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ORIGINAL ARTICLE

Direct oral anticoagulants or vitamin K antagonists in emergencies: comparison of management in an observational study

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Abstract

Background: Restoring hemostasis in patients on oral anticoagulants presenting with major hemorrhage (MH) or before surgical intervention has changed, with the replacement of vitamin K antagonist (VKA) with direct oral anticoagulants (DOACs).

Objectives: To observe the difference in urgent hemostatic management between patients on VKA and those on DOACs.

Methods: A multicenter observational study evaluated the variation in laboratory testing, hemostatic management, mortality, and hospital length of stay (LOS) in patients on VKA or DOACs presenting with MH or urgent hemostatic restoration.

Results: Of the 1194 patients analyzed, 783 had MH (61% VKA) and 411 required urgent hemostatic restoration before surgery (56% VKA). Compared to the international normalized ratio (97.6%), plasma DOAC levels were measured less frequently (<45%), and the time taken from admission for the coagulation sample to reach the laboratory varied widely (median, 52.3 minutes; IQR, 24.8-206.7). No significant plasma DOAC level (<50 ng/mL) was found in up to 19% of patients. There was a poor relationship between plasma DOAC level and the usage of a hemostatic agent. When compared with patients receiving VKA (96.5%) or dabigatran (93.7%), fewer patients prescribed a factor Xa inhibitor (75.5%) received a prohemostatic reversal agent. The overall 30-day mortality for MH (mean: 17.8%) and length of stay (LOS) (median: 8.7 days) was similar between VKA and DOAC patients.

Conclusion: In DOAC patients, when compared to those receiving VKA, plasma DOAC levels were measured less frequently than the international normalized ratio and had a poor relationship with administering a hemostatic reversal agent. In addition, following MH, mortality and LOS were similar between VKA and DOAC patients.

KEYWORDS
anticoagulants, coagulation, dabigatran, hemorrhage, hemostatics

Essentials

- We compared urgent reversal strategies between direct oral anticoagulants (DOACs) and vitamin K antagonists (VKA).
- No significant plasma DOAC level (<50 ng/mL) was found in approximately 1 of 5 patients.
- A poor relationship exists between plasma DOAC level and the use of a hemostatic agent.
- Mortality from major bleeding is concerning and is similar between vitamin K antagonist and DOAC patients.

1 | INTRODUCTION

The number of patients on long-term oral anticoagulants (OAC) is steadily increasing by approximately 10% per year because of the age-dependent rise in the incidence of atrial fibrillation (AF) and venous thromboembolism (VTE) [1,2]. Until recently, vitamin K antagonists (VKAs), such as warfarin, were the mainstay of OAC treatment [3]. However, the compelling reason for a change to direct oral anticoagulants (DOACs), such as the direct thrombin inhibitor dabigatran, or direct factor Xa (FXa) inhibitors, such as rivaroxaban, apixaban, and edoxaban, has been an overall reduction in major hemorrhage (MH), particularly the halving of the risk of intracerebral hemorrhage [4,5]. As a result, DOACs account for most OACs currently administered, with recent studies suggesting that DOACs are prescribed rather than VKA in >80% of new patients with AF and VTE [1,2].

However, excessive bleeding is the most concerning side effect of OACs. Data from randomized clinical trials and observational clinical studies show that MH occurs at a rate of 2.1 per 100 patient years [6,7], which is reduced by approximately 30% with DOACs [4,8,9]. Urgent surgery on OACs is estimated to occur in 20% of patients annually

[10,11]. Hospital protocols for MH and urgent hemostatic restoration (UHR) before surgery vary depending on the hospital referral pattern; availability of coagulation tests; access to specific prohemostatic reversal agents, such as prothrombin complex concentrates (PCC; 3 or 4 factor), activated prothrombin complex concentrates (aPCC; FEIBA [Takeda Pharmaceuticals]), recombinant factor VIIa (Novoseven [Novo Nordisk]); and, more recently, specific reversal agents to dabigatran (idarucizumab) and FXa inhibitors (andexanet alfa) [7,12–15].

While monitoring the international normalized ratio (INR) is essential for the safe and effective management of warfarin therapy, patients on DOACs usually do not require laboratory monitoring because of its predictable pharmacokinetics. However, plasma DOAC level can be helpful in exceptional circumstances, such as patients with extremes in body weight, presence of renal disease, using concomitant medications that induce or inhibit liver enzymes, in acute bleeding, prior to urgent surgery, or before instituting thrombolysis for ischemic stroke [12,14,16]. In an emergency, for a plasma DOAC level to have a beneficial impact, the turnaround time (TAT) would need to be the same as an urgent head computed tomography (CT) scan for an intracerebral hemorrhage.

It is unusual to have a normal INR in an emergency for a patient on VKA. In contrast, because DOACs have a short biological half-life, it is expected that in some patients, there will be no detectable plasma DOAC either from poor medication adherence or delay in time from the last dose. Indeed, in DOAC reversal studies in patients with MH or UHR, 21% of patients had no significant plasma dabigatran detected [17,18], 28% had prespecified low anti-FXa levels of <75 ng/mL for rivaroxaban and apixaban [19], and 21.8% had a prespecified low anti-FXa level of <40 ng/mL for edoxaban [20]. These patients were excluded from the efficacy analysis as these levels were considered not clinically relevant for OAC-related bleeding. The International Society on Thrombosis and Haemostasis (ISTH) also recommends only to consider anticoagulation reversal in patients with severe bleeding and a DOAC level of >50 ng/mL and for patients requiring an invasive procedure with a high bleeding risk of >30 ng/mL [21].

