Stroke

CLINICAL TRIAL

Patent Foramen Ovale Closure Decreases the Incidence but Not the Size of New Brain Infarction on Magnetic Resonance Imaging

An Analysis of the REDUCE Trial

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BACKGROUND AND PURPOSE: Randomized patent foramen ovale closure trials have used open-label end point ascertainment which increases the risk of bias and undermines confidence in the conclusions. The Gore REDUCE trial prospectively performed baseline and follow-up magnetic resonance imaging (MRIs) for all subjects providing an objective measure of the effectiveness of closure.

METHODS: We performed blinded evaluations of the presence, location, and volume of new infarct on diffusion-weighted imaging of recurrent clinical stroke or new infarct (>3 mm) on T2/fluid attenuated inversion recovery from baseline to follow-up MRI at 2 years, comparing closure to medical therapy alone. We also examined the effect of shunt size and the development of atrial fibrillation on infarct burden at follow-up.

RESULTS: At follow-up, new clinical stroke or silent MRI infarct occurred in 18/383 (4.7%) patients who underwent closure and 19/177 (10.7%) medication-only patients (relative risk, 0.44 [95% CI, 0.24–0.81], *P*=0.02). Clinical strokes were less common in closure patients compared with medically treated patients, 5 (1.3%) versus 12 (6.8%), *P*=0.001, while silent MRI infarcts were similar, 13 (3.4%) versus 7 (4.0%), *P*=0.81. There were no differences in number, volumes, and distribution of new infarct comparing closure patients to those treated with medication alone. There were also no differences of number, volumes, and distribution comparing silent infarcts to clinical strokes. Infarct burden was also similar for patients who developed atrial fibrillation and for those with large shunts.

CONCLUSIONS: The REDUCE trial demonstrates that patent foramen ovale closure prevents recurrent brain infarction based on the objective outcome of new infarcts on MRI. Only clinical strokes were reduced by closure while silent infarctions were similar between study arms, and there were no differences in infarct volume or location comparing silent infarcts to clinical strokes.

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GRAPHIC ABSTRACT: An online graphic abstract is available for this article.

Patent foramen ovale (PFO) is associated with otherwise cryptogenic stroke in young patients, presumably by allowing systemic venous thromboemboli to cross the atrial septum and enter the left atrium and the systemic arterial circulation.[1,2] Closure of the PFO to eradicate right-to-left shunting was

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Nonstandard Abbreviations and Acronyms

FLAIR	fluid attenuated inversion recovery
MRI	magnetic resonance imaging
PFO	patent foramen ovale

proposed as an intervention to reduce recurrent stroke risk in patients with presumed PFO-associated stroke and transcatheter closure devices have been used in clinical practice before definitive evidence proving their efficacy.[3] Randomized trials were undertaken to confirm or refute the benefit of PFO closure and up to this point 6 studies have been completed.[4–9] To ensure study feasibility, each of these trials used an open-label design with both patients and treating clinicians aware of the treatment assignment and actual treatment received. However, this methodological approach increases the risk of bias and potentially undermines the confidence in the conclusions of the studies. The Gore REDUCE study was the only trial that required all patients to undergo magnetic resonance imaging (MRI) at baseline and after a clinical neurological event or at 2-years of follow-up. The change in volume of infarct from baseline to follow-up MRI is an objective outcome which could provide additional support for the important findings of this clinical trial. The initial publication reported that while clinical stroke was reduced by PFO closure compared with medical therapy alone, the number of patients with new silent MRI infarcts were not significantly different between the study arms.[7] However, there was no assessment of whether PFO closure reduced the size and number, or altered the location of infarcts. We performed an analysis of MRI data from the REDUCE trial, assessing volumes, numbers, and locations of new brain infarcts on follow-up MRI compared with the baseline MRI. Our hypothesis was that patients who underwent closure would have fewer numbers and smaller volumes of infarct compared with subjects who only took medication.

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METHODS

The study data may be made available upon reasonable request to the sponsor.

