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Effectiveness of patent foramen ovale occlusion devices versus medical therapy: An indirect comparison based on reconstructed individual patient data

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ABSTRACT

Background: Percutaneous closure of patent foramen ovale (PFO) reduces the risk of recurrent stroke in selected patients with cryptogenic stroke. However, direct comparative data among different occlusion devices are lacking.

Objective: Our study aimed to compare the efficacy PFO closure plus medical therapy versus medical therapy alone in patients with cryptogenic stroke using data from randomized controlled trials (RCTs).

Methods: Randomized controlled trials with ≥36 months of follow-up evaluating PFO closure with Abbott or Gore devices versus medical therapy were identified. Individual patient data were reconstructed from published Kaplan–Meier curves using the IPDfromKM artificial intelligence–based method. Time-to-event analyses were performed using hazard ratios (HRs) with 95% confidence intervals (CIs). Between-trial heterogeneity was assessed on control arms.

Results: Three randomized trials were included. No significant heterogeneity was observed among medical therapy control groups. When all devices were pooled, PFO closure significantly reduced recurrent stroke compared with medical therapy alone (HR 0.4288; 95%CI, 0.2533 to 0.7258; $p = 0.0016$). Both Abbott devices (HR 0.4631 (95% CI, 0.2597 to 0.8258; $p = 0.00909$) and Gore devices (HR= 0.3457 (95%CI, 0.1354 to 0.8826) were associated with a significantly lower risk of recurrent stroke. The indirect comparison between devices showed no significant difference.

Conclusions: In this indirect comparison based on reconstructed individual patient data, PFO closure with occlusion devices significantly reduced recurrent stroke compared with medical therapy alone. Abbott and Gore devices demonstrated comparable long-term efficacy.

Introduction

Patent foramen ovale (PFO), an incomplete apposition of the two septa that creates a 'tunnel' between right atrium (RA) and left atrium (LA), is present approximately in one quarter of the adult population and is more frequently observed in patients with cryptogenic stroke.[1] Cryptogenic stroke, as defined by the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification, is a brain infarction not attributable to a clearly recognized cardioembolic event, carotid or intracranial artery disease, or other diseases after appropriate vascular, cardiac, and serological investigations. Although PFO is often an incidental finding, paradoxical embolism is considered a plausible mechanism linking PFO to ischemic stroke.[1,2] Closure of a PFO has been shown to reduce the risk of recurrent stroke in selected patients.[3] Over the past decade, randomized controlled trials (RCTs) have demonstrated that percutaneous PFO closure reduces recurrent stroke compared with medical therapy alone in carefully selected patients. Several occlusion devices have been evaluated in RCTs.[4-6] After the withdrawal of earlier

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systems, two devices have become predominant in clinical practice: the Amplatzer PFO Occluder (Abbott) and the Gore Helex/Cardioform Septal Occluders. To date, no head-to-head randomized trials have compared these devices, and comparative evidence is therefore indirect.

This short communication presents an indirect comparison of PFO closure devices versus medical therapy using reconstructed individual patient data derived from published Kaplan–Meier curves. A methodological feature of our comparative analysis consisted in the use of a new artificial intelligence (AI) technique called the "IPDfromKM" method.[7] This method is an AI tool that reconstructs individual patient data from the graph of Kaplan-Meier curves, thus allowing cross-study comparisons based on reconstructed patient data.[8] This method yields an easy-to-understand summary of the results by generating a unique multi-curve plot containing the Kaplan-Meier curves of all reconstructed patients. Treatments are compared statistically using standard parameters such as the hazard ratio (HR) and confidence interval (CI). The analysis focuses on long-term prevention of recurrent ischemic stroke in patients with cryptogenic stroke. In this context, an advantage of the IPDfromKM method is that the value of the HR considers the time course of the curves projected over the entire follow-up period.

Methods, results and discussion

Study design and data reconstruction

A systematic search of PubMed (last search run on 15 December 2025) and complementary sources identified RCTs evaluating PFO closure plus medical therapy versus medical therapy alone with at least 36 months of follow-up and available Kaplan–Meier curves for recurrent ischemic stroke. The search terms ("patent foramen ovale" AND (occlusion OR occlude) were employed in combination with the filter "randomized controlled trials".

