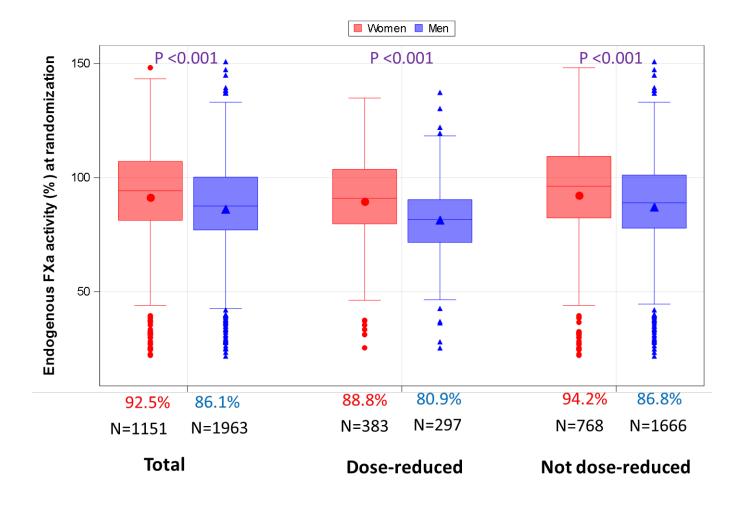
Appendix

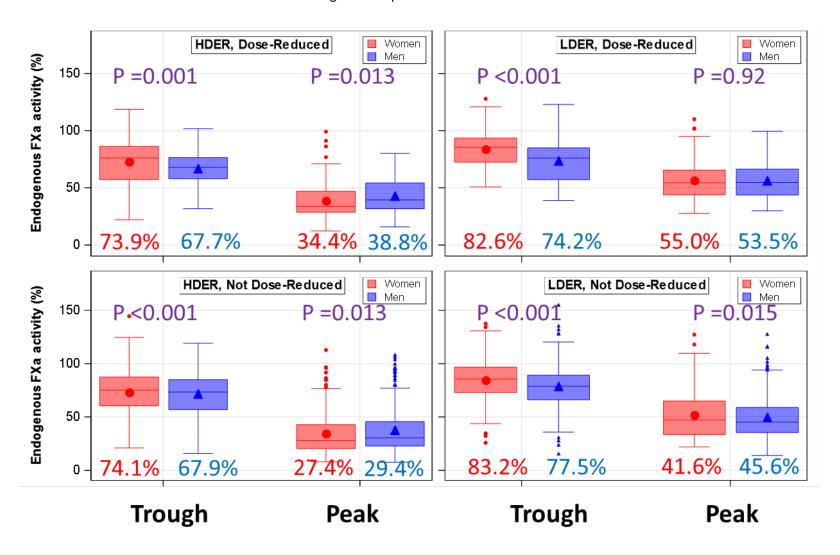
Supplemental Figure I: Baseline endogenous Factor Xa activity according to dose-reduction criteria in men and women.

The difference between men and women was tested using the non-parametric Wilcoxon rank-sum test. DR = dose reduction



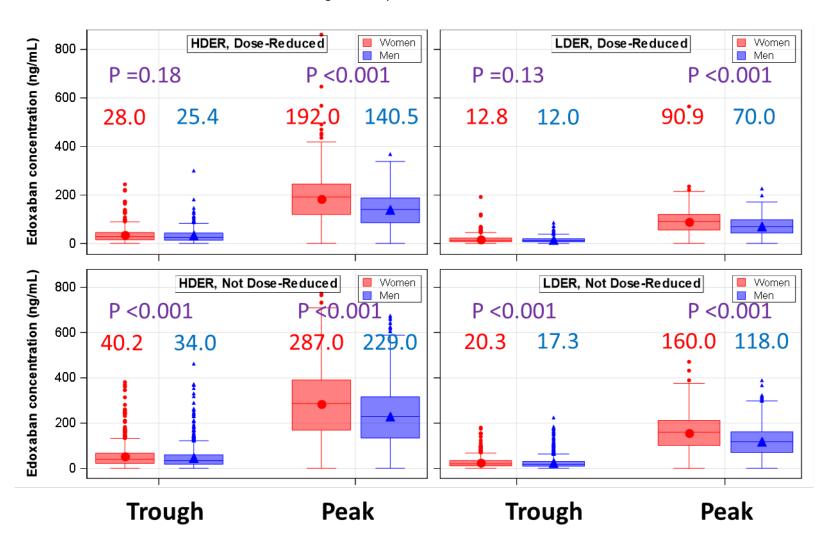
Supplemental Figure II: Endogenous Factor Xa activity with higher-dose (HDER) and lower-dose edoxaban regimen (LDER) according to dose-reduction criteria.

