SUPPLEMENTAL MATERIAL

Supplementary Table S1. Edoxaban Trough Concentration and Anti-FXa Activity at Trough by Age and Dose Reduction

		<65 year	65-74 year	≥75 year
Edoxaban Concentration at trough (ng/mL)	HDER No DR (60mg)	29.4[15.3-53.1]	36.1[20.0-63.8]	42.6[25.4-68.4]
	HDER DR (30mg)	18.2[10.0-38.8]	25.1[13.0-41.4]	28.8[16.5-45.8]
	LDER No DR (30mg)	14.0[7.3-27.3]	18.5[10.6-31.7]	22.8[13.4-36.0]
	LDER DR (15mg)	8.2[3.6-14.3]	11.6[6.6-19.6]	13.5[8.4-22.2]
Anti FXa Activity at trough (IU/mL)	HDER No DR (60mg)	0.5[0.3-1.0]	0.7[0.4-1.1]	0.8[0.5-1.3]
	HDER DR (30mg)	0.5[0.2-1.0]	0.5[0.3-0.9]	0.5[0.3-0.8]
	LDER No DR (30mg)	0.3[0.2-0.5]	0.4[0.2-0.5]	0.4[0.3-0.7]
	LDER DR (15mg)	0.2[0.2-0.3]	0.3[0.2-0.5]	0.3[0.2-0.5]

DR; dose reduction, HDER; higher dose edoxaban regimen, LDER; lower dose edoxaban regimen.

Supplementary Table S2. Primary Outcomes by Dose Reduction (Higher dose edoxaban regimen (60/30 mg)

Outcomes	Age	Event Rates (%/pt-yrs)				Higher dose edoxaban regimen vs. warfarin			
		Did not meet edoxaban dose reduction criteria*		Met edoxaban dose reduction criteria*		Did not meet edoxaban dose reduction criteria*	Met edoxaban dose reduction criteria*		3 way
		Edox 60mg	Warfarin	Edox 30mg	Warfarin	HR [95% CI]	HR [95% CI]	P_{int}†	P_{int}‡
Stroke or SEE	***<65 years***	1.1	1.1	1.0	1.7	0.99 [0.67-1.47]	0.62 [0.20-1.90]	0.43	0.52
	65-74 years	1.4	1.6	2.6	2.5	0.85 [0.62-1.16]	1.01 [0.59-1.70]	0.60	
	≥75 years	1.6	1.9	2.4	2.9	0.82 [0.60-1.12]	0.84 [0.61-1.15]	0.91	
Major Bleeding	***<65 years***	1.4	1.8	1.9	1.9	0.79 [0.56-1.11]	1.04 [0.39-2.76]	0.62	0.09
	65-74 years	2.4	3.3	2.7	3.5	0.75 [0.58-0.96]	0.76 [0.45-1.30]	0.95	
	≥75 years	4.4	4.1	3.4	6.0	1.06 [0.84-1.33]	0.58 [0.43-0.77]	0.0013	

*In the higher-dose edoxaban regimen, patients with moderate renal dysfunction, weight ≤ 60 mg, or use of strong P-gp inhibitors received 30 mg instead of 60 mg edoxaban once daily. There was no “dose reduction” for warfarin; instead the dose of warfarin was titrated to a target INR of 2.0-3.0.

†p-interaction for dose reduction and treatment effect

‡3 way p-interaction for dose reduction, treatment effect and age

Supplementary Table S3. Primary Outcomes by Dose Reduction (Lower dose edoxaban regimen 30/15 mg)

