Appendix B10. Outcome Exploratory Subgroup Analyses
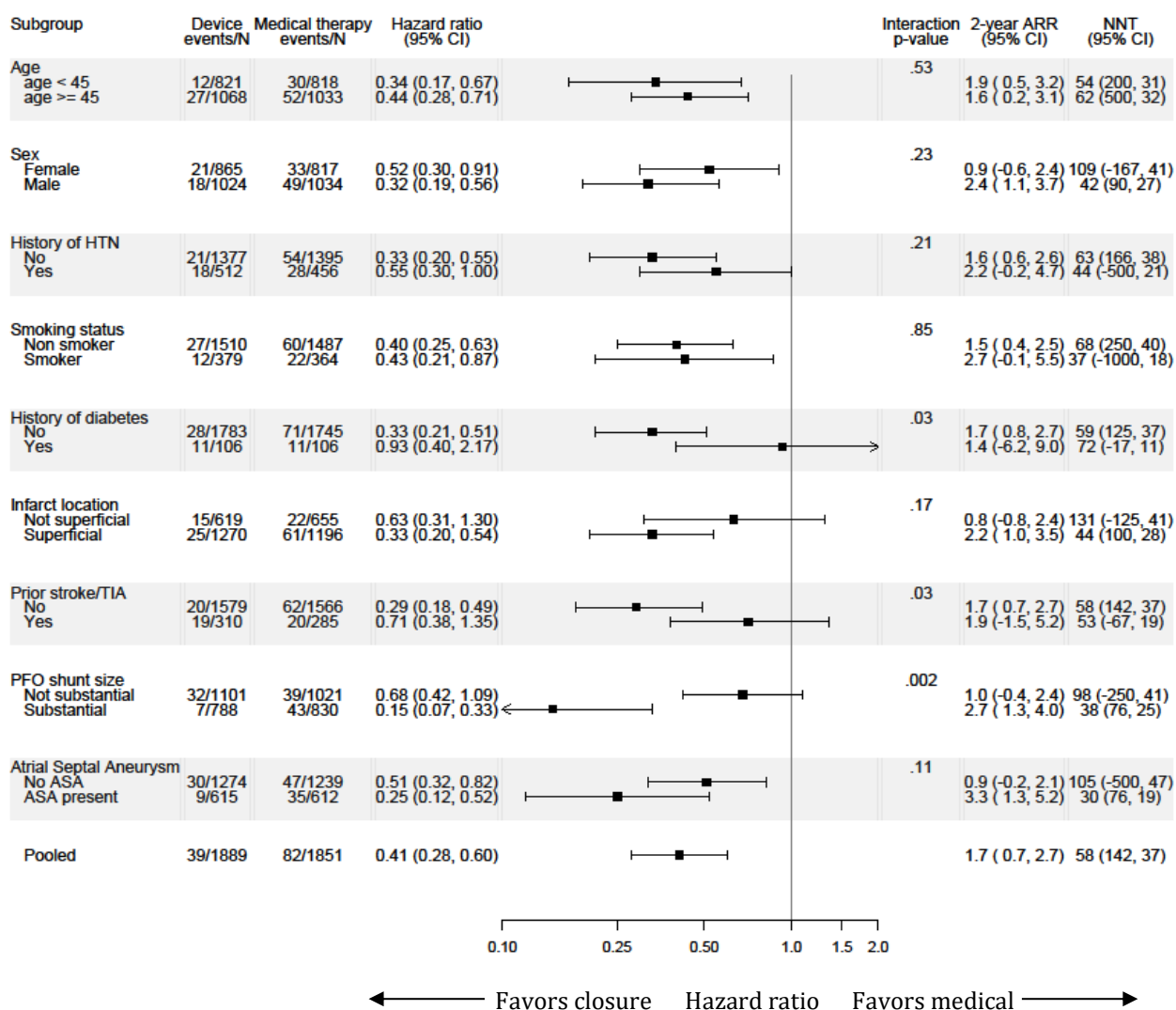
Appendix Figure 5. Recurrent Ischemic Stroke Exploratory Subgroup Analyses.