The difference between men and women was tested using the non-parametric Wilcoxon rank-sum test.



Supplemental Figure III: Edoxaban concentrations with higher-dose (HDER) and lower-dose edoxaban regimen (LDER) according to dose-reduction (DR) criteria.

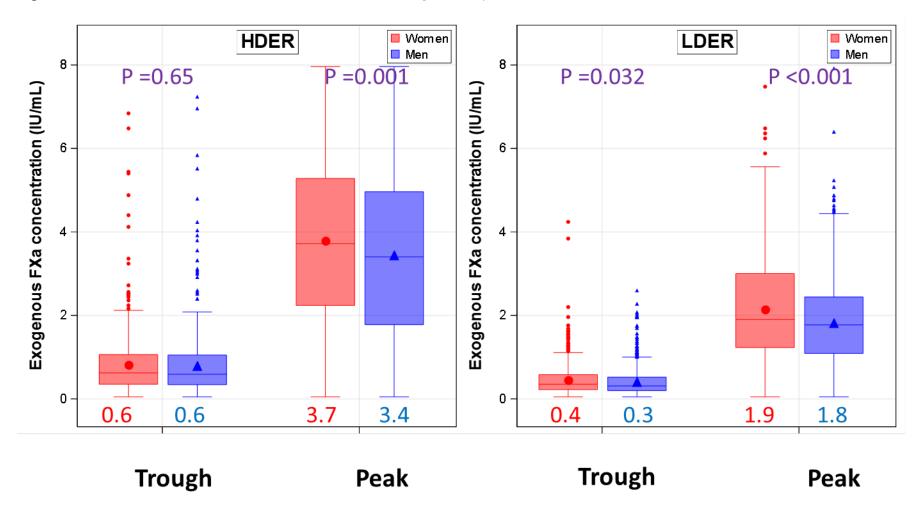
The difference between men and women was tested using the non-parametric Wilcoxon rank-sum test.



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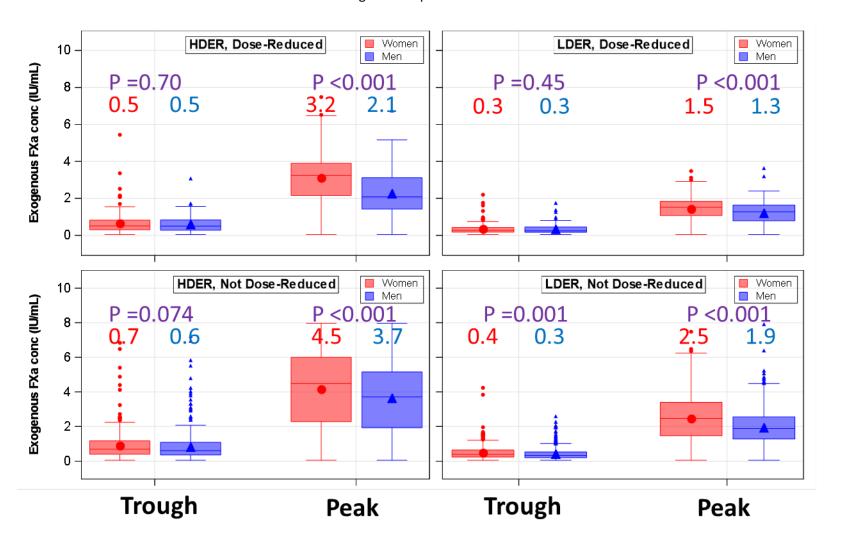
Supplemental Figure IV: Exogenous Factor Xa Concentrations with higher-dose (HDER) and lower-dose edoxaban (LDER)

regimen. The difference between men and women was tested using the non-parametric Wilcoxon rank-sum test.



