (94%). PCC and tranexamic acid were the additional antidotes administered.

Andexanet alfa

Adherence to the hospital protocol was "moderate" (67%), with lack of indication (used for urgent procedures instead of bleeding) being the only reason for non-adherence. Andexanet alfa is only registered for bleeding and not for urgent procedures. Moreover, two dosages of andexanet alfa was used, i.e. 400 mg (low dose) and 800 mg (high dose) boluses followed by 280 or 960 mg in 2 h, respectively. PCC and tranexamic acid were given as additional antidotes.

Overall adherence

Overall adherence to the hospital protocol for bleeding was "moderate" (71%).

Urgent procedures

Detailed information on the use of reversal agents for patients needing an urgent procedure is shown in Table 3. In 65% of the patients to whom a reversal agent was administered, the type of DOAC used was dabigatran. Furthermore, laparoscopy and orthopaedic surgery accounted for 36 and 15% of the urgent procedures, respectively.

PCC

Adherence to the protocol was "low" (45%), with underdosing, a lack of indication (patient using dabigatran), and missing lab data (apixaban, rivaroxaban, and edoxaban blood levels) as the main reasons for non-adherence. PCC was administered in a dose range of 25–50 IE/kg, with 50 IE/kg being the most frequently used (in 50% of the cases). Tranexamic acid was the only prohemostatic agent given.

Idarucizumab

Missing lab data (dabigatran blood levels) on the dabigatran plasma concentration before administering the reversal agents was the main reason for a "low" adherence (26%). One patient received an overdose of idarucizumab (10 g). One hospital in which two patients were treated had no protocol for the use of reversal agents for urgent interventions in patients using DOAC (Table 3).

Table 2. Details on the use of reversal agents in bleeding patients* using DOAC.

	PCC ($n = 151$)	Idarucizumab ($n = 68$)	Andexanet alfa ($n = 9$)	Total ($n = 228$)
DOAC type, no. (%)				
Apixaban	70 (46)	1 (1)	6 (67)	77 (34)
Dabigatran	0 (0)	67 (99)	0 (0)	67 (30)
Edoxaban	7 (5)	0 (0)	0 (0)	7 (3)
Rivaroxaban	74 (49)	0 (0)	3 (33)	77 (34)
Site of bleeding, no. (%)*				
Gastrointestinal	44 (29)	20 (29)	3 (33)	67 (30)
Intracranial	78 (52)	29 (43)	6 (66)	113 (50)
Muscosceletal	14 (9)	5 (7)	0 (0)	19 (8)
Pulmonal	6 (4)	5 (7)	0 (0)	11 (4)
Cardial	2 (1)	4 (6)	0 (0)	6 (3)
Other	7 (5)	5 (7)	0 (0)	12 (5)
Bleeding category, no. (%)				
Minor	31 (21)	21 (31)	1 (11)	53 (23)
Major	108 (72)	42 (62)	8 (89)	158 (69)
Unknown	12 (8)	5 (7)	0 (0)	17 (7)
Administration of antidote				
PCC, no. (%)				151 (66)
<25 IE/kg	12 (8)			
25 IE/kg	30 (20)			
25–50 IE/kg	12 (8)			
50 IE/kg	93 (62)			
>50 IE/kg	4 (3)			
Idarucizumab, no. (%)				68 (30)
2.5 gr		3 (4)	7 (78)	9 (4)
5 gr		64 (94)	2 (22)	
10 gr		1 (1)		
Andexanet alfa, no. (%)				
400 mg bolus + 280 mg/2 h				
800 mg bolus + 960 mg/2 h				
In accordance with hospital protocol				
Yes, no. (%)	92 (61)	65 (96)	6 (67)	163 (71)
No, no. (%)	59 (39)	3 (4)	3 (33)	65 (29)
Underdose, no. (% of No)	40 (68)	1 (33)	0 (0)	
Overdose	7 (12)	1 (33)	0 (0)	
No indication	8 (14)	1 (33)	3 (100)	
Other	4 (7)	0 (0)	0 (0)	
Additional prohemostatic, no. (%)				
PCC	0 (0)	3 (4)	2 (22)	
Tranexamic acid	35 (23)	14 (21)	1 (11)	
Eptacog Alfa	0 (0)	1 (1)	0 (0)	
Fibrinogen	0 (0)	0 (0)	0 (0)	
Andexanet alfa	1 (1)	0 (0)	0 (0)	
Vitamin K	2 (1)	0 (0)	0 (0)	
Type of hospital in which treatment has taken place, no. (%)				
General	27 (18)	10 (15)	0 (0)	37 (16)
Teaching	72 (48)	41 (60)	1 (11)	114 (50)
Academic	52 (34)	17 (25)	8 (89)	77 (34)

*Most common bleedings were described. Least common are grouped with 'Other.'
Abbreviations. no., number; DOAC, direct oral anticoagulant; PCC, prothrombin concentration complex.