Subgroup	Device events/N	Medical therapy events/N	Hazard ratio (95% CI)		Interaction p-value	2-year ARR (95% CI)	NNT (95% CI)
Age					.53		
age < 45	12/821	30/818	0.34 (0.17, 0.67)			1.9 (0.5, 3.2)	54 (200, 31)
age >= 45	27/1068	52/1033	0.44 (0.28, 0.71)			1.6 (0.2, 3.1)	62 (500, 32)
Sex					.23		
Female	21/865	33/817	0.52 (0.30, 0.91)			0.9 (-0.6, 2.4)	109 (-167, 41)
Male	18/1024	49/1034	0.32 (0.19, 0.56)			2.4 (1.1, 3.7)	42 (90, 27)
History of HTN					.21		
No	21/1377	54/1395	0.33 (0.20, 0.55)			1.6 (0.6, 2.6)	63 (166, 38)
Yes	18/512	28/456	0.55 (0.30, 1.00)			2.2 (-0.2, 4.7)	44 (-500, 21)
Smoking status					.85		
Non smoker	27/1510	60/1487	0.40 (0.25, 0.63)			1.5 (0.4, 2.5)	68 (250, 40)
Smoker	12/379	22/364	0.43 (0.21, 0.87)			2.7 (-0.1, 5.5)	37 (-1000, 18)
History of diabetes					.03		
No	28/1783	71/1745	0.33 (0.21, 0.51)			1.7 (0.8, 2.7)	59 (125, 37)
Yes	11/106	11/106	0.93 (0.40, 2.17)			1.4 (-6.2, 9.0)	72 (-17, 11)
Infarct location					.17		
Not superficial	15/619	22/655	0.63 (0.31, 1.30)			0.8 (-0.8, 2.4)	131 (-125, 41)
Superficial	25/1270	61/1196	0.33 (0.20, 0.54)			2.2 (1.0, 3.5)	44 (100, 28)
Prior stroke/TIA					.03		
No	20/1579	62/1566	0.29 (0.18, 0.49)			1.7 (0.7, 2.7)	58 (142, 37)
Yes	19/310	20/285	0.71 (0.38, 1.35)			1.9 (-1.5, 5.2)	53 (-67, 19)
PFO shunt size					.002		
Not substantial	32/1101	39/1021	0.68 (0.42, 1.09)			1.0 (-0.4, 2.4)	98 (-250, 41)
Substantial	7/788	43/830	0.15 (0.07, 0.33)			2.7 (1.3, 4.0)	38 (76, 25)
Atrial Septal Aneurysm					.11		
No ASA	30/1274	47/1239	0.51 (0.32, 0.82)			0.9 (-0.2, 2.1)	105 (-500, 47)
ASA present	9/615	35/612	0.25 (0.12, 0.52)			3.3 (1.3, 5.2)	30 (76, 19)
Pooled	39/1889	82/1851	0.41 (0.28, 0.60)			1.7 (0.7, 2.7)	58 (142, 37)

