APPENDIX

Table of Contents

Appendix Table 1. Event rates and effects of closure versus medical therapy for individual trials (intention-to-treat analyses)

Analysis	Outcome rate		Log-rank Test	Cox PH model	Covariate-adjusted Cox PH model
	Device closure Rate per person-year (events/total person-years)	Medical therapy Rate per person-year (events/total person-years)	p-value	Hazard ratio* (95% CI); p-value	Hazard ratio† (95% CI); p-value
	Analyses of data from individual trials				
	CLOSURE (N = 909)				
Primary composite outcome	2.9% (23/783)	4.0%(31/771)	p= 0.294	0.75 (0.44 to 1.29); p = 0.296	0.72 (0.42 to 1.24); p = 0.238
Recurrent ischemic stroke	1.5% (12/798)	1.6% (13/795)	p= 0.865	0.93 (0.43 to 2.05); p = 0.865	0.84 (0.37 to 1.89); p =0.673
Secondary composite outcome (ischemic stroke, TIA, early death)	2.9% (23/783)	3.8% (29/771)	p= 0.433	0.80 (0.46 to 1.39); p= 0.434	0.77(0.44 to 1.34); p= 0.350
	PC Trial (N = 414)				
Primary composite outcome	0.8%(7/827)	1.4% (11/804)	p= 0.328	0.63 (0.24 to 1.62); p =0.333	0.62 (0.24 to 1.64); p = 0.340
Recurrent ischemic stroke	0.1% (1/841)	0.9% (7/814)	p= 0.033	0.14 (0.02 to 1.15) p = 0.068	0.16 (0.02 to 1.34); p = 0.090
Secondary composite outcome (ischemic stroke, TIA, early death)	0.6% (5/827)	1.4% (11/804)	p= 0.129	0.45 (0.16 to 1.30); p= 0.139	0.47(0.16 to 1.36); p= 0.164
	RESPECT (N = 980)				
Primary composite outcome	1.0% (15/1447)	1.7% (21/1217)	p= 0.163	0.63 (0.32 to 1.22); p =0.167	0.63 (0.32 to 1.24); p =0.182
Recurrent ischemic stroke	0.6% (9/1460)	1.3% (16/1231)	p= 0.081	0.49 (0.22 to 1.11); p = 0.088	0.50 (0.22 to 1.14); p = 0.100
Composite outcome (stroke, TIA, early death)	1.0% (15/1447)	1.7% (21/1217)	p= 0.163	0.63 (0.32 to 1.22); p= 0.167	0.63(0.32 to 1.24); p= 0.182

* Unadjusted hazard ratios and p-values from Cox PH models; source study was included in the model as a stratification term.
†Adjusted Hazard ratios estimated using Cox PH models combined from ten multiply imputed datasets. Source study was included in the model as a stratification term. Covariates used for adjustment included age, sex, race, coronary artery disease, diabetes, hypertension, hyperlipidemia, prior stroke, smoking status, index event (stroke versus transient ischemic attack), hypermobile septum, and PFO shunt size (large versus small).
CI = confidence interval; N = number of patients; NA = not applicable; PH = proportional hazards.

Appendix Table 2. Safety Outcomes (intention-to-treat analyses)

Safety Outcomes	**Device closure** Rate per person-year (events/total person-years)	**Medical therapy** Rate per person-year (events/total person-years)	**Hazard ratio* (95% CI)**	**p-value***
Analyses using data from all 3 trials (N = 2303)	**N = 1150**	**N = 1153**		
Procedural complications†	3.3% (37/1105)	NA	NA	NA
Bleeding	0.45% (14/3097)	0.31% (9/2860)	1.56 (0.68 to 3.61)	0.296
Atrial fibrillation	1.49% (45/3024)	0.46% (13/3853)	3.41 (1.84 to 6.33)	<0.0001
Analyses limited to trials of the Amplatzer device (N = 1394) ‡	**N = 703**	**N = 691**		
Procedural complications†	3.4% (24/703)	NA	NA	NA
Bleeding	0.13% (3/2315)	0.14% (3/2082)	0.95 (0.19 to 4.72)	0.952
Atrial fibrillation	0.93% (21/2265)	0.48% (10/2070	1.94 (0.91 to 4.12)	0.086