To assess the real-world change in hemostatic management from VKA to DOACs, the Anticoagulation Reversal and Events Study (ARES) Collaborative was performed. It aimed to observe the emergency management of OAC patients presenting across major tertiary hospitals in Australia and New Zealand (ANZ). Hospitals implemented widely established ANZ guidelines for VKA-related events [22,23] in contrast to evolving management guidelines for DOACs [24]. In addition, the real-world management pathways for patients presenting on VKA were compared to DOACs, particularly around the utility of OAC levels and the type of prohemostatic and specific reversal agents.

2 | METHODS

2.1 | Study design

The ARES Collaborative Study was an observational cohort study that collected data from ANZ tertiary hospitals on emergency presentations with MH or UHR before surgery or thromboembolism (TE). The study was divided into ARES 1, which recruited 287 patients between October 2012 and April 2015, and ARES 2, which recruited 1201 patients from October 2015 to September 2019. In total, 1488 eligible patients were enrolled. During this study period, the OACs available in ANZ were VKA, dabigatran, rivaroxaban, and apixaban. PCC (Prothrombinex-VF [CSL-Behring], 3-factor PCC) and aPCC (FEIBA) were utilized for VKA and DOAC presentations at a recommended guideline dose of 25 to 50 IU/kg with or without fresh frozen plasma (FFP) [22,23]. Idarucizumab (Praxbind [Boehringer Ingelheim]) at a bolus dose of 5 mg (2 × 2.5 mg) for dabigatran reversal was approved in New Zealand in December 2015 and in Australia in May 2016. VKA is the only approved OAC for patients with mechanical heart valves. Andexanet alfa (Andexxa [AstraZeneca]) was not approved for use in ANZ during the study period. Seventeen sites around ANZ contributed data to this study. Standard-of-care protocols for anticoagulant management and reporting of serious adverse events were administered by each contributing hospital according to local institutional requirements. Participation in the study had no impact on the clinical decisions made. Human research institutional ethics review approval was obtained in each site according to the National Health and Medical Research Council guidelines, which included the category of negligible risk research and waiver of consent for the nonidentifiable data collection. This approval ensures the collection of the most critical events.

2.2 | Selection and enrolment of subjects

Inclusion criteria included patients aged ≥18 years presenting to the emergency department with significant bleeding and TE or requiring hemostatic restoration for urgent surgery and who have taken a DOAC or VKA in the last 7 days. Patients were excluded from further analysis if they had minor hemorrhage controlled by local measures not requiring hospital admission or change in anticoagulant management or if they had TE.

2.3 | Clinical and laboratory evaluation

Clinical record chart review identified baseline demographics, including age and sex, type and main indication for anticoagulation, type of emergency (MH or UHR for surgery or intervention), calculated creatinine clearance (estimated glomerular filtration rate), CHA_2DS_2-VASC score, documentation of the event including adjudication of ISTH bleeding severity definition (life-threatening and MH, minor bleeding) [25], and site of bleeding.

Outcome measures include standard laboratory testing parameters (full blood count, liver function tests, urea, creatinine and electrolytes, activated partial thromboplastin time [aPTT], prothrombin time [PT], INR), dabigatran level (standardized dilute thrombin time [Haemoclot, Hyphen-BioMed], calibrated anti-Xa chromogenic assays

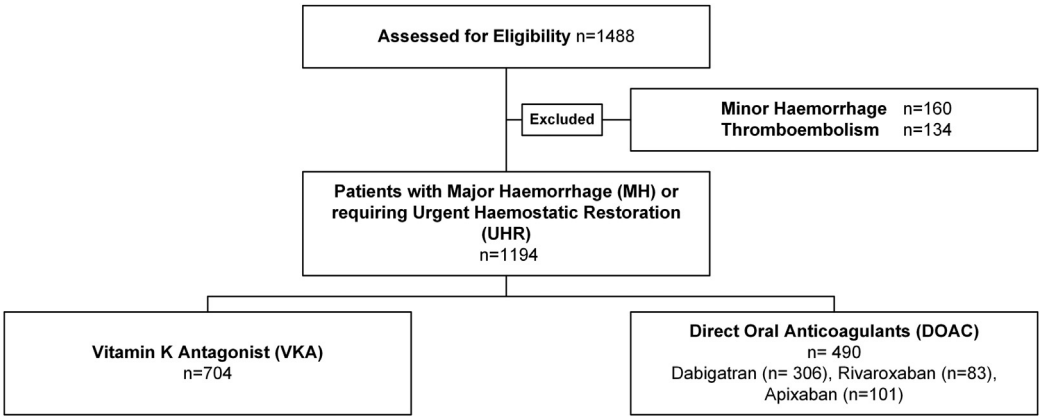

FIGURE 1 Anticoagulation Reversal and Events Study (ARES) Collaborative recruitment strengthening the reporting of observational studies in epidemiology (STROBE) diagram. DOAC, direct oral anticoagulant; MH, major hemorrhage; UHR, urgent hemostatic restoration; VKA, vitamin K antagonist.

specific to rivaroxaban and apixaban, type of nonspecific reversal agent used for hemorrhage (3-factor PCC [Prothrombinex-VF] and aPCC [FEIBA]), specific antidote agent (idarucizumab), hemostatic blood product use (FFP and cryoprecipitate [cryoppt]), other hemostatic agents (tranexamic acid and vitamin K), length of hospital admission stay, and day 30 clinical outcome.

TABLE 1 Demographics of patients with major hemorrhage or urgent hemostatic restoration before surgery.

