	Genotype	Caucasians n=3261	Blacks n=152	East Asians <sup>a</sup> n=168
VKORC1	G/G	1220 (37.4)	128 (84.2)	2 (1.2)
	G/A	1533 (47.0)	24 (15.8)	38 (22.6)
	A/A	508 (15.6)	0	128 (76.2)
	*1/*1	2101 (64.4)	146 (96.1)	155 (92.3)
CYP2C9	*1/*2	689 (21.1)	3 (2.0)	0
	*1/*3, *2/*2, *2/*3, or *3/*3	471 (14.4)	3 (2.0)	13 (7.7)

Supplemental Table 1. Genotype Frequencies by Race

All values are n (%)

<sup>a</sup> Includes subjects from Japan, China, Taiwan, and Korea only

	Normal ResponderEdoxabanWarfarin		Sensitive Responder		Highly Sensiti	ive Responder	Overall	
			Edoxaban Warfarin		Edoxaban	Warfarin	Edoxaban	Warfarin
Bleeding Events	(n=1212)	(n=1247)	(n=691)	(n=675)	(n=75)	(n=56)	(n=1978)	(n=1978)
Major	7 (0.6%)	3 (0.2%)	3 (0.4%)	1 (0.2%)	2 (2.7%)	0 (0.0%)	12 (0.6%)	4 (0.2%)
Major or CRNM	22 (1.8%)	33 (2.7%)	18 (2.6%)	28 (4.2%)	3 (4.0%)	3 (5.4%)	43 (2.2%)	64 (3.2%)
All	96 (7.9%)	121 (9.7%)	61 (8.8%)	101 (15.0%)	11 (14.7%)	9 (16.1%)	168 (8.5%)	231 (11.7%)

Supplemental Table 2. Bleeding Events During the First 28 Days of Treatment Across Genotype Categories

CRNM = clinically relevant nonmajor

Supplemental Figure 1. Participant Disposition Flow Diagram



**Supplemental Figure 2.** The incidence and hazard ratios for bleeding events for edoxaban vs warfarin during the first 90 days of treatment and during the entire the duration of the study across the 3-bin warfarin sensitivity groups (A) and 2-bin warfarin sensitivity groups (B)

Α	Bleeding Events During First 90 Days of Treatment						Bleeding Events During the Entire Study					
	Edoxaban	Warfarin		Adj. HR (95% Cl)ª	<b>P</b> int <sup>b</sup>	Edoxaban	Warfarin		Adj. HR (95% CI)ª	<b>P</b> int <sup>b</sup>		
Total bleeds					0.0747					0.4455		
Normal	14.4%	15.6%	-•-	0.91 (0.739, 1.110)		21.7%	22.8%	-•-	0.93 (0.783, 1.094)			
Sensitive	13.7%	20.9%		0.62 (0.479, 0.806)		22.3%	27.0%		0.78 (0.628, 0.967)			
Highly sensitive	22.7%	26.8%		0.84 (0.417, 1.707)		28.0%	30.4%		- 0.89 (0.466, 1.686)			
Major and CRNM	bleeds				0.1886					0.1659		
Normal	5.8%	4.5%		1.27 (0.894, 1.808)		9.2%	8.1%	-+	1.12 (0.857, 1.466)			
Sensitive	5.4%	6.5%		0.81 (0.522, 1.257)		7.8%	10.2%		0.75 (0.524, 1.073)			
Highly sensitive	8.0%	12.5% —	•	— 0.61 (0.201, 1.844)		12.0%	16.1%	•	- 0.69 (0.273, 1.761)			
		0.25	0.5 1	2			0.25	0.5 1	2			
		Edoxa	aban safer 🛛	Varfarin safer			Edoxab	an safer W	arfarin safer			
В	Blee	ding Event	s During Fi	rst 90 Days of Treatme	nt	I	Bleeding E	vents Durin	g the Entire Study			
	Edoxaban	Warfarin		Adj. HR (95% CI)ª	$P_{int}^{b}$	Edoxaban	Warfarin		Adj. HR (95% CI)ª	<b>P</b> <sub>int</sub> <sup>b</sup>		
Total bleeds					0.0377					0.2392		
Normal	14.4%	15.6%	-•	0.91 (0.739, 1.110)		21.7%	22.8%	-•	0.93 (0.783, 1.094)			
Pooled Sensitive	14.6%	21.3%	-•	0.65 (0.508, 0.826)		22.8%	27.2%	-•-	0.79 (0.644, 0.969)			
Major and CRNM	bleeds				0.0861					0.0693		
Normal	5.8%	4.5%	+•	— 1.27 (0.894, 1.808)		9.2%	8.1%		1.12 (0.857, 1.466)			
Pooled Sensitive	5.6%	7.0%	-•	0.79 (0.524, 1.187)		8.2%	10.7%	-•	0.75 (0.537, 1.046)			
		0.25	0.5 1	2			0.25	0.5 1	2			
		Edoxa	ban safer W	/arfarin safer			_ Edoxab	an safer W	—► arfarin safer			

