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## Review

## Bleeding with direct oral anticoagulants vs warfarin: clinical experience ☆☆☆☆

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## ARTICLE INFO

## ABSTRACT

The risk of bleeding in the setting of anticoagulant therapy continues to be re-evaluated following the introduction of a new generation of direct oral anticoagulants (DOACs). Interruption of DOAC therapy and supportive care may be sufficient for the management of patients who present with mild or moderate bleeding, but in those with life-threatening bleeding, a specific reversal agent is desirable. We review the phase 3 clinical studies of dabigatran, rivaroxaban, apixaban, and edoxaban in patients with nonvalvular atrial fibrillation, in the context of bleeding risk and management.

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The vitamin K antagonists (VKAs), such as warfarin, have been the standard and indeed, only, option for oral anticoagulant therapy for decades. However, their use requires routine coagulation monitoring because genetic variation and interactions between warfarin and diet, other drugs, and comorbidities produce variable and unpredictable anticoagulant effects [1–3]. The time in therapeutic range is a determinant of the efficacy and safety of warfarin [4]. In 1 representative study, 62% of warfarin-treated patients with nonvalvular atrial fibrillation (NVAF) who were admitted to the emergency department for ischemic strokes had international normalized ratios (INRs) that were outside of the desired therapeutic range [5].

The new generation of direct oral anticoagulants (DOACs) offers important advantages over warfarin, but the risk of bleeding with these drugs—as with all anticoagulants—remains an ongoing safety concern. The DOACs currently approved by the U.S. Food and Drug Administration (FDA) include the direct thrombin inhibitor dabigatran, which

was approved in 2010, and the more recently introduced direct factor Xa (FXa) inhibitors rivaroxaban, apixaban, and edoxaban. In contrast to warfarin, DOACs have a more rapid onset, predictable anticoagulant effect, shorter half-life, [6–9] and few drug–drug and dietary interactions [10–13]. Hence, they can be given in fixed doses without routine coagulation monitoring.

The severity of bleeding events with anticoagulant use ranges from minor bleeding to life-threatening intracranial hemorrhages (ICHs) or exsanguinating hemorrhages. Supportive measures for bleeding management in anticoagulated patients vary depending on the setting and specific on-board therapy. Identifying the optimal management strategy is a critical component of bleeding management. The landscape has recently changed with the introduction of a specific rapidly acting reversal agent for dabigatran in the United States [14]. In this article we briefly review the phase 3 clinical studies of dabigatran, rivaroxaban, apixaban, and edoxaban as compared with warfarin in the context of bleeding risk and management. This article focuses on studies performed in patients with NVAF. Postmarketing and “real-world” data are presented by Villines et al [15] in this special issue. We will also briefly discuss the current strategies for assessing coagulation and general measures for managing DOAC bleeding. Discussions of specific DOAC reversal agents are presented by Pollack [16] and Milling et al [17], elsewhere in this special issue.

## Bleeding Risks in Phase 3 NVAF Trials of DOACS vs Warfarin

In phase 3 clinical trials, dabigatran, rivaroxaban, apixaban, and edoxaban were compared with VKAs for the prevention of stroke or systemic embolism in NVAF. The incidence of major bleeding or a composite of major and nonmajor clinically relevant bleeding were the primary safety end points in these trials.