Between-trial heterogeneity was evaluated on medical therapy control arms using likelihood ratio and Wald tests. Individual patient data were reconstructed from published Kaplan–Meier curves using the IPDfromKM method.[7]; HRs and 95%CIs were calculated using standard survival analysis techniques. In our pooled analysis of RCTs, we evaluated long-term outcomes associated with PFO closure using percutaneous occlusion devices compared with medical therapy alone, and we indirectly explored potential differences between the two most widely used systems: the Amplatzer PFO Occluder (Abbott Vascular, formerly St. Jude Medical) and the Helex/Cardioform septal occluders (Gore & Associates). By reconstructing individual patient data from published Kaplan–Meier curves according to the IPDfromKM method, we were able to perform time-to-event analyses across studies with extended follow-up durations.

Three trials met inclusion criteria: RESPECT, PC Trial, and REDUCE (Table 1). Trials using multiple heterogeneous devices or complex multiarm designs were excluded to limit methodological heterogeneity.[4] The RESPECT trial evaluating PFO closure with the Amplatzer PFO Occluder was the largest, enrolling 980 patients, and provided the longest follow-up, with a median duration of 5.9 years.[9] Similarly, the PC Trial assessed patients with PFO randomized to closure using the Amplatzer device or to medical therapy alone.[10] The REDUCE trial evaluated PFO closure using initially the Helex occluder and subsequently the Cardioform septal occluder; in both cases, the trial compared device closure plus long-term antiplatelet therapy with antiplatelet therapy alone.[5] The CLOSE trial was excluded from our analysis because of its more complex three-arm design, which included PFO closure plus long-term antiplatelet therapy, antiplatelet therapy alone, and an anticoagulation arm

Table 1
Main characteristics of the three included trials. The event is recurrent stroke.

Author	Trial	Main inclusion criteria	Device	Follow up	Endpoint	Crude event rates	Hazard ratio in the original trial	Hazard ratio recomputed from reconstructed patients	Notes
Saver 2017[9]	RESPECT trial	PFO confirmed by transesophageal echocardiography and cryptogenic ischemic stroke.	Abbott device: Amplatzer	5.9 years	Recurrent ischemic stroke o	*T* = 18/499 *C* = 28/481	0.55 (95% CI, 0.31 to 0.999)	0.5567 (95%CI, 0.2949 to 1.051, *p* = 0.0709)	
Meier 2013[10]§	PC trial	PFO documented on transesophageal echocardiography and no other identifiable cause and ischemic stroke, a TIA with a neuroradiologically verified cerebral ischemic lesion, or a clinically and radiologically verified extracranial peripheral thromboembolic event.	Abbott device: Amplatzer	4.1/4 years	§Recurrent ischemic stroke	*T* = 1[&]/204 *C* = 5[&]/210	0.20 (95% CI, 0.02 to 1.72; *P* = 0.14).	0.2549 (95%CI, 0.02849 to 2.281, *p* = 0.222)	Data from Figure S5 in the Appendix
Søndergaard 2017[5]	REDUCE trial	PFO assessed by means of transesophageal echocardiography and cryptogenic ischemic stroke.	Gore device: the Helex Septal Occluder (HELEX; W.L. Gore and Associates) device (implanted through late 2012) or the Cardioform Septal Occluder (GSO; W.L. Gore and Associates) device (implanted from late 2012 onward).	3.2 years	Recurrent ischemic stroke	*T* = 6/441 *C* = 12/223	0.23 (95% CI, 0.09 to 0.62)	0.227 (95%CI, 0.07887 to 0.6533)	

Symbols and abbreviations: PFO, patent foramen ovale; *T*= (rate in the treatment group); *C*= (rate in the control group).
§In this trial, the primary endpoint was a composite of death, nonfatal stroke, TIA, or peripheral embolism; the results based on this endpoint were the following: *T* = 7/204 vs *C* = 11/210; HR=0.63; (95% CI, 0.24 to 1.62; *P* = 0.34) .
& These 6 events included no cardiovascular deaths.

compared with antiplatelet therapy.[4]; in addition, a variety of closure devices were permitted although 53% of patients received the Amplatzer PFO Occluder, introducing further heterogeneity.

