Clinical Trial Perspective

CLINICAL INVESTIGATION

Design of patent foramen ovale closure trials: the importance of patient-reported outcomes

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Clinical trials assessing the safety and comparative effectiveness of catheter-delivered device closure of patent foramen ovale are active in multiple common disorders including migraine headaches and cryptogenic stroke. Trials began with multiple single-center studies using historical controls, a few prospective studies and, more recently, randomized clinical trials sponsored by the medical device industry in order to gain regulatory approval. While numerous problems have frustrated investigators and sponsors of identifying the appropriate target population and suboptimally performing devices, during the current period of redesigning future trials there has been a new focus on incorporating better measures of outcomes. The need for, and value of, patient-report outcomes are discussed in this article. While subjective symptoms have been used as clinical end points in some studies the broader application of patient-report outcomes is necessary to understand treatment differences more comprehensively and gather data that will assist in clinical decision making and the determination of patient preferences. These issues are discussed in the context of new clinical trials but also in the post-approval period when longitudinal outcomes must be studied over a prolonged period of time with these chronic disorders with disabling manifestations, high personal socioeconomic burdens, and large societal costs.

Keywords: clinical trial design • medical devices • migraine • outcomes • patent foraman ovale • patient-reported outcomes • stroke

The goals of recently reported and ongoing clinical trials of patent foramen ovale (PFO) closure have been, broadly speaking, to improve the care of patients with different clinical syndromes that are thought to be related to the presence of a PFO. The underlying premise has been that the PFO is causative, not simply associated or incidental, and by closing the PFO the patient's condition should improve. The 'proof of principle' has been accepted by many but the scientific rigor of the proof has been questioned with calls for randomized trials and pooling of data to create a large registry [1]. Clinical trials have not focused on understanding pathophysiology but rather device efficacy and safety for US FDA approval. In the USA there are no devices approved for PFO closure, off-label closure has become common practice and a controversial issue, and enrollment in randomized trials has been slow [2,3]. Recent efforts to address these issues, better understand pathophysiology, and improve methodology for future trials have included a PFO Summit organized by patients [101].

Clinical trials of PFO closure have included many nonrandomized trials that have been positive, specifically those treated with a device that had superior outcomes. The nonrandomized trials and case studies have been numerous but uncontrolled, retrospective and rarely prospective, single-center reports on the

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efficacy and safety of PFO closure to prevent recurrent stroke, to reduce the migraine burden and to alleviate hypoxemia [4–10].

Randomized trials and their status are listed in Table 1. To date only one randomized trial has been published and that was performed in England (MIST) [11]. Another randomized trial has been publically presented [102] but not yet published (CLOSURE I). Both trials failed to meet their primary end point and have been roundly criticized for inadequate rigor in patient selection, exclusion of high-risk patients more likely to benefit, high rates of device- and procedure-related complications, high frequency of incomplete PFO closure, inadequate statistical power, inappropriately short-term follow-up, and lack of echocardiographic core laboratory with standardized methodology [6,8].

These medical device trials must show efficacy and safety. Defining measures of efficacy and safety relevant to patient care and to patients are self-evident and obvious but need to be prioritized over other measures that can be used. Measures of device performance in terms of completeness of closure of the PFO are needed but the most valuable outcomes to be studied are those that measure both the clinical benefit to the patient as well as any potential harm. Alternative treatments exist for these conditions and the outcomes of patients in a PFO closure device arm must be compared with patients receiving these alternative treatments. The US FDA has demanded that all randomized trials of PFO closure devices demonstrate superiority over current therapy. The outcomes included in determination of superiority have included subjective patient-centric metrics in migraine trials but not in trials assessing the impact of PFO closure in patients with stroke and hypoxemia. Some traditional clinical measures of PFO closure, such as detailed echocardiographic assessment of device performance, may have minimal relevance to the day-to-day functioning of patients with chronic diseases, such as migraine and hypoxemia caused by intracardiac shunting via a PFO.

The use of patient-reported outcomes

The use of patient-centric measures of outcomes or patient-reported outcomes (PROs) should reveal treatment differences in clinically meaningful outcomes but potentially can also be used to study the burden of the disease [12]. The impact on the patient's physical and psychological state, activity level, employment and other issues, such as pregnancy, are broader outcomes on a patient's life often poorly understood, not usually collected during clinical trials and not represented in disease management guidelines. Yet, it is often these broader impacts on a patient's life that are central to a patient deciding between therapies. Major implications for non-medical costs associated with different treatment strategies can drive a patient's choice. An example is the airline pilot who has a stroke with complete recovery, a PFO is found and is implicated as playing a causative role, and the pilot will lose his or her pilot's license and job unless the defect is closed. The negative implications of not being able to undergo PFO closure are clearly defined and the patient's decision making is clearly influenced by this non-medical issue.