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Dabigatran

In the Randomized Evaluation of Long-term anticoagulation therapy (RE-LY) study, 18,113 patients who had NVAF and risk of stroke were randomized to dabigatran 110 mg twice daily or 150 mg twice daily, or warfarin (adjusted doses with a target INR of 2-3), and were followed for a median of 2.0 years [18]. In the primary publication of the RE-LY study, rates of major bleeding were 3.11% per year in the dabigatran 150-mg-twice-daily group (relative risk 0.93; 95% confidence interval [CI], 0.81-1.07;  $P = .31$ ) and 2.71% per year in the dabigatran 110-mg-twice-daily group (relative risk 0.80; 95% CI, 0.69-0.93;  $P = .003$ ) vs 3.36% per year in the warfarin group [18]. Dabigatran 150 mg twice daily and 110 mg twice daily reduced the relative risk of intracranial bleeding (both doses  $P < .001$ ), and only dabigatran 150 mg twice daily increased the relative risk of major gastrointestinal (GI) bleeding ( $P < .001$ ) vs warfarin (Table 1) [18-22]. After completion of the study, additional primary efficacy and safety outcome events were identified, and the rates of major bleeding were revised to 3.32% in the dabigatran 150 mg twice-daily group (relative risk 0.93; 95% CI, 0.81-1.07;  $P = .32$ ) and 2.87% in the dabigatran 110-mg-twice-daily group (relative risk 0.80; 95% CI, 0.70-0.93;  $P = .003$ ) vs 3.57% in the warfarin group [23]. Inclusion of the newly identified events did not change the study conclusions [23]. Overall, these results contributed to the FDA approval of dabigatran etexilate for prevention of stroke and systemic embolism in patients with NVAF [10]. As dabigatran etexilate is predominantly eliminated in the urine (80% renal excretion), [10] renal impairment can increase the exposure to dabigatran, and thus, dose adjustment may be considered in this patient population. For patients with a creatinine clearance (CrCl) of 15-30 mL/min, the recommended dosage of dabigatran etexilate in the United States is 75 mg twice daily. Patients with a CrCl of  $\leq 30$  mL/min were excluded from the RE-LY trial [24] and dosing recommendations for patients with a CrCl of  $< 15$  mL/min or on dialysis are not provided [10] (Table 2). Outside of the United States, dabigatran 110 mg twice daily is recommended for patients deemed to be at risk of stroke, including: elderly patients (age  $\geq 80$  years), concomitant use of interacting drugs (eg, verapamil), high bleeding risk (HAS-BLED score  $\geq 3$ ), or moderate renal impairment (30-50 mL/min) [25-27].

In a subgroup analysis of the RE-LY study, the risk of major bleeding was assessed according to age [28]. Dabigatran 110 mg twice daily compared with warfarin was associated with a lower risk of major bleeding in younger patients (aged  $< 75$  years; 1.89% vs 3.04%;  $P < .001$ ) and a similar risk in older patients (aged  $\geq 75$  years; 4.43% vs 4.37%;  $P = .89$ ). Dabigatran 150 mg twice daily compared with warfarin was associated with a lower risk of major bleeding in younger patients (2.12% vs 3.04%;  $P < .001$ ) and a trend toward a higher risk of major bleeding in older patients (5.10% vs 4.37%;  $P = .07$ ). The similar or higher risk of major bleeding was driven by rates of extracranial bleeding, primarily GI bleeding; the risk of ICH was lower with both doses of dabigatran compared with warfarin, irrespective of age. In a separate subgroup analysis of the RE-LY cohort, the incidence of ICH during anticoagulation therapy was evaluated by site (intracerebral, subdural, or subarachnoid), risk factors, and outcomes [29]. The relative risk of intracerebral hemorrhage was reduced with dabigatran 150 mg twice daily (relative risk 0.23; 95% CI, 0.12-0.45;  $P < .001$ ) and dabigatran 110 mg twice daily (relative risk 0.30; 95% CI, 0.16-0.54;  $P < .001$ ) compared with warfarin. The relative risk of subdural hemorrhages was only reduced with dabigatran 110 mg twice daily compared with warfarin (relative risk 0.27; 95% CI, 0.12-0.55;  $P < .001$ ). Dabigatran 150 mg twice daily and 110 mg twice daily did not significantly reduce the risk of subarachnoid hemorrhages compared with warfarin. Mortality following ICH was similar in patients treated with dabigatran 150 mg twice daily (35%), dabigatran 110 mg twice daily (41%), or warfarin (36%).

