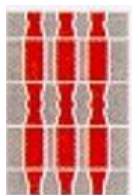




**Accordo di collaborazione tra Ministero della Salute
- Direzione Generale dei dispositivi medici, del
Servizio farmaceutico e della Sicurezza delle cure
e
l'Agencia Nazionale per i Servizi Sanitari Regionali**

**Rapid HTA Report - Implantable devices for the
closure of patent foramen ovale (PFO) in adults**



Regione Umbria

Implantable devices for the closure of patent foramen ovale (PFO) in adults

– Rapid HTA report –

July 2013

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Prefazione

Il concetto di “rapid assessment” di una tecnologia sanitaria non è nuovo. Per quanto riguarda i prodotti farmaceutici, per i quali gli Stati membri dell’UE utilizzano l’HTA come parte del processo decisionale, sono stati chiaramente definiti dei limiti temporali, ma parlando di altre tecnologie sanitarie i confini sono molto sfocati. Seguendo la logica dell’ottimizzazione delle risorse e auspicando un precoce utilizzo dei risultati dell’assessment all’interno dei processi decisionali, si rendono urgenti misure di definizione e intervento anche in questi ambiti. Naturalmente, è necessario affrontare alcuni inconvenienti che caratterizzano qualsiasi valutazione rapida, come la perdita di dettagli e il potenziale rischio di minore affidabilità del prodotto.

Agenas ritiene che il programma italiano di HTA potrebbe beneficiare di linee guida chiare, che raggiungano un certo consenso, su come condurre una valutazione rapida e sul suo significato pratico.

Per questi motivi Agenas ha sviluppato, per conto del Ministero della Salute, una breve relazione per descrivere le pratiche attuali in ambito di rapid HTA e ha prodotto la prima esperienza italiana di rapid HTA report sui dispositivi utilizzati per la chiusura del forame ovale pervio (PFO). Questo lavoro è frutto della ormai instaurata collaborazione con alcune delle regioni italiane unite nel network RIHTA (Rete Italiana di Health Technology Assessment) e del confronto con esperti locali e revisori internazionali.

Fulvio Moirano

Direttore Generale, Agenas



Foreword

The concept of “rapid assessment” of a health technology is not new. With respect to the medicinal products, for which EU Member States use HTA as part of the decision-making process, time limits have been clearly defined but talking about “non-drug” technologies the borders are quite blurred. Following the rationale of resource-saving and the possibility of inputting in real-time into the decision-making process, clarification and implementation in this field seem to be urgent. Of course, it is necessary to face some drawbacks of any rapid assessment, such as loss of detail and perhaps lower reliability of the product.

Agenas believes that the Italian HTA programme could benefit from clear guidance on how to conduct a rapid assessment to achieve some consensus on the practice and its practical meaning.

For this reasons Agenas developed a short report to describe current practices in rapid HTA and produced the first Italian experience of rapid HTA report on the devices used for the closure of the patent foramen ovale (PFO) on behalf of the Italian Ministry of Health. Such report comes from the established collaboration with some of the Italian regions joined in the RIHTA network (Rete Italiana di Health Technology Assessment) and from consultation with local experts and international reviewers.

Fulvio Moirano

Executive Director, Agenas



Sommario

La chiusura percutanea del forame ovale pervio (*patent foramen ovale, PFO*) è una delle opzioni di trattamento per quei pazienti nei quali è stato identificato un PFO e che soffrono di attacchi ischemici transitori, ictus o emicrania criptogenetica persistente. Ad oggi nessuno degli occlusori cardiaci per il trattamento del PFO marcati CE è stato approvato dalla Food and Drug Administration (FDA). Sul mercato italiano ci sono 12 diversi occlusori per il PFO e si stima che nel 2012, siano state eseguite 2.541 procedure di chiusura del PFO. Il prezzo del singolo occlusore può variare da 5.535 a 6.868 Euro (IVA esclusa) e l'impatto stimato sul bilancio del Servizio Sanitario Nazionale (SSN) ha raggiunto i 15 milioni di Euro nel 2012. Abbiamo effettuato una revisione sistematica e una meta-analisi di studi clinici comparativi in cui gruppi di pazienti con PFO che manifestavano attacchi ischemici transitori, ictus o emicrania criptogenetica persistente sono stati sottoposti a chiusura percutanea del PFO e confrontati con gruppi di pazienti trattati con cure tradizionali. Abbiamo incluso 6 studi primari: 5 studi clinici controllati (*controlled clinical trial, CCT*), e 1 studio randomizzato controllato (*randomised controller trial, RCT*). I 5 CCT mostravano che la chiusura percutanea del PFO era migliore del trattamento medico relativamente alla riduzione di ictus, di attacchi ischemici transitori e alla combinazione di entrambi. Tuttavia, la scarsa qualità metodologica e l'eterogeneità degli studi hanno influito pesantemente sull'attendibilità e sulla generalizzabilità dei risultati di questa revisione sistematica. La stratificazione dei dati degli studi per tipo di dispositivo ha provocato una ulteriore perdita di significatività e frammentazione della base di evidenza a noi disponibile. Emergono inoltre questioni legate alla sicurezza della tecnologia dato che l'unico RCT incluso nella revisione riportava il 4,7% di eventi avversi riconducibili direttamente al dispositivo o alla procedura. Si raccomanda la pianificazione di studi clinici randomizzati, multicentrici e sufficientemente dimensionati che tengano in particolare considerazione l'adeguata selezione dei pazienti e il rapporto rischio/beneficio della procedura.