	Major hemorrhage		Urgent hemostatic restoration		Total
Type of anticoagulant	Vitamin K antagonist	DOAC (dabigatran, rivaroxaban, and apixaban)	Vitamin K antagonist	DOAC (dabigatran, rivaroxaban, and apixaban)	
Number	476	307	228	183	1194
Sex, *n* (%)					
Male	270 (56.7)	170 (55.4)	140 (61.4)	102 (55.7)	682 (57.1)
Female	206 (43.3)	137 (44.6)	88 (38.6)	81 (44.3)	512 (42.9)
Age (y), median (25th to 75th percentile)	81 (72-86)	79 (74-86)	78 (72-86)	79 (71-85)	
Age (y), *n* (%)					
<65	60 (12.6)	28 (9.1)	37 (16.2)	20 (10.9)	145 (12.1)
65-75	100 (21.0)	64 (20.8)	57 (25.0)	51 (27.9)	272 (22.8)
>75	316 (66.4)	215 (70.1)	134 (57.8)	112 (61.2)	777 (65.1)
CHA_2DS_2-VASC score, mean ± SD	3.1 ± 2.3	3.5 ± 1.9	3.1 ± 2.5	3.5 ± 1.9	
eGFR (mL/min/1.73 m^2) mean ± SD	48.8 ± 23.8	58.4 ± 20.3	49.1 ± 26.3	51.0 ± 23.1	
Main indication for oral anticoagulant, *n* (%)					
AF and stroke	309 (64.9)	255 (83.1)	134 (58.8)	154 (84.2)	852 (71.4)
DVT	53 (11.1)	23 (7.5)	32 (14.0)	7 (3.8)	115 (9.6)
PE	30 (6.4)	10 (3.3)	12 (5.3)	9 (4.9)	61 (5.1)
MHV	43 (9.0)	2 (0.6)	24 (10.5)	2 (1.1)	71(5.9)
Other	41 (8.6)	17 (5.5)	26 (11.4)	11 (6.0)	95 (8.0)

CHA2DS2-VASC score is a scoring system to assess the risk of thromboembolism with atrial fibrillation.

AF, atrial fibrillation; DOAC, direct oral anticoagulant including dabigatran, rivaroxaban, and apixaban; DVT, deep vein thrombosis; eGFR, estimated glomerular filtration rate; MHV, mechanical heart valve; PE, pulmonary embolism.

TABLE 2 Site of the event for major hemorrhage by oral anticoagulant (n = 783).

	Vitamin K antagonist	All DOACs	Dabigatran, *N* (% of DOAC)	Rivaroxaban, *N* (% of DOAC)	Apixaban, *N* (% of DOAC)	Total
Type of hemorrhage						
Gastrointestinal hemorrhage, *N* (%)	170 (35.7)	117 (38.1)	74 (46.8)	18 (27.7)	25 (29.8)	287
Intracerebral hemorrhage, *N* (%)	194 (40.8)	121 (39.4)	61 (38.6)	29 (44.6)	31 (36.9)	315
Other sites of hemorrhage (retroperitoneal, urinary tract, muscle/joint, chest, or other), *N* (%)	112 (23.5)	69 (22.5)	23 (14.6)	18 (27.7)	28 (33.3)	181
Total	476	307	158	65	84	783

DOAC, direct oral anticoagulant.

MH was defined following the ISTH major bleeding criteria [25]: for patients enrolled in the study with intracranial hemorrhage, a head CT or magnetic resonance imaging scan revealing hemorrhagic stroke was required.

2.4 | Statistical analysis

Descriptive statistics and associations between the variables and OAC were assessed using chi-squared tests or Fisher's exact tests when assumptions of the chi-squared tests were violated. Qualitative data (eg, whether a patient did or did not receive a specific coagulation test) were converted into quantitative data to allow for statistical analysis. The quantitative data were assessed for normality with the D'Agostino and Pearson tests. Subsequently, the Kruskal-Wallis test was used to determine whether significant differences in the mean (eg, the number of patients who received a specific coagulation test) existed. Dunn's multiple comparisons test was applied when examining multiple comparisons between groups. For nonparametric data, a Mann–Whitney U-test was used to analyze the differences. Statistical significance was set at 5%. All statistical analyses were performed using Stata IC/14 (StataCorp) or Prism 7.04 (GraphPad Software Inc).

3 | RESULTS

3.1 | Patient characteristics and demographics

A flowchart of all ARES-eligible patients is shown in Figure 1. Of the 1488 patients recruited, after excluding those with minor hemorrhage

TABLE 3 Coagulation tests performed on patients with major hemorrhage and urgent hemostatic restoration before surgery by oral anticoagulant.

	VKA	Dabigatran	Factor Xa inhibitor	Total
No. of eligible patients	704	306	184	1194
Any coagulation test performed, no. of subjects (%)[a]	687 (97.6)	287 (93.7)[b]	167 (90.7)[c]	1141
Specific coagulation test for the type of OAC, no. of subjects (%)[d]	687 (97.6)	79 (25.8)[e]	83 (45.1)[e,f]	849
Time from presentation for the coagulation test to arrive for analysis (min), median (IQR)	50.2 (24.0-168.2)	52.4 (24.0-288.4)	60.3 (29.5-219.5)	
VKA INR <1.5 or DOAC <50 ng/mL, *n* (%)	13 (1.9)	15 (19.0)[e]	12 (14.4)[e]	40
VKA INR >1.5, DOAC >50 ng/mL, *n* (%)	674 (98.1)	64 (81)[e]	71 (85.6)[e]	809

IQR = 25th to 75th percentile.

DOAC, direct oral anticoagulant; INR, international normalized ratio; OAC, oral anticoagulant; VKA, vitamin K antagonist; Anti Xa inhibitor, rivaroxaban and apixaban.

[a]Any coagulation test arising from a blood test at presentation, including activated partial thromboplastin time, prothrombin time, international normalized ratio, thrombin time, calibrated chromogenic factor Xa, and calibrated dilute thrombin time.

[b]$P < .05$, significant difference from warfarin.

[c]$P < .001$, significant difference from warfarin.

[d]Number of patients with a specific coagulation test to measure the intensity of anticoagulation, including vitamin K antagonist (international normalized ratio), direct oral anticoagulant dabigatran level (calibrated dilute thrombin time), or rivaroxaban or apixaban levels (calibrated chromogenic factor Xa).