Bleeding management and outcomes were evaluated in a separate analysis of the RE-LY cohort [30]. More patients in the dabigatran 150-mg-twice-daily (61.4%) vs warfarin group (49.9%) were treated

**Table 1** Primary Safety Outcome Data from Phase 3 Studies of DOACs vs Warfarin by Type of Bleeding

Primary Safety Outcome (Percentage of Patients with an Adverse Event)*	RE-LY [18]†		ROCKET AF [19, 20]		ARISTOTLE [21]		ENGAGE-AF TIMI 48 [22]		
	Dabigatran 150 mg (n = 6076)	Warfarin (n = 6022)	Rivaroxaban (n = 7111)	Warfarin (n = 7125)	Apixaban (n = 9088)	Warfarin (n = 9052)	Edoxaban 60 mg (n = 7012)	Edoxaban 30 mg (n = 7002)	Warfarin (n = 7012)
Major bleeding	3.11% per y	3.36% per y	3.6% per y	3.4% per y	2.13% per y	3.09% per y	2.75% per y	1.61% per y	3.43% per y
Hazard ratio (95% CI)	0.93 (0.81-1.07)	—	1.04 (0.90-1.20)	—	0.69 (0.60-0.80)	—	0.80 (0.71-0.91)	0.47 (0.41-0.55)	—
P-value	.31	—	.58	—	<.001	—	<.001	<.001	—
Intracranial bleeding	0.30% per y	0.74% per y	0.5% per y	0.7% per y	0.33% per y	0.80% per y	0.39% per y	0.26% per y	0.85% per y
Hazard ratio (95% CI)	0.40 (0.27-0.60)	—	0.67 (0.47-0.93)	—	0.42 (0.30-0.58)	—	0.47 (0.34-0.63)	0.30 (0.21-0.43)	—
P-value	<.001	—	.02	—	<.001	—	<.001	<.001	—
Gastrointestinal bleeding	1.51% per y	1.02% per y	2.00% per y	1.24% per y	0.76% per y	0.86% per y	1.51% per y	0.82% per y	1.23% per y
Hazard ratio (95% CI)	1.50 (1.19-1.89)	—	1.61 (1.30-1.99)	—	0.89 (0.70-1.15)	—	1.23 (1.02-1.50)	0.67 (0.53-0.83)	—
P-value	<.001	—	<.0001	—	.37	—	.03	<.001	—

ARISTOTLE = Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; CI = confidence interval; DOAC = direct oral anticoagulant; ENGAGE-AF-TIMI 48 = Effective Anticoagulation with Factor-Xa next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction study 48; RE-LY = Randomized Evaluation of Long-term anticoagulation therapy; ROCKET AF = Rivaroxaban Once daily oral direct factor-Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation.

\* Data are presented as reported in each publication. Proportion of patients with an adverse event is described as an event rate (percentage/year) [18,21,22] or event rate number/100 patient-years [19,20].

† Rates of the primary safety outcomes from the RE-LY trial are reported as relative risk, not hazard ratios.

**Table 2**  
Dosage and Administration of DOACs for Patients with NVAf According to Renal Function\*

Drug	Renal Function (CrCl)	Dosage and Administration
Dabigatran etexilate [10]	>30 mL/min 15-30 mL/min <15 mL/min or on dialysis	150 mg BID 75 mg BID Not provided <sup>†</sup>
Rivaroxaban [13]	>50 mL/min 15-50 mL/min <15 mL/min	20 mg QD with evening meal 15 mg QD with evening meal Not provided <sup>‡</sup>
Apixaban [11]	No dose adjustment is recommended for patients with RI alone (including patients with ESRD [ $<15$ mL/min] and maintained on hemodialysis) For patients with at least 2 of the following characteristics: $\geq 80$ y of age, weight $\leq 60$ kg, or serum creatinine $\leq 1.5$ mg/dL	5 mg BID 2.5 mg BID
Edoxaban [12]	>95 mg/dL >50 to $\leq 95$ mL/min 15-50 mL/min <15 mL/min	Avoid use 60 mg QD 30 mg QD Not recommended

BID = twice daily; CrCl = creatinine clearance; DOAC = direct oral anticoagulant; NVAf = nonvalvular atrial fibrillation; QD = once daily; RI = renal impairment.