Subjects

As described in a previous publication, the Gore REDUCE clinical trial enrolled 664 patients under age 60 with a PFO with right-to-left shunt, an embolic-appearing ischemic stroke within the past 6 months, and no alternative mechanism identified after a complete work up.[7] Written informed consent was obtained, and subjects were randomized in a 2:1 ratio to closure with the GORE HELEX/CARDIOFORM Septal Occluder plus antiplatelet medical therapy or antiplatelet medical therapy alone. Institutional review boards at enrolling centers approved this study. Per the protocol, all subjects underwent brain MRI before randomization and again at 2 years if they remained free of clinical stroke symptoms. At every follow-up timepoint, patients were assessed for a new stroke which included use of a validated questionnaire to objectively detect new stroke symptoms. If screening for symptoms was positive or a clinical stroke was suspected, MRI was required by protocol to confirm or refute an infarct. A blinded MRI core lab reviewed all brain MRIs for evidence of new ischemic injury of 3 mm or greater comparing T2/fluid attenuated inversion recovery (FLAIR)-sequences between the screening MRI and follow-up MRI. For this analysis, we included all 37 patients with clinical stroke or core lab identified new ischemic injury comparing baseline to follow-up T2/FLAIR-sequence MRI. If there was no clinical event and no follow-up MRI, these cases were excluded from the analysis. Figure 1 shows the CONSORT (Consolidated Standards of Reporting Trials) flow diagram for this analysis.

Imaging Analyses

New infarcts, defined as acute diffusion-weighted imaging lesion at time of recurrent clinical stroke or new T2/FLAIR lesion >3 mm in any dimension from baseline to follow-up MRI at 2 years, were identified and segmented using a semi-automated methodology blinded to treatment assignment. T2/FLAIR scans were automatically corrected for image inhomogeneities, and baseline scans were linearly registered with follow-up timepoints.[10,11] New infarcts were identified and segmented on the follow-up timepoint by a radiologist using ITK-Snap.[12] The baseline apparent diffusion coefficient and diffusion-weighted imaging scans of each subject were also used to identify new lesions, if the information on T2/FLAIR scans was not sufficient alone for the decision. A multi-atlas skull stripping algorithm was applied for the removal of extra-cranial material on T1-weighted scans.[13] Each scan was segmented into a set of anatomic regions of interest using a multi-atlas label fusion method.[14] Regional infarct volumes and counts were calculated within each regions of interest, as well as in larger anatomic regions obtained by grouping single regions of interests within a hierarchical representation. Vascular distributions, anterior or posterior, were then determined using these regions of interest maps. To evaluate the effect on shunt size on infarct outcomes, we used the echocardiography core lab assessment of shunt size (occluded, trivial [0–5 bubbles in left atrium], moderate [6–25 bubbles], or large [>25]). If there was no core lab assessment, we used the site assessment of the shunt. For patients in the medical arm, we used the baseline shunt size assessment, for the closure arm we used the assessment from the study closest to the 12-month follow-up visit.

Statistical Analyses

The event rates between patients assigned to medical therapy alone and those assigned to PFO closure were compared using the risk difference Z test (Wald method), χ^2, or Fisher exact tests, as appropriate. Infarct volumes were compared between study arms using Wilcoxon rank sum given that these data were not normally distributed. The comparison of the distribution of

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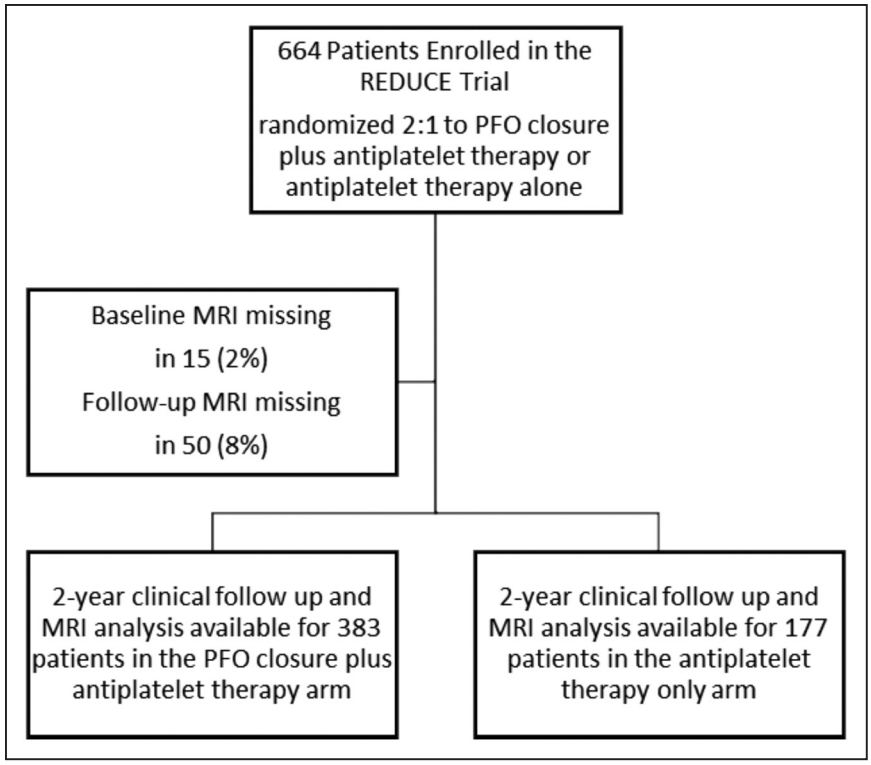