Hazard ratio scale: 0.10 0.25 0.50 1.0 1.5 2.0

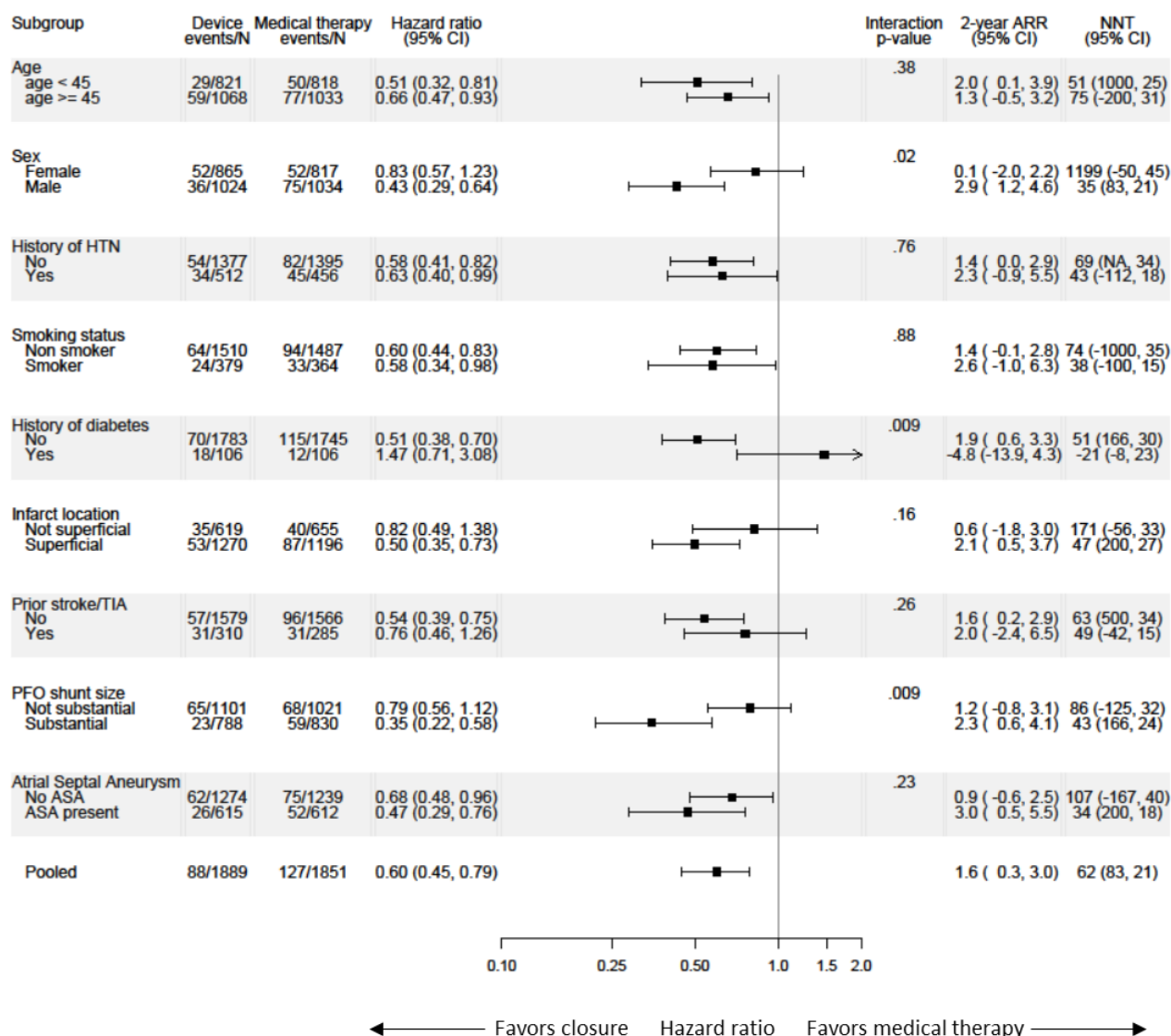⟵ Favors closure   Hazard ratio   Favors medical ⟶

Legend:

Primary outcome recurrent ischemic stroke. HR accounting for: age, sex, prior myocardial infarction, diabetes, hypertension, hyperlipidemia, prior stroke or TIA, smoking status, index event (stroke versus TIA), atrial septal aneurysm on trans-esophageal echocardiography (definition in Appendix A5), PFO shunt size (large versus small, definition in Appendix A5) and superficial infarction on neuroimaging (present versus absent). 2-year ARR calculated as differences in Kaplan Meier event rates at two years. Median time to the primary outcome of recurrent ischemic stroke was 13.7 months (n=121; interquartile range 4.8 to 29.7). Note: p-values from exploratory analyses are provided for descriptive purposes.

ARR, absolute risk reduction; CI, confidence interval; HR, hazard ratio; NNT, number-needed-to-treat.