\* Information in this table is based on the U.S. prescribing information for the available agents. Please see individual prescribing information for warnings and precautions.

<sup>†</sup> Dosing recommendations cannot be provided for patients with CrCl  $<15$  mL/min or on dialysis [10].

<sup>‡</sup> Clinical efficacy and safety studies with Xarelto did not enroll patients with end-stage renal disease on dialysis [13].

with blood transfusions ( $P < .001$ ), and fewer patients in both dabigatran groups were administered fresh frozen plasma (FFP) (dabigatran 150 mg twice daily, 21.6% and dabigatran 110 mg twice daily, 17.8%) vs warfarin (30.2%;  $P < .005$  and  $P < .001$ , respectively). The proportion of major bleeding events requiring hospitalization was similar between dabigatran 110 mg twice daily and 150 mg twice daily compared with warfarin (51.2%, 61.8%, and 56.5%, respectively).

**Rivaroxaban**

In the Rivaroxaban Once daily oral direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF), 14,264 patients with NVAf who were at moderate-to-high risk for stroke were randomized to rivaroxaban or warfarin and followed for a median of 1.94 years [19]. Patients received fixed-dose rivaroxaban (20 mg once daily or 15 mg once daily in patients with a CrCl of 30–49 mL/min) or adjusted doses of warfarin (target INR of 2–3). The rates of any major bleeding event (number per 100 patient-years) were similar between the rivaroxaban group (3.6) and the warfarin group (3.4) (hazard ratio [HR] 1.04; 95% CI, 0.90–1.20;  $P = .58$ ) [19]. Rivaroxaban compared with warfarin reduced the rate of ICH (HR 0.67; 95% CI, 0.47–0.93;  $P = .02$ ) [19,20] and increased the rate of major GI bleeding (HR 1.61; 95% CI, 1.30–1.99,  $P < .001$ ) [20] (Table 1). Based on these safety and efficacy data, the FDA approved rivaroxaban 20 mg once daily for NVAf patients with a CrCl of  $>50$  mL/min and 15 mg once daily for those with a CrCl of 15–50 mL/min [13] (Table 2).

In a separate analysis of the ROCKET AF cohort, baseline factors that were independently associated with major bleeding were: age, sex, diastolic blood pressure, history of chronic obstructive pulmonary disease, prior GI bleeding, prior aspirin use, and anemia [31]. The relative risk of major bleeding with rivaroxaban vs warfarin treatment was similar regardless of age, whereas the risk of ICH was reduced irrespective of age. Rivaroxaban was associated with reductions in various subtypes of ICH, including intraparenchymal, intraventricular, and subdural compared with warfarin (all  $P < .05$ ; no HRs provided). Patients with a history of GI bleeding who were treated with rivaroxaban were at higher risk of major bleeding than those treated with warfarin (HR 2.33; 95% CI, 1.39–3.88; interaction  $P = .002$ ), whereas the risk of GI bleeding was similar between rivaroxaban and warfarin if there was no history of GI bleeding (HR 1.00; 95% CI, 0.86–1.16).

Bleeding management and outcomes were evaluated in a separate analysis of the ROCKET AF cohort [32]. Among patients who experienced major bleeding, rivaroxaban compared with warfarin was associated with less frequent use of FFP (45 vs 81 units; odds ratio 0.43; 95% CI, 0.29–0.66;  $P < .0001$ ) and prothrombin complex concentrate (PCC) (4 [0.9%] vs 9 [2.2%] patients). Outcomes after major bleeding, including duration of hospitalization (5 days vs 6 days) and all-cause death (20.4% vs 26.1%; HR 0.688; 95% CI, 0.455–1.042) were similar among patients treated with rivaroxaban or warfarin.