Sintesi in italiano

La chiusura anatomica del forame ovale è incompleta in approssimativamente un adulto su quattro. In assenza di specifiche condizioni cliniche, la presenza di un forame ovale pervio (*patent foramen ovale, PFO*) deve essere considerata una variante anatomica normale e non un segno patologico^[4]. Tuttavia, è stata suggerita un'associazione tra PFO e ictus embolico cerebrale^[1] come anche l'associazione tra PFO e emicrania cronica^[2]. Assieme alla terapia medica e alla chiusura chirurgica, la chiusura percutanea del PFO è una delle opzioni di trattamento per i pazienti con PFO che soffrono di attacchi ischemici transitori, ictus o emicrania criptogenetica persistente. La procedura è minimamente invasiva e viene eseguita dopo ecocardiografia e esame fluoroscopico per determinare la dimensione e il tipo di occlusore più adatto al paziente, così come le caratteristiche anatomiche del difetto^[1].

Dalla loro prima introduzione, diversi dispositivi per la chiusura del PFO sono stati sviluppati e marcati CE. Tuttavia, nessuno di questi dispositivi è stato ancora approvato dalla FDA e negli Stati Uniti la procedura di chiusura percutanea del PFO viene eseguita *off-label*, utilizzando dispositivi approvati per altre indicazioni^[4].

Attualmente in Italia 7 produttori offrono 12 diversi dispositivi per la chiusura del PFO e si stima che nel 2012, siano state eseguite 2.541 procedure di chiusura del PFO^[14]. Il prezzo del singolo occlusore può variare da 5.535 a 6.868 Euro (IVA esclusa) e l'impatto stimato sul bilancio del Servizio Sanitario Nazionale (SSN) ha raggiunto i 15 milioni di Euro nel 2012.

Abbiamo effettuato ricerche bibliografiche per identificare studi comparativi in cui gruppi di pazienti con PFO che manifestavano attacchi ischemici transitori, ictus o emicrania criptogenetica persistente erano stati sottoposti a chiusura percutanea del PFO e confrontati con gruppi di pazienti trattati con cure tradizionali (ad esempio, terapia medica, sintomatica o secondariamente preventiva, come anticoagulanti o fibrinolitici). Gli studi eligibili sono stati estratti ed è stata valutata la loro qualità metodologica.

Dall'iniziale lista di 197 citazioni abbiamo identificato: 3 revisioni sistematiche^[17-19], 2 report di horizon scanning^[20,21] e 6 studi primari. Di questi ultimi, 5 erano *controlled clinical trial, CCT*^[22,24-27] e uno era *randomised controlled trial, RCT*^[28].

Abbiamo effettuato una meta-analisi degli studi primari e riscontrato che la chiusura del PFO aveva ridotto significativamente l'incidenza di ictus in un solo studio^[25], e l'incidenza di attacchi ischemici transitori in due studi^[22,25]. L'incidenza della combinazione di attacchi ischemici transitori, ictus, e mortalità appariva ridotta in un solo studio^[27]. Combinando i 5 studi CCT, è

emerso che la chiusura percutanea del PFO era migliore del trattamento medico nel ridurre attacchi ischemici transitori, ictus o la combinazione di entrambi, anche se in presenza di eterogeneità significativa. La scarsa qualità metodologica e l'eterogeneità degli studi hanno influito pesantemente sull'attendibilità e sulla generalizzabilità dei risultati di questa revisione sistematica. La stratificazione dei dati degli studi per tipo di dispositivo ha provocato un'ulteriore perdita di significatività e frammentazione della base di evidenza a noi disponibile. Il profilo di sicurezza della procedura è stato valutato esaminando gli eventi avversi gravi riportati negli studi: l'unico RCT incluso nella nostra revisione^[28] riportava il 4,7% di eventi avversi riconducibili direttamente al dispositivo o alla procedura.

In conclusione, date le evidenze di efficacia e sicurezza disponibili, sosteniamo che l'impiego clinico della tecnologia in questione, in special modo per la prevenzione secondaria di eventi cardiovascolari, non possa prescindere dalla pianificazione di studi clinici randomizzati, multicentrici e sufficientemente dimensionati che tengano in particolare considerazione l'adeguata selezione dei pazienti, il rapporto rischio/beneficio della procedura e che includano elementi utili per successive analisi economiche una volta accertato e definito il profilo di efficacia e sicurezza del trattamento.

Abstract

Percutaneous closure of patent foramen ovale (PFO) is one of the treatment options for patients with PFO suffering from transient ischemic attacks (TIA), cryptogenic stroke or persistent migraine. At time of writing, none of the several CE marked PFO closure devices have been approved by the US Food and Drug Administration (FDA). Currently there are 12 different PFO closure devices available on the Italian market and it has been estimated, that in 2012, 2,541 PFO procedures were performed. The price for a single PFO closure device ranged from € 5,535 to € 6,868 (excluding VAT), resulting in an estimated impact on the Servizio Sanitario Nazionale (SSN) budget of € 15 millions in 2012. We performed a systematic review and a meta-analysis of clinical studies in which patients with PFO suffering from TIAs, cryptogenic stroke or persistent migraine underwent insertion of percutaneous devices for the closure of PFO were compared to patients treated by usual care. We included 6 primary studies: 5 controlled clinical trials (CCT), and 1 randomised controlled trial (RCT). In the 5 CCTs we found that percutaneous closure of PFO was better than medical treatment in reducing stroke, TIA or the combination of both even if in the presence of significant heterogeneity. Poor methodological study quality and heterogeneity undermines our confidence in the results of this review. We attempted to stratify by device type the overall pooling of study data but it resulted in loss of power and further fragmentation of the evidence base. The safety profile of the technology appears to be of concern, in that 4.7% of device- or procedure-related serious adverse events were observed in the only RCT included. We recommend that large multicentre, sufficiently powered, and properly randomised trials be carried out in Europe with particular attention to patient selection and risk/benefit ratio.