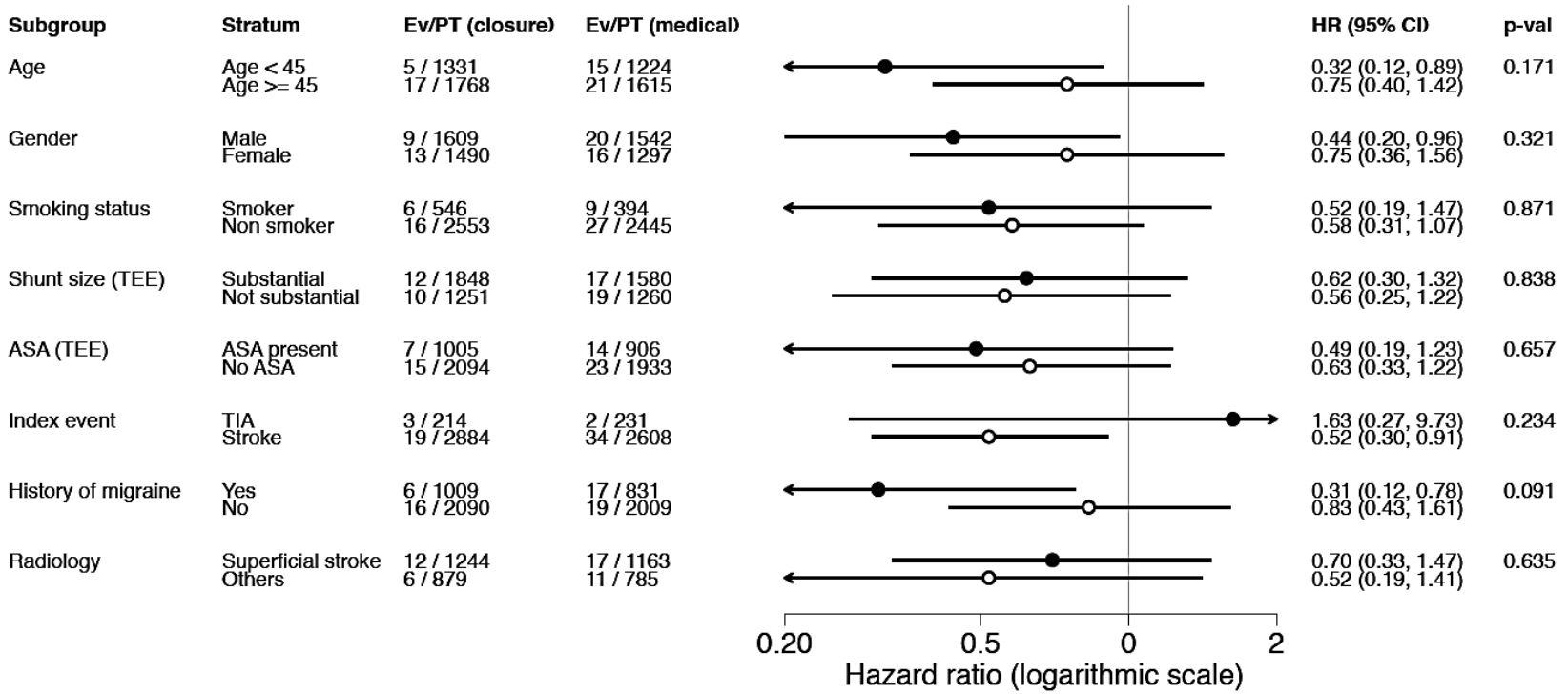
* Unadjusted hazard ratios and p-values from Cox PH models; source study was included in the model as a stratification term.
†Data for procedural complications abstracted from original study publications.
‡ Excludes CLOSURE.
CI = confidence interval; N = number of patients; NA = not applicable; PH = proportional hazards.

Appendix Table 3. Stability analyses, excluding either of the Amplatzer device trials, for recurrent stroke, composite outcome rates and effects of closure (intention-to-treat analyses)

