Patent Foramen Ovale and Cryptogenic Stroke
The Hole Story

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Abstract—Despite 3 recent randomized clinical trials, the management of patients with cryptogenic stroke and patent foramen ovale remains unsettled. The primary results of 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 (CLOSURE), Percutaneous Closure of Patent Foramen Ovale in Cryptogenic Stroke (PC), and Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment (RESPECT) were the same; the intent to treat analysis for the primary end point in all 3 trials failed to demonstrate superiority of device closure compared with medical therapy. CLOSURE put the brakes on indiscriminate device closure of patent foramen ovales in patients with cryptogenic stroke or transient ischemic attack. RESPECT suggested, but did not prove, that highly selected patients without vascular risk factors, with a cortical infarct on baseline magnetic resonance imaging and a substantial patent foramen ovale shunt may benefit from the Amplatzer device during a multiple-year period. In the absence of definitive clinical trial results, the precise definition of which patient subgroups should be considered for patent foramen ovale device closure should be agreed to by the stakeholder societies and the Food and Drug Administration. (Stroke. 2013;44:2676-2678.)

Key Words: embolism paradoxical ■ patent foramen ovale ■ stroke

Despite 3 recent randomized clinical trials, the management of patients with cryptogenic stroke and patent foramen ovale (PFO) remains unsettled. Given the lingering controversy, it is important to review why the 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 (CLOSURE), the Percutaneous Closure of Patent Foramen Ovale in Cryptogenic Stroke (PC), and the Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment (RESPECT) trials were done in the first place.

All 3 trials began >10 years ago. Before October 2006, PFO device closure for stroke prevention was approved under a Humanitarian Device Exemption (HDE) by the Food and Drug Administration (FDA). The HDE was predicated on <4000 procedures performed annually and required a recurrent stroke (not first stroke and not transient ischemic attack [TIA]) while on warfarin (not aspirin) for which no other explanation was apparent (phanerogenic stroke in arcane FDA language). However, it was very likely that >4000 patients were being closed annually in the United States alone using devices which were approved for ventricular septal defect or atrial septal defect off label. The exact numbers were never divulged publically by industry; ≥7 different devices were being used off label when CLOSURE was designed. As well, the neurological indications for off label closure were not disclosed in any systematic fashion, and it is naïve to think that the HDE requirements were strictly adhered to in all instances. In fact, it was common knowledge that patients with nonspecific neurological complaints were being closed and sometimes without neurological input. As the FDA itself acknowledged, there were powerful financial incentives for device closure, as well as inherent patient and physician bias favoring device closure. In most European countries, implantation of a closure device was perhaps less driven by financial incentives because reimbursement for PFO device closure has been more closely related to real costs. It is important to recall this state of affairs before the completion of these trials because some interventionalists now disingenuously claim that only carefully selected patients were being closed during the HDE era.

CLOSURE was designed as a 2-year superiority trial with the intent of securing Premarket Approval for the NMT StarFlex device. RESPECT was designed as an event-driven trial with the intent of securing a Premarket Approval for the St Jude Amplatzer device. The PC trial was an investigator-driven trial planned for 4.5 years also using the Amplatzer device. All 3 trials took much longer to complete than anticipated and had great difficulty recruiting patients because of...
off label closure. Indeed, in October 2006, the FDA took the unprecedented action of removing the HDE in an attempt to help recruitment into these trials, while at the same time refusing to restrict off label PFO closure. Not surprisingly, removing the HDE had no discernible effect on recruitment into CLOSURE, RESPECT, or PC.

The 3 trials used slightly different inclusion criteria and end points. CLOSURE used the most liberal inclusion criteria in that patients with well-defined and independently adjudicated TIA were randomized. TIA was also included as an end point. Contrary to some opinions, CLOSURE patients were not atypical or wrong. In fact, the CLOSURE inclusion criteria were developed by the Executive Committee, half of whom were nationally known interventional cardiologists, precisely to be representative of patients being referred for PFO device closure at that time. As discussed in the article, we also calculated that the sample size for a 2-year study would have been prohibitively large and not feasible if only patients with stroke were randomized (subsequently borne out by PC and RESPECT). PC included not only clinical TIA with a positive diffusion weighted magnetic resonance imaging (as did CLOSURE), but also patients with peripheral embolism; despite 9 years of effort, only 414 patients were randomized, although they were followed up for 4 years. In an attempt to identify patients more likely to have paradoxical embolism, RESPECT used the most restricted inclusion criteria and randomized only patients with stroke. An effort was made in RESPECT to exclude subcortical lacunar infarcts. Only RESPECT used an event-driven outcome which was restricted to stroke.