Outcomes	Age	Event Rates (%/pt-yrs)				Lower dose edoxaban regimen vs. warfarin			
		Did not meet edoxaban dose reduction criteria*		Met edoxaban dose reduction criteria*		Did not meet edoxaban dose reduction criteria*	Met edoxaban dose reduction criteria*		3 way
		Edox 30mg	Warfarin	Edox 15 mg	Warfarin	HR [95% CI]	HR [95% CI]	P_{int}*	P_{int}**
Stroke or SEE	***<65 years***	1.5	1.1	2.3	1.7	1.43 [0.99-2.08]	1.34 [0.55-3.29]	0.89	0.82
	65-74 years	1.6	1.6	3.0	2.5	0.94 [0.70-1.28]	1.16 [0.70-1.93]	0.49	
	≥75 years	2.0	1.9	3.3	2.9	1.07 [0.80-1.45]	1.15 [0.86-1.54]	0.74	
Major Bleeding	***<65 years***	0.8	1.8	0.5	1.9	0.43 [0.28-0.65]	0.24 [0.05-1.13]	0.48	0.05
	65-74 years	1.6	3.3	1.8	3.5	0.48 [0.36-0.63]	0.51 [0.29-0.93]	0.82	
	≥75 years	2.7	4.1	1.6	6.0	0.65 [0.51-0.84]	0.27 [0.18-0.39]	0.0001	

*In the lower-dose edoxaban regimen, patients with moderate renal dysfunction, weight ≤ 60 mg, or use of strong P-gp inhibitors received 15 mg instead of 30 mg edoxaban once daily. There was no “dose reduction” for warfarin; instead the dose of warfarin was titrated to a target INR of 2.0-3.0.

†p-interaction for dose reduction and treatment effect

‡3 way p-interaction for dose reduction, treatment effect and age

Supplementary Table S4 Patient Characteristics in Very Elderly Population (≥ *80 years*)

Characteristics	< 80 years (N=17514, 83.0%)	≥ 80 years (N=3591, 17.1%)
Age -- years	70 [63.0-75.0]	82 [81.0-85.0]
Weight -- kg	83.8 [71.5-97.1]	74 [64.1-84.0]
Female Sex	6386 (37)	1654 (46)
Hypertension	16433 (94)	3321 (93)
Dyslipidemia	9215 (53)	1843 (51)
Diabetes	6717 (38)	907 (25)
Current Smoking	1443 (8.2)	109 (3.0)
Prior PCI	1162 (6.6)	278 (7.7)
Prior Stroke or TIA	5017 (29)	956 (27)
Congestive Heart Failure	10501 (60)	1623 (45)
Type of AF		
Paroxysmal	4452 (25)	914 (26)
Permanent	9018 (52)	1847 (52)
CrCl (ml/min) at randomization	75.6 [59.1-96.8]	49.8 [41.0-60.8]
≤50	2256 (13)	1818 (51)
>50-80	7593 (43)	1572 (44)
> 80	7665 (44)	201 (5.6)
Race		
White	14007 (80)	3060 (85)
Asian	2588 (15)	321 (8.9)
Black	250 (1.4)	28 (0.8)
Other	669 (3.8)	181 (5.0)
$CHADS_2$ Score		
Mean (SD)	2.8 (0.9)	3.2 (1.1)
4-6	3593 (21)	1175 (33)
CHA_2DS_2-VASc Score		
Mean (SD)	4.2 (1.4)	5.0 (1.3)
4-6	11718 (67)	3201 (89)
HAS-BLED Score ≥3	7751 (44)	2051 (57)
Time in Therapeutic range	68.2 [56.3-77.2]	69.5 [57.8-78.5]
Dose reduction at randomization	3465 (20)	1891 (53)
Prior VKA experience	10274 (59)	2167 (60)
Medication at randomization		
Aspirin	5110 (29)	1070 (30)
Thienopyridine	393 (2.2)	94 (2.6)

*See Figure 1 Legend for abbreviations and for data presentation.

p value <0.001 for all comparisons except for hypertension (p=0.003), dyslipidemia (p=0.158), prior PCI (p=0.016), prior stroke or TIA (p=0.014), Type of AF (p=0.996), Time in therapeutic range (p=0.225), prior VKA experience (p=0.062), aspirin use (p=0.455), and thienopyridine use (p=0.174).