1. Technology and current treatments

1.1 Clinical problem

The foramen ovale is a hole in the wall that divides the two upper chambers of the heart at the level of the atria. The hole is present in the heart of a developing foetus, but normally closes up soon after birth. If it fails to close it is known as a patent foramen ovale (PFO). For patients with a PFO as an isolated finding, no special treatment is given, as in most people, the persistence of a PFO does not cause any complications. However, there have been a number of studies suggesting an association between PFO and cerebral embolic stroke. The presence of a PFO increases the chance of thromboemboli crossing from the right side into the left side of the heart, and from there into the arterial circulation system, which may block blood vessels and cause serious problems such as a stroke^[1]. PFO is thought to be associated with chronic migraines and PFO closure aims to prevent the recurrence of such events^[2].

1.2 Epidemiological data

A pooled analysis of autopsy studies yielded an average prevalence of PFO of 26% (range 17% to 35%; the highest prevalence was in subjects younger than age 30 years)^[3]. As anatomic closure is incomplete in approximately 1 of every 4 adults, in the absence of specific clinical conditions, PFO should be considered a normal anatomic variant and not a pathological finding^[4].

1.3 Treatments and clinical pathways

Transoesophageal echocardiography (TOE) is used for the diagnosis of a PFO and delineation of its morphologic details^[5].

Treatment options include medical treatment with anticoagulation therapy, surgical closure (open heart surgery), and percutaneous closure^[1].

1.4 Description and regulatory status of the technology

Percutaneous closure of PFO involves making a small incision in the groin under intravenous sedation. A guide wire and delivery sheath is then introduced into the vein and passed into the heart across the PFO. A closure device (also known as occluder) which may resemble a tiny

two-ended umbrella is then inserted through the defect via the delivery sheath. The device is inserted through the flap and released, closing the PFO. Echocardiography and fluoroscopic guidance are used to determine the size and position of the defect and to place the occluder^[1].

The first report of percutaneous closure of PFO was published in 1992^[6]. Since then, several devices have been developed, refined, and CE marked. At time of writing, none of the available PFO closure devices have been approved by the FDA and the procedure in the United States is performed off-label, using devices approved for other indications^[4].

This rapid HTA report focuses on the devices commercially available in Italy and registered within the General Repertory of medical devices (RDM).

2. Report's objectives: policy and research questions

This rapid HTA report has been developed to answer the following questions:

Policy question: what is the optimal use of the devices for PFO closure?

Research question: Are the devices used for the closure of PFO safe and effective?

3. Context overview

3.1 PFO closure devices on the Italian market

A search of the RDM was conducted on February 2013 using the National Classification of Medical Devices (CND) code associated with PFO closure devices: "P07040303 - PROTESI PER FORAMI OVALI PERVI E PER DOTTO DI BOTALLO" (the Global Medical Device Nomenclature, GMDN, code is "45418 - Cardiac Occluder"). Results of this search and those of searches on the internet (i.e., manufacturers' websites) are summarised in Table 3.1.

Table 3.1: Devices for the closure of the patent foramen ovale (PFO) commercially available in Italy as of 1st February 2013 and registered within the General Repertory of medical devices (RDM).

Manufacturer	Device name
AGA MEDICAL CORPORATION*	AMPLATZER PFO OCCLUDER
CARDIA INC.	ULTRASEPT PFO
CARDIA INC.	ATRIASEPT II
COHEREX MEDICAL INC.	COHEREX FLATSTENT EF
LIFETECH SCIENTIFIC CO., LTD.	CERA PFO CLOSURE SYSTEM
OCCLUTECH GMBH	FIGULLA FLEX PFO
OCCLUTECH GMBH	FIGULLA FLEX II PFO
OCCLUTECH GMBH	FIGULLA PFO OCCLUDER N
OCCLUTECH GMBH	FIGULLA PFO OCCLUDER
ST. JUDE MEDICAL	PREMERE PFO OCCLUDER
STARWAY MEDICAL TECHNOLOGY INC.	CARDI-O-FIX PFO OCCLUDER
W.L.GORE & ASSOCIATES INC.	GORE HELEX SEPTAL OCCLUDER

*AGA Medical Corporation is part of St. Jude Medical since 2010.

Source: Data from General Repertory of medical devices and internet searches performed by Agenas.

3.2 Technical description of the devices identified

In alphabetical order by manufacturer:

CARDIA INC.

Intrasept, Atriasept I, Atriasept II, and Ultrasept

Cardia's PFO closure devices represent different generations (i.e. seven) of the same basic concept^[7]. The pioneer device was the Intrasept, the first occluder device employing the articulating sail concept. It was constructed on a nitinol and titanium frame covered on the right and left atrial sides with polyvinyl alcohol (PVA) sails. The sails are designed to inhibit

the flow of blood between the atria. Atrisept II and Ultrasept are the sixth and the latest generation, respectively and are the only Cardia Inc PFO closure devices registered on the RDM. They received CE mark in 2008 and 2009 respectively. They are circular, low profile, fully retrievable, repositionable, and available for transcatheter closure of the PFO and ASD. In particular, in the Ultrasept device, the right atrial struts and end caps have been completely replaced with a second rounded sail^[8].

COHEREX MEDICAL INC.

