Appendix B4. Patient Characteristics in Each Study

Appendix Table 7. CLOSURE.

Variable	N	Full Sample	Device	Medication Therapy
Recurrent ischemic strokes (primary outcome), events/N		25/909	12/447	13/462
			HR (95% CI) = 0.93 (0.43, 2.05)	
Age in years, mean (sd)	909	45.47 (9.34)	45.75 (9.63)	45.19 (9.06)
Male Gender	909	471 (51.8%)	233 (52.1%)	238 (51.5%)
White Race	909	812 (89.3%)	398 (89.0%)	414 (89.6%)
Smoke	907	138 (15.2%)	69 (15.4%)	69 (15.0%)
Diabetes	909	71 (7.8%)	41 (9.2%)	30 (6.5%)
High Cholesterol	909	401 (44.1%)	212 (47.4%)	189 (40.9%)
Hypertension	909	282 (31.0%)	151 (33.8%)	131 (28.4%)
Prior Stroke	909	51 (5.6%)	26 (5.8%)	25 (5.4%)
Prior Stroke or TIA	909	114 (12.5%)	55 (12.3%)	59 (12.8%)
Atrial Septal Aneurysm	873	311 (35.6%)	153 (35.8%)	158 (35.4%)
Large Sized Shunt[a]	777	154 (19.8%)	88 (22.9%)	66 (16.8%)
Presence of a Superficial Infarct[b]	556	289 (52.0%)	127 (49.2%)	162 (54.4%)
Index Stroke (vs. TIA)	907	653 (72.0%)	324 (72.6%)	329 (71.4%)

[a]>20 bubbles for all trials except CLOSURE (>25) and CLOSE (>30).
[b]Not reported in PC Trial.
HR indicates hazard ratio comparing device to medication therapy; SD, standard deviation; TIA indicates transient ischemic attack.

Appendix Table 8. PC Trial.

Variable	N	Full Sample	Device	Medication Therapy
Recurrent ischemic strokes (primary outcome), events/N		8/414	1/204	7/210
			HR (95% CI) = 0.14 (0.02, 1.15)	
Age in years, mean (sd)	414	44.48 (10.17)	44.32 (10.23)	44.63 (10.13)
Male Gender	414	206 (49.8%)	92 (45.1%)	114 (54.3%)
White Race	NR			
Smoke	414	99 (23.9%)	52 (25.5%)	47 (22.4%)
Diabetes	414	11 (2.7%)	5 (2.5%)	6 (2.9%)
High Cholesterol	414	112 (27.1%)	50 (24.5%)	62 (29.5%)
Hypertension	414	107 (25.8%)	49 (24.0%)	58 (27.6%)
Prior Stroke	NR			
Prior Stroke or TIA	414	155 (37.4%)	76 (37.3%)	79 (37.6%)
Atrial Septal Aneurysm	414	98 (23.7%)	47 (23.0%)	51 (24.3%)

Appendix B: Supplementary Results

Large Sized Shunt[a]	369	80 (21.7%)	43 (23.2%)	37 (20.1%)
Presence of a Superficial Infarct[b]	NR			
Index Stroke (vs. TIA)	414	414 (100%)	204 (100%)	210 (100%)

[a]>20 bubbles for all trials except CLOSURE (>25) and CLOSE (>30).
[b]Not reported in PC Trial.
NR, not reported; SD, standard deviation; TIA indicates transient ischemic attack.

Appendix Table 9. RESPECT.