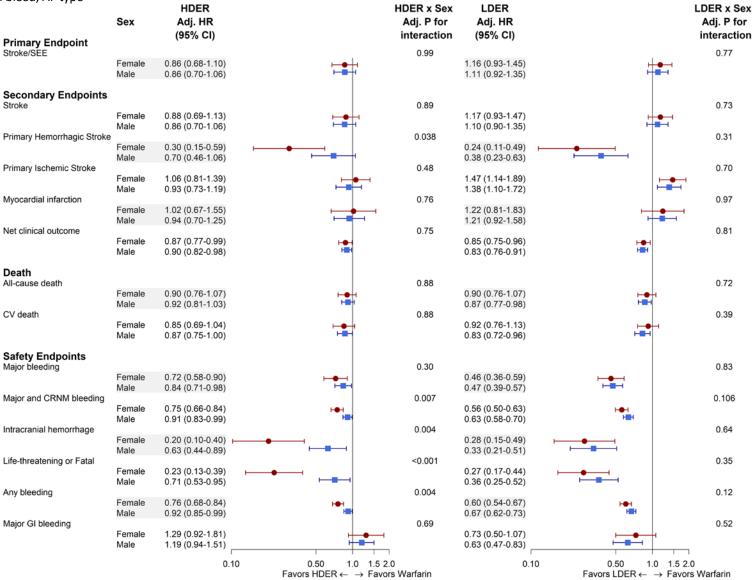
Supplemental Figure V: Exogenous Factor Xa concentrations with higher-dose (HDER) and lower-dose edoxaban regimen (LDER) according to dose-reduction (DR) criteria.

The difference between men and women was tested using the non-parametric Wilcoxon rank-sum test.



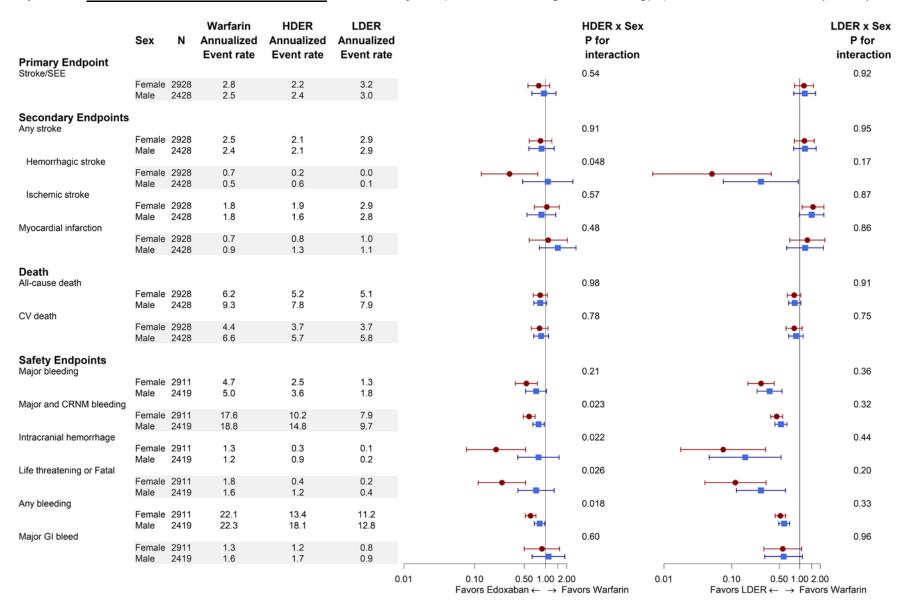
Supplemental Figure VI: Efficacy and safety of edoxaban versus warfarin stratified by sex using multivariable adjusted* Cox model. (The x-axis of the forest plot represents hazard ratio.)

*Adjusted for age, body mass index, race, smoking, history of stroke or TIA, diabetes, heart failure, hypertension, coronary artery disease, peripheral artery disease, dyslipidemia, hepatic disease, non-ICH bleed, AF type