Heterogeneity assessment

Reconstructed Kaplan–Meier curves for medical therapy arms across the three included trials showed no statistically significant heterogeneity (likelihood ratio test = 3.04 on 2 df, $p = 0.20$; Wald's test = 2.84 on 2 df, $p = 0.20$; Fig. 1). This finding supports the methodological appropriateness of pooling control groups and performing indirect comparisons.

Main analysis: device closure versus medical therapy

When patients treated with any occlusion device were pooled and compared with those receiving medical therapy alone, PFO closure was associated with a significant reduction in recurrent ischemic stroke (HR=0.4288; 95%CI, 0.2533 to 0.7258; $p = 0.0016$); Fig. 2A). This result is consistent with previously published randomized trials and meta-analyses supporting device closure in selected patients with cryptogenic stroke. Separate comparisons of each device versus pooled medical therapy controls demonstrated significant benefit for both systems. Closure with Abbott devices was associated with a HR of 0.4631 (95%CI, 0.2597 to 0.8258; $p = 0.00909$), while Gore devices showed a HR of 0.3457 (95%CI, 0.1354 to 0.8826); Fig. 2B). The wider confidence interval for Gore devices likely reflects smaller sample size and shorter follow-up. The indirect comparison between Abbott and Gore devices showed no statistically significant difference (HR=0.746, 95%CI, 0.248 to 2.246), indicating comparable efficacy and excluding meaningful superiority of one device over the other. The strong concordance between HRs reported in the original trials and those recomputed from reconstructed data (Table 1) supports the validity of the IPDfromKM approach.

A key finding of our study is the absence of significant heterogeneity among the medical therapy arms across the three included trials. Kaplan–Meier curves for patients treated with medical therapy alone demonstrated comparable event rates, with no statistically significant differences in survival distributions. This observation supports the methodological validity of pooling control groups and suggests that background medical therapy and baseline risk profiles were sufficiently similar to allow meaningful comparative analyses using the IPDfromKM method.

When all device-treated patients were pooled and compared with medical therapy alone, PFO closure was associated with a significant reduction in the risk of recurrent events. The observed HR (0.4288; 95% CI, 0.2533 to 0.7258; $p = 0.0016$) is consistent with prior randomized trials demonstrating the superiority of device closure plus medical therapy over medical therapy alone in carefully selected patients with cryptogenic stroke. Current meta-analytic evidence and consensus guidelines similarly support consideration of PFO closure in patients at highest risk, with no clear evidence favoring one specific closure device over another. A novel aspect of the present study is the indirect comparison between Abbott and Gore devices. In the three-arm analysis (Fig. 2 Panel B), both devices were associated with a statistically significant reduction in recurrent events compared with pooled medical therapy controls. Our study was not designed or powered for a head-to-head comparison, and differences in patient characteristics, trial design, and follow-up duration may have influenced these results; however, our results based on this indirect comparison clearly exclude any hypothesis of superiority of one device over the other. Importantly, both devices demonstrated a clinically meaningful benefit compared with medical therapy alone.

Another limitation of our analysis relates to the use of reconstructed individual patient data derived from published Kaplan–Meier curves. Although this approach allows recovery of time-to-event information and enables detailed survival analyses when original datasets are unavailable, it does not permit reconstruction of baseline covariates or adjustment for patient-level characteristics across trials. Consequently, indirect comparisons between treatment strategies should be interpreted