Variable	N	Full Sample	Device	Medication Therapy
Recurrent ischemic strokes (primary outcome), events/N		46/980	18/499	28/481
			HR (95% CI) = 0.55 (0.31, 1.00)	
Age in years , mean (sd)	968	45.44 (9.84)	45.24 (9.67)	45.65 (10.01)
Male Gender	980	536 (54.7%)	268 (53.7%)	268 (55.7%)
White Race	NR			
Smoke	980	130 (13.3%)	75 (15.0%)	55 (11.4%)
Diabetes	980	74 (7.6%)	33 (6.6%)	41 (8.5%)
High Cholesterol	980	391 (39.9%)	196 (39.3%)	195 (40.5%)
Hypertension	980	313 (31.9%)	160 (32.1%)	153 (31.8%)
Prior Stroke	979	104 (10.6%)	53 (10.6%)	51 (10.6%)
Prior Stroke or TIA	980	182 (18.6%)	93 (18.6%)	89 (18.5%)
Atrial Septal Aneurysm	980	349 (35.6%)	179 (35.9%)	170 (35.3%)
Large Sized Shunt[a]	969	478 (49.3%)	247 (50.0%)	231 (48.6%)
Presence of a Superficial Infarct[b]	897	706 (78.7%)	357 (80.0%)	349 (77.4%)
Index Stroke (vs. TIA)	980	980 (100%)	499 (100%)	481 (100%)

[a]>20 bubbles for all trials except CLOSURE (>25) and CLOSE (>30).
[b]Not reported in PC Trial.
NR, not reported; SD, standard deviation; TIA indicates transient ischemic attack.

Appendix Table 10. REDUCE.

Variable	N	Full Sample	Device	Medication Therapy
Recurrent ischemic strokes (primary outcome), events/N		20/664	8/441	12/223
			HR (95% CI) = 0.31 (0.13, 0.76)	
Age in years, mean (sd)	664	45.22 (9.36)	45.42 (9.26)	44.83 (9.56)
Male Gender	664	399 (60.1%)	261 (59.2%)	138 (61.9%)
White Race	664	615 (92.6%)	412 (93.4%)	203 (91.0%)
Smoke	664	161 (24.2%)	105 (23.8%)	56 (25.1%)
Diabetes	664	28 (4.2%)	18 (4.1%)	10 (4.5%)
High Cholesterol	664	317 (47.7%)	214 (48.5%)	103 (46.2%)
Hypertension	664	171 (25.8%)	113 (25.6%)	58 (26.0%)

Prior Stroke	664	55 (8.3%)	42 (9.5%)	13 (5.8%)
Prior Stroke or TIA	664	85 (12.8%)	62 (14.1%)	23 (10.3%)
Atrial Septal Aneurysm	538	143 (26.6%)	98 (27.4%)	45 (25.0%)
Large Sized Shunt[a]	642	168 (26.2%)	123 (28.9%)	45 (20.8%)
Presence of a Superficial Infarct[b]	626	449 (71.7%)	304 (72.7%)	145 (69.7%)
Index Stroke (vs. TIA)	664	664 (100%)	441 (100%)	223 (100%)

[a]>20 bubbles for all trials except CLOSURE (>25) and CLOSE (>30).
[b]Not reported in PC Trial.
SD, standard deviation; TIA indicates transient ischemic attack.

Appendix Table 11. DEFENSE.

Variable	N	Full Sample	Device	Medication Therapy
Recurrent ischemic strokes (primary outcome), events/N		5/120	0/60	5/60
Age in years , mean (sd)	120	51.75 (13.78)	49.27 (14.74)	54.23 (12.37)
Male Gender	120	67 (55.8%)	33 (55.0%)	34 (56.7%)
White Race	NR			
Smoke	120	26 (21.7%)	10 (16.7%)	16 (26.7%)
Diabetes	120	14 (11.7%)	6 (10.0%)	8 (13.3%)
High Cholesterol	120	43 (35.8%)	18 (30.0%)	25 (41.7%)
Hypertension	120	29 (24.2%)	12 (20.0%)	17 (28.3%)
Prior Stroke	120	6 (5.0%)	3 (5.0%)	3 (5.0%)
Prior Stroke or TIA	120	10 (8.3%)	4 (6.7%)	6 (10.0%)
Atrial Septal Aneurysm	120	58 (48.3%)	29 (48.3%)	29 (48.3%)
Large Sized Shunt[a]	120	96 (80.0%)	50 (83.3%)	46 (76.7%)
Presence of a Superficial Infarct[b]	120	104 (86.7%)	56 (93.3%)	48 (80.0%)
Index Stroke (vs. TIA)	120	120 (100%)	60 (100%)	60 (100%)

[a]>20 bubbles for all trials except CLOSURE (>25) and CLOSE (>30).
[b]Not reported in PC Trial.
NR, not reported; SD, standard deviation; TIA indicates transient ischemic attack.