**Apixaban**

In the Apixaban for Reduction In Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) study, 18,201 patients with AF and at least one additional risk factor for stroke were randomized to apixaban or dose-adjusted warfarin (target INR 2–3) and followed for a median of 1.8 years [21]. Apixaban was administered twice daily as fixed doses of either 5 mg or 2.5 mg according to age, body weight, and serum creatinine level. The rates of major bleeding were 2.13% per year in the apixaban group vs 3.09% per year in the warfarin group (HR 0.69; 95% CI, 0.60–0.80;  $P < .001$ ). The rate of intracranial bleeding was reduced with apixaban compared with warfarin (0.33% vs 0.80% per year; HR 0.42; 95% CI, 0.30–0.58;  $P < .001$ ). In contrast, the rate of GI bleeding did not differ between apixaban and warfarin (0.76 vs 0.86% per year; HR 0.89; 95% CI, 0.70–1.15;  $P = .37$ ) (Table 1) [21]. These safety data contributed to the FDA approval of apixaban 5 mg twice daily for patients with NVAf [11]. Apixaban 2.5 mg twice daily is recommended for patients with at least 2 of the following characteristics:  $\geq 80$  years of age, weight  $\leq 60$  kg, or serum creatinine  $\leq 1.5$  mg/dL (Table 2).

In a separate analysis, Hylek et al [33] evaluated clinical outcomes associated with major bleeding in patients enrolled in ARISTOTLE. Baseline factors that were independently associated with major hemorrhage were: older age, prior hemorrhage, prior stroke or transient ischemic attack, diabetes, a lower CrCl ( $<85$  mL/min/1.73 m<sup>2</sup>), decreased hematocrit level ( $<45\%$ ), use of aspirin therapy, and use of nonsteroidal anti-inflammatory drugs [33]. Adverse events following major extracranial hemorrhage occurred less frequently in the apixaban than in the warfarin group, including fewer hospitalizations (1.05% vs 1.41% per 100 patient-years; HR 0.75; 95% CI, 0.61–0.92;  $P = .0052$ ) and fewer transfusions (0.89% vs 1.25% per 100 patient-years; HR 0.71; 95% CI, 0.57–0.89;  $P = .0025$ ) [33]. In addition, death within 30 days following major

hemorrhage occurred half as often with apixaban vs warfarin (36 vs 71 events; HR 0.50; 95% CI, 0.33–0.74;  $P < .001$ ).

### Edoxaban

In the Effective aNticoaGulation with factor xA next GEneration in Atrial Fibrillation-Thrombolysis in Myocardial Infarction study 48 (EN-GAGE-AF TIMI 48), 21,105 patients with moderate-to-high-risk AF were randomized to warfarin, high-dose (HD) edoxaban (60 mg) once daily or low-dose (LD) edoxaban (30 mg) once daily, and followed for a median of 2.8 years [22]. The dose of edoxaban was reduced by 50% in patients with an estimated CrCl of 30–50 mL/min, body weight of  $\leq 60$  kg, or the concomitant use of potent P-glycoprotein inhibitors at baseline or during the course of the study. The annualized rate of major bleeding in patients receiving HD edoxaban was 2.75% (HR 0.80; 95% CI, 0.71–0.91;  $P < .001$ ) and 1.61% in patients receiving LD edoxaban (HR 0.47; 95% CI, 0.41–0.55;  $P < .001$ ), compared with 3.43% in the warfarin group. Rates of ICH were reduced with HD edoxaban (0.39%; HR 0.47; 95% CI, 0.34–0.63) and LD edoxaban (0.26%; HR 0.30; 95% CI, 0.21–0.43) relative to warfarin (0.85%; both doses  $P < .001$ ). Gastrointestinal bleeding occurred more frequently with HD edoxaban (1.51%; HR 1.23; 95% CI, 1.02–1.50;  $P = .03$ ) and less frequently with LD edoxaban than warfarin (0.82% vs 1.23%; HR 0.67; 95% CI, 0.53–0.83;  $P < .001$ ) (Table 1). Based on these data, edoxaban 60 mg once daily was approved by the FDA for patients with NVAF and a CrCl of  $>50$  to  $\leq 95$  mL/min [12]. A dose adjustment to edoxaban 30 mg once daily is recommended in patients with a CrCl of 15–50 mL/min (Table 2).