Coherex FlatStent EF

The Coherex FlatStent EF received the CE mark in 2009. It has an expandable stent design and is made with a polymer filling to aid endothelialisation and includes radio-opaque markers to guide deployment. The device is retrievable and redeployable and has the theoretical advantage of an “in-tunnel” design that may reduce complications including left atrial device surface thrombus formation and device perforation. The “in-tunnel” design makes the Coherex FlatStent more effective in PFO tunnels of 4 mm or longer (limiting its use as a device for all PFO closure anatomy)^[9].

LIFETECH SCIENTIFIC CO., LTD.

Cera PFO Closure System, CeraFlex PFO Closure System

The Lifetech Scientific's PFO occluders (Cera and CeraFlex) received the CE mark in 2012. At the time of searching, the CeraFlex PFO Closure System was not registered on the RDM. Lifetech closure systems are self-expandable double disc devices, which are made of a nitinol wire mesh that is shaped into two flat discs and a waist between the two discs. Polyethylene terephthalate (PET) membranes are sewn into each disc help to seal the hole and provide a foundation for growth of tissue over the occluder after placement. A special feature of this devices is the ceramic coating (titanium nitride, TiN) on the wire mesh that theoretically reduces the ability of the device to produce a thrombus, providing faster endothelialisation and improved biocompatibility. The CeraFlex differs from the predecessor by the mesh design, and the connection system to the delivery cable^[10].

OCCLUTECH GMBH

Figulla PFO Occluder, Figulla PFO Occluder N, Figulla Flex PFO Occluder, Figulla Flex II PFO Occluder

Occlutech's PFO closure devices represent three different generations of the same basic concept. The Figulla PFO Occluder, launched in 2007, and its improved version Figulla PFO

Occluder N, launched in the same year represent the first generation. The Figulla PFO occluders consist of nitinol wires tightly woven into 2 flat discs creating a smooth and flexible outer layer. The two retention discs allow for a single central pin on the right atrial side. The discs are connected by a waist in the centre. Two polyethylene terephthalate (PET) patches assure complete closure after implantation. The left atrial disc consists only of a single layer without a hub, thereby minimising the amount of material on the left atrial side. The device is self-centring, repositionable, and retrievable^[11]. The improvements in the latest generations (i.e., Figulla Flex and Figulla Flex II) are mainly visible in the delivery system that allows a tilted angle of 45° (Figulla Flex, CE-marked in 2009) and 50° (Figulla Flex II, CE-marked in 2012) during the placement before the device is released. Figulla Flex II also has a mesh design with different patterns along the occluder, which theoretically gives the product a lower profile^[12].

ST. JUDE MEDICAL

Amplatzer PFO Occluder

The Amplatzer PFO Occluder, originally developed by AGA Medical Corporation, now part of St. Jude Medical, is a self-expanding device made of a nitinol wire mesh that received the CE mark in 1998. It consists of a right atrial and a slightly smaller left atrial disc connected together by a bond bridge made of nitinol wire. To increase its closing ability, the discs contain thin polyester (dacron) fabric. It is radio-opaque, retrievable and redeployable. The Amplatzer PFO Occluder is the most commonly used device worldwide and as such, many recently developed devices have similar design and implantation characteristics^[9].

Premere PFO Occluder

The Premere PFO occluder received CE marking in 2005. It is a flexible, low profile device with two independent self-expandable anchors made of nitinol. The right anchor is enclosed between two veils made of knitted polyester fabric. The device is suitable for long PFO tunnels. It has an adjustable tether connecting the anchors and can conform to different septal anatomies. It has the advantage of minimal left atrial material, theoretically reducing potential thrombus formation^[9].

STARWAY MEDICAL TECHNOLOGY INC.

Cardi-O-Fix PFO Occluder

The Cardi-O-Fix PFO Occluder received the CE mark in 2007. It is a self-expandable, double disc implant device made of shape-memorising nitinol wire mesh. The two discs are linked together by a short connecting waist. In order to increase its closing ability, the discs and

the waist are filled with polyester fabric (PET). The polyester fabric is securely sewn to each disc by a polyester thread^[13].

W.L.GORE & ASSOCIATES INC.

Gore HELEX Septal Occluder

The HELEX septal occluder received the CE mark in 2011. It's a low-profile, double-disc occluder device designed to close PFOs and secundum ASDs. The device is comprised of an expanded polytetrafluoroethylene membrane, bonded to a single nitinol wire frame which can be delivered through a femoral venous sheath. The HELEX is compliant and non-self-centring, making it theoretically capable of conforming to the curvilinear surfaces of the atrial septum. The delivery system allows for repositioning or retrieval of the device after deployment. A safety cord attached to the device provides for removal of the occluder even after device release in the unlikely case of device embolism^[9].

There are several new dedicated PFO closure devices with varying numbers of patients treated to date. A full description of each device is beyond the scope of this rapid HTA report. They include the Cierra PFX™ (Cierra, Inc., CA, USA), SeptRx (Stout Medical, PA, USA), Heartstitch (Sutura, CA, USA), Nitocclud (PFM Medical, CA, USA), Edwards Suture (Edwards Lifesciences, IR, CA, USA), Coaptus RF (Coaptus Medical, WA, USA)^[9], Spider™ PFO Occluder (Lifetech Scientific Co., Ltd., China), CeraFlex PFO Occluder (Lifetech Scientific Co., Ltd., China).

3.3 Use of the technology in Italy

To quantify the real number of PFO closure procedures performed in Italy a survey should be carried out among all the centres providing the procedure. This was outside the aims of the present rapid HTA report. According to the data collected by GISE (Italian Society of Invasive Cardiology), 2,541 PFO closure procedures were performed in 2012 in Italy (personal communication from Sergio Berti, MD, based on unpublished data from GISE^[14]). According to the data available to the Ministry of Health, in 2012 the price for a single PFO closure system ranged from € 5,535 to € 6,868 (prices are excluding VAT). Considering the cost of the technology alone, the impact on the SSN budget in 2012 was estimated to be around € 15 millions.