[e]$P < .0001$, significant difference from warfarin.

[f]$P < .0001$, significant difference from dabigatran.

and patients with TE, 1194 had MH (*n* = 783) or required UHR (*n* = 411). Seven hundred four patients were on VKA and 490 patients were on a DOAC—dabigatran (*n* = 306) or FXa inhibitor (*n* = 184; rivaroxaban [*n* = 83] and apixaban [*n* = 101]). Patient demographics are shown in Table 1. Most patients taking OACs were elderly, aged >75 years. The main indication for anticoagulation was AF, followed by VTE. In both VKA and DOAC patients, the CHA_2DS_2-VASC score was elevated, suggesting that the highest-risk patients for stroke were included. As expected, VKA was almost exclusively used for mechanical heart valves.

3.2 | Site of MH by oral anticoagulants

The most common sites of MH are shown in Table 2. The majority occurred in the gastrointestinal tract or the brain. There was a similar proportion of patients with intracerebral and gastrointestinal hemorrhage between VKA and all DOAC patients (range, 35.7%-40.8%). Relatively less gastrointestinal hemorrhage occurred in the patients on rivaroxaban and apixaban (27.7% and 29.8%, respectively) than in patients on VKA (35.7%) and dabigatran (46.8%), whereas patients on rivaroxaban and apixaban (27.7% and 33.3%, respectively) had more other sites of MH than patients on VKA (23.5%) and dabigatran (14.6%).

3.3 | Coagulation testing

Patients who underwent any coagulation test after admission (aPTT, PT, INR, thrombin time, calibrated chromogenic FXa, and calibrated dilute thrombin time) or specific preintervention OAC coagulation performed (VKA [INR], dabigatran [calibrated dilute thrombin time and FXa inhibitor], and rivaroxaban/apixaban [calibrated chromogenic FXa assay]) are listed in Table 3. A significantly greater number of VKA patients (*n* = 687; 97.6%) underwent any coagulation test when compared with dabigatran patients (*n* = 287; 93.7%; *P* = .021) and FXa inhibitor patients (*n* = 167; 90.7%; *P* = .0002). No significant difference was observed in the coagulation testing rate between patients on dabigatran and those on a FXa inhibitor.

There was a wide range of time for the laboratory to receive any coagulation test with the median time from presentation for VKA (50.2 minutes; IQR, 24.0-168.2), dabigatran (52.4 minutes; IQR, 24.0-288.4), FXa inhibitor (60.3 minutes; IQR, 29.5-219.5), and overall OAC (median, 52.3 minutes; IQR, 24.8-206.7). However, some coagulation samples were received quickly, suggesting that a rapid TAT is feasible.

For the specific assessment of the intensity of OAC, compared to VKA where almost all patients who had a coagulation test had an INR performed (*n* = 687; 97.6%), a significantly lower number of dabigatran patients (*n* = 79; 25.8%; *P* < .0001) and FXa inhibitor patients (*n* = 83; 45.1%; *P* < .0001) had a specific DOAC level. Furthermore, the number of VKA patients at presentation who had an INR of <1.5 or

TABLE 4 Hemostatic interventions for major hemorrhage and urgent hemostatic restoration before surgery by oral anticoagulant.

	Vitamin K antagonist	Dabigatran	Factor Xa inhibitor
No. of patients (*N*)	704	306	184
Total no. of patients given a hemostatic agent[a]	680 (96.5%)	287 (93.7%)	139 (75.5%)[b]
Type of medication administered[c]			
PCC/aPCC	579 (82.2%)	24 (7.8%)	123 (66.8%)
Idarucizumab	0	236 (77.1%)	0
Vitamin K	532 (62.2%)	31 (10.1%)	34 (18.4%)
Tranexamic acid	24 (3.4%)	25 (8.2%)	26 (14.1%)
FFP or cryoppt	180 (25.6%)	29 (9.5%)	41 (22.3%)
Dose of PCC/aPCC administered			
Dose of PCC (IU), median (IQR)	MH, 2000 (1500-3000) UHR, 2500 (1475-2500) *N* = 579	MH, 2850 (1750-3875) UHR, 1750 (500-2500) *N* = 14	MH, 3000 (2000-3500)[d] UHR, 2500 (1500-3125) *N* = 118
Dose of aPCC (IU), median (IQR)	0	4000 (3125-4000) *N* = 10	3000 (3000-3500) *N* = 5

Factor Xa inhibitor includes rivaroxaban and apixaban.

aPCC, activated prothrombin complex concentrate (FEIBA); cryoppt, cryoprecipitate; FFP, fresh frozen plasma; MH, major hemorrhage; PCC, prothrombin complex concentrate; UHR, urgent hemostatic restoration.

[a]Hemostatic reversal agent includes prothrombin complex concentrate, activated prothrombin complex concentrate, fresh frozen plasma, cryoprecipitate, or idarucizumab.

[b]*P* < .0001 compared with Vitamin K antagonist and dabigatran.

[c]Multiple medications were administered together for hemostasis.

[d]*P* < .002 compared with Vitamin K antagonist.