Figure 1. The CONSORT (Consolidated Standards of Reporting Trials) flow diagram for patients included in this analysis. MRI indicates magnetic resonance imaging; and PFO, patent foramen ovale.

infarct locations were also tested using similar nonparametric methods. Finally, we assessed whether the development of atrial fibrillation after PFO closure was associated with increased risk of new infarcts or increased infarct volume and also whether shunt size was associated with increased infarct volume as well using similar methods. Analysis was performed using STATA 16 (College Station, TX).

RESULTS

Baseline MRI was performed in 649 patients (97.7%). During the 2-year follow-up period, MRIs were performed for suspected new stroke or TIA events in 105 subjects (15.8%) overall, 59 (13.4%) in the closure group, and 46 (20.6%) in the medical therapy group (P=0.02). At the end of the 2-year study period, there were 50 (7.5%) patients with missing MRI follow-up data, 29 (6.6%) in the closure arm, and 21 (9.4%) in the medical arm (P=0.19).

After blinded review comparing the diffusion-weighted imaging and T2-weighted sequences between baseline and follow-up, new clinical stroke or silent MRI infarct occurred in 18/383 (4.7%) patients who underwent closure and 19/177 (10.7%) medically treated patients (relative risk [RR], 0.44 [95% CI, 0.24–0.81], P=0.02). Clinical strokes were reported in 5 (1.3%) patients assigned to closure and 12 (6.8%) medically treated patients (RR, 0.19 [95% CI, 0.07–0.54], P=0.001), while silent brain infarction occurred in 13/383 (3.4%) versus 7/177 (4.0%), (RR, 0.86 [95% CI, 0.35–2.11], P=0.81). Sensitivity analyses including those patients without clinical stroke and missing follow-up MRIs did not alter the primary findings, assuming they all had silent infarct (RR, 0.52 [95% CI, 0.35–0.79]) or none of them did (RR, 0.47 [95% CI, 0.25–0.89]).

There were 3 subjects with MRI-negative clinically determined strokes in this study, 1 subject (0.4%) in the medical arm and 2 (0.5%) in the closure arm. Excluding patients with MRI-negative clinical events, among those with new infarct, the total and discrete infarct lesion volumes and number of lesions were not different between treatment arms (Table 1). Figure 2 presents the distribution of total infarct volumes dichotomized by treatment arm. A sensitivity analysis including the MRI-negative clinical strokes and assigning them minimally detectable volumes (30 mm3), did not change these findings (Table I in the Data Supplement). Infarct distribution was also similar for patients in the closure arm compared with patients given medical treatment only (Table 2). Tables 3 and 4 demonstrate that across patients in both arms of the study, there were no differences in total and discrete infarct lesion volume, number, or distribution comparing patients with clinical stroke to those with silent infarct.