<sup>a</sup>Covariates used in the Cox proportional hazards model included presenting diagnosis (PE with or without DVT vs DVT only), baseline risk factors (temporary risk vs other), and the need for edoxaban dose adjustment

<sup>b</sup>P-values for interactions are based on the Cox proportional hazards model with additional interaction terms for applicable genotype and treatment

CI = confidence intervals; CRNM = clinically relevant non-major; DVT = deep vein thrombosis; HR = hazard ratios; PE = pulmonary embolism

**Supplemental Figure 3.** The incidence and hazard ratios for major bleeding events for edoxaban vs warfarin during the first 90 days of treatment and during the entire the duration of the study across the 3-bin warfarin sensitivity groups (A) and 2-bin warfarin sensitivity groups (B)

	Major Bleeding Events During First 90 Days of Treatment					Major Bleeding Events During the Entire Study					
	Edoxaban	Warfarin		Adj. HR (95% CI) <sup>a</sup>	<b>P</b> int <sup>b</sup>	Edoxaban	Warfarin	1	Adj. HR (95% CI) <sup>a</sup>	<b>P</b> int <sup>b</sup>	
3-Bin Analysis					_					<0.0001	
Normal	1.2%	0.6%	<b>⊢−</b> −1	1.83 (0.770, 4.341)		1.7%	1.6%	<b>⊢ ♦</b>	1.01 (0.545, 1.863)		
Sensitive	0.9%	0.3%		_		1.0%	1.3%	<b>⊢</b> ●	0.76 (0.284, 2.035)		
Highly sensitive	2.7%	0%		—		2.7%	0%		—		
2-Bin Analysis					_					0.9536	
Normal	1.2%	0.6%	⊢ <b>−</b> −−	1.83 (0.770, 4.341)		1.7%	1.6%	<b>⊢ ♦</b> − 1	1.01 (0.545, 1.863)		
Pooled Sensitive	e <sup>c</sup> 1.0%	0.3%		_		1.2%	1.2%		0.96 (0.380, 2.409)		
			0.5 1 2 4	8				0.5 1 2	4 8		
	Edoxaban safer Warfarin safer					Edoxaban safer Warfarin safer					

<sup>a</sup> Covariates used in the Cox proportional hazards model included presenting diagnosis (PE with or without DVT vs DVT only), baseline risk factors (temporary risk vs other), and the need for edoxaban dose adjustment

<sup>b</sup>P-values for interactions are based on the Cox proportional hazards model with additional interaction terms for applicable genotype and treatment

<sup>c</sup> There were too few major bleeding events to reliably establish estimates of the risk of major bleeding or to estimate the  $P_{int}$  values CI = confidence intervals; DVT = deep vein thrombosis; HR = hazard ratios; PE = pulmonary embolism

**Supplemental Figure 4.** Kaplan-Meier curve for the incidence of bleeding events in warfarin treated patients across 2-bin warfarin sensitivity genotypes



CI = confidence intervals; HR = hazard ratio