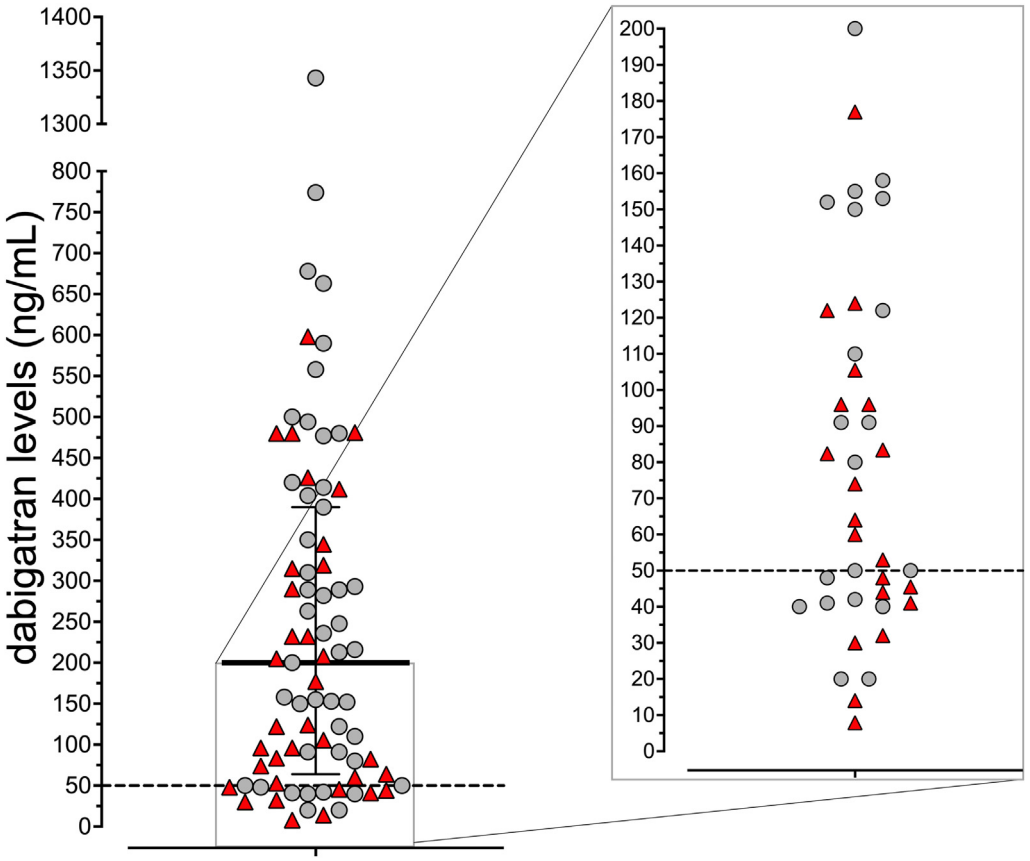

FIGURE 2 Patients with major hemorrhage or urgent hemostatic restoration who had a dabigatran drug level and were administered idarucizumab. There were a total of 79 patients with insert (n = 34). The median dabigatran level is 200 ng/mL (solid line; IQR, 64-390 ng/mL). A dashed line at 50 ng/mL represents a level where if over, hemostatic agents or an oral anticoagulant antidote is recommended. Red triangles, idarucizumab administered; grey circles, no idarucizumab administered.

the number of DOAC patients with a level of <50 ng/mL who are likely to not require any hemostatic agent was significantly different for dabigatran patients (n = 15; 19.0%; $P < .0001$) and FXa inhibitor patients (n = 12 [14.4%]; $P < .0001$) when compared with VKA patients (n = 13; 1.9%).

3.4 | Comparison of urgent hemostatic management between VKA and DOACs

The type of hemostatic intervention for patients is shown in Table 4. More patients on VKA (96.5%) and dabigatran (93.7%) were given a hemostatic reversal agent (which includes PCC, aPCC, FFP, cryoppt, or idarucizumab) when compared to the FXa inhibitors (75.5%; $P < .0001$). The administration of a PCC/aPCC or idarucizumab does not appear to relate to the plasma DOAC level, as shown in Figure 2 (dabigatran and idarucizumab) and Figure 3 (FXa inhibitors rivaroxaban and apixaban and PCC/aPCC). However, patients frequently had high DOAC levels of >350 ng/mL with dabigatran (n = 22; 27.8%) or FXa inhibitors (n = 11; 13.2 %), indicating that bleeding will likely be a problem from the DOAC without the administration of a hemostatic agent.

Tranexamic acid was used more commonly in FXa inhibitor patients (14.1%) when compared with VKA (3.4%) or dabigatran (8.2%). Less FFP and cryoppt were used in the dabigatran patients (9.5%) than in VKA (25.6%) or FXa inhibitor patients (22.3%). For MH, the dose of PCC administered was significantly ($P < .002$) higher in patients on FXa inhibitors (median, 3000 IU; IQR, 2000-3500) than the VKA median dose of 2000 IU (IQR, 1500-3000) but not that of dabigatran (median, 2850 IU; IQR, 1750-3875). As expected, all the PCC and aPCC doses were in the ANZ recommended range of 25 to 50 IU/kg, assuming an average body weight of 80 kg.

3.5 | Mortality and length of hospital stay for MH patients

Overall, 30-day mortality for MH on any OAC (VKA or DOAC) was substantial (median: 17.8%), as shown in Figure 4. However, mortality was evenly divided between those with intracerebral hemorrhage and gastrointestinal bleeding (data not shown). Number of overall days of hospitalization after the MH event was a median of 8 days (IQR, 4-18) and was similar between the types of OACs.