4. Effectiveness and safety

4.1 Methods

A search strategy was conducted in February 2013 to identify studies in which patients (adults aged 16 years or more) with PFO, suffering from TIAs, cryptogenic stroke or persistent migraine who underwent insertion of percutaneous devices for the closure of PFO compared to patients treated with standard care (i.e., medical treatment, symptomatic or secondarily preventive such as anticoagulants or fibrinolytics). The search strategy is reported in Appendix 1 – Search Strategy.

The primary outcome of included studies was the effect of PFO closure devices on the recurrence of cryptogenic strokes, transient ischaemic attacks, headache or any ischaemic abnormalities leading to clinical symptoms. HTA reports, systematic reviews and comparative prospective primary studies (trials and cohort studies) in the English language with no time restrictions were included for assessment.

Two authors (IA and AMo) screened potential citations for inclusion and extracted data on standardised sheets (see Appendix 2 – Data extraction sheet). Differences of opinion were resolved by discussion with a third author (TJ).

Assessment of methodological quality for randomised controlled trials was carried out using criteria from the *Cochrane Handbook for Systematic Reviews of Interventions*^[15]. Quality was assessed according to randomisation, generation of the allocation sequence, allocation concealment, blinding and reporting of adequate follow-up.

The quality of non-randomised studies was assessed in relation to the presence of potential confounders using the appropriate Newcastle-Ottawa Scales (NOS)^[16]. Quality was used at the analysis stage as a means of interpreting the results. Risk of bias categories were assigned on the basis of the number of NOS items judged inadequate in each study: low risk of bias - up to one inadequate item; medium risk of bias - up to three inadequate items; high risk of bias - more than three inadequate items; very high risk of bias - when there was no description of methods.

4.2 Results of literature review

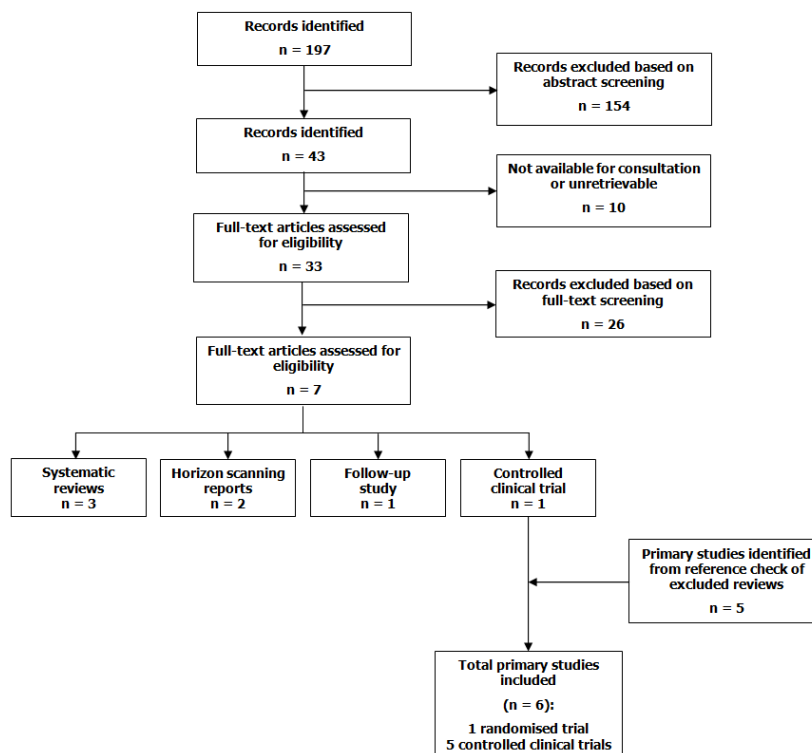
Studies identified by the search strategy are summarised in the flow-chart in Figure 4.1. A total of 197 records were identified and, based on the relevance of titles and abstracts, 43 articles

were considered for full-text evaluation. However, 10 full-text articles, several of which were conference abstracts, were unable to be accessed. Of the remaining 33 studies available for assessment, 26 studies were excluded for reasons stated in Appendix 3 – Excluded studies.

Of the 7 studies considered for inclusion, 3 were systematic reviews^[17,18,19], 2 were horizon scanning reports^[20,21], and 2 were controlled clinical trials (CCTs)^[22,23]. A review of the references of the included systematic reviews and the excluded reviews, HTA reports or guideline reports, identified 4 other primary studies that were CCTs^[24,25,26,27]. A search of clinicaltrial.gov identified a randomised controlled trial (RCT) that was completed and recently published^[28]. One CCT^[23] was an extension of the Windecker's study^[24]. The cohort of patients was followed for 10 years and, using a propensity score-matched approach, the authors showed that percutaneous PFO closure was more effective than medical treatment for the secondary prevention of recurrent cerebrovascular events among patients with PFO-related transient ischemic attack or stroke.

A total of 6 primary studies (Figure 4.1) were included for assessment in this report. Agreement for included studies between reviewers was excellent: Kappa = 0.843 (95% CI 0.635 - 1.000).

Figure 4.1: Flow-chart of the studies.



Data from systematic reviews

Agarwal et al.^[18] performed a systematic review including 39 studies of which 10 were apparently comparative and 5 of them were considered in our analysis. These studies were controlled clinical trials (CCT). Khairy et al.^[17] produced a systematic review and included 10 studies that performed percutaneous closure of PFO but none were comparative. Kitsios et al.^[19] in a systematic review identified 7 non-randomised studies all of which were considered in Agarwal's review^[18].

