Comparison of Antiplatelet Therapies for Prevention of Patent Foramen Ovale-Associated Stroke

Scott E. Kasner, MD,* Bryan Randall, MS,† Grethe Andersen, MD,‡ Helle K. Iversen, MD,§ Risto O. Roine, MD,|| Christina Sjostrand, MD, PhD,¶ John F. Rhodes, MD,** and Lars Søndergaard, MD††, The Gore REDUCE Study Investigators

Aims: The REDUCE study demonstrated a reduction in the risk of recurrent stroke with patent foramen ovale closure and antiplatelet therapy compared to antiplatelet therapy alone. The clinicians were allowed to choose among aspirin, clopidogrel, or aspirin/dipyridamole with the expectation that all antiplatelet therapies would have similar efficacy in this population. We tested that presumption by comparing recurrent stroke rates among antiplatelet agents within the control arm of the trial. *Methods:* We evaluated patients in REDUCE study who were randomized to the medical arm. The primary endpoint for this analysis was freedom from clinical ischemic stroke through at least 2 years of follow-up, to a maximum of 5 years. In the primary analysis, antiplatelet treatment was defined as the agent during the week prior to a recurrent stroke or last known contact. *Results:* Of 223 patients in the medical treatment arm, the initial agent was aspirin 52%, clopidogrel 30%, and aspirin/dipyridamole 12%. Patients treated with aspirin were similar to those treated with alternatives, but were more likely to be enrolled in the United States. The last reported agent was aspirin alone in 55%, clopidogrel alone in 31%, aspirin/dipyridamole in 7%, and other/nothing/missing in 7%. Recurrent stroke rates were similar for all 3 antiplatelet regimens in unadjusted and adjusted analyses, with no overall difference among agents (P= .17). *Conclusions:* Among patients with patent foramen ovale-associated stroke who were managed medically, there were no differences among antiplatelet agents in the risk of recurrent stroke, though confidence intervals were wide.

Key Words: Stroke—patent foramen ovale—antiplatelet agents—prevention

Introduction

The Gore REDUCE clinical study demonstrated a reduction in the risk of recurrent stroke with patent foramen ovale (PFO) closure and antiplatelet therapy compared to antiplatelet therapy alone.[1] The clinicians were allowed to choose among aspirin, clopidogrel, or aspirin/dipyridamole. The trial was designed with the expectation that all antiplatelet therapies would have similar efficacy in this population,[2] since the absolute differences in efficacy among these agents in prior stroke trials were small[3,4] and generally most evident among patients with vascular risk factors and atherosclerotic disease.[5,6] We hypothesized that patients with PFO-associated stroke would have similar recurrent stroke rates when treated with aspirin compared to other antiplatelet agents.

Methods

The REDUCE study was a multinational prospective, randomized, controlled, open-label trial with blinded adjudication of outcome events.[1] Patients were eligible if

From the *University of Pennsylvania, Philadelphia, Pennsylvania; †WL Gore and Associates, Flagstaff, Arizona; ‡Aarhus University, Aarhus, Denmark; §University of Copenhagen, Copenhagen, Denmark; ||Turku University Hospital and University of Turku, Turku, Finland; ¶Karolinska Institute, Stockholm, Sweden; **Medical University of South Carolina, Charleston, South Carolina; and ††Rigshospitalet, Copenhagen, Denmark.

Received November 23, 2019; accepted December 22, 2019.

Funding: This work was supported by WL Gore and Associates.

Address correspondence to Scott E. Kasner, MD, Department of Neurology, University of Pennsylvania, 3400 Spruce Street, Philadelphia, PA 19014. E-mails: kasner@mail.med.upenn.edu, kasner@pennmedicine.upenn.edu.