Of the 383 patients who underwent closure and had follow-up MRI, 28 developed atrial fibrillation (7.3%) including 20 patients who experienced atrial fibrillation within 30 days of the procedure and 8 after this period, with 1 of these patients developing a clinical stroke during follow-up. Of the 28 who developed atrial fibrillation after closure, 17 (61%) were placed on an oral anticoagulant at least temporarily. There was no increased risk of recurrent clinical stroke or silent infarct among those who developed atrial fibrillation compared with those who did not, 1/28 (3.6%) versus 16/355 (4.5%), risk difference, −0.9% (95% CI, −8.1% to 6.3%), P=0.79. Among those

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Table 1. Infarct Volumes and Numbers of New Infarcts on Follow-Up MRI Comparing Patients Who Underwent Closure to Those Who Only Received Antiplatelet Medication

	Overall	Antiplatelet only	Closure	*P* value
Total infarct volume for subjects with clinical stroke or silent MRI infarct, mm³, median (IQR)	N=34	N=18	N=16	0.60
	442 (148–1809)	369 (148–1211)	504 (155–3387)	
Total infarct volume for subjects with clinical stroke, mm³, median (IQR)	N=14	N=11	N=3	0.70
	369 (148–966)	352 (148–966)	550 (144–2284)	
Total infarct volume for subjects with silent infarct, mm³, median (IQR)	N=20	N=7	N=13	0.84
	528 (138–3625)	596 (76–2760)	460 (165–4491)	
Number of discrete new infarcts for subjects with clinical stroke or silent MRI infarct, median (IQR, min/max)	N=34	N=18	N=16	0.07
	1 (1–1, 1/4)	1 (1–1, 1/4)	1 (1–2, 1/4)	
Number of discrete new infarcts for subjects with clinical stroke, median (IQR, min/max)	N=14	N=11	N=3	0.37
	1 (1–1, 1/4)	1 (1–1, 1/4)	1 (1–2, 1/2)	
Number of discrete new infarcts for subjects with silent MRI infarct, median (IQR, min/max)	N=20	N=7	N=13	0.11
	1 (1–1, 1/4)	1 (1–1, 1/1)	1 (1–2, 1/4)	
Discrete lesion infarct volume for subjects with clinical stroke or silent MRI infarct, mm³, median (IQR)	N=34	N=18	N=16	0.88
	284 (102–1089)	319 (105–966)	232 (71–2225)	
Discrete lesion infarct volume for subjects with clinical stroke, mm³, median (IQR)	N=14	N=11	N=3	1.0
	284 (105–642)	284 (105–643)	347 (102–1388)	
Discrete lesion infarct volume for subjects with silent infarct, mm³, median (IQR)	N=20	N=7	N=13	0.75
	305 (76–2760)	596 (76–2760)	232 (71–4491)	

IQR indicates interquartile range; min/max, minimum and maximum values; and MRI, magnetic resonance imaging.

with new clinical stroke or silent clinical infarct, infarct size was not different comparing the patient with atrial fibrillation to those without atrial fibrillation, median 550 mm³ versus 425 mm³, *P*=0.94. Finally, including patients in both arms of the study with new clinical stroke or silent clinical infarct, there was no association between shunt size, dichotomized as none/small (n=16) versus moderate/large (n=18), and total volume of new ischemic injury, median 587 versus 369 mm³, *P*=0.43.

DISCUSSION

This preplanned analysis of blinded MRI data from the REDUCE trial provides objective confirmation that undergoing PFO closure with the GORE HELEX/CARDIOFORM Septal Occluder is associated with a reduction in new brain infarct, cutting the risk by about half. As was described in the initial publication, there was a significant reduction in recurrent clinical strokes but no difference in the number of patients with silent subclinical infarcts comparing patients randomized to closure with patients who only received antiplatelet medication.[7] The explanation for this discrepancy between clinical strokes and subclinical infarcts is not clear. Catheter-based cardiac procedures may lead to embolization and findings of small infarcts on MRI are not uncommon after such procedures.[15] Thus, some patients who underwent PFO closure may have had small subclinical periprocedural infarcts, or infarcts with clinical symptoms that were not identified or were attributed to anesthesia effects. In contrast, patients who did not undergo closure would have slowly accumulated these lesions over time, and the follow-up duration was not long enough to show a distinction between the groups. Finally, it is possible that the differential impact on clinical stroke versus subclinical infarct reflects ascertainment bias, if the patients' and clinicians' expectation is that closure is effective. Regardless of the cause for this finding, this analysis reaffirms that PFO closure reduces the combination of clinical stroke and subclinical infarct overall.