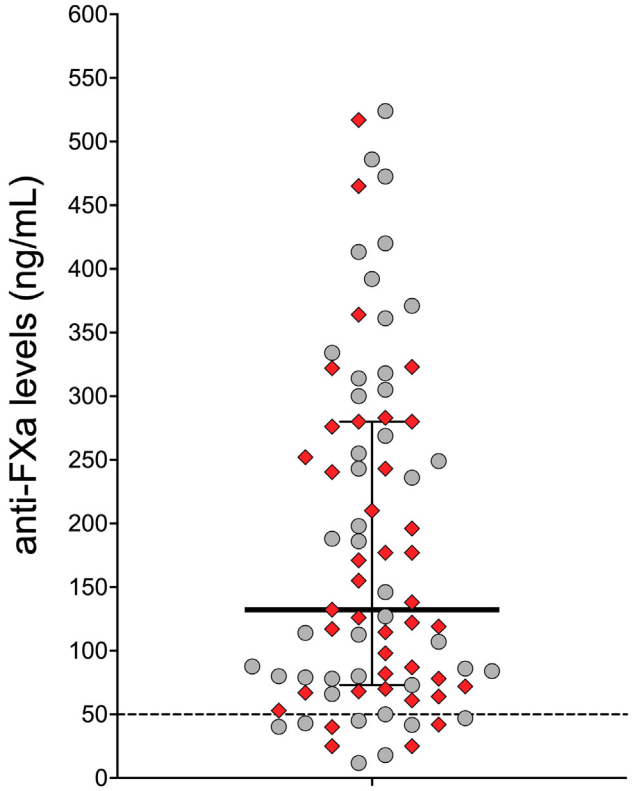

FIGURE 3 Patients with major hemorrhage or urgent hemostatic restoration who had a factor Xa (FXa) inhibitor (rivaroxaban and apixaban) drug level and were administered prothrombin complex concentrate (PCC). There were a total of 83 patients. The overall median anti-FXa level is 132 ng/mL, represented by the solid line (IQR, 73-280/mL). Dashed line at 50 ng/mL represents a level where if over, hemostatic agents or an oral anticoagulant antidote is recommended. Red triangles, PCC administered; grey circles, no PCC administered.

4 | DISCUSSION

The ARES Collaborative study demonstrates a change in real-world practice in urgent hemostatic management of patients on DOACs compared to VKA. Unlike VKA, where almost all the patients had an INR to identify the intensity of anticoagulation, <50% of DOAC patients had a specific DOAC level. Most importantly, up to one-fifth of patients with MH or UHR had a low DOAC level (<50 mg/mL), where a hemostatic agent is unlikely to be required. These data are consistent with the number obtained from the idarucizumab and andexanet alfa reversal studies [17–19], other observational studies [26–28], and DOAC levels immediately before surgery after stopping before 24 hours [29]. Our study demonstrates that without a plasma DOAC measure, some patients in the real world will receive unnecessary, expensive, and potentially harmful hemostatic agents (such as PCC, aPCC, FFP, idarucizumab, or andexanet alfa) when no significant plasma DOAC is present. Highlighting these data will likely motivate the organization's engagement to consider rapid plasma DOAC testing in the context of patient safety, clinical outcomes, and cost-effectiveness.

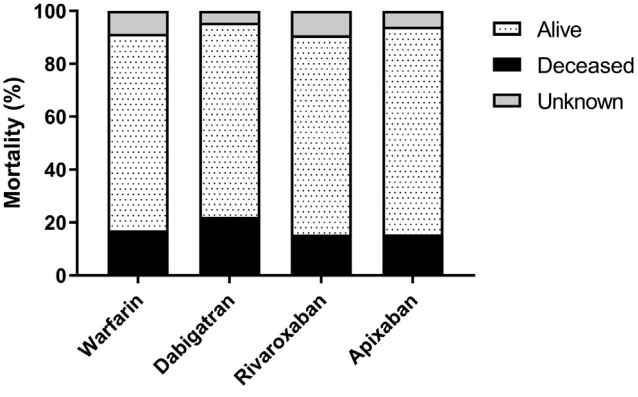

FIGURE 4 Thirty-day mortality for patients with major hemorrhage. All oral anticoagulants (n = 139; 17.8%), warfarin (vitamin K antagonist, n = 81; 17.0%), dabigatran (n = 35; 22.2%), rivaroxaban (n = 10, 15.4%), and apixaban (n = 13, 15.5%).

There is currently a difference in the perceived role of the results of INR and plasma DOAC levels on urgent hemostatic management. In VKA emergency treatment, the INR informs appropriate decisions about the use and dose of PCC and vitamin K. Ideally, knowledge of a plasma DOAC level should have an equal impact on DOAC hemostatic management. Our study confirms that regardless of the type of OAC (VKA or DOAC), 30-day mortality from MHs is substantial (17.8%), equally divided between gastrointestinal and intracerebral bleeding. This is despite having long experience with VKA PCC clotting factor replacement and vitamin K therapy. We also show no overall difference in length of stay in hospital (median 8 days) after MH between patients on VKA and those on a DOAC. After major bleeding, underlying medical comorbidities and failure to restart OAC may contribute to mortality. In an emergency, clinicians face the time trade-off for a decision to institute anticoagulant reversal treatment with or without a coagulation test to achieve the right balance between controlling bleeding and not causing thrombosis.

Defining the best treatment with an informative plasma DOAC level and identifying the most appropriate hemostatic intervention for the subtype of bleed could improve these outcomes.

Selecting the correct patient for the best treatment in the shortest time is critical for stopping the bleeding with excessive anticoagulation. To be useful, the TAT for an urgent laboratory INR or plasma DOAC result should be as rapid as stroke recommendations of the door-to-imaging time of 25 minutes, interpreting the CT result and implementing treatment within 45 minutes [30]. In our study, the laboratory took much longer to receive the coagulation specimen than the door-to-imaging time for a CT scan (median, 52.3 minutes; IQR, 24.8-206.7). This difference limits the application of a DOAC test on critical clinical decisions. Once the blood specimen has arrived, a DOAC or INR result could be available after a 5-minute 4000 × g centrifugation of a blood sample [31] with a 10-minute analytical time. The variables contributing to faster TATs for coagulation laboratory testing were laboratory control of specimen handling and rapid transport time [31]. Reagent and labor costs, test licensing, specimen transport, and the lack of trained laboratory staff for DOAC testing are major logistic and organizational issues [32–34]. These reasons

could explain the low uptake of specific DOAC testing compared to INR results. As in stroke patients where a Code Stroke protocol is initiated, perhaps Code Bleed for OAC could be activated to focus the whole hospital on setting standards for hemostatic management, including an audit of the TAT of plasma DOAC and INR results. A median TAT of ≤40 minutes for urgent DOAC level has been achieved in several centers [28,35].