Patient-reported outcomes have become important in the assessment of chronic disease and their treatments including non-cardiac conditions, such as

Table 1. Randomized trials of patent foramen ovale closure.

Trial	ClinicalTrials.gov identifier and sponsor	Condition studied	Status 2011
RESPECT	NCT00465270; AGA Medical Corporation	Cryptogenic stroke	Recruiting
CLOSURE	NCT00201461; NMT Medical	Cryptogenic stroke and TIA	Completed, presented, but not yet published
REDUCE	NCT00738894; WL Gore & Associates	Cryptogenic stroke	Recruiting
PC Trial	NCT00166257; initiated by Bern University Hospital and sponsored by AGA Medical	Cryptogenic stroke	Recruitment completed and currently completing follow-up
PREMIUM	NCT00355056; AGA Medical Corporation	Migraine	Recruiting
ESCAPE	NCT00267371; St Jude Medical	Migraine	Stopped due to poor enrollment
MIST 2	NCT00283738; NMT Medical	Migraine	Stopped due to poor enrollment and sponsor finances
Coherex FlatStent EF PFO Migraine Registry	NCT01280578; Coherex Medical	Migraine	Not yet recruiting
PRIMA PFO Migraine Trial	NCT00505570; AGA Medical Corporation	Migraine	Recruiting

TIA: Transient ischemic attack.
Data taken from [104].

cancer, neurodegenerative disorders, depression and arthritis, but also cardiac conditions including congestive heart failure, atrial fibrillation and coronary artery disease [13]. The use of PROs in cardiovascular research has been thought to be lagging but increasingly used in more recently designed trials.

The use of PROs in clinical trials of PFO closure have appeared in some but certainly not all trials. There are differences in the use of PROs in clinical trial design of reported and ongoing trials of PFO closure in two major patient populations: patients with cryptogenic stroke and patients with migraine. In migraine–PFO closure trials PROs are central since the major symptom is self-reported and subjective in nature (i.e., a migraine headache). There remains no objective measures of migraine that can complement these PROs. In Table 2 some of the common PROs instruments used in migraine trials are listed and include those that are disease specific as well as broader measures of quality of life.

In Table 3 the results of the MIST trial are replicated with a focus on measures that try to quantify the burden of migraine headache in terms of frequency, duration, severity and impact. Despite being a negative trial, MIST stands out as the first completed and published randomized trial of PFO closure for any condition. Randomized migaine trials have included a sham procedure for those randomized to the control, that is, a no PFO closure device arm. This is part of the blinding design for both patients and their migraine doctors. This has been necessary because of the known high placebo response rate in medication trials for migraine.

Table 2. Examples of patient-reported outcome tools used in migraine–patent foramen ovale closure trials.

Instrument	Description	Ref.
Headache impact test	Disease-specific disability scores	[14]
MIDAS questionnaire	Disease-specific disability scores	[15]
Migraine-specific QOL	Disease-specific QOL	[16]
SF-36v2 QOL questionnaire	Generic QOL	[17]

MIDAS: Migraine disability assessment; QOL: Quality of life; SF-36: Short-form 36.
Adapted from [11].

What needs to be included in optimally designed PROs?

The specific types of PROs needed for the optimally designed PFO closure trials need to build on the first generation trials that used more traditional measures. Broader measures of health-related quality of life, and general psychological and physical state should be identified as well as disease-specific assessments of functional state and symptoms.

New therapies for migraine should be evaluated as to whether they succeed in allowing a reduction of medications and reduce the frequency and severity of secondary mental illness, such as depression. Thus PROs must capture the risks associated with the migraine medications as well as the psychological (suicide/depression) disability associated with chronic and episodic migraine. Current trials that look at outcomes over brief periods of time may better capture procedure complications and underestimate ongoing risks associated with medications and secondary depression.

In stroke trials there has been a lack of emphasis on PROs with priority given to traditional measures of death and recurrent stroke rates. Other patient-centric outcomes are yet to be defined with a collection of data that accurately represent the patient experience with device closure or medical therapy. Next-generation trials should employ tools to document physical disability from recurrent stroke and a quality of life tool that documents PROs, such fatigue and emotional distress. Long-term complications with devices, medications, such as warfarin, and other burdens of different treatment strategies need data prospectively gathered and analyzed in the context of patent experiences not only traditional serious adverse effects.