Andexanet alfa

Andexanet alfa was administered in three patients and in all of them, a clear indication (not registered for urgent interventions) for the use of this reversal agent was lacking, resulting in low adherence (0%).

Overall adherence

Overall adherence to the hospital protocol for urgent procedures is "low" (31%).

Tranexamic acid

Frequent use of tranexamic acid as an additional prohemostatic treatment was observed in one hospital. Further analysis of the data showed that tranexamic acid was used according to the protocol for bleeding only in 13% of cases. Inappropriate dosing and a lack of indication (used for indications that are not specified in a specific hospital protocol) were the main reasons for non-adherence.

Discussion

We found moderate (61%), full (96%), and moderate (67%) adherence to the bleeding protocols for PCC, idarucizumab, and andexanet alfa, respectively. Adherence to urgent protocols was "low" at 45, 26, and 0% for PCC, idarucizumab, and andexanet alfa, respectively (Figure 1). Overall adherence to treatment protocols was "moderate" in patients with bleeding and "low" in those needing an urgent procedure. However, for idarucizumab, a "high" adherence to the bleeding protocol was found. The main reasons for non-adherence to the bleeding protocol were underdosing and off-label use

Table 3. Details on the use of reversal agents for patients needing (urgent) intervention using DOAC.

	PCC ($n = 20$)	Idarucizumab ($n = 39$)	Andexanet alfa ($n = 3$)	Total ($n = 62$)
DOAC type, no. (%)				
Apixaban	11 (55)	0 (0)	2 (67)	13 (21)
Dabigatran	1 (5)	39 (100)	0 (0)	40 (65)
Edoxaban	3 (15)	0 (0)	0 (0)	3 (5)
Rivaroxaban	5 (25)	0 (0)	1 (33)	6 (10)
Intervention type, no. (%)				
Vascular surgery	2 (10)	0 (0)	0 (0)	2 (3)
Wound rinsing	2 (10)	1 (3)	0 (0)	3 (5)
Drainage	3 (15)	5 (13)	0 (0)	8 (13)
Laminectomy	2(10)	0 (0)	0 (0)	2 (3)
Transplantation	1 (5)	0 (0)	0 (0)	1 (2)
Laparoscopy	8 (40)	13 (33)	0 (0)	21 (34)
Amputation	1 (5)	0 (0)	0 (0)	1 (2)
Groin rupture	1 (5)	3 (8)	0 (0)	4 (6)
Orthopedic surgery	0 (0)	9 (23)	0 (0)	9 (15)
Trauma surgery	0 (0)	1 (3)	0 (0)	1 (2)
Pacemaker implantation	0 (0)	3 (8)	0 (0)	3 (5)
Biopsy	0 (0)	3 (8)	2 (67)	5 (8)
Mastoidectomy	0 (0)	1 (3)	0 (0)	1 (2)
Necrosectomy	0 (0)	0 (0)	1 (33)	1 (2)
Administration of antidote PCC, no. (%)				20 (32)
<25 IE/kg	6 (30)			
25 IE/kg	0 (0)			
25–50 IE/kg	4 (20)			
50 IE/kg	10 (50)			
>50 IE/kg	0 (0)			
Idarucizumab, no. (%)		0 (0)		39 (63)
2.5 g		38 (97)		
5 g		1 (3)		
10 g				
Andexanet alfa, no. (%)				
400 mg bolus + 280 mg/2 h			0 (0)	3 (5)
800 mg bolus + 960 mg/2 h			3 (100)	
In accordance with hospital protocol				
Yes, no. (%)	9 (45)	10 (26)	0 (0)	19 (31)
No, no. (%)	11 (55)	27 (69)	3 (100)	41 (66)
Underdose, no. (% of No)	2 (18)	0 (0)	0 (0)	
Overdose	0 (0)	1 (4)	0 (0)	
No indication	1 (9)	0 (0)	3 (100)	
Missing lab data	7 (64)	26 (96)	0 (0)	
Other	1 (9)	0 (0)	0 (0)	
Other	0 (0)	2 (5)	0 (0)	2 (3)
Protocol not present				
Additional prohemostatic no. (%)				
Tranexamic acid	7 (35)	0 (0)	0 (0)	
Type of hospital in which treatment has taken place, no. (%)				
General	0 (0)	2 (5)	0 (0)	2 (3)
Teaching	10 (50)	35 (90)	0 (0)	35 (56)
Academic	10 (50)	2 (5)	3 (100)	15 (24)