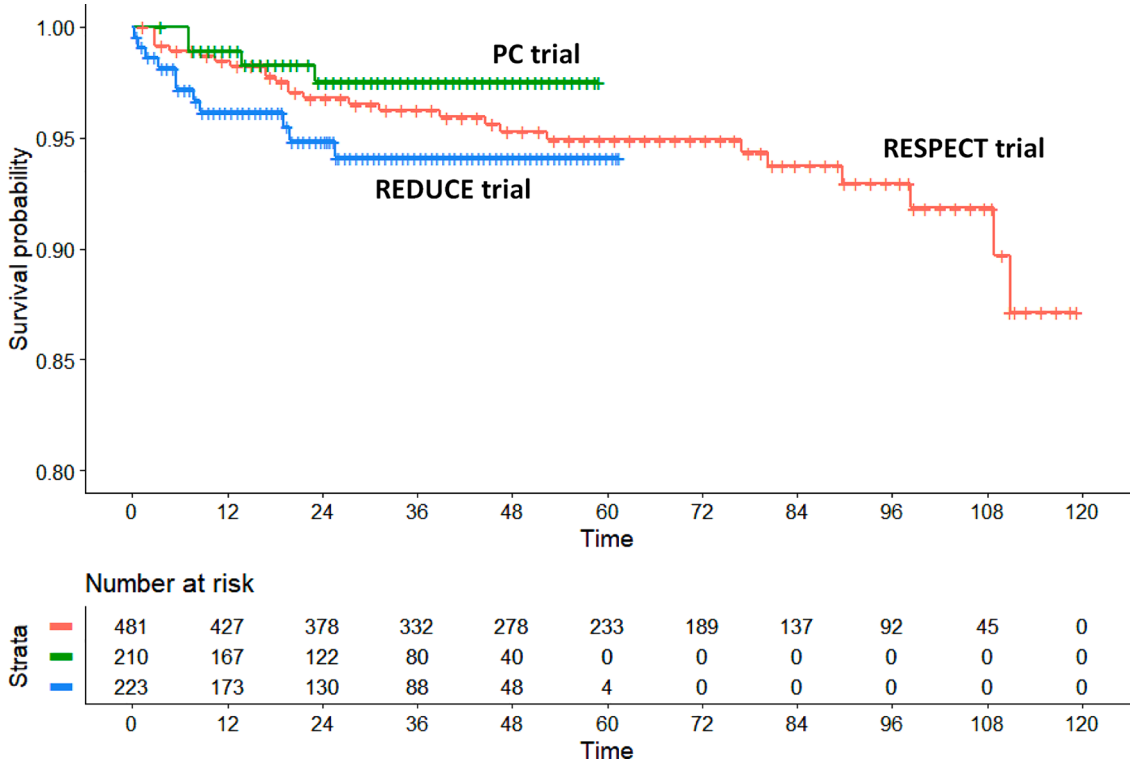

Fig. 1. Heterogeneity assessment based on the control arms of the three trials. Endpoint, recurrent stroke. Time in months.