Table 3. Efficacy analysis in MIST using patient-report outcomes.

Measures of patient-reported outcomes	Implant (n = 64)		Sham (n = 70)	
	Baseline	Analysis phase	Baseline	Analysis phase
Patients with no migraine attacks, n	0	3	1	3
Frequency of migraine attacks over a month, mean ± SD	4.88 ± 2.43	3.26 ± 1.82	4.552 ± 0.18	3.552 ± 0.14
Total MIDAS score, median (range)	40 (3–108)	16 (0–270)	34 (2–189)	18 (0–240)
Headache days over 3 months (MIDAS),median (range)	26 (0–70)	19 (0–90)	30 (5–80)	21 (0–80)
HIT-6 total score, mean ± SD	67 ± 4.6	60 ± 10	66 ± 4.9	59 ± 0.8
Total migraine headache days over a month, median (range)	6.0 (1–17.0)	3.8 (0–13.3)	5.0 (0–20.0)	3.7 (0–16.7)

HIT-6: Headache impact test; MIDAS: Migrain disability assessment.
Adapted from [11].

The lifestyle impacts and risks of PFO closure versus medical treatments are often more complex and individualized on the patient level. For example the impact and risks of warfarin therapy versus PFO closure may be quite different when considering women of childbearing age, physical laborers at risk of injury, participants in sports with high-accident risk, scuba divers, astronauts, patients undergoing noncardiac surgeries associated with palpable rates of embolism, including air embolism, patients with comorbidities increasing bleeding risks and genetic factors determining warfarin dosing difficulties.

For trials in migraine, stroke and other conditions associated with PFO the PROs also need to address the broader issues of costs rather than the narrowly defined medical costs that currently dominate the trials addressing costs. Indirect costs of stroke and migraine are often over 50% of the total cost and are dominated by the reduced productivity of survivors, lost earnings and secondarily long-term informal care giving. These patient and family-centric outcomes are not captured in comparative effectiveness/safety analysis. Further studies that focus on long-term and indirect expenditures are essential to assess the impact of any new preventative treatments on total stroke and migraine costs.

The NIH Patient-Reported Outcomes Measurement Information System

The Patient-Reported Outcomes Measurement Information System (PROMIS) initiative is relevant to future clinical trials of PFO closure [103]. PROMIS is a component of the NIH Roadmap for Medical Research and has the goal to improve the reporting and quantification of changes in PROs. PROMIS is developing new ways to measure PROs, such as pain, fatigue, physical functioning, emotional distress and social role participation that have a major impact on quality of life across a variety of chronic diseases.

Other aspects of PROMIS are appealing to apply in PFO-related research. Both written and internet accessible patient input is possible using an established infrastructure for data acquisition and tabulation. Both improved clinical trial efficiency and data validity have been shown with PROMIS and existing PROs. Conducting validation studies on new PROs developed for the PFO field would be possible in large-scale clinical trials in a variety of clinical populations.

Additional future directions

Clinical trials designed for FDA device approval often do not adequately address the issues that arise when a new therapy emerges into routine clinical care. Clinical decision making is more complex and individualized to the patient. Patient choices between treatment options are often major driving forces but have not been studied in the PFO field. Thus the development of new PROs and collection of PROs data for analysis not only improves clinical trials designed for a regulatory process but will add valuable information to bring to patients and providers. Furthermore, postapproval studies should be mandated that provide longitudinal patient-centered outcome data that will augment that derived from the pivotal trial. With this focus of patient-centric issues there can be more sophisticated approaches to practice guidelines that not only incorporate traditional evidence but also incorporate the need to individualize treatment decisions with a better understanding of patient preferences.

Future perspective

PRO are expected to be increasingly used in clinical trial design as general and disease-specific measures are developed and validated. Furthermore advances in commercial IT infrastructure and user-friendly interfaces will enable internet-based input of PRO data from patients in their homes and other locations. PROs will not only have a greater role in clinical trials but should increasingly be used to make regulatory and health policy decisions.

Financial & competing interests disclosure

JD Carroll is a consultant for AGA Medical Corporation and serves on the steering committee for the clinical trial RESPECT sponsored by AGA Medical Corporation. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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Executive summary

- Clinical trials assessing the safety and effectiveness of device closure of patent foramen ovale are active in multiple common disorders, including migraine headaches and cryptogenic stroke.
- Patient-report outcomes are discussed in this article as being important as clinical end points in future clinical trials in studying novel treatments, such as patent foramen ovale closure.
- Patient-report outcomes also provide a framework that will assist after new therapies become approved when there is the need to facilitate clinical decision making with the determination of patient preferences.

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