We also found that there were no differences in the size and locations of new infarcts, comparing patients who underwent closure to those who received medicine alone. These findings are in contrast to the RESPECT trial (Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment) which performed a post hoc analysis of infarct size of recurrent ischemic strokes and reported that there was a trend towards fewer large infarcts in patients who underwent closure compared with patients treated medically, 1/7 (14%) versus 9/13 (69%), *P*=0.06.[16] However, only patients with recurrent clinical strokes underwent MRI in that study whereas all patients in the REDUCE trial were expected to have protocol-mandated MRI studies, with only 7.5% failing to do so.

We found that neither shunt size nor postclosure atrial fibrillation was associated with subsequent infarct burden. Importantly, overall we also saw no difference in the volume, number, or distribution of new subclinical MRI infarcts compared with clinically apparent strokes. This finding is in contrast with numerous prior studies evaluating the relationship between clinical stroke and infarct volume on MRI. Among patients who present with

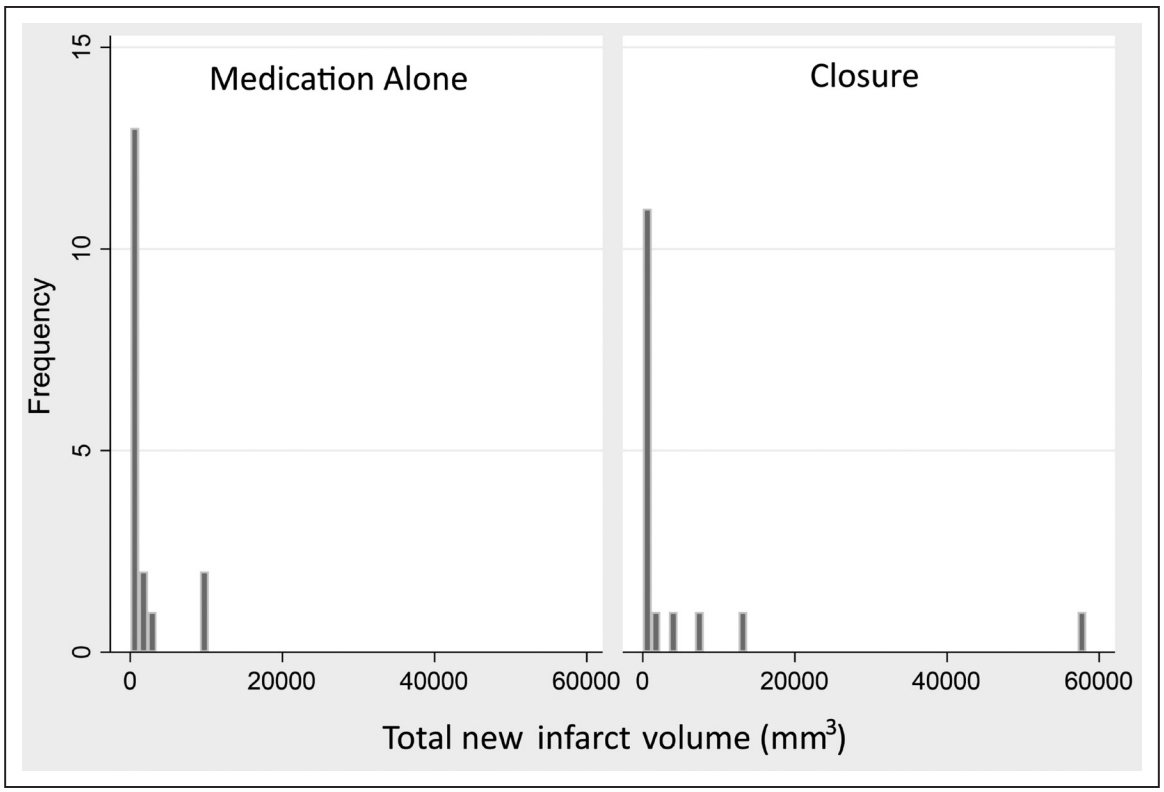

Figure 2. The distribution of total new ischemic injury comparing baseline to follow-up magnetic resonance imaging (MRI) in patients who underwent closure and patients who only received antiplatelet therapy.

symptoms of stroke, acute infarct size on MRI has been strongly correlated with symptom severity and long-term outcome from stroke.[17,18] Similarly, multiple studies of patients who receive screening MRIs and clinical assessments for stroke after a surgical procedure have reported that patients with clinical stroke have significantly larger infarct volumes compared with those with clinically silent lesions.[19–21] As such, our finding of the lack of difference in volume between clinical stroke and silent infarction together with the observation that only clinical stroke events were reduced by closure, supports the possibility that open-label end point ascertainment may have resulted in bias, with more medically treated patients, or fewer patients assigned to closure, being referred for clinical stroke end point adjudication.