Supplementary Table S5 Patient Characteristics in Very Elderly Population (≥*85 years*)

Characteristics	< 85 years (N=20206, 95.7%)	≥ 85 years (N=899, 4.3%)
Age -- years	71 [64.0-77.0]	86 [85.0-88.0]
Weight -- kg	82 [70.0-95.7]	72 [63.0-81.2]
Female Sex	7634 (38)	406 (45)
Hypertension	18927 (94)	827 (92)
Dyslipidemia	10607 (53)	451 (50)
Diabetes	7438 (37)	186 (21)
Current Smoking	1533 (7.6)	19 (2.1)
Prior PCI	1379 (6.8)	61 (6.8)
Prior Stroke or TIA	5716 (28.3)	257 (29)
Congestive Heart Failure	11700 (58)	424 (47)
Type of AF		
Paroxysmal	5146 (26)	220 (25)
Permanent	10405 (52)	460 (51)
CrCl (ml/min) at randomization	71.7 [55.3-93.1]	44.3 [37.0-53.3]
≤50	3473 (17)	601 (67)
>50-80	8881 (44)	284 (32)
> 80	7852 (39)	14 (1.6)
Race		
White	16291 (81)	776 (86)
Asian	2844 (14)	65 (7.2)
Black	271 (1.3)	7 (0.8)
All others	799 (4.0)	51 (5.7)
$CHADS_2$ Score		
Mean (Sd)	2.8 (1.0)	3.2 (1.1)
4-6	4467 (22)	301 (34)
CHA_2DS_2-VASc Score		
Mean (Sd)	4.3 (1.4)	5.0 (1.3)
4-6	14129 (70)	790 (88)
HAS-BLED Score ≥3	9279 (46)	523 (58)
Time in Therapeutic range	68.4 [56.5-77.4]	68.4 [57.9-77.4]
Dose reduction at randomization	4754 (24)	602 (67)
Prior VKA experience	11912 (59)	529 (59)
Medication at randomization		
Aspirin	5912 (29)	268 (30)
Thienopyridine	461 (2.3)	26 (2.9%)

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p value <0.001 for all comparisons except for hypertension (p=0.044), dyslipidemia (p=0.172), prior PCI (p=0.962), prior stroke or TIA (p=0.864), Type of AF (p=0.630), time in therapeutic range (p=0.238), prior VKA experience (p=0.946), aspirin use (p=0.725), and thienopyridine use (p=0.233)..

Supplementary Table S6 Outcomes in Very Elderly Population (≥ *80 years*)