One strategy to increase the availability of real-time DOAC results is to adopt near-patient plasma DOAC testing. Preliminary data support point-of-care coagulation devices to detect DOAC (except for apixaban) levels of >50 ng/mL [36–39]. Another alternative is using global hemostatic assays, such as thrombin generation or a modified DOAC thromboelastogram, which are reported to be sensitive to low DOAC levels [40,41]. However, further work is needed in larger MH and UHR cohorts to explore whether the point-of-care thrombin generation [42] or modified thromboelastogram strategy would be helpful for DOAC emergency management. Recently, urine detection of the type of DOAC could assist in overcoming the uncertainty of which DOAC was taken in an unconscious patient. Still, it gives no further information on the degree of anticoagulation from the DOAC [43].

Differences in clinical interpretation of plasma DOAC level are more challenging than an INR result with VKA for these reasons.

First, unlike VKA, DOACs have a maximal peak of 2 to 3 hours after ingestion and a relatively short terminal half-life, relying on renal function [44]. Emergency management includes establishing the time and amount of the last DOAC dose and the type of DOAC taken. Obtaining this information can be difficult if the patient is poorly compliant, confused, critically unwell, or unconscious. In addition, renal function can rapidly deteriorate in a resuscitated hypovolemic bleeding patient or before acute surgery, leading to DOAC drug accumulation. These situations can create further clinical uncertainty about the time taken to clear the DOAC to a level that will have little impact on normal hemostasis. Unless a plasma DOAC level is measured, it is unknown if the DOAC is present and to what level.

Second, although specific quantification of plasma DOAC drug levels determined by specific coagulation assays (dilute thrombin time [TT], ecarin clotting time for dabigatran, and calibrated anti-FXa chromogenic assays) is well validated for precision and monitored by external quality assurance programs [32,40,45–48], the clinical demand and hospital awareness for implementing a rapid DOAC level, such as an INR result in an emergency, are lacking. One recent advance to simplify obtaining an anti-FXa result to make it more feasible in an emergency is the current data supporting using the low-molecular-weight heparin anti-FXa calibration curve to calculate a conversion factor for plasma rivaroxaban, apixaban, and edoxaban levels [49,50].

Third, recent studies show that aPTT or PT is not likely to detect DOAC levels under 100 to 150 ng/mL [40,51], and a trivial dabigatran level causes a very prolonged TT [40]. In our study, this uncertainty is a likely contributor to the decrease in ordering any coagulation testing in DOAC patients (FXa inhibitors, 90.7%; $P < .0001$; dabigatran, 93.7%; $P < 05$) when compared to VKA (97.6%). Nevertheless, obtaining an aPTT, PT, and TT are still valuable because the pattern and extent of the prolongation could provide a clue of the type and excess of DOAC present [33,45]. However, the aPTT and PT could also be abnormal in patients with severe bleeding or consumptive coagulopathy requiring other hemostatic support. Therefore, each emergency department should know the expected pattern DOACs produce on their aPTT, PT, and TT results calibrated for their coagulation instrument and specific reagents.

In our study, most detected plasma levels of DOACs were within the "on therapy" target range [11,15,16,36,52]. The levels were consistent with those observed in patients enrolled in the andexanet alfa study [19] and almost double (median, 200 ng/mL) compared with those in the idarucizumab study (median, 95.3 ng/mL) [18]. However, elevated plasma DOAC levels of >350 ng/mL were also found in up to a quarter of patients with MH and UHR. These higher levels would alert most clinicians to consider upfront hemostatic agents and perhaps to repeat plasma DOAC levels later to detect significant rebound anticoagulation occurring once the specific reversal agent disappears.

Whether a plasma DOAC result obtained in ARES impacted the clinical decision for a hemostatic product is uncertain, as demonstrated by the poor relationship with the use of idarucizumab or PCC/aPCC regardless of the DOAC level. Almost all VKA and dabigatran patients had a prohemostatic reversal agent (PCC, aPCC, FFP, and cryoppt) and, once available, idarucizumab. However, the uptake for using a prohemostatic reversal agent was significantly much less for FXa inhibitors (75.5%; $P < .001$) and more for tranexamic acid (19.7%; $P < .0001$). The possible reasons include more patients had a gastrointestinal hemorrhage on VKA and dabigatran, the lack of availability of andexanet alfa, the negligible effect of apixaban on standard coagulation assays, and the significantly more use and reassurance of obtaining an anti-FXa result (45.1%) when compared with dabigatran (27.5%). In addition, without access to andexanet alfa for MH or UHR, most clinicians used PCC or aPCC as their preferred hemostatic agent for an FXa inhibitor at a significantly higher amount (median, 3000 IU) than VKA (median, 2000 IU; $P < .0001$) frequently combined with FFP (29.4%).

There is still uncertainty as to whether giving any hemostatic agents or antidotes changes mortality [53–59] or progression of intracerebral bleeding [60–62], with the time to administration being a key uncontrolled variable in most studies [47,48]. However, physician assessment of the hemostatic response is positive and generally effective after PCC, aPCC, idarucizumab, or andexanet alfa [4,8,9,63]. Therefore, the European and the American Heart Association/American Stroke Association 2022 guidelines have a moderate to strong recommendation based on low- to moderate-quality evidence to use specific antidotes idarucizumab and andexanet alfa and, if not available, PCC or aPCC [12,64,65].