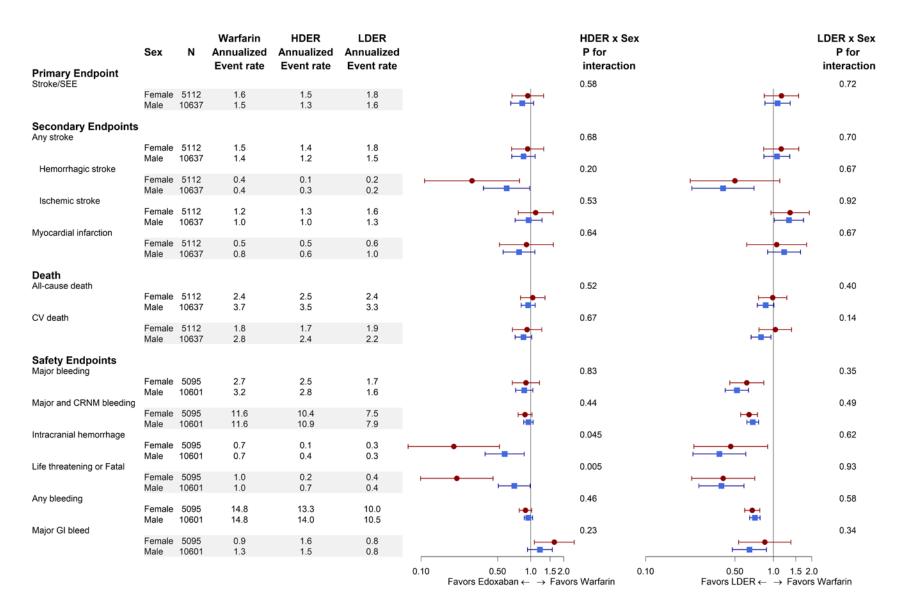


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Supplemental Figure VII: Efficacy and safety of higher dose edoxaban regimen (HDER) and lower dose edoxaban regimen (LDER) versus warfarin in patients who met criteria for dose reduction stratified by sex (i.e., HDER 30 mg, LDER 15 mg). (The x-axis of the forest plot represents hazard



Supplemental Figure VIII: Efficacy and safety of higher dose edoxaban regimen (HDER) and lower dose edoxaban regimen (LDER) in patients who did <u>not</u> meet criteria for dose-reduction versus warfarin stratified by sex (i.e., HDER 60 mg, LDER 30 mg). (The x-axis of the forest plot represents hazard ratio.)



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Supplemental Figure IX: Edoxaban versus warfarin on stroke and systemic embolic events in women by major subgroups. (The x-axis of the forest plot represents hazard ratio.)

		Total N	Warfarin Annualized Event rate	HDER Annualized Event rate	LDER Annualized Event rate	HDER x Subgrp P for interaction	LDER x Sex P for interaction
Age (yrs)							
	<65	1510	1.1	0.9	1.6	REF H	REF
	65-<75	2753	1.8	1.5	2.1	1.00	0.48
	>=75	3777	2.5	2.3	2.8	0.86	0.44
Weight (kg)							
	<74	3914	2.5	2.2	2.9	REF H	REF
OLIABOO	>=74	4126	1.5	1.3	1.8	0.99	0.80
CHADS2	<=3	6052	1.5	1.4	2.0	REF H	REF
	<=3 >3	6052 1988	1.5 3.5	1.4 2.8	3.4	0.53	0.23
Region	-3	1900	3.5	2.0	3.4	0.55	0.23
Region	N. America	1598	1.8	1.9	2.1	REF H	REF
	S. America	1081	2.2	1.8	2.3	0.61	0.72
	W. Europe	1233	1.8	2.3	2.1	0.47	0.93
	E. Europe	3008	1.7	1.5	2.6	0.70	0.47
	Asia	1120	3.1	1.6	2.3	0.15	0.24
Diabetes							
	No	5258	2.2	1.8	2.4	⊢ ■ ⊢ REF ⊢ ■ −	REF
	Yes	2782	1.5	1.7	2.2	0.23	0.24
Heart Failure							
	No	3464	2.0	1.9	2.4	⊢ ■ REF	REF
	Yes	4576	2.0	1.7	2.3	0.51	0.71
Stroke/TIA							
	No	5761	1.5	1.4	1.9	REF +	REF
	Yes	2279	3.4	2.8	3.5	0.62	0.37
AF type	D	0.400	0.0	0.0	4.0	-	DEE
	Paroxysmal	2432 1825	0.9 2.4	2.0 1.4	1.9 1.7	REF 0.001	REF 0.007
	Persistent Permanent	3780	2.4	1.4	2.9	0.001	0.007
Hypertension	remanent	3700	2.5	1.0	2.5	0.001	0.109
пурецензіон	No	409	2.2	2.3	4.4	REF REF	REF
	Yes	7631	2.0	1.7	2.2	0.60	0.11
Prior MI	100	7001	2.0			3.55	0.11
	No	7457	1.9	1.7	2.2	⊢ REF ⊢	REF
	Yes	582	3.1	2.0	3.1	0.42	0.81
Dose reduced							
	No	5112	1.6	1.5	1.8	⊢■ REF ⊢■	REF
	Yes	2928	2.8	2.2	3.2	0.52	1.00
Aspirin use							
	No	5903	1.9	1.8	2.3	⊢ ≠ → REF	REF
	Yes	2135	2.4	1.6	2.3	0.12	0.31
Amiodarone use		7070					555
	No	7073	2.0	1.8	2.4	REF	REF
	Yes	967	1.7	1.2	1.6	0.55	0.47
					0	1.10 0.50 1.0 3.0 0.10 0.50 1.0 1.5 3.0	
					0	Favors HDER \leftarrow \rightarrow Favors Warfarin Favors LDER \leftarrow \rightarrow Favors Warfarin	n