1052-3057/$ - see front matter

https://doi.org/10.1016/j.jstrokecerebrovasdis.2019.104632

Table 1. *Choice of initial antiplatelet agent in relation to baseline characteristics*

Characteristic	Aspirin (n = 117)	Clopidogrel (n = 67)	Aspirin + dipyridamole (n = 26)
Age, years (mean ± s.d.)	44.5 ± 10.4	44.5 ± 9.0	45.7 ± 7.3
Male sex	76 (65%)	36 (54%)	17 (65%)
Medical history			
Current smoking	27 (23%)	18 (27%)	8 (31%)
Hypertension	32 (27%)	17 (25%)	5 (19%)
Diabetes mellitus	4 (3%)	5 (7%)	1 (4%)
Stroke or TIA prior to index event	10 (9%)	10 (15%)	1 (4%)
Region			
United States	79 (68%)	13 (19%)	11 (42%)
Europe, United Kingdom, Canada	38 (32%)	54 (81%)	15 (58%)
Patent foramen ovale shunt grade	(n = 115)	(n = 65)	(n = 25)
Grade I small (1-5 bubbles)	26 (23%)	10 (15%)	3 (12%)
Grade II moderate (6-25 bubbles)	53 (46%)	29 (45%)	8 (32%)
Grade III large (>25 bubbles)	36 (31%)	26 (40%)	14 (56%)

they were aged 18-59 years, had a cryptogenic ischemic stroke within 180 days prior to randomization, had a PFO with right-to-left shunt, and provided informed consent to participate. Patients were randomly assigned in a 2:1 ratio to closure of the PFO and antiplatelet therapy, or to antiplatelet therapy alone. Antiplatelet therapy was chosen by the local investigator, and at each site, antiplatelet therapy was mandated to be the same in both treatment groups, consisting of aspirin alone (75-325 mg once daily), combination aspirin (50-100 mg daily) dipyridamole (225-400 mg daily), or clopidogrel (75 mg once daily). Other combinations of antiplatelet drugs and anticoagulants were not permitted. All patients were expected to continue antiplatelet therapy for the duration of follow-up in the trial.

Patients were followed for a minimum of 2 years and a maximum of 5 years. Visits with a study neurologist occurred at 1, 6, 12, 18, 24, 36, 48, and 60 months. If a TIA or stroke was suspected on clinical grounds at any time, an evaluation was performed by a neurologist, who was aware of treatment assignment, and brain imaging was required at that time. A recurrent ischemic stroke event was defined as a focal neurological deficit, presumed due to ischemia, persisting longer than 24 hours, or a deficit associated with MRI or CT evidence of a new brain infarction consistent with the clinical syndrome. All suspected recurrent stroke or TIA events were reviewed and adjudicated by the clinical events committee.

For this investigation, we evaluated the cohort of patients who were randomized to the medical arm of the trial, and censored those who crossed over to closure. The primary endpoint for this analysis, as in the main trial report, was freedom from clinical ischemic stroke through at least 2 years of follow-up, to a maximum of 5 years. In the primary analysis, antiplatelet treatment was defined as the agent during the week prior to a recurrent stroke or last known contact. In secondary analysis, antiplatelet agent was treated as a time-dependent covariate. Cox regression was employed to adjust for age, sex, prior stroke or TIA, and global region (United States versus all others). All analyses were considered exploratory and post hoc.

Results

In the REDUCE study, 664 patients were enrolled, 441 randomly assigned to the closure group and 223 assigned to the medical therapy only group. Of those randomized to the medical arm, the initial agent chosen on the date of enrollment was aspirin in 52%, clopidogrel 30%, aspirin/dipyridamole 12%, and other/nothing/missing in 6%.

Patients treated with aspirin were similar to those treated with alternatives, but were more likely to be enrolled in the United States (Table 1). The last reported agent was aspirin alone in 55%, clopidogrel alone in 31%, aspirin/dipyridamole in 7%, and other/nothing/missing in 7%.

Recurrent stroke rates and hazard ratios for antiplatelet agents compared to aspirin are summarized in Table 2 and Figure 1, with no overall difference among agents (P= .17). Concordant results were obtained using antiplatelet agent as a time-dependent covariate.