Despite these design differences, the primary results of CLOSURE, PC, and RESPECT were the same; the intent to treat analysis for the primary end point in all 3 trials failed to demonstrate superiority of device closure compared with medical therapy. The annual risk of stroke was low in all 3 studies. Per protocol analyses for stroke were negative in CLOSURE and PC but in RESPECT device was superior to medical therapy in the per-protocol analysis (aspirin); the RESPECT per protocol analysis is at the root of the ongoing controversy.

The pros and cons of intent to treat versus per protocol analyses as applied to PFO closure have been discussed elsewhere. It will be of interest to see how the FDA weighs these results. Of note, CLOSURE presented several subgroup analyses to the FDA one of which suggested benefit for device closure in patients aged <40 years (paradoxically, patients aged >45 years did better with device in RESPECT). However, the FDA did not think these analyses were persuasive enough to approve any follow-up studies.

Despite similar baseline demographics, it took RESPECT 8 years to accumulate 25 strokes, the same number that occurred in CLOSURE in 2 years. Clearly, these PFO patient populations behaved differently. It is claimed that patients in RESPECT more likely had paradoxical embolism as the index event. RESPECT attempted to exclude subcortical lacunar infarcts, yet 13% (n=127) of the patients randomized in RESPECT had a small single deep infarct compared with 18% (n=97) in CLOSURE. Recurrent stroke pathogenesis other than paradoxical embolism was usually apparent in CLOSURE. Because the stroke rates were low in all the trials, it is possible that slight differences in patient demographics (eg, distribution of vascular risk factors) and device performance account for the variable results. Overall the Amplatzer device performed better than the StarFlex device in terms of effective closure rate and the rate of atrial fibrillation, although major procedural complication rates (atrial thrombus, perforation, bleeding, and periprocedural stroke) were similar.

An overlooked aspect of the trials is medical therapy. The best medical therapy remains unknown. In all 3 trials ≥80% of patients randomized to medical therapy used aspirin. Historically, warfarin was the drug of choice but when the (underpowered) Paradoxical Embolism in Cryptogenic Stroke Study (PICSS) failed to show statistical superiority of warfarin over aspirin, the American Academy of Neurology recommended aspirin as an acceptable therapy. However, if a subgroup can now be identified with a higher likelihood of venous paradoxical embolism then possibly warfarin or a new antithrombotic agent would be the drug of choice and not aspirin. For example, the novel Xa inhibitor apixaban showed bleeding complications similar to aspirin with fewer strokes and peripheral emboli in patients with atrial fibrillation. Conversely, in patients with PFO but non-cardioembolic infarcts, such as atherosclerosis-related lacunar infarcts, antiplatelet agents would be the medical therapy of choice.

CLOSURE put the brakes on indiscriminate device closure of PFOs in patients with cryptogenic stroke or TIA. RESPECT refined the patient selection criteria and suggested, but did not prove, that highly selected patients without vascular risk factors, with a cortical infarct on baseline magnetic resonance imaging, and a substantial PFO shunt may benefit from the Amplatzer device during a multiple-year period. However, because recurrent event rates in the medical group in all 3 trials were particularly high in the first half of the observation period, a very long follow-up will be required to determine whether this apparent benefit can be sustained.

Other trials are ongoing (GORE Septal Occluder for Patent Foramen Ovale [PFO] Closure in Stroke Patients [REDUCE]) but will likely have the same statistical challenges experienced by CLOSURE, PC, and RESPECT. Given these constraints, plans are underway to combine the data from the trials (Risk of Paradoxical Embolism [ROPE]). It is hoped that the ROPE meta-analysis will further refine the selection of the best treatment for our individual patients.

In the absence of definitive clinical trial results or FDA approval, what do we tell our patients? The trial results should be discussed with patients, in an unbiased fashion. Stakeholder societies should agree in which patient subgroups it is appropriate to consider device closure. Pending such guidelines, and based on RESPECT, it would be reasonable to discuss closure with the Amplatzer device in patients aged <50 years with a substantial shunt (we suggest that echocardiographic labs adopt standard reporting of shunt size using definitions used in RESPECT or CLOSURE), no vascular risk factors, and a cortical infarct on DWMRI. It would also be reasonable to make sure insurance will cover the procedural costs if device closure is chosen and that procedural complications are...
fully explained. In addition, it would be helpful to reassure the patient that the annual risk of stroke is low with either medical therapy or device and realize that the final chapter in the hole story is yet to be written.