In a subgroup analysis, both doses of edoxaban were associated with reductions in various subtypes of ICH, including parenchymal, sub-arachnoid, and subdural or epidural bleeds [34]. Both edoxaban doses also reduced the composite outcome of death, nonfatal stroke, or ICH (HR 0.88;  $P = .003$  for HD edoxaban, and HR, 0.90;  $P = .021$  for LD edoxaban) compared with warfarin. In a separate subgroup analysis, Ruff et al [35] reported that reducing edoxaban dose based on prespecified clinical factors (defined above) maintained the anticoagulant efficacy of edoxaban and was associated with a reduced risk of major bleeding compared with warfarin.

In summarizing all the above studies, major bleeding risk was reduced with apixaban (5 or 2.5 mg) twice daily, edoxaban (60 mg and 30 mg) once daily, and dabigatran 110 mg twice daily vs warfarin, and rivaroxaban (20 or 15 mg) once daily and dabigatran 150 mg twice daily had a similar bleeding risk vs warfarin. The risk of major GI bleeding was similar with apixaban (5 or 2.5 mg) twice daily and dabigatran 110 mg twice daily vs warfarin, and increased with rivaroxaban (20 or 15 mg) once daily and dabigatran 150 mg twice daily vs warfarin. The risk of GI bleeding with edoxaban was greater with edoxaban 60 mg once daily and lower with edoxaban 30 mg once daily. Intracranial bleeding risk was reduced with all DOACs that were compared with warfarin.

### Current Strategies for the Assessment and Management of DOAC Bleeding

DOACs do not require routine monitoring [18–22] as is necessary with warfarin, but laboratory measurement of blood levels or anticoagulant activity may be helpful during an emergent bleeding situation or in a number of other settings. Liquid chromatography tandem mass spectrometry is a quantitative method of measuring DOAC concentration but is not a practical option for routine clinical use. In some circumstances, commonly available coagulation tests such as the activated partial thromboplastin time (aPTT), prothrombin time, and thrombin time (TT) can provide qualitative assessments of the presence or absence of an anticoagulant effect, but their sensitivity differs depending on the agent. Specific assays, including dilute thrombin time, ecarin clotting time (ECT), ecarin chromogenic assays, and chromogenic anti-FXa assays can be used to quantify drug levels accurately but are not

**Table 3**  
Available Assays for Measurement of DOAC Activity

Useful Laboratory Test	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Strong	ECT	Chromogenic anti-FXa	Chromogenic anti-FXa	Chromogenic anti-FXa
Weak	TT/dTT aPTT PT/INR	PT*		PT

aPTT = activated partial thromboplastin time; DOAC = direct oral anticoagulant; dTT = dilute thrombin time; ECT = ecarin clotting time; FXa = factor Xa; INR = international normalized ratio; PT = prothrombin time; TT = thrombin time.

\* PT reagent neoplastin has the most linear correlation.

yet widely available in the United States [36–39]. Applications of these assays to specific DOACs are summarized in Table 3 and will be discussed in further detail by Levy et al [40] in this special issue.

### Rescue Therapies for Life-Threatening Bleeding Events in DOAC-Anticoagulated Patients

Until recently there was no DOAC-specific reversal agent available, and nonspecific hemostatic products have been used in bleeding management of DOAC-anticoagulated patients. Strategies for managing bleeding complications with nonspecific hemostatic agents are different in patients anticoagulated with DOACs compared with warfarin. In the presence of warfarin, which has a long half-life, nonspecific hemostatic products including FFP and PCCs replenish clotting factors and their effects can be sustained with the addition of vitamin K [41]. In contrast, circulating DOACs will also inhibit the exogenous clotting factors, and FFP may not effectively counteract DOAC-mediated anticoagulation.[27,42] The PCCs contain high concentrations of vitamin K-dependent coagulation factors (Table 4), [27, 43–47] whereas recombinant FVIIa (rFVIIa) contains high concentrations of coagulation factor VIIa. Vitamin K does not reverse the anticoagulant effect of DOACs [10–13]. Antifibrinolytic agents can be used in patients with bleeding, [48] but their efficacy is unproven [43].