Appendix Figure 6. Secondary Outcome Exploratory Subgroup Analyses.

Subgroup	Device events/N	Medical therapy events/N	Hazard ratio (95% CI)		Interaction p-value	2-year ARR (95% CI)	NNT (95% CI)
Age					.38		
age < 45	29/821	50/818	0.51 (0.32, 0.81)			2.0 (0.1, 3.9)	51 (1000, 25)
age >= 45	59/1068	77/1033	0.66 (0.47, 0.93)			1.3 (-0.5, 3.2)	75 (-200, 31)
Sex					.02		
Female	52/865	52/817	0.83 (0.57, 1.23)			0.1 (-2.0, 2.2)	1199 (-50, 45)
Male	36/1024	75/1034	0.43 (0.29, 0.64)			2.9 (1.2, 4.6)	35 (83, 21)
History of HTN					.76		
No	54/1377	82/1395	0.58 (0.41, 0.82)			1.4 (0.0, 2.9)	69 (NA, 34)
Yes	34/512	45/456	0.63 (0.40, 0.99)			2.3 (-0.9, 5.5)	43 (-112, 18)
Smoking status					.88		
Non smoker	64/1510	94/1487	0.60 (0.44, 0.83)			1.4 (-0.1, 2.8)	74 (-1000, 35)
Smoker	24/379	33/364	0.58 (0.34, 0.98)			2.6 (-1.0, 6.3)	38 (-100, 15)
History of diabetes					.009		
No	70/1783	115/1745	0.51 (0.38, 0.70)			1.9 (0.6, 3.3)	51 (166, 30)
Yes	18/106	12/106	1.47 (0.71, 3.08)			-4.8 (-13.9, 4.3)	-21 (-8, 23)
Infarct location					.16		
Not superficial	35/619	40/655	0.82 (0.49, 1.38)			0.6 (-1.8, 3.0)	171 (-56, 33)
Superficial	53/1270	87/1196	0.50 (0.35, 0.73)			2.1 (0.5, 3.7)	47 (200, 27)
Prior stroke/TIA					.26		
No	57/1579	96/1566	0.54 (0.39, 0.75)			1.6 (0.2, 2.9)	63 (500, 34)
Yes	31/310	31/285	0.76 (0.46, 1.26)			2.0 (-2.4, 6.5)	49 (-42, 15)
PFO shunt size					.009		
Not substantial	65/1101	68/1021	0.79 (0.56, 1.12)			1.2 (-0.8, 3.1)	86 (-125, 32)
Substantial	23/788	59/830	0.35 (0.22, 0.58)			2.3 (0.6, 4.1)	43 (166, 24)
Atrial Septal Aneurysm					.23		
No ASA	62/1274	75/1239	0.68 (0.48, 0.96)			0.9 (-0.6, 2.5)	107 (-167, 40)
ASA present	26/615	52/612	0.47 (0.29, 0.76)			3.0 (0.5, 5.5)	34 (200, 18)
Pooled	88/1889	127/1851	0.60 (0.45, 0.79)			1.6 (0.3, 3.0)	62 (83, 21)

←———— Favors closure   Hazard ratio   Favors medical therapy ————→

Legend:

Secondary outcome recurrent ischemic stroke, TIA, or vascular death. HR accounting for: age, sex, prior myocardial infarction, diabetes, hypertension, hyperlipidemia, prior stroke or TIA, smoking status, index event (stroke versus TIA), atrial septal aneurysm on trans-esophageal echocardiography (definition in Appendix A5), PFO shunt size (large versus small, definition in Appendix A5) and superficial infarction on neuroimaging (present versus absent). 2-year ARR calculated as differences in Kaplan Meier event rates at two years. Note: p-values from exploratory analyses are provided for descriptive purposes.

ARR, absolute risk reduction; CI, confidence interval; HR, hazard ratio; NNT, number-needed-to-treat.

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Appendix B: Supplementary Results

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