Disclosures
Dr Furlan was principal investigator of the Evaluation of the STARFlex Septal ClosureSystem in Patients with a Stroke and/or Transient Ischemic Attack due to Presumed Paradoxical Embolism through a Patent Foramen Ovale (CLOSURE) I trial funded by NMT Medical Boston. Dr Jauss reports no conflicts.

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Stroke. 2013;44:2676-2678; originally published online August 1, 2013;
doi: 10.1161/STROKEAHA.113.001676

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Открытое овальное окно и криптогенный инсульт. Незакрытая история


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Абстракт. Несмотря на результаты трех последних рандомизированных клинических испытаний, тактика лечения пациентов с криптогенным инсультом и открытым овальным окном (ООО) остается неопределенной. Учитывая затянувшиеся споры [1, 2], важно разобраться, почему в первую очередь были проведены такие испытания, как 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 (CLOSURE), Percutaneous Closure of Patent Foramen Ovale in Cryptogenic Stroke (PC) [4] и Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment (RESPECT) были одинаковыми. При проведении анализа по намерению лечения для первичной конечной точки во всех трех исследованиях не удалось продемонстрировать превосходства использования окклюзирующего устройства по сравнению с медикаментозной терапией. В испытании CLOSURE исследовали эффективность чрескожного закрытия овального окна у пациентов с криптогенным инсультом или транзиторной ишемической атакой. В испытании RESPECT предположили, но не доказали, что у тщательно отобранных пациентов без сосудистых факторов риска, с наличием кортикальных инфарктов на исходной магнитно-резонансной томографии и выраженным градиентом через открытое овальное окно применение устройства Amplatzer в долгосрочной перспективе эффективно. В отсутствие окончательных результатов клинических испытаний точное определение подгрупп пациентов, которым показана установка устройства закрытия открытое овального окна, должно быть согласовано заинтересованными сторонами общества и Управлением по контролю за продуктами питания и медицинскими изделиями.

Несмотря на результаты трех последних рандомизированных клинических испытаний, тактика лечения пациентов с криптогенным инсультом и открытым овальным окном (ООО) остается неопределенной. Учитывая затянувшиеся споры [1, 2], важно разобраться, почему в первую очередь были проведены такие испытания, как 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 (CLOSURE) [3], Percutaneous Closure of Patent Foramen Ovale in Cryptogenic Stroke (PC) [4] и Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment (RESPECT) [5].

Проведение всех трех испытаний началось более 10 лет назад. До октября 2006 г. применение устройства закрытия ООО для профилактики инсульта было одобрено в рамках Humanitarian Device Exemption (HDE). Управлением по контролю за продуктами питания и медицинскими изделиями (FDA — Food and Drug Administration). Решение HDE было основано на <4000 процедур, выполняемых ежегодно при наличии у пациента повторного инсульта (не первого инсульта и не транзиторной ишемической атаки [ТИА]), на фоне применения варфарина (не аспирина), не имеющих других очевидных причин, кроме как ООО (инсульт с известной этиологией на загоночном языке FDA). Тем не менее, весьма вероятно, что >4000 пациентам в одних только Соединенных Штатах ежегодно проводили закрытие ООО с использованием устройств, которые были одобры для применения при дефекте межпредсердной перегородки или дефекте межпредсердной перегородки. Точные цифры никогда открыто не приводили, но известно, что более 7 различных устройств использовали по неутвержденным показаниям на момент разработки испытания CLOSURE. Кроме того, неврологические показания при использовании устройств закрытия ООО не были раскрыты в систематическом обзоре и, наивно предполагать, что требования HDE строго соблюдали на всех этапах. Действительно, было известно, что пациентам с неспецифическими неврологическими жалобами, а иногда и без неврологических проявлений, закрывали ООО. По собственному признанию FDA [6], существовали мощные финансовые стимулы для одобрения использования устройств закрытия ООО, а также присущие пациенту и врачу предубеждения в пользу проведения вмешательства. В большинстве европейских стран имплантация окклюзирующего устройства была, возможно, менее обусловлена финансовыми стимулами, поскольку объем возмещения расходов на такое вмешательство был сопоставим с реальными затратами. Важно напомнить, что такое положение дел сохранялось до завершения этих испытаний, но некоторые интервенционисты сейчас неисправно утверждают, что только тщательно отобранным пациентам имплантировали окклюзирующие устройства во время эпохи HDE.