Discussion

In the REDUCE trial, the observed rate of recurrent clinical ischemic stroke with PFO closure was 0.39 per 100 person-years compared to 1.71 per 100 person-years with antiplatelet therapy alone (hazard ratio 0.23; 95% confidence interval 0.09-0.62).[1] The majority of patients were treated with aspirin, though clopidogrel and aspirin/dipyridamole were more frequently used in Europe. Among those who were managed on medical therapy, there were no prominent differences among these 3 antiplatelet regimens. This analysis had limited power to detect such differences, but the results are nonetheless reassuring. In broader secondary stroke prevention trials

Table 2. *Recurrent clinical ischemic stroke and antiplatelet agent*

Antiplatelet treatment	Recurrent clinical ischemic stroke (per 100 person-years)	Hazard ratio, unadjusted (95% CI)	Hazard ratio, adjusted* (95% CI)
Aspirin (n = 123)	1.4	(reference)	(reference)
Clopidogrel (n = 69)	3.6	2.5 (0.78-7.7)	3.2 (0.81-12.5)
Aspirin/dipyridamole (n = 17)	0	0 (0.00-. . .)	0 (0.00-. . .)

*Adjusted for age, sex, prior stroke or TIA, and US versus non-US site. When antiplatelet agents were analyzed as time-varying covariates, the adjusted hazard ratio for clopidogrel alone versus aspirin alone was 3.2 (95% CI: 0.80-12.7).