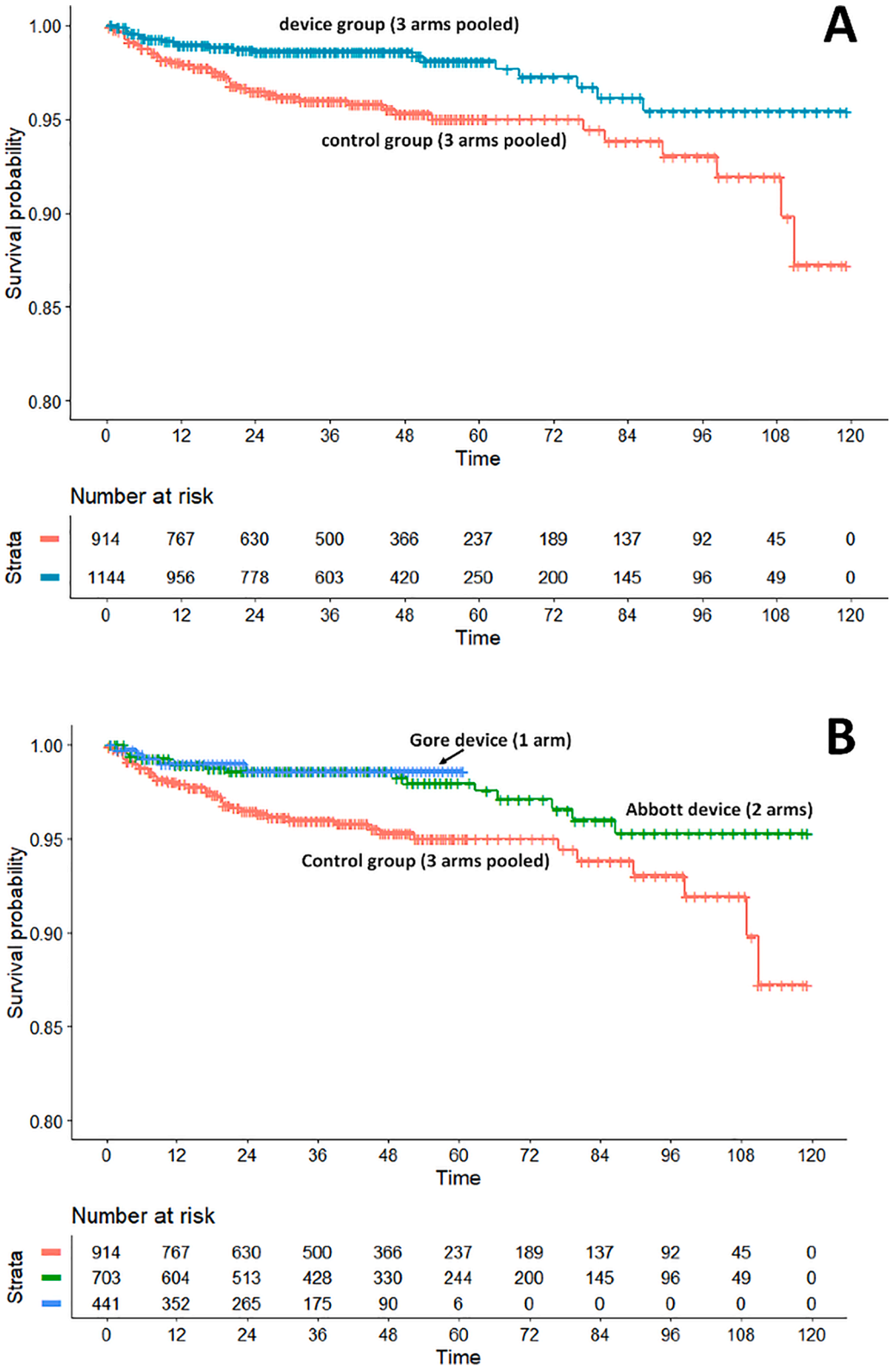

Fig. 2. Panel A. Main analysis: comparison between patients treated with an occlusion device plus medical therapy with those treated with medical therapy alone. Endpoint, recurrent ischemic stroke. Time in months. **Panel B: C**urves of the two devices reported separately. Endpoint, recurrent stroke. Time in months.

with caution, as residual differences in patient populations or trial design cannot be completely excluded.

On the other hand, the absence of substantial heterogeneity across the medical therapy arms suggests that the underlying risk of recurrent stroke was reasonably similar among the trial populations. Although this observation does not fully exclude differences in baseline characteristics, it provides supportive evidence that the study populations were broadly comparable and therefore strengthens the validity of the planned indirect comparisons.

A methodological strength of this study is represented by the use of

the IPDfromKM method.[6], a technique that has increasingly been used in recent years, particularly in cardiology and oncology.[11] Nevertheless, reconstructed data cannot fully substitute original individual patient data from RCTs of direct comparison and are subject to the limitations inherent in indirect comparisons. Several limitations should therefore be acknowledged. First, the analysis included a limited number of trials, reflecting strict inclusion criteria and the requirement for long-term Kaplan–Meier data. Second, unmeasured confounders, such as PFO anatomical characteristics, procedural techniques, or differences in adjunctive medical therapy, could not be accounted for. Finally, several PFO closure devices with different characteristics are currently available, including the Occlutech PFO occluder; however, according to the European consensus document.[3], most of the evidence supporting PFO closure is based on the Amplatzer PFO Occluder and the GORE Cardioform Septal Occluder. Consequently, device selection should be guided primarily by this evidence, while alternative devices may be considered in selected patients based on specific anatomical, technical, or clinical factors, within a shared decision-making framework.

In conclusion, this pooled analysis confirmed that percutaneous PFO closure using occlusion devices is associated with a significant reduction in recurrent events compared with medical therapy alone. Both Abbott and Gore devices demonstrated favorable long-term outcomes, with no evidence of heterogeneity among control groups.

CRediT authorship contribution statement

Melania Rivano: Writing – original draft, Data curation. **Roberto Brunoro:** Visualization, Supervision, Investigation. **Marco Cesca:** Writing – review & editing. **Andrea Ossato:** Validation, Software. **Andrea Messori:** Software, Methodology, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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