Data from HTA reports, horizon scanning reports, and guideline reports

In 2006 a report by the Australian and New Zealand Horizon Scanning Network (ANZHSN)^[20] identified a randomised trial that assessed the efficacy of STARFlex (MIST trial) and a case-control study^[29]. Another report from the National Horizon Scanning Centre (NHSC)^[21] of the University of Birmingham considered only the MIST trial^[30].

Primary studies included

The characteristics of the included primary studies (n = 6) are reported in Table 4.1. Five studies reported sufficient design elements to classify them as controlled clinical trials^[22,24-27]. The number of included patients ranged from 92 to 308, with a mean age ranging from 46 to 51 years. All studies considered the recurrence of stroke as a primary outcome. Follow-up ranged between 2 to 6 years. While one of the CCT studies^[22] used only one type of device for PFO closure (i.e., Amplatzer) the remaining studies used a variety of devices; in one study 42% of the patients in the intervention group received STARFlex^[25]. One study^[28] was a randomised trial and compared the efficacy of percutaneous PFO closure (using Amplatzer) in 980 patients.

Table 4.1: Characteristics of included studies.

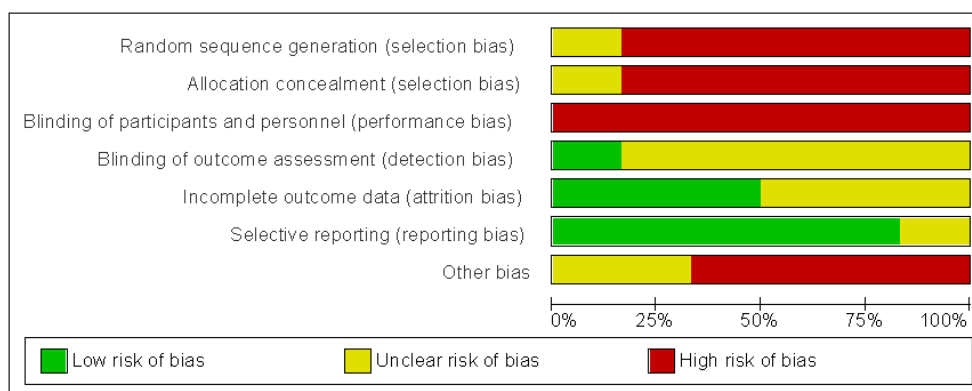
Author [ref.]	Type of study	Population	Intervention	Type of device	Outcome	Follow-up duration	Notes
Carroll 2013 [28]	RCT	980 subjects between 18 and 60 years of age (mean 45.9±9.9), with history of a cryptogenic ischemic stroke and a PFO identified by means of transesophageal echocardiography.	Medical therapy alone (aspirin, warfarin, clopidogrel, and aspirin combined with extended-release dipyridamole; n=488) vs Transcatheter closure of the PFO (n=481).	Amplatzer PFO Occluder.	Primary efficacy end point: a composite of recurrent nonfatal ischemic stroke, fatal ischemic stroke, or early death after randomisation. Secondary efficacy end points: complete closure of the PFO on the 6-month follow-up transesophageal echocardiogram, the absence of recurrent symptomatic nonfatal ischemic stroke or cardiovascular death, and the absence of a transient ischemic attack.	Median 2.1±2 years	-
Casabaun 2007 [27]	CCT	121 consecutive patients with cryptogenic stroke or TIA and PFO. Age 46 (mean).	Antiplatelet agents (acetylsalicylic acid 81 mg or 325 mg, clopidogrel, or combination dipyridamole/acetylsalicylic acid; n=41), anticoagulation with warfarin (n=20), percutaneous device closure (CardioSEAL and Amplatzer ASD Occluder; n=47) or surgical closure. (n=13).	CardioSEAL and Amplatzer.	1) recurrent stroke; 2) a composite of recurrent stroke, TIA, and death from vascular causes.	6 years (from 1997 to 2003)	-
Harrer 2006 [26]	CCT	124 patients with cryptogenic cerebral ischemia and PFO. Age 51 (±15).	Transcatheter PFO closure (n=34) vs medical treatment (n=83) or surgical closure (n=7).	Rashkind, the ASDOS and the Sideris buttoned device in the early phase of the study and the Amplatzer, the CardioSEAL and the PFO STARFlex systems in the later phase.	1) recurrent stroke; 2) risk factors for recurrence;	4.2 years (mean follow-up 52 ± 32 months)	-
Schuchlenz 2005 [25]	CCT	280 consecutive patients with cryptogenic cerebrovascular events and a PFO (mean age: 46 aspirin; 50 Coumandin; 44 device; p=0.006).	Platelet inhibitors (n=66) or anticoagulation (n=47) vs underwent device closure (n=167).	Rashkind Occluder (7 patients), Amplatzer (90 patients), and CardioSEAL or STARFlex devices (70 patients).	1) recurrence cerebrovascular events; 2) death; 3) severe treatment complications.	Mean follow-up of 2.6 years	STARFlex devices used in 70 patients
Thanopoulos 2006 [22]	CCT	92 consecutive patients with a PFO and at least one documented TIA or stroke of recent origin (<30 days).	Antiplatelet agents (n=44) vs Transcatheter PFO closure with Amplatzer PFO occluder (n=48).	Amplatzer.	1) embolic events; 2) haemorrhagic events; 3) adverse events.	Follow-up 24 months.	-
Windecker 2004 [24]	CCT	308 patients with cryptogenic stroke and PFO (mean age 50). <i>The individual treatment decision was based on patient and physician preference.</i>	Percutaneous closure vs medical treatment.	Six different device types used: Amplatzer PFO Occluder (n 54), PFO STARFlex (n 42), Sideris buttoned device (n 27), Angel Wing device (n 10), Amplatzer ASD Occluder (n 9), and CardioSEAL (n 8).	Recurrent thromboembolic events.	6 years (follow-up: between 1994 and 2000)	The cohort was followed for 10 years ²³ ; PFO closure was more effective than medical treatment for the secondary prevention of recurrent cerebrovascular events among patients with PFO-related transient ischemic attack or stroke.