		Warfarin	HDER	LDER	HDER vs. War		LDER vs. War	
		Event rate (%/yr)	Event rate (%/yr)	Event rate (%/yr)	HR (95% CI)	Pint	HR (95% CI)	Pint
Stroke/SEE	< *80 yr*	1.6	1.4	1.9	0.87 (0.73 - 1.04)	0.97	1.17 (0.99 - 1.39)	0.39
	≥ *80 yr*	2.9	2.5	2.8	0.88 (0.64 - 1.20)		1.01 (0.75 - 1.36)	
Ischemic Stroke	< *80 yr*	1.1	1.1	1.7	1.03 (0.84 - 1.27)	0.54	1.49 (1.23 - 1.81)	0.23
	≥ *80 yr*	2.1	1.8	2.4	0.90 (0.63 - 1.30)		1.18 (0.84 - 1.65)	
Hemorrhagic Stroke	< *80 yr*	0.4	0.2	0.2	0.55 (0.37 - 0.82)	0.93	0.37 (0.23 - 0.59)	0.31
	≥ *80 yr*	0.8	0.4	0.2	0.53 (0.26 - 1.06)		0.21 (0.08 - 0.56)	
Fatal Stroke	< *80 yr*	0.4	0.4	0.3	0.96 (0.67 - 1.37)	0.75	0.84 (0.58 - 1.22)	1.00
	≥ *80 yr*	0.8	0.7	0.7	0.86 (0.48 - 1.53)		0.84 (0.47 - 1.50)	
Major bleeding	< *80 yr*	3.0	2.5	1.5	0.83 (0.71 - 0.96)	0.54	0.49 (0.41 - 0.58)	0.37
	≥ *80 yr*	6.2	4.6	2.6	0.75 (0.58 - 0.98)		0.42 (0.31 - 0.56)	
ICH	< *80 yr*	0.7	0.4	0.2	0.49 (0.34 - 0.69)	0.64	0.31 (0.20 - 0.47)	0.88
	≥ *80 yr*	1.6	0.6	0.5	0.41 (0.22 - 0.77)		0.29 (0.15 - 0.57)	
Fatal bleeding	< *80 yr*	0.3	0.2	0.1	0.57 (0.35 - 0.94)	0.79	0.28 (0.15 - 0.54)	0.27
	≥ *80 yr*	0.8	0.4	0.4	0.50 (0.21 - 1.15)		0.50 (0.22 - 1.13)	
Major GI bleeding	< *80 yr*	1.1	1.3	0.7	1.19 (0.95 - 1.5	0.41	0.66 (0.51 - 0.85)	0.87
	≥ *80 yr*	1.9	2.7	1.3	1.44 (0.97 - 2.13)		0.69 (0.43 - 1.09)	
Net clincal outcome:	< *80 yr*	7.0	6.5	6.1	0.92 (0.85 - 1.01)	0.17	0.87 (0.79 - 0.95)	0.09
Primary	≥ *80 yr*	14.2	11.6	10.5	0.82 (0.71 - 0.95)		0.75 (0.65 - 0.87)	
Net clincal outcome:	< *80 yr*	4.4	4.0	3.8	0.91 (0.82 - 1.02)	0.30	0.86 (0.78 - 0.96)	0.24
Secondary	≥ *80 yr*	9.6	7.8	7.2	0.82 (0.69 - 0.97)		0.76 (0.64 - 0.91)	
Net clincal outcome:	< *80 yr*	5.1	4.6	4.8	0.90 (0.81 - 0.99)	0.43	0.93 (0.84 - 1.03)	0.10
Tertiary	≥ *80 yr*	10.7	8.8	8.3	0.83 (0.71 - 0.98)		0.79 (0.67 - 0.93)	

HDER; Higher dose edoxaban regimen, LDER; lower dose edoxaban

*See Table 1 for abbreviations.