To varying degrees, the completed PFO closure trials attempted to mitigate the effects of unblinded end point ascertainment. Most of the trials used validated stroke symptom detection questionnaires, adjudication of outcome events by a blinded center Clinical Events Committee, and protocol-mandated MRI if an event was suspected. The REDUCE trial used all of these strategies and, while this analysis of infarct size raises the possibility that there was ascertainment bias, there were other data from this trial that were more reassuring. As noted in the Appendix of the initial publication, a total of 176 subjects (26.5%) had one or more adverse events submitted to the Clinical Event Committee for possible primary end point adjudication: 104 (23.6%) in the closure group and 72 (32.5%) in the medical-therapy group. Unscheduled MRIs were performed for suspected new stroke or TIA events in 59 (13.4%) patients in the closure group and 46 (20.6%) in the medical-therapy group while the final confirmed stroke rates following blinded adjudication was 1.4% in the closure arm and 5.4% in the medication alone arm. This suggests that there was

Table 2. Locations of the 44 Discrete New Infarcts Seen on Follow-Up MRI in 34 Subjects Comparing Patients Who Underwent Closure to Those Who Only Received Antiplatelet Medication

	Overall	Antiplatelet only	Closure	*P* value
Left hemisphere	17/44 (39%)	7/21 (33%)	10/23 (43%)	0.55
Right hemisphere	22/44 (50%)	12/21 (57%)	10/23 (43%)	0.55
Brain stem/cerebellum	5/44 (11%)	2/21 (10%)	3/23 (13%)	1.0
Anterior circulation (ACA or MCA)	36/44 (82%)	18/21 (86%)	19/23 (83%)	1.0

ACA indicates anterior cerebral artery; MCA, middle cerebral artery; and MRI, magnetic resonance imaging.

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Table 3. Infarct Volumes and Numbers of New Infarcts on Follow-Up MRI Comparing Patients With Clinical Stroke to Those With Silent Infarct

	Overall	Clinical stroke	Silent infarct	*P* value
Total infarct volume for all subjects, mm³, median (IQR)	N=34	N=14	N=20	0.62
	442 (148–1809)	369 (148–966)	528 (138–3625)	
Total infarct volume for subjects in the closure arm, mm³, median (IQR)	N=16	N=3	N=13	0.95
	505 (155–3387)	550 (144–2284)	460 (165–4491)	
Total infarct volume for subjects in the medical arm, mm³, median (IQR)	N=18	N=11	N=7	0.86
	369 (148–1211)	352 (148–966)	596 (76–2760)	
Number of discrete new infarcts for all subjects, median (IQR, min/max)	N=34	N=14	N=20	.99
	1 (1–1, 1/4)	1 (1–1, 1/4)	1 (1–1, 1/4)	
Number of discrete new infarcts for subjects in the closure arm, median (IQR, min/max)	N=16	N=3	N=13	1.0
	1 (1–2, 1/4)	1 (1–2, 1/2)	1 (1–2, 1/4)	
Number of discrete new infarcts in the medical arm, mm³, median (IQR, min/max)	N=18	N=11	N=7	1.0
	1 (1–12/4)	1 (1–1, 1/4)	1 (1–1, 1/1)	
Discrete lesion infarct volume for all subjects, mm³, median (IQR)	N=34	N=14	N=20	0.76
	284 (102–1089)	284 (105–643)	305 (76–2760)	
Discrete lesion infarct volume for subjects in the closure arm, mm³, median (IQR)	N=16	N=3	N=13	0.94
	232 (71–2225)	347 (102–1388)	232 (71–4491)	
Discrete lesion infarct volume for subjects in the medical arm, mm³, median (IQR)	N=18	N=11	N=7	0.60
	319 (105–966)	284 (105–643)	596 (76–2760)	

IQR indicates interquartile range; min/max, minimum and maximum values; and MRI, magnetic resonance imaging.