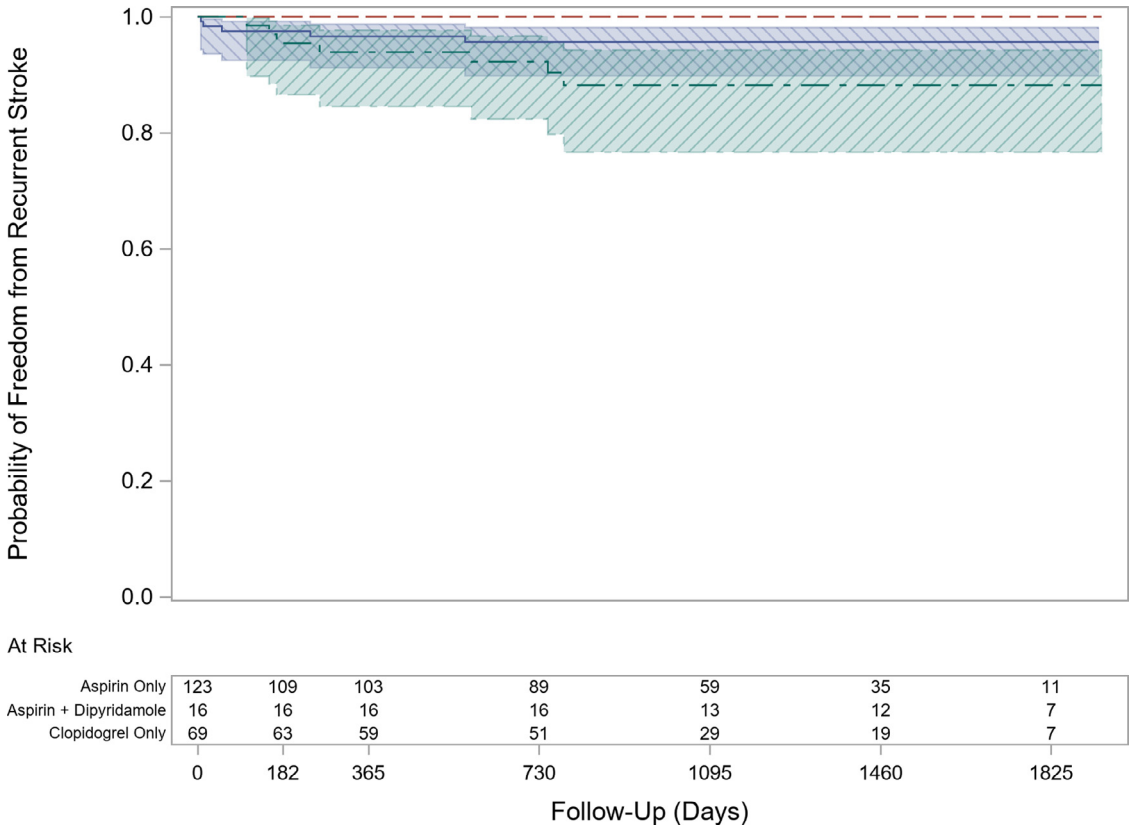

Figure 1. *Probability of freedom from recurrent clinical ischemic stroke. Shown are Kaplan-Meier plots based on last reported antiplatelet agent. (Blue/solid line = aspirin, green/long and short dashed line = clopidogrel, red/dashed line = aspirin + dipyridamole.) (Color version of figure is available online.)*

of noncardioembolic stroke, both clopidogrel[3] and aspirin-dipyridamole[4] have been shown to reduce the risk of stroke and other major vascular events compared to aspirin alone. However, the absolute risk reductions were small, and seemed to be accentuated among patients with vascular risk factors and manifest atherosclerotic disease.[5,6] Conversely, patients with PFO-associated stroke are relatively young with few risk factors,[7] and therefore the differences among agents would be expected to be quite modest. In the REDUCE study, the most commonly used agent was either aspirin or clopidogrel, which accounted for the vast majority of patients and all of the recurrent events, and that pairwise comparison did not suggest a benefit of clopidogrel in this patient population. However, there were too few patients on aspirin-dipyridamole to draw any conclusions about this strategy.

In addition to the low power, this analysis was also potentially limited by confounding by indication. Patients treated with an agent other than aspirin may have been deemed high risk by their clinicians. We found that those treated with clopidogrel were more likely to be from Europe due to regional guidelines for secondary stroke prevention but were otherwise similar. Nevertheless, adjusting for region along with age, sex, and prior cerebrovascular event had no discernable effect on the relative efficacy of clopidogrel compared to aspirin. Residual confounding by unmeasured factors remains a potential limitation.

In conclusion, this study supports the hypothesis that there are no significant differences in efficacy among antiplatelet agents for patients with PFO-associated stroke. Further, these findings emphasize the relative benefit of closure over antiplatelet therapy.

Declaration of Competing Interest

Drs. Kasner, Andersen, Iversen, Roine, Sjostrand, Rhodes, and Sondergaard received grant funding from WL Gore and Associates. Bryan Randall is an employee of WL Gore and Associates.

References

1. Sondergaard L, Kasner SE, Rhodes JF, et al. Patent foramen ovale closure or antiplatelet therapy for cryptogenic stroke. N Engl J Med 2017;377:1033-1042.
2. Kasner SE, Thomassen L, Sondergaard L, et al. Patent foramen ovale closure with gore helex or cardioform septal occluder vs. antiplatelet therapy for reduction of recurrent stroke or new brain infarct in patients with prior cryptogenic stroke: design of the randomized gore reduce clinical study. Int J Stroke 2017;12:998-1004.
3. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (caprie). Lancet 1996;348:1329-1339.
4. Diener HC, Cunha L, Forbes C, et al. European stroke prevention study. 2. Dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. J Neurol Sci 1996;143:1-13.
5. Hirsh J, Bhatt DL. Comparative benefits of clopidogrel and aspirin in high-risk patient populations: lessons from the caprie and cure studies. JAMA Intern Med 2004;164:2106-2110.
6. Leonardi-Bee J, Bath PMW, Bousser M-G, et al. Dipyridamole for preventing recurrent ischemic stroke and other vascular events. Stroke 2005;36:162-168.
7. Kent DM, Ruthazer R, Weimar C, et al. An index to identify stroke-related vs incidental patent foramen ovale in cryptogenic stroke. Neurology 2013;81:619-625.