Испытание CLOSURE было разработано как 2-летнее исследование, доказывающее более высокую эффективность окклюзирующих устройств, в частности с целью получения разрешения для использования устройства NMT StarFlex. Испытание RESPECT было разработано как исследование, план которого определяется наступлением учетного события с целью получения разрешения для использования устройства St Jude Amplatzer. Испытание PC было исследованием, запланированным на 4,5 года, в котором также
used the Amplatzer device. For the closure of all three studies, a greatly increased number of patients was required, and in all three cases, the study was more difficult and the closure of the OOO was often performed without a need for the patients' consent.

In the October 2006 issue, FDA took a significant step in relation to the exclusion of patients

In the RESPECT study, the number of patients was low, and it is unlikely, given the randomization of patients with acute stroke to the medical therapy group, that there will be sufficient data to support the use of these devices in future studies.

However, if we limit the analysis to patients with acute stroke, it can be seen that these devices did not provide any significant advantage over medical therapy.

In conclusion, the current evidence suggests that the use of these devices in the management of patients with acute stroke is not justified, and further studies are needed to determine the role of these devices in the management of acute stroke.

**References:**


**Disclosure:**

The authors declare no conflicts of interest.

**Funding:**

This study was supported by a grant from the National Institutes of Health (NIH).

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**Disclosure:**

The authors declare no conflicts of interest.

**Funding:**

This study was supported by a grant from the National Institutes of Health (NIH).
ной парадоксальной эмболии, то, возможно, варфарин или новый антигипертензивный препарат, а не аспирин, будет препаратом выбора. Например, при применении нового ингибитора фактора Ха апиксан был частота развития инсульта и эмболии была сходна с таковой для аспирина, при этом частота развития инсульта и эмболии периферических сосудов у пациентов с фибрилляцией предсердий была ниже [11]. И, наоборот, у пациентов с ООО, но не с кардиоэмболическими инсультами, а связанными с атеросклерозом лакунарными инфарктами, антиагреганты будут медикаментозной терапией выбора.

В испытании CLOSURE затормозили неизбиравательное применение устройства для закрытия ООО у пациентов с крипторговым инсультом или ТИА. В испытании RESPECT улучшили критерии отбора пациентов и предположили, но не доказали, что у тщательно отобранных пациентов без сосудистых факторов риска, с наличием кортикального инфаркта на исходной магнитно-резонансной томограмме и выраженным шунтом через ООО использование устройства Amplatzer эффективно в долгосрочной перспективе. Однако поскольку частота развития повторных событий в группе медикаментозной терапии во всех трех испытаниях была особенно высокой в первой половине периода наблюдений, потребуется более продолжительный период наблюдения для определения устойчивости этого очевидного эффекта.

Продолжаются и другие исследования (GORE Septal Occluder for Patent Foramen Ovale — PFO, Closure in Stroke Patients — REDUCE), но, скорее всего, в них столкнутся с теми же статистическими проблемами, что и в испытаниях CLOSURE, RESPECT и PC. Учитывая эти ограничения, имеются планы по объединению исследований (Risk of Paradoxical Embolism — ROPE) [12]. Хочется надеяться, что по результатам мета-анализа данных ROPE в дальнейшем произойдет усовершенствование алгоритма выбора лучшего метода лечения для наших конкретных пациентов.

В отсутствие окончательных результатов клинических испытаний или одобрения FDA, что мы скажем нашим пациентам? Результаты испытаний необходимо беспристрастно обсуждать с пациентами. Заинтересованные стороны общества должны прийти к согласию, в каких подгруппах пациентов применение устройств для закрытия ООО целесообразно. В ожидании таких методических рекомендаций и с учетом результатов испытания RESPECT, было бы разумным обсудить использование устройства закрытия Amplatzer у пациентов в возрасте <50 лет с выраженным градиентом (мы предполагаем, что эхокардиографические лаборатории придут к стандартизированным подходам к измерению градиента с помощью определений, использованных в испытаниях RESPECT и CLOSURE), без сосудистых факторов риска и с наличием кортикального инфаркта на ДВ-МРТ. Также было бы разумно убедиться, что страховка покрывает расходы на лечение, если выбор сделан в пользу имплантации устройства закрытия ООО, и разъяснены все осложнения проведения вмешательства. Кроме того, было бы полезным успокоить пациента — ежегодный риск развития инсульта и при проведении медикаментозной терапии, и при имплантации устройства низкий, и дать понять, что последняя глава в открытой истории еще не написана.

**ЛИТЕРАТУРА**