Supplementary Table S7 Outcomes Very Elderly Population (≥ *85 years*)

		Warfarin	HDER	LDER	HDER vs. warfarin		LDER vs. warfarin	
		Event rate (%/yr)	Event rate (%/yr)	Event rate (%/yr)	HR (95% CI)	Pint	HR (95% CI)	Pint
Stroke / SEE	*<85 year*	1.7	1.5	2.0	0.88 (0.75 - 1.03)	0.56	1.14 (0.98 - 1.33)	0.68
	≥85 year	3.5	2.5	3.4	0.73 (0.40 - 1.33)		1.01 (0.58 - 1.76)	
Ischemic Stroke	*<85 year*	1.2	1.2	1.7	1.01 (0.84 - 1.22)	0.50	1.42 (1.19 - 1.69)	0.80
	≥85 year	2.4	1.9	3.0	0.79 (0.39 - 1.60)		1.30 (0.69 - 2.47)	
Hemorrhagic Stroke	*<85 year*	0.5	0.3	0.2	0.53 (0.37 - 0.76)	0.78	0.35 (0.23 - 0.54)	N/A
	≥85 year	0.8	0.5	0.0	0.64 (0.18 - 2.28)		N/A	
Fatal Stroke	*<85 year*	0.4	0.4	0.4	0.96 (0.70 - 1.31)	0.40	0.82 (0.59 - 1.14)	0.64
	≥85 year	1.0	0.5	1.0	0.56 (0.16 - 1.91)		1.07 (0.38 - 3.05)	
Major bleeding	*<85 year*	3.3	2.7	1.6	0.82 (0.72 - 0.94)	0.17	0.48 (0.41 - 0.56)	0.35
	≥85 year	8.8	5.0	3.1	0.58 (0.35 - 0.94)		0.36 (0.20 - 0.64)	
ICH	*<85 year*	0.8	0.4	0.2	0.46 (0.33 - 0.62)	0.62	0.29 (0.20 - 0.42)	0.38
	≥85 year	1.6	0.9	0.8	0.61 (0.20 - 1.88)		0.51 (0.15 - 1.70)	
Fatal bleeding	*<85 year*	0.4	0.2	0.1	0.52 (0.33 - 0.82)	0.45	0.31 (0.18 - 0.53)	0.17
	≥85 year	0.6	0.6	0.6	0.99 (0.20 - 4.91)		1.03 (0.21 - 5.12)	
Major GI blding	*<85 year*	1.1	1.5	0.8	1.29 (1.05 - 1.57)	0.14	0.70 (0.56 - 0.89)	0.15
	≥85 year	3.8	2.8	1.3	0.76 (0.39 - 1.50)		0.36 (0.15 - 0.87)	
Net clincal outcome	*<85 year*	7.7	7.0	6.5	0.90 (0.84 - 0.98)	0.25	0.84 (0.78 - 0.91)	0.41
Primary	*≥85 year*	19.2	14.6	14.0	0.77 (0.60 - 1.00)		0.75 (0.58 - 0.98)	
Net clincal outcome	*<85 year*	4.9	4.4	4.2	0.89 (0.81 - 0.98)	0.52	0.84 (0.76 - 0.93)	0.73
Secondary	*≥85 year*	13.3	10.5	10.2	0.81 (0.60 - 1.08)		0.80 (0.59 - 1.08)	
Net clincal outcome	*<85 year*	5.7	5.0	5.2	0.89 (0.81 - 0.97)	0.48	0.90 (0.82 - 0.99)	0.41
Tertiary	*≥85 year*	14.6	11.4	11.2	0.80 (0.60 - 1.06)		0.79 (0.59 - 1.06)	

