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Device Closure of Patent Foramen Ovale After Stroke

Pooled Analysis of Completed Randomized Trials

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ABSTRACT

BACKGROUND The comparative effectiveness of percutaneous closure of patent foramen ovale (PFO) plus medical therapy versus medical therapy alone for cryptogenic stroke is uncertain.

OBJECTIVES The authors performed the first pooled analysis of individual participant data from completed randomized trials comparing PFO closure versus medical therapy in patients with cryptogenic stroke.

METHODS The analysis included data on 2 devices (STARFlex [umbrella occluder] [NMT Medical, Inc., Boston, Massachusetts] and Amplatzer PFO Occluder [disc occluder] [AGA Medical/St. Jude Medical, St. Paul, Minnesota]) evaluated in 3 trials. The primary composite outcome was stroke, transient ischemic attack, or death; the secondary outcome was stroke. We used log-rank tests and unadjusted and covariate-adjusted Cox regression models to compare device closure versus medical therapy.

RESULTS Among 2,303 patients, closure was not significantly associated with the primary composite outcome. The difference became significant after covariate adjustment (hazard ratio [HR]: 0.68; $p = 0.049$). For the outcome of stroke, all comparisons were statistically significant, with unadjusted and adjusted HRs of 0.58 ($p = 0.043$) and 0.58 ($p = 0.044$), respectively. In analyses limited to the 2 disc occluder device trials, the effect of closure was not significant for the composite outcome, but was for the stroke outcome (unadjusted HR: 0.39; $p = 0.013$). Subgroup analyses did not identify significant heterogeneity of treatment effects. Atrial fibrillation was more common among closure patients.

CONCLUSIONS Among patients with PFO and cryptogenic stroke, closure reduced recurrent stroke and had a statistically significant effect on the composite of stroke, transient ischemic attack, and death in adjusted but not unadjusted analyses. (J Am Coll Cardiol 2016;67:907–17) © 2016 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

ITT = intention to treat

PFO = patent foramen ovale

TIA = transient ischemic attack

Approximately 30% of ischemic strokes are "cryptogenic," an etiologically heterogeneous class. Approximately one-half of patients <60 years of age with cryptogenic stroke have a patent foramen ovale (PFO), nearly double the prevalence in the general population. For these patients, cryptogenic stroke may be caused by paradoxical embolism, in addition to other occult etiologies.

Controversy exists over the preferred management strategy for patients with cryptogenic stroke and PFO. Three randomized clinical trials investigating 2 devices—STARFlex (umbrella occluder) (NMT Medical, Inc., Boston, Massachusetts) in CLOSURE I (Evaluation of the STARFlex Septal Closure System in Patients with a Stroke and/or Transient Ischemic Attack due to Presumed Paradoxical Embolism through a Patent Foramen Ovale) (1), and Amplatzer PFO Occluder (disc occluder) (AGA Medical/St. Jude Medical, St. Paul, Minnesota) in the RESPECT (Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment) (2) and PC (Percutaneous Closure of Patent Foramen Ovale in Cryptogenic Embolism) (3) trials—have now been completed. The trials did not report statistically significant differences between device closure and medical therapy. Meta-analyses using published aggregate data have generally reported results suggestive of a protective effect of closure on stroke or on the composite outcome of recurrent stroke, transient ischemic attack (TIA), or death, but the data have been contradictory as to the statistical significance of these associations (1–5). We performed a meta-analysis of individual participant data to better synthesize data from the 3 randomized trials (6–8).

Individual participant data meta-analysis holds several advantages over meta-analysis using aggregate results extracted from trial publications (9), including the ability to standardize outcome definitions and analyses across studies without any reliance on numerical approximations, which are often necessary when extracting data from publications. Additionally, access to participant-level data allows the use of statistical methods to address missing data, perform covariate-adjusted analyses (which often have greater power than unadjusted analyses for time-to-event outcomes [10–12]), and assess heterogeneity of treatment effects across subgroups.

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METHODS

We pre-specified our analytical plan and registered the study protocol with PROSPERO, the international prospective register of systematic reviews (CRD42014013895). The Tufts Medical Center Institutional Review Board approved the study.

We used individual participant data from 3 randomized trials that, to our knowledge, represent the totality of randomized evidence on percutaneously implanted PFO closure devices versus medical therapy in patients with PFO and cryptogenic stroke. The CLOSURE I trial (6) randomized 909 patients ages 18 to 60 years between 2003 and 2008 with a planned follow-up of 2 years. The RESPECT trial (7) randomized 980 patients in the same age range between 2003 and 2011. The trial's primary analysis was performed as planned after the 25th outcome event; the mean duration of follow-up was 2.6 years (range 0 to 8.1 years). The PC trial (8) randomized 414 patients age <60 years between 2000 and 2009. The mean duration of follow-up was 4.1 years in the closure group and 4.0 years in the medical therapy group.

received payments on the basis of clinical trial contracts for the number of subjects enrolled; and he serves as an unpaid consultant to Genentech advising on the design and conduct of the PRISMS trial (neither the University of California nor Dr. Saver received any payments for this voluntary service). Dr. Smalling receives funding from St. Jude Medical. Dr. Jüni is an unpaid steering committee or statistical executive committee member of trials funded by AstraZeneca, Abbott Vascular, Biotronik, Biosensors, Medtronic, The Medicines Company, and St. Jude Medical; has received research grants to his institution from AstraZeneca, Biotronik, Biosensors International, Eli Lilly, and The Medicines Company; and CTU Bern, which is part of the University of Bern, has a staff policy of not accepting honoraria or consultancy fees but is involved in design, conduct, or analysis of clinical studies funded by Abbott Vascular, Ablynx, Amgen, AstraZeneca, Biosensors, Biotronik, Boehringer Ingelheim, Eisai, Eli Lilly, Exelixis, Geron, Gilead Sciences, Nestlé, Novartis, Novo Nordisk, Padma, Roche, Schering-Plough, St. Jude Medical, and Swiss Cardio Technologies. Dr. Mattle is supported by grants to his institution from and served on the speakers bureau of Bayer, Biogen Idec, Boehringer Ingelheim, Bristol-Myers Squibb, Covidien, Daiichi-Sankyo, Genzyme, Merck-Serono, Neuravi, Novartis, Pfizer, Sanofi, Teva, St. Jude, and the Swiss Heart Foundation. Dr. Meier is supported by research grants to his institution and by personal speakers bureau honoraria from AstraZeneca, Bayer, Bristol-Myers Squibb, Boehringer Ingelheim, Daiichi-Sankyo, Eli Lilly, Pfizer, and St. Jude Medical. Dr. Thaler is a member of the national steering committees of 2 trials sponsored by St. Jude Medical (RESPECT, ACP Trial) and 1 trial sponsored by Coherex (WaveCrest). All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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