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Bleeding with Direct Oral Anticoagulants vs Warfarin: Clinical Experience

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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

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

	RE-LY[18,†]			ROCKET AF[19, 20]		ARISTOTLE[21]		ENGAGE-AF TIMI 48[22]		
Primary Safety Outcome (Percentage of Patients with an Adverse Event)*	Dabigatran 150 mg (n = 6076)	Dabigatran 110 mg (n = 6015)	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	2.71% 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)	0.80 (0.69-0.93)	—	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	.003		.58		<.001		<.001	<.001	
Intracranial bleeding	0.30% per y	0.23% 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)	0.31 (0.20-0.47)	—	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	<.001		.02		<.001		<.001	<.001	
Gastrointestinal bleeding	1.51% per y	1.12% 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)	1.10 (0.86-1.41)	—	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	.43		<.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.