Key: RCT = Randomised clinical trials; CCT = Controlled clinical trial; TIA = transient ischemic attack; PFO = patent foramen ovale.

Methodological quality of the studies

The assessment of the methodological quality of the studies is reported in Appendix 4 – Quality assessment. The generation sequence of randomisation and allocation concealment was unclear in the one included RCT. All the CCTs were considered at high risk of bias by default, however whether the outcome assessor was blinded or not was not reported, therefore it remains unclear as to whether these studies were free from detection bias (Figure 4.2).

Figure 4.2: Bias risk analysis of the studies.



Meta-analysis of the results

PFO closure significantly reduced the incidence of stroke in only 1 study^[25] and the incidence of TIA in 2 studies^[22,25]. PFO closure reduced the incidence of combined outcomes including stroke, TIA and vascular mortality in only 1 study^[27]. By combining the 5 CCT studies, percutaneous closure of PFO was better than medical treatment in reducing stroke (Figure 4.3), TIA (Figure 4.4) or the combination of both, however there was significant heterogeneity (Figure 4.5, $P= 0.002$). By combining 3 studies, PFO closure was better than medical treatment in reducing mortality (Figure 4.6).

Figure 4.3: Incidence of stroke.

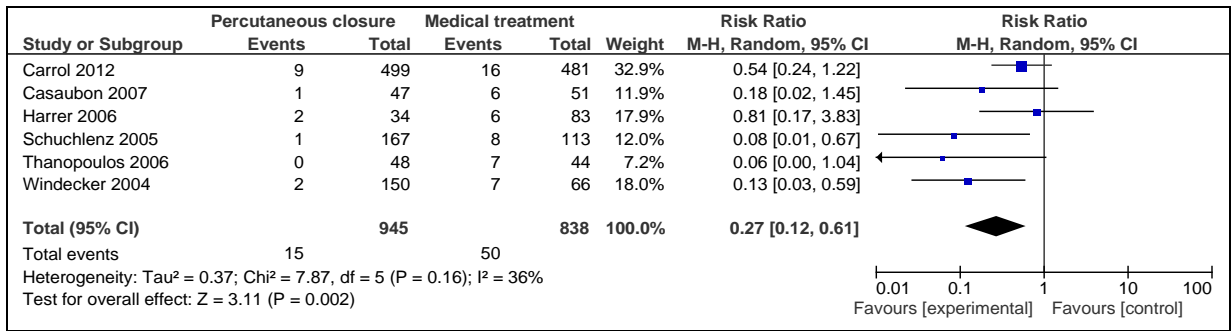


Figure 4.4: Incidence of transient ischemic attack (TIA).

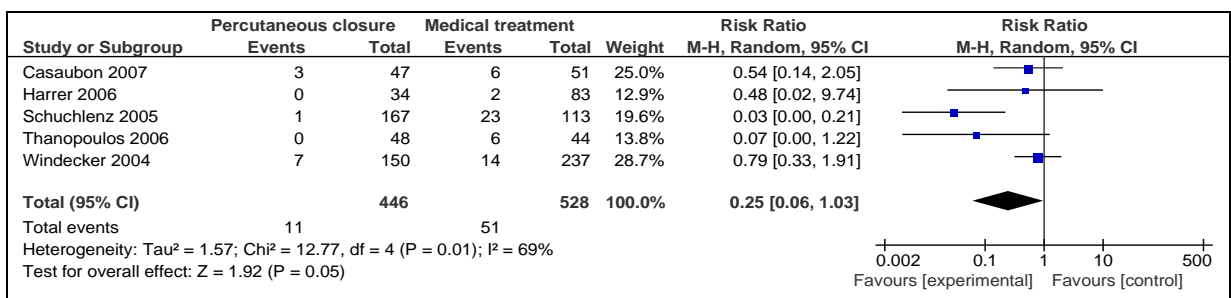


Figure 4.5: Combined incidence of stroke and transient ischemic attack (TIA).

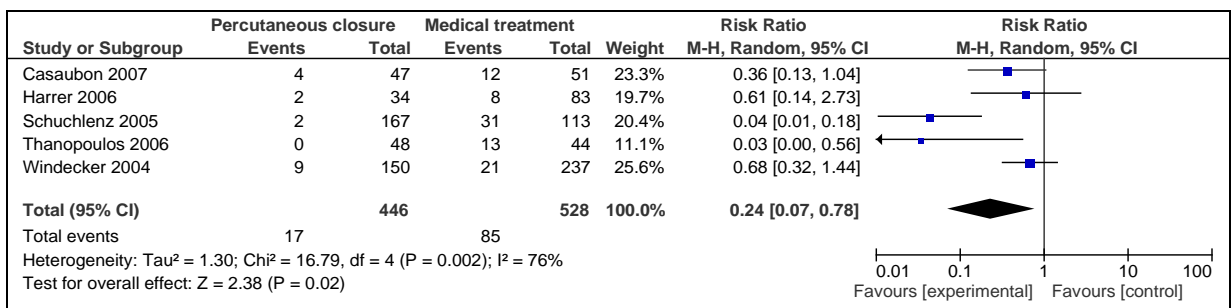
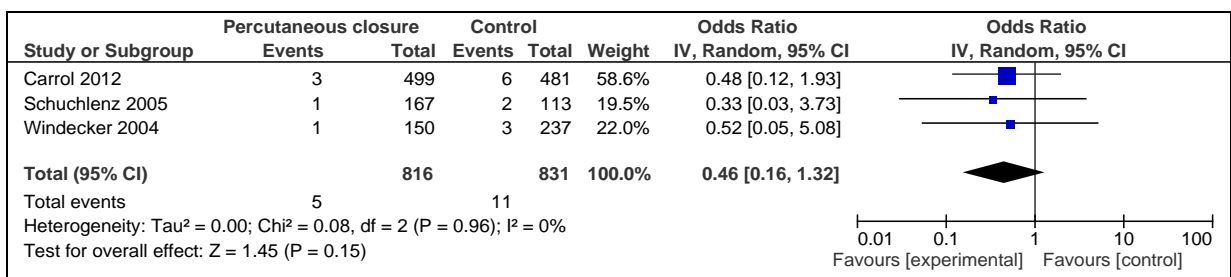