Our results have several limitations inherent in an observational study, including potential bias of case ascertainment, retrospective data collection, and the variation in the standard of care for hemostatic management among centers. Another limitation is that race and ethnicity data were not collected. However, we have captured a real-

world and not a highly selected clinical trial population of elderly patients in a multicenter study who have been appropriately prescribed VKA or DOACs. Idarucizumab was available for dabigatran reversal during the study period, and our study indicates that, if available, specific reversal drugs would be preferred rather than PCC. All OAC presentations were included because low-risk research ethical approval makes our findings more applicable to current practice, mainly when specific reversal agents are introduced.

5 | CONCLUSION

Further research is required to improve mortality in patients presenting with the life-threatening event of OAC-related bleeding, including additional evidence about the role of laboratory and near-patient testing to measure DOAC levels. This information will inform the best strategy for appropriately using hemostatic reversal agents to achieve better outcomes safely and effectively in these critically ill patients.

APPENDIX

Thrombosis and Haemostasis Society of Australia and New Zealand Clinical Trial Group Anticoagulation Reversal and Events Study Collaborative participating principal investigators and sites are as follows: Vivien Chen (Concord Repatriation General Hospital, Sydney, Australia), Laura Young (Auckland City Hospital, Auckland New Zealand), Eileen Merriman (North Shore Hospital, Auckland New Zealand), Jennifer Curnow (Westmead Hospital, Sydney, Australia), Alexander Gallus and Jirping Boey (Flinders Medical Centre, Adelaide, Australia), Chee Wee Tan and Simon McRae (Royal Adelaide Hospital, Adelaide, Australia), Amanda Hugman (St George Hospital, Sydney, Australia), Joanne Joseph (St Vincent Hospital, Sydney, Australia), Paul Harper (Palmerston North Hospital, Palmerston North, New Zealand), Timothy Brighton (Prince of Wales Hospital, Sydney, Australia), Gordon Royle (Middlemore Hospital), Helen Crowther (Blacktown Hospital, Sydney, Australia), Huyen Tran (Alfred Hospital, Melbourne, Australia), Philip Campbell (University Hospital, Geelong, Victoria, Australia), and Ross Baker (Royal Perth Hospital and Hollywood Private Hospital, Perth Australia).

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ETHICS STATEMENT

Human research institutional ethics review approval was obtained in each site according to the National Health and Medical Research Council guidelines, which included the category of negligible risk research and waiver of consent for the nonidentifiable data collection.

AUTHOR CONTRIBUTIONS

All authors contributed to the study concept and design, analysis and interpretation of data, and critical writing or revision of the intellectual content and read and approved the final version of the paper.

RELATIONSHIP DISCLOSURE

R.I.B. reports grants to the institution from Bayer, Takeda, Pfizer, Daiichi Sankyo, CSL Behring, Roche, Amgen, Celgene, Rigel Pharmaceuticals, AbbVie, Sanofi, MorphoSys AG, Acerta Pharma, Janssen-Cileg, Bristol-Myers Squibb, Boehringer Ingelheim, Alexion, and Technoclone; reports payment or honoraria to the institution from Bayer, Bristol-Myers Squibb, and Cardinal Health; and reports participation on a Data Safety Monitoring Board or Advisory Board for Roche, Janssen-Celeg, and CSL Behring. V.C. reports honoraria for presentations from Bayer and Pfizer. L.Y. reports unpaid participation on a COVID-19 Independent Vaccine Safety Monitoring Board not relevant for this paper. E.M. reports payment or honoraria for lecture at International Society on Thrombosis and Haemostasis 2019 from Boehringer Ingelheim and for presentations from Bayer, reports accommodation support for International Society on Thrombosis and Haemostasis 2019 from Boehringer Ingelheim and Sanofi, and reports leadership role (president) in the Thrombosis and Haemostasis Society of Australia and New Zealand from 2011 to 2021. J.J. reports personal fees for speaking on heparin induced thrombocytopenia at International Society on Thrombosis and Haemostasis 2019 from Aspen Australia and reports participation on an Advisory Board for manuscript writing (Hammett C, Badve SV, Kerr PG, Tran HA, Dundon BK, Lo S, et al. Oral anticoagulant use in patients with atrial fibrillation and chronic kidney disease: a review of the evidence with recommendations for Australian clinical practice. Heart Lung Circ 2022;31:1604–11.) for Bayer Australia. J.C. reports research funding paid to institution from Bayer Australia, reports fees for participation on an Advisory Board for Pfizer/BMS, is the education subcommittee chair (unpaid) for the Thrombosis and Haemostasis Society of Australia and New Zealand, and is a governance committee member (unpaid) of International Society on Thrombosis and Haemostasis. P.H.

is a member of the Pharmac Haematology advisory committee, New Zealand. A.H. was a panel member on the filmed educational session "Cancer associated thrombosis, what general practitioners need to know" for MD Briefcase in July 2022 and is a member of the Data Monitoring Committee for track trial "Treatment of cardiovascular disease with low dose rivaroxaban in patients with chronic kidney disease." G.H. reports personal fees from Bayer for consulting about Stroke Prevention Initiative, reports personal fees from Bristol Myers Squibb for serving as a member of the Steering Committee of the AXIOMATIC-SSP trial of milvexian, a factor XIa inhibitor, added to dual antiplatelet therapy to prevent ischemic stroke after transient ischemic attack and mild ischemic stroke, reports personal fees from Janssen for serving as a member of the Executive Committee of the LIBREXIA Stroke trial of milvexian, a factor XIa inhibitor, vs placebo, added to antiplatelet therapy to prevent ischemic stroke after transient ischemic attack and mild ischemic stroke and for a lecture at sponsored scientific symposium about antithrombotic therapy for secondary stroke prevention, and reports personal fees from the American Heart Association for serving as an Associate Editor of *Circulation*. H.T. reports payment or honoraria from AstraZeneca.

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