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Supplemental Figure X: Edoxaban versus warfarin on major bleeding in women by major subgroups. (The x-axis of the forest plot represents hazard ratio.)

		Total N	Warfarin Annualized Event rate	HDER Annualized Event rate	LDER Annualized Event rate	HDE i	LDER x Sex P for interaction	
Age (yrs)								
	<65	1506	1.7	1.6	0.5	⊢	REF -	REF
	65-<75	2745	2.8	2.2	1.4	- ■ 	0.64	0.28
	>=75	3755	4.7	3.2	2.1	⊢-≡	0.40 ⊢■ー	0.36
Weight (kg)								
	<74	3890	3.9	2.6	1.5	⊢-■	REF ⊢■ー	REF
	>=74	4116	2.9	2.3	1.6	⊢ +	0.43	0.20
CHADS2								
	<=3	6022	3.1	2.3	1.5	⊢≣ →	REF ⊢■	REF
	>3	1984	4.2	3.2	1.7	⊢ ■-	0.89	0.60
Region								
0	N. America	1591	4.4	4.4	2.8	⊢	REF ⊢■	REF
	S. America	1078	3.7	2.6	1.3	⊢	0.37	0.22
	W. Europe	1227	4.0	2.7	1.4	⊢	0.32	0.18
	E. Europe	2997	2.3	1.3	1.0	⊢	0.090	0.31
	Asia	1113	4.3	3.0	1.6	⊢	0.34	0.21
Diabetes								
	No	5232	3.2	2.4	1.4	⊢ ■	REF ⊢■→	REF
	Yes	2774	3.6	2.5	1.8	⊢ ■	0.69	0.58
CHF								
	No	3442	3.7	2.9	1.6	⊢ ■	REF ⊢■	REF
	Yes	4564	3.1	2.2	1.5	⊢ ■	0.75	0.56
Stroke/TIA								
	No	5733	3.3	2.3	1.6	⊢ ■→	REF ⊢■ー	REF
	Yes	2273	3.4	3.0	1.3	⊢	0.36	0.38
AF type								
7/1	Paroxysmal	2421	3.0	3.4	1.1	<u> </u>	REF ⊢■	REF
	Persistent	1815	3.9	1.5	1.5	──	0.002	0.74
	Permanent	3770	3.3	2.3	1.9	⊢ ■	0.072	0.12
Hypertension								
,,	No	407	4.1	2.9	1.5	———	REF -	REF
	Yes	7599	3.3	2.5	1.5	⊢ ■→	0.96 ⊢■→	0.76
Prior MI								
	No	7424	3.5	2.5	1.5	⊢■ →	REF ⊢■→	REF
	Yes	581	1.8	2.9	1.8		0.11	0.11
Dose reduced								
	No	5095	2.7	2.5	1.7	⊢ ■	REF ⊢■→	REF
	Yes	2911	4.7	2.5	1.3	⊢	0.028	0.003
Aspirin use								
	No	5885	3.0	2.4	1.3	⊢ ■	REF ⊢■→	REF
	Yes	2120	4.5	2.8	2.3	⊢	0.32	0.55
Amiodarone use								
	No	7042	3.4	2.5	1.6	⊢■ →	REF ⊢■→	REF
	Yes	964	2.6	2.5	0.8	—	0.41	0.42
					Г			
					0.1	0.50 1.0 3.0	0.10 0.50 1.0 1	.5 3.0

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