a higher sensitivity for clinical stroke in the closure arm given that more patients who were referred for adjudication were determined to not have a stroke, compared with patients in the medical arm. Other PFO closure trials have reported mixed results in this regard. One trial noted numerically more referred stroke events in the medical arm negated by adjudication, while another reported similar referrals of possible stroke events for adjudication when using a validated stroke questionnaire.[5,22]

The potential for bias in study design is a prominent consideration for developers of clinical practice guidelines. During the systematic review of available evidence addressing a particular clinical question, guideline developers rate the risk of bias for each study, which then informs the strength of the related recommendations. The Cochrane Handbook for Systematic Reviews of Interventions specifically notes that, "The outcome assessment is potentially influenced by knowledge of intervention received" and that the reviewers must make a judgement, "whether it is likely that participants' reporting of the outcome was influenced by knowledge of intervention received, in which case risk of bias is considered high."[23] Similarly, the American Academy of Neurology guideline development manual recommends classifying randomized studies with open-label end point ascertainment as class II evidence regardless of blinded adjudication of events.[24] Guidelines that relied on data from the initial 3 closure trials did not recommend routine PFO closure.[25–27] With the accumulation of positive randomized trial data, more recent guidelines have supported PFO closure in select patients, although there has remained a concern about the open-label methodologies in these trials.[28] This analysis using objective neuroimaging-based outcome data strongly supports the conclusion that PFO closure reduces the risk of recurrent brain infarct in select patients with otherwise cryptogenic embolic-appearing stroke.

This study has important limitations. Given that MRI was obtained at the time of suspected clinical stroke, which occurred more often in the medical arm, it is possible that we have underestimated the benefit of closure as there may have been a larger number of infarcts and

Table 4. Locations of the 44 Discrete New Infarcts Seen on Follow-Up MRI in 34 Subjects Comparing Clinical Stroke to Silent Infarction

	Overall	Clinical stroke	Silent infarction	*P* value
Left hemisphere	17/44 (39%)	7/18 (39%)	10/26 (38%)	0.98
Right hemisphere	22/44 (50%)	11/18 (61%)	11/26 (42%)	0.22
Brain stem/cerebellum	5/44 (11%)	0/18 (0%)	5/26 (19%)	0.07
Anterior circulation (ACA or MCA)	36/44 (82%)	17/18 (94%)	20/26 (77%)	0.21

ACA indicates anterior cerebral artery; MCA, middle cerebral artery; and MRI, magnetic resonance imaging.

total infarct volume for medically treated patients with additional follow-up time. However, acute diffusion-weighted imaging infarct size is typically larger than late final infarct volume measured on T2/FLAIR which would bias our results in favor of closure.[29] In addition, although our focus on both clinical and MRI silent infarction did result in more events than the purely clinical outcomes of other PFO closure trials, we were likely underpowered to rule out potentially clinically meaningful associations such as small differences in size or location of infarcts for the comparison between treatment arms. We were similarly underpowered to demonstrate differences in size or location of infarcts comparing clinical stroke and silent infarct. Also, MRI data were missing in 7.5% of patients overall which may impact generalizability of our results, although sensitivity analyses suggest that the findings are unlikely to have been meaningfully different. Our conclusions regarding clinical strokes and subclinical infarcts in patients who developed atrial fibrillation after closure compared with those who did not should be interpreted with caution as over half of patients who developed atrial fibrillation were treated with anticoagulation, which would mitigate much of this risk. Finally, we utilized a cutoff of >3 mm for detection of new infarcts in this analysis, as this what was used by the core lab in this trial MRI and has been cited as a reasonable threshold in the American Heart Association statement on stroke definitions.[30] Moreover, the measurement of lesions smaller than this threshold becomes less reliable due to MRI noise, motion artifacts, and other sources of error when we approach the level of the voxel size used in our semi-automated method. As a result, we may have overlooked smaller infarcts.

CONCLUSIONS

The REDUCE study demonstrated that new brain infarcts on MRI, an objective outcome measure of efficacy, were significantly reduced by PFO closure. Overall, only clinical strokes were reduced by closure while there were similar rates of subclinical infarcts between treatment arms. In addition, clinical and silent infarcts were similar in volume, number, and distribution, raising the possibility of ascertainment bias of clinical outcomes in open-label PFO closure studies. Objective measures should be used in open-label stroke prevention trials whenever possible.

ARTICLE INFORMATION

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Supplemental Materials

Online Table I

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