Appendix Table 12. CLOSE-A (randomization group 2: had contraindications to oral anticoagulants).

Variable	N	Full Sample	Device	Medication Therapy
Recurrent ischemic strokes (primary outcome), events/N		7/129	0/65	7/64
Age in years, mean (sd)	129	40.61 (11.18)	39.59 (11.89)	41.65 (10.40)
Male Gender	129	84 (65.1%)	41 (63.1%)	43 (67.2%)
White Race	NR			

Smoke	129	36 (27.9%)	16 (24.6%)	20 (31.3%)
Diabetes	129	3 (2.3%)	1 (1.5%)	2 (3.1%)
High Cholesterol	129	22 (17.1%)	10 (15.4%)	12 (18.8%)
Hypertension	129	10 (7.8%)	5 (7.7%)	5 (7.8%)
Prior Stroke	129	4 (3.1%)	2 (3.1%)	2 (3.1%)
Prior Stroke or TIA	129	12 (9.3%)	5 (7.7%)	7 (10.9%)
Atrial Septal Aneurysm	129	53 (41.1%)	28 (43.1%)	25 (39.1%)
Large Sized Shunt[a]	129	120 (93.0%)	60 (92.3%)	60 (93.8%)
Presence of a Superficial Infarct[b]	129	85 (65.9%)	41 (63.1%)	44 (68.8%)
Index Stroke (vs. TIA)	129	129 (100%)	65 (100%)	64 (100%)

[a]>20 bubbles for all trials except CLOSURE (>25) and CLOSE (>30).
[b]Not reported in PC Trial.
NR, not reported; SD, standard deviation; TIA indicates transient ischemic attack.

Appendix Table 13. CLOSE-B (randomization group 1: had no contraindications to PFO closure or oral anticoagulants).

Variable	N	Full Sample	Device	Medication Therapy
Recurrent ischemic strokes (primary outcome), events/N		10/524	0/173	10/351
Age in years , mean (sd)	524	44.25 (9.66)	44.13 (9.08)	44.31 (9.95)
Male Gender	524	295 (56.3%)	96 (55.5%)	199 (56.7%)
White Race	NR			
Smoke	524	153 (29.2%)	52 (30.1%)	101 (28.8%)
Diabetes	524	11 (2.1%)	2 (1.2%)	9 (2.6%)
High Cholesterol	524	66 (12.6%)	20 (11.6%)	46 (13.1%)
Hypertension	524	56 (10.7%)	22 (12.7%)	34 (9.7%)
Prior Stroke	524	19 (3.6%)	8 (4.6%)	11 (3.1%)
Prior Stroke or TIA	524	37 (7.1%)	15 (8.7%)	22 (6.3%)
Atrial Septal Aneurysm	524	172 (32.8%)	53 (30.6%)	119 (33.9%)
Large Sized Shunt[a]	524	486 (92.7%)	156 (90.2%)	330 (94.0%)
Presence of a Superficial Infarct[b]	524	341 (65.1%)	118 (68.2%)	223 (63.5%)
Index Stroke (vs. TIA)	524	524 (100%)	173 (100%)	351 (100%)

[a]>20 bubbles for all trials except CLOSURE (>25) and CLOSE (>30)..
[b]Not reported in PC Trial.
NR, not reported; SD, standard deviation; TIA indicates transient ischemic attack.