The nonactivated PCCs, including 4-Factor PCC and 3-Factor PCC may be effective for management of bleeding in patients anticoagulated with apixaban, [11] dabigatran, [10] rivaroxaban, [13] or edoxaban [49,50]. The PCCs raise the levels of coagulation factors that have been inhibited by DOACs. Their use in patients treated with DOACs is primarily based on studies of 4-Factor PCC in animal models of bleeding [51–53] and healthy subjects [44,45,50,54]. A retrospective study of 18 patients treated with rivaroxaban or apixaban and experiencing traumatic ICH suggested that 4-Factor PCC reduces hemorrhagic complications and hematoma expansion [55]. In a bleeding model of pigs anticoagulated with dabigatran, 4-Factor PCC reduced blood loss and

**Table 4**  
Currently Available Blood Products for Rescue Management in DOAC Bleeding (Rivaroxaban and Apixaban)

Product	Factors	Dosage and Administration*
3-Factor PCC	II, IX, X	50 U/kg, IV May repeat Q 12 h
4-Factor PCC	II, VII, IX, X, Proteins C and S	50 U/kg, IV; One time dose

DOAC = direct oral anticoagulant; IV = intravenous; PCC = prothrombin complex concentrate; Q 12 h = every 12 hours.

\* Dosage and administration recommendations are based on clinical information [25, 43–45] and expert opinion, as the use of PCCs to reverse the anticoagulant effects of DOACs is not an approved indication in the United States [46,47].

the risk of mortality; high-dose 4-Factor PCC resulted in overcorrection of thrombin generation, but no thromboembolic complications were observed [53]. Four-Factor PCC had no impact on laboratory tests of the anticoagulant action of dabigatran in a study of nonbleeding healthy subjects (PCC did not restore aPTT, ECT, or TT) despite evidence that it improves hemostasis. In the same study, 4-Factor PCC immediately and completely normalized the prothrombin time [45]. In phase 1 studies of healthy volunteers treated with edoxaban that underwent punch biopsy, 4-Factor PCC completely reversed bleeding, restored endogenous thrombin potential, and partially reversed thrombin time [50]. Transient and dose-dependent increases in prothrombin fragment 1 and 2 (F1+2) with 3-Factor PCC may reflect possible procoagulant risk [49].

Administration of the procoagulant rFVIIa is suggested for anticoagulated bleeding patients in the U.S. prescribing information for dabigatran etexilate [10] and apixaban [11]. In an ex vivo study of healthy volunteers, rFVIIa normalized levels of coagulation markers, however, it failed to restore fibrin generation [56]. The impact of this finding on restoration of hemostasis is unclear.

Specific reversal agents are being developed with the goal of improving the management and outcomes of bleeding in DOAC-treated patients. In addition to idarucizumab, a specific reversal agent for dabigatran, [57] andexanet alfa is under evaluation for reversal of indirect or direct FXa inhibitors, [58,59] while ciraparantag [60] is in clinical trials for reversal of DOACs as well as other anticoagulants. These reversal agents will be discussed in the papers by Pollack [16] and Milling et al [17] in this special issue.

## Conclusion

DOACs offer important safety advantages over VKAs because they are at least as effective for the prevention of thromboembolism, are associated with lower rates of life-threatening and intracranial bleeding, and are more convenient because they can be given in fixed doses without routine coagulation monitoring. Commonly available general coagulation tests have limitations for measurement of the anticoagulant effects of DOACs. Specific assays are commercially available [61] but have not been widely implemented. Specific reversal agents are being introduced into clinical practice and will help to streamline the management of patients with bleeding and those who require urgent surgery.

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