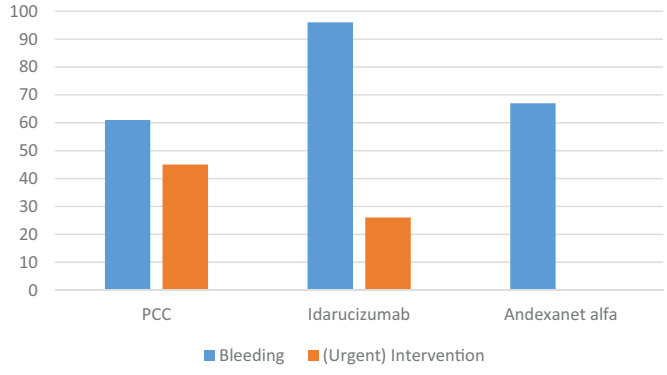

Figure 1. Use of reversal agents in accordance with hospital protocols (%). Abbreviation. PCC: prothrombin concentration complex.

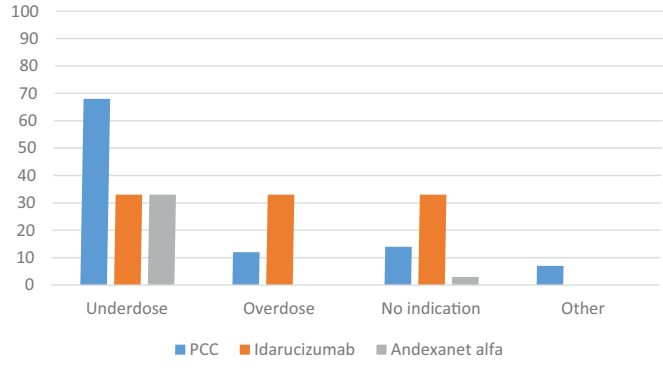

Figure 2. Deviations from hospital protocols in use of reversal agents for bleeding (%).

(Figure 2). In urgent procedures, laboratory assays for measuring drug concentrations mentioned in the protocols were seldom performed (Figure 3).

Currently, there are no studies that have published results on the extent to which PCC usage complies with protocols in patients using DOAC. Additionally, for the vitamin K

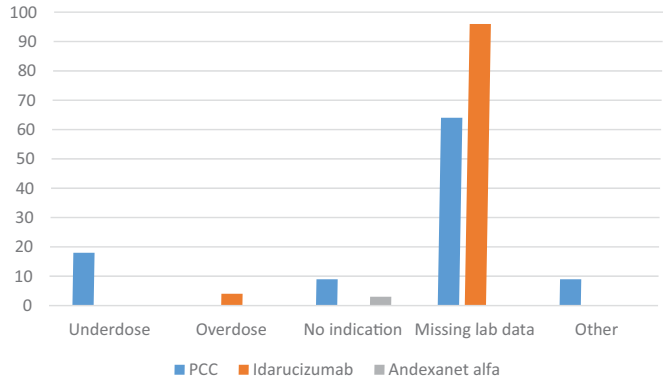

Figure 3. Deviations from hospital protocols in the use of reversal agents for (urgent) intervention (%).

antagonist (VKA), studies on compliance are limited. Barillari et al. described the use of PCC in 47 patients (VKA users) in a clinical setting in Italy[11]. He observed that guidelines were not always followed, and vitamin K was only used in a quarter of all patients. Toth et al. found that the majority of VKA patients who did not achieve a post-treatment INR below 1.5 received little to no vitamin K or lower dosages of PCC than recommended[12]. They also showed that, in a potentially significant group of patients that underwent urgent surgery, the use of PCC could have been avoided by better planning and prompt use of vitamin K. In part, these findings could also be relevant for reversal in DOAC patients.