Supplementary Table S8 Outcomes by patients aged <75 and ≥75 years

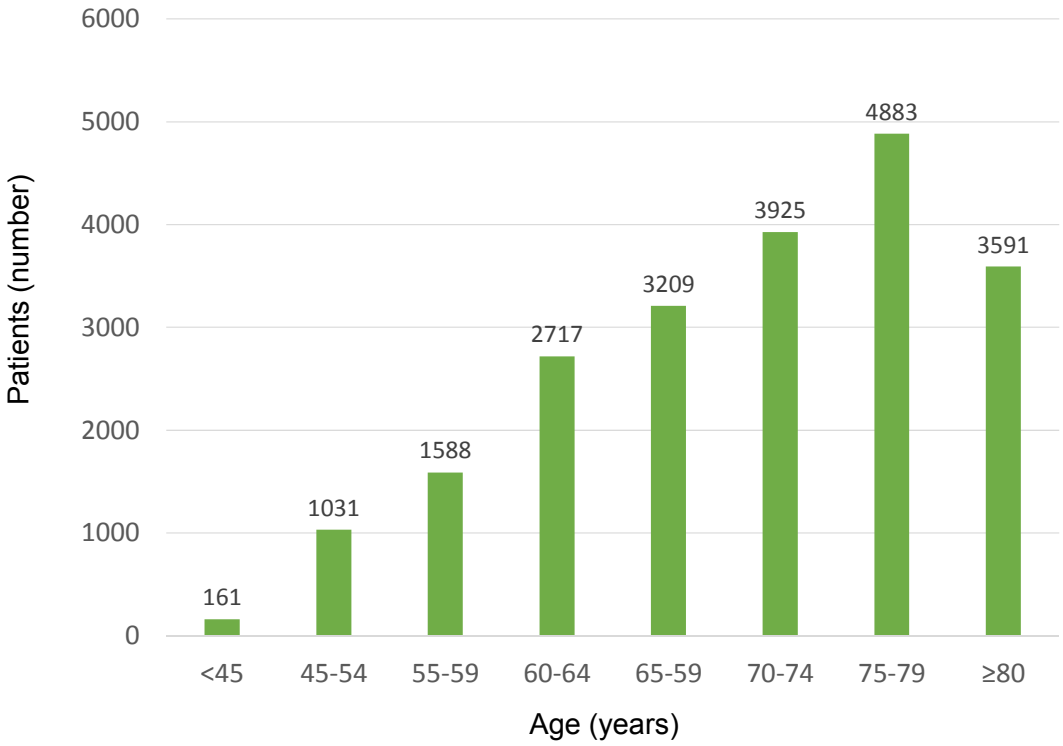
		Warfarin	HDER	LDER	HDER vs. Warfarin			LDER vs. Warfarin		
		Event rate (%/pt-yrs)	Event rate (%/pt-yrs)	Event rate (%/pt-yrs)	HR (95% CI)		P-int	HR (95% CI)		P-int
Stroke / SEE	< 75 yr	1.5	1.4	1.7	0.91	(0.73 - 1.13)	0.59	1.14	(0.93 - 1.40)	0.87
	≥ 75yr	2.3	1.9	2.6	0.83	(0.67 - 1.04)		1.12	(0.91 - 1.37)	
Ischemic Stroke	< 75 yr	1.0	1.1	1.5	1.10	(0.86 - 1.42)	0.26	1.52	(1.20 - 1.93)	0.39
	≥ 75yr	1.7	1.5	2.2	0.90	(0.69 - 1.16)		1.31	(1.03 - 1.66)	
Hemorrhagic Stroke	< 75 yr	0.4	0.2	0.1	0.51	(0.32 - 0.82)	0.71	0.31	(0.18- 0.54)	0.74
	≥ 75yr	0.5	0.3	0.2	0.58	(0.35 - 0.97)		0.36	(0.19 - 0.66)	
Fatal Stroke	< 75 yr	0.3	0.3	0.3	1.00	(0.64 - 1.56)	0.64	0.88	(0.56 - 1.39)	0.81
	≥ 75yr	0.6	0.5	0.5	0.86	(0.57 - 1.31)		0.81	(0.53 - 1.24)	
Major bleeding	< 75 yr	2.6	2.0	1.2	0.77	(0.64 - 0.93)	0.57	0.47	(0.38 - 0.58)	0.95
	≥ 75yr	4.8	4.0	2.3	0.83	(0.70 - 0.99)		0.47	(0.38 - 0.58)	
ICH	< 75 yr	0.6	0.3	0.2	0.54	(0.35 - 0.82)	0.34	0.30	(0.18 - 0.51)	0.99
	≥ 75yr	1.2	0.5	0.4	0.40	(0.26 - 0.62)		0.31	(0.19 - 0.49)	
Fatal bleeding	< 75 yr	0.3	0.2	0.1	0.66	(0.36 - 1.22)	0.40	0.30	(0.14 - 0.67)	0.66
	≥ 75yr	0.6	0.3	0.2	0.46	(0.25 - 0.84)		0.38	(0.20 - 0.73)	
Major GI bleeding	< 75 yr	1.0	1.1	0.6	1.15	(0.87 - 1.51)	0.47	0.61	(0.44 - 0.85)	0.48
	≥ 75yr	1.7	2.2	1.2	1.32	(1.01 - 1.72)		0.72	(0.53 - 0.98)	
Net clinical outcome:	< 75 yr	6.2	5.7	5.6	0.91	(0.82 - 1.02)	0.55	0.90	(0.80 - 1.00)	0.07
--Primary	≥ 75yr	11.2	9.7	8.7	0.87	(0.79 - 0.97)		0.78	(0.7- 0.87)	
Net clinical outcome:	< 75 yr	4.0	3.7	3.7	0.91	(0.80 - 1.04)	0.49	0.90	(0.79 - 1.03)	0.11
--Secondary	≥ 75yr	7.2	6.1	5.5	0.86	(0.76 - 0.97)		0.78	(0.68 - 0.88)	
Net clinical outcome:	< 75 yr	4.6	4.2	4.5	0.91	(0.80 - 1.03)	0.46	0.97	(0.86 - 1.10)	0.05
--Tertiary	≥ 75yr	8.2	7.0	6.7	0.85	(0.76 - 0.96)		0.82	(0.73- 0.92)	

HDER; Higher dose edoxaban regimen, LDER; lower dose edoxaban

*See Table 1 for abbreviations.

