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CORRESPONDENCE

Five-Year Outcomes of PFO Closure or Antiplatelet Therapy for Cryptogenic Stroke

TO THE EDITOR: Closure of a patent foramen ovale (PFO) has been shown to reduce the risk of recurrent stroke in selected patients.[1] Data on outcomes of PFO closure in patients who were followed for a median of 5.9 years after the procedure are available; however, these data are limited to closure with a single device.[2] We have reported the results of the Gore REDUCE Clinical Study,[3] a prospective, randomized, open-label trial that compared the efficacy and safety of two closure devices plus antiplatelet agents (PFO closure group) with those of antiplatelet agents alone (antiplatelet-only group) for reducing the risk of recurrent ischemic stroke; the median duration of follow-up was 3.2 years, and outcome events were adjudicated in a blinded manner (the protocol is available with initial 2017 report[3]). Here, we report the results of the planned 5-year outcome analysis.

A total of 441 patients were randomly assigned to the PFO closure group and 223 to the antiplatelet-only group (Fig. S1 in the Supplementary Appendix, available with the full text of this letter at NEJM.org). In an intention-to-treat analysis, the rate of stroke recurrence was compared between groups. During the initial follow-up period of 3.2 years, 18 patients had recurrent strokes (6 [1.4%] in the PFO closure group and 12 [5.4%] in the antiplatelet-only group). After the end of the initial follow-up period, two strokes occurred (both in the PFO closure group) during the extended follow-up period. Thus, during a median duration of follow-up of 5.0 years (interquartile range, 4.8 to 5.2), a total of 20 patients had recurrent ischemic strokes — 8 patients (1.8%) in the PFO closure group (0.39 strokes per 100 patient-years) and 12 patients (5.4%) in the antiplatelet-only group (1.26 strokes per 100 patient-years) (hazard ratio, 0.31; 95% confidence interval, 0.13 to 0.76) (Fig. 1). Similar results were observed in the per-protocol and as-treated analysis populations, and there was no evidence of heterogeneity of treatment effect across key subgroups (Fig. S3 in the Supplementary Appendix). Data on new infarction on magnetic resonance imaging (the second primary outcome) were not collected at 5 years.

The incidence of serious adverse events was similar in the two trial groups, as was the incidence of death, major bleeding, and deep-vein thrombosis or pulmonary embolism (Table S5 in the Supplementary Appendix). There were no fractures, thromboses, or embolizations of the device, nor were there cardiac erosions, during the extended follow-up period. However, atrial fibrillation or flutter occurred in a higher percentage of patients in the PFO closure group than in the antiplatelet-only group (6.8% [30 patients] vs. 0.4% [1 patient]); 12 patients (2.7%) in the PFO closure group had prolonged atrial

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fibrillation or flutter lasting 30 days or more, 1 of whom had recurrent stroke while receiving anticoagulation. Predictors of atrial fibrillation or flutter related to PFO closure and subsequent stroke risk require further investigation, and a patient-level meta-analysis relating to these predictors is under way.[4]

With the two additional strokes in the PFO closure group that occurred between the last report and this one, the absolute difference in risk between the trial groups at 5 years was 3.6 percentage points in favor of PFO closure, and the number needed to treat to prevent one stroke in 5 years was approximately 25 patients.

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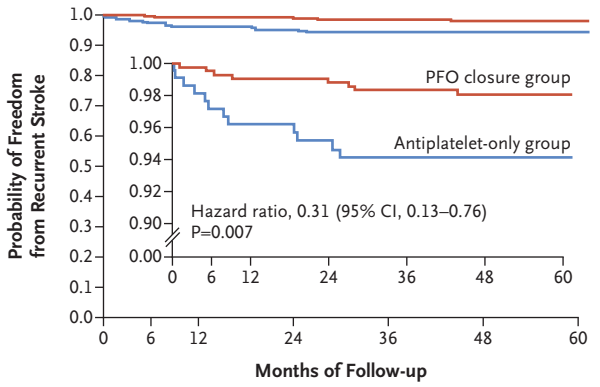

No. at Risk

PFO closure group	441	442	417	411	400	391	235
Antiplatelet-only group	223	202	194	185	180	174	76

Figure 1. Probability of Freedom from Clinical Evidence of Recurrent Ischemic Stroke.

Shown are Kaplan–Meier estimates in the intention-to-treat population. The inset shows the same data on an enlarged y axis.

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*A complete list of the Gore REDUCE Clinical Study investigators and participating organizations is provided in the Supplementary Appendix of the initial 2017 report, available at NEJM.org.

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Microsatellite-Instability–High Advanced Colorectal Cancer

TO THE EDITOR: The KEYNOTE-177 trial, the results of which were reported by André et al. (Dec. 3 issue),[1] represents a practice-changing step in the treatment of patients with microsatellite-instability–high (MSI-H) or mismatch-repair–deficient (dMMR) metastatic colorectal cancer, for whom pembrolizumab should now be considered the preferred first-line therapy. These re-