Van der Wall et al. found that inappropriate usage of idarucizumab occurred in 28% of patients; 14 of 35 patients (40%) required intervention and 11 of 53 patients (21%) presented with bleeding[13]. They concluded that in all the intervention cases, the procedure could have been delayed (for at least 8 h) and in eight of the bleeding complications, the situation was not considered "uncontrollable." Dabigatran plasma levels were not measured in other patients; either they had a last intake >72 h and a normalized aPTT or they used rivaroxaban. A global study on the use of idarucizumab in clinical practice by Fanikos et al. found a low frequency of unapproved idarucizumab dosage regimens (3.3%) and minimal off-label use[14]. Life-threatening bleeding was the most frequent indication for idarucizumab (57.7%), followed by urgent intervention (35.9%). Among the life-threatening bleeding events, the most frequent was gastrointestinal tract bleeding (44.4%). No information was provided on whether the appropriateness of the urgent intervention was considered, while analysing the possibility of delaying the intervention or specific laboratory assays.

Studies on the adherence to protocols of andexanet alfa are very limited. In their study, Sobolewski et al. evaluated the adherence to institutional restriction criteria in patients with an indication for andexanet alfa[15]. The restriction criteria intended to promote judicious prescribing due to safety concerns and significant costs. During the study, there were 16 requests for andexanet alfa, of which seven were denied for a lack of an approved indication. Drug spending for andexanet alfa was approximately $319,000. A reduction in drug spending by $203,280 was achieved due to the implementation of the restriction criteria.

Our results are largely consistent with those in the above-mentioned studies. A wide range of dosages for PCC in bleeding protocols is advised due to scarce scientific data on the most effective dose regime. Idarucizumab is less prone to inappropriate dosing because of its simple approved dosage regimen for bleeding and urgent intervention. The low protocol adherence rates in urgent interventions and PCC usage are due to missing lab data. We hypothesize that clinicians prescribing these agents for an urgent intervention are not aware of the criteria for reversal agent use (intervention delay possibilities and specific laboratory assays available) in their local hospital. Andexanet alfa is the newest reversal agent available and is only registered and reimbursed in case of life-threatening bleeding. Unfamiliarity with specific restriction criteria in clinicians and a lack of dispensing control for andexanet alfa by pharmacists, in bleeding and incomplete intervention protocols, could be the main reasons for low adherence scores. Low compliance scores for tranexamic acid, used as an additional prohemostatic treatment (in one hospital), could be attributed to similar reasons.

To our knowledge, this is one of the few studies that investigated whether the reversal agents (idarucizumab, PCC, and andexanet alfa) are applied according to the protocol in DOAC users. The limitation of this study is that the protocols were not validated with strong evidence. We have also not collected data on their year of introduction. This hampered our ability to determine if these characteristics caused non-adherence to the protocol and should be a focus of future research. Furthermore, we were not able to judge adherence in cases where a reversal agent was not used, making our analysis incomplete. Retrospective design is also one of the limitations that limited the depth of our analysis. It also introduces the possibility of underreporting and the risk of bias. The strengths of this study are the large number of included patients (290) and diversity of included hospital types (academic, teaching, and general). Although this was a single-country study, we feel that our findings are representative and therefore, relevant to other countries as well.

We hope that our research contributes to a better understanding of compliance to described protocols and further optimization of the correct use of antidotes.

Conclusion

This study evaluated the use of reversal agents in 290 patients on DOAC who experienced bleeding or underwent (surgical) intervention in seven hospitals across the Netherlands. We found moderate (61%), full (96%), and moderate (67%) adherence to the bleeding protocols for PCC, idarucizumab, and andexanet alfa, respectively. Adherence to urgent protocols was low at 45, 26, and 0% for PCC, idarucizumab, and andexanet alfa, respectively. In bleeding patients, the overall protocol adherence was moderate, and in patients in need of an urgent procedure, it was low. The main reasons for the lack of adherence were underdosing, off-label use, and a lack of specific lab testing. These results can assist in improving protocol implementation.

Transparency

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Declaration of financial/other relationships

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Author contributions

M.v.E, A.R, and N.v.R gathered data; D.M, N.V, and E.v.R designed and initiated the research; M.v.E analyzed protocols and performed statistical analysis; D.M, N.V, M.v.E, and E.v.R analyzed the results; D.M, L.V, P.v.d.B, M.v.H, H.L, K.M, N.V, and E.v.R contributed to writing or reviewed this this article.

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