Supplementary Figure S1. Age distribution

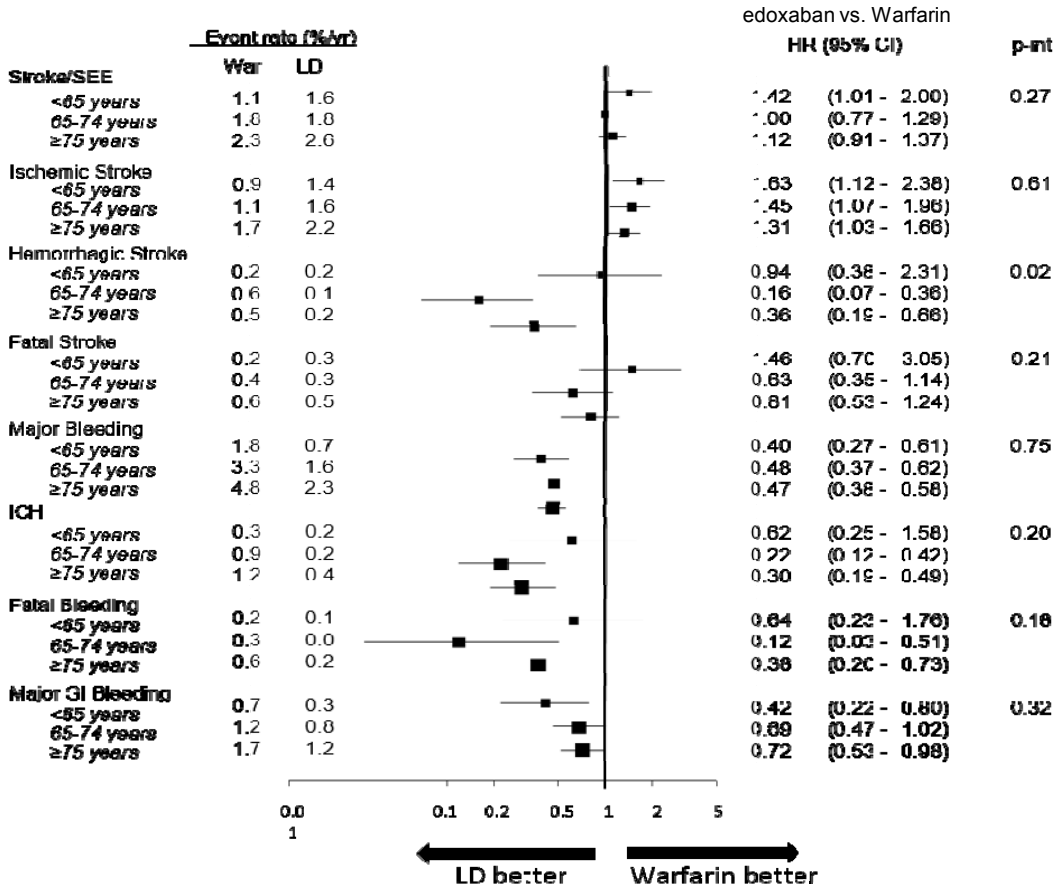
The median age was 72 years (interquartile range, 64 to 78). 40.2% were aged ≥75 years including 899 (4.3%) in age group ≥85 years