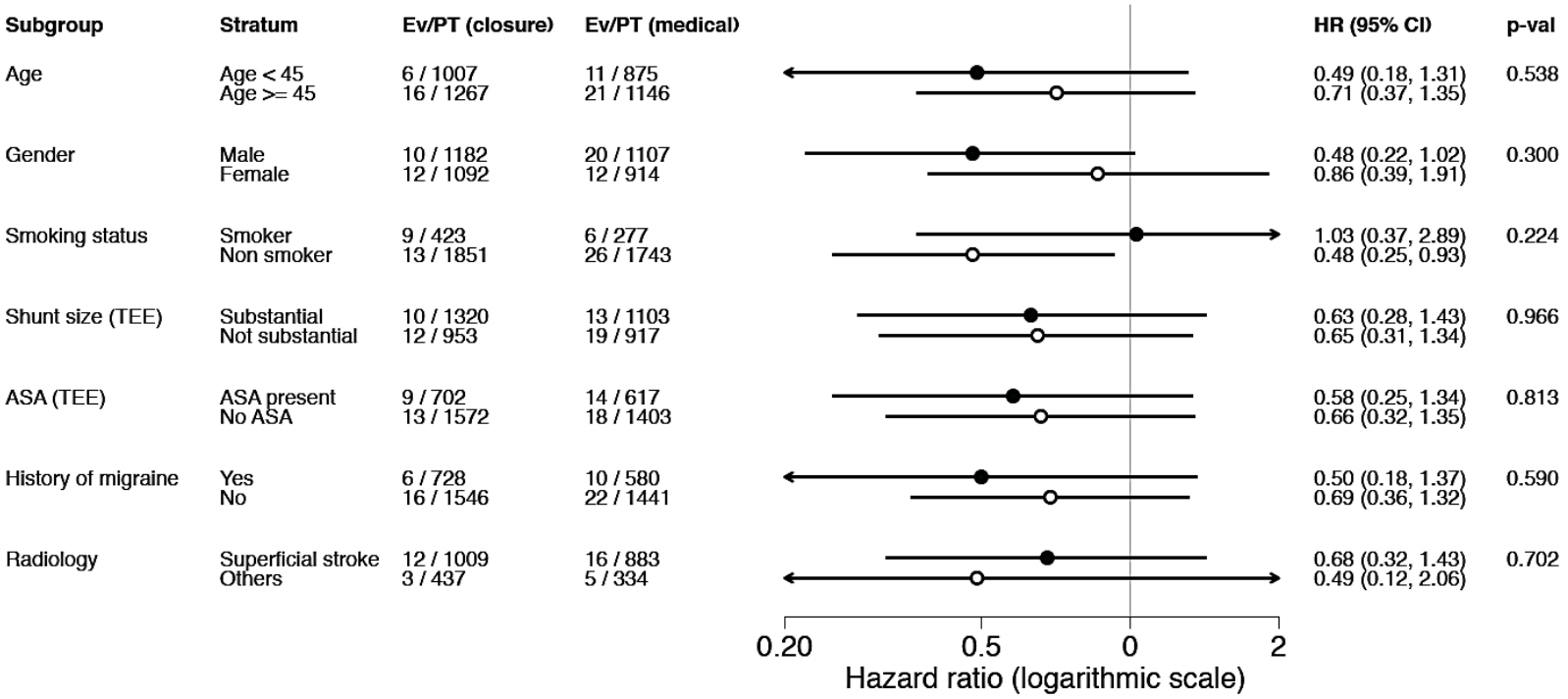
Analysis	Event Rate		Cox PH model	Covariate-adjusted Cox PH model*
	Device closure Rate per person-year (events/total person-years)	**Medical therapy** Rate per person-year (events/total person-years)	**Hazard ratio**† (95% CI); p-value	**Hazard ratio**† (95% CI); p-value
Analyses limited to data from the CLOSURE and RESPECT trials				
Primary composite outcome	1.70% (38/2230)	2.62% (52/1988)	0.70 (0.46 to 1.06); p = 0.092	0.69 (0.45 to 1.05); p = 0.080
Recurrent ischemic stroke	0.93% (21/2258)	1.43% (29/2026)	0.68 (0.39 to 1.19); p = 0.179	0.67 (0.38 to 1.18); p = 0.165
Analyses limited to data from the CLOSURE and PC Trials				
Primary composite outcome	1.86% (30/1610)	2.67% (42/1575)	0.72 (0.45 to 1.15); p = 0.164	0.70 (0.44 to 1.12); p = 0.134
Recurrent ischemic stroke	0.79% (13/1640)	1.24% (20/1609)	0.65 (0.33 to 1.32); p = 0.235	0.61 (0.30 to 1.23); p = 0.168

* Adjusted for age, sex, race, coronary artery disease, diabetes, hypertension, hyperlipidemia, prior stroke, smoking status, index event (stroke versus transient ischemic attack), hypermobile septum, and PFO shunt size (large versus small).
†Hazard ratios estimated using Cox PH models combined from ten multiply imputed datasets. For pooled results, the study was included in the model as a stratification term.
CI = confidence interval; PFO = patent foramen ovale; PH = proportional hazards.

Appendix Figure 1. Subgroup analysis for recurrent ischemic stroke (intention-to-treat analyses)



Appendix Figure 2. Subgroup analysis for composite outcome (Amplatzer device trials)



Appendix Figure 3. Subgroup analysis for recurrent stroke (Amplatzer device trials)