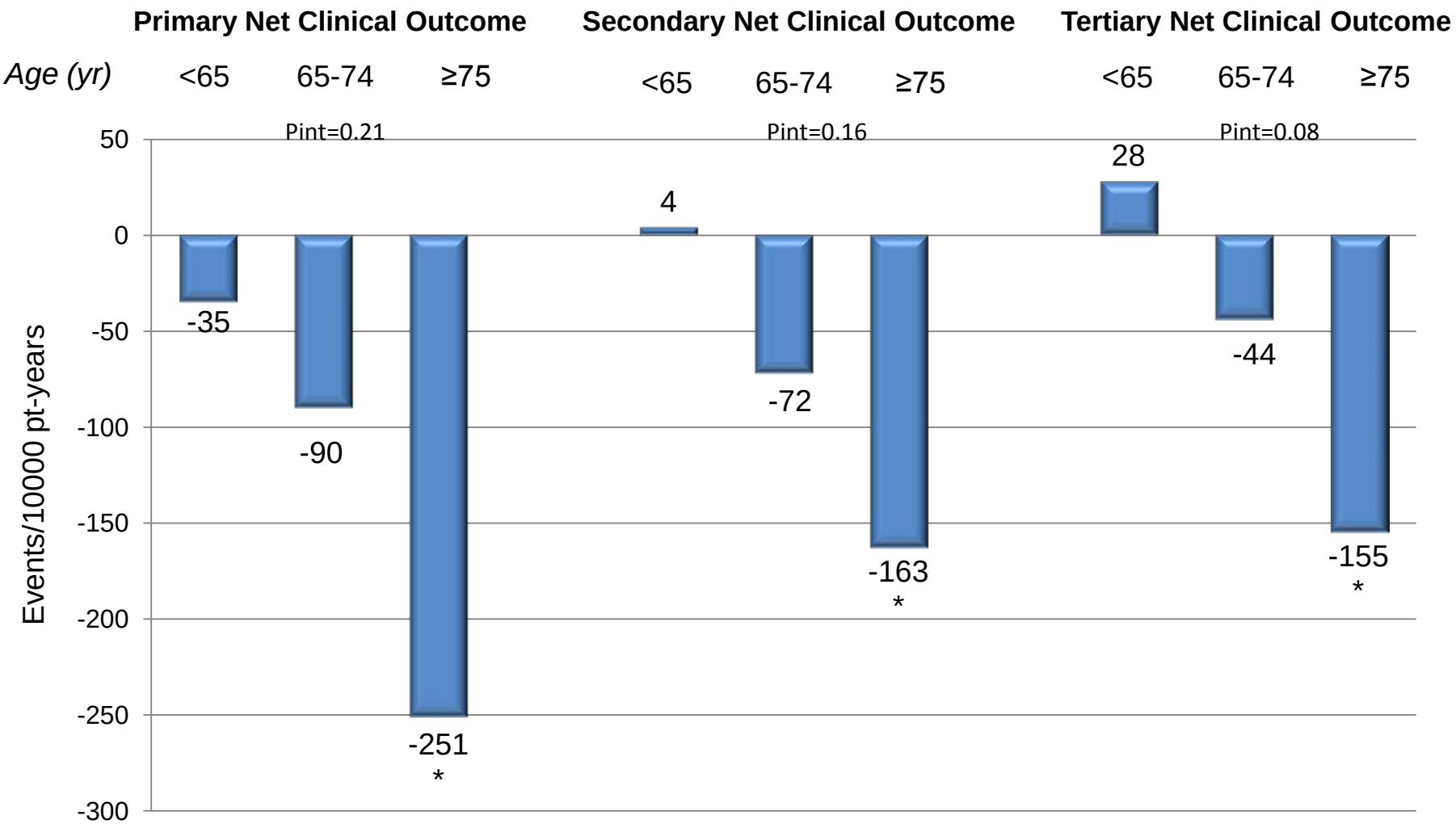
Supplementary Figure S2. Efficacy and Safety Outcomes Comparing the Lower Dose Edoxaban Regimen vs. Warfarin by Age

In the elderly, the risks of ISTH major bleeding (HR 0.47 [0.38-0.58]) and ICH (HR 0.30 [0.19-0.49]) were significantly reduced with the lower dose edoxaban regimen as compared to warfarin.

See Figure 1 and 3 for abbreviations.



Supplementary Figure 3.
Net Clinical Outcomes of the Lower Dose Edoxaban Regimen Compared to Warfarin



Event rates (%/yr)

Age (yr)	<65	65-74	≥75	<65	65-74	≥75	<65	65-74	≥75
Warfarin	4.9	7.3	11.2	3.0	4.8	7.2	3.6	5.5	8.2
LDER	4.5	6.4	8.7	3.1	4.1	5.5	3.9	5.0	6.7