Figure 4.6: Incidence of mortality.



Safety

The RCT by Carroll et al.^[28], reported 22/464 (4.7%) serious adverse events were developed in the closure group and considered as device- or procedure-related. Six patients developed pulmonary embolism compared to one in the control group. In addition, two patients developed pericardial tamponade that was treated during the course of the procedure, and two patients developed cardiac thrombus in the right atrium, resulting in abandonment of the procedure in one.

In the CCT by Harrer et al.^[26], apart from femoral hematomas (3/34) due to the vascular access, there were no further device- or procedure-related complications.

In Casaubon et al.^[27], among the 47 patients that received PFO, device post-procedure arrhythmia was reported in 8 (7%) patients, chest pain in 3 (2%) patients and groin hematoma in 1 patient (1%). Two patients with device closure developed thrombus on the device and subsequently underwent surgical closure without further complications.

In Schuchlenz et al.^[25], 13 of the 167 patients (8%) developed complications related to device or procedure including hemopericardium, embolisation and bleeding.

In Windecker et al.^[24], periprocedural complications occurred in 9 of 150 patients (6%), and embolisation of the device in 4 patients, air embolism in 3 patients, and vascular access site problems in 2 patients.

In Thanopoulos et al.^[22] one of the 48 patients developed hemopericardium that was successfully managed by pericardiocentesis and no other complications were observed.

4.3 Discussion of results

The studies included in this systematic review showed that percutaneous closure of PFO was better than medical treatment in reducing stroke, TIA or the combination of both, even if heterogeneity between the studies was considerable. Poor methodological study quality and heterogeneity undermines our confidence in the results of this review.

We attempted to stratify by device type the overall pooling of study data but it resulted in loss of power and further fragmentation of the evidence base. A sub-group analysis was performed, using the data from the two studies^[22,28] that used only one type of device (Amplatzer). Given the differences in the size of the studies (980 vs 92 patients) and in the number of events observed (15 cases of TIA across all arms of the two trials) the results were not significant.

The safety profile of the technology is also an issue. The only RCT included for assessment^[28] reported 4.7% of patients who underwent PFO closure experienced a serious adverse event that was considered device- or procedure-related. In one CCT^[25] 8% of the patients developed complications related to device or procedure. These observations are of particular concern given

the type of patient enrolled in these studies –subjects in their 40s with one episode or more of stroke. Some of the most commonly observed harms such as arrhythmias could be reversible and harmless, although worrying. Although no deaths were recorded, serious events such a pulmonary embolism and haemopericardium could be fatal.

5. Conclusions

Anatomic closure of foramen ovale is incomplete in approximately 1 of every 4 adults. In the absence of specific clinical conditions, a PFO should be considered a normal anatomic variant and not a pathological finding^[4]. However, association between PFO and cerebral embolic stroke has been suggested^[1] as well as its association with chronic migraines^[2].

Together with medical therapy and surgical closure, percutaneous closure of PFO is one of the treatment options for patients with PFO suffering from TIAs, cryptogenic stroke or persistent migraine. The procedure is minimally invasive and is performed after echocardiography and fluoroscopic examination to determine the size and type of the PFO, and the anatomy of the defect^[1].

Since their introduction, several PFO closure devices have been developed, refined, and CE marked. However, none of these devices have been approved by the FDA and the procedure in the United States is performed off-label, using devices approved for other indications^[4].

In Italy, at time of writing, 7 manufacturers were offering 12 different PFO closure devices and it has been estimated that 2,541 PFO procedures were performed in 2012^[14]. Considering that the price for a single PFO closure device ranged from € 5,535 to € 6,868 (excluding VAT), this resulted in an impact on the SSN budget of € 15 millions.

We performed searches to identify studies in which patients with PFO suffering from TIAs, cryptogenic stroke or persistent migraine underwent insertion of percutaneous devices for the closure of PFO were compared to patients treated by usual care (i.e., medical treatment, symptomatic or secondarily preventive such as anticoagulants or fibrinolytics). Eligible studies were extracted and their methodological quality was assessed.

From the initial list of 197 records and from references checking we identified 3 systematic reviews^[17,18,19], 2 horizon scanning reports^[20,21], and 6 primary studies. The 6 primary studies were 5 controlled clinical trials (CCT)^[22,24-27], and 1 randomised clinical trial (RCT)^[28].

We performed a meta-analysis of the primary studies and found that PFO closure significantly reduced the incidence of stroke in only 1 study^[25] and the incidence of TIA in 2 studies^[22,25]. PFO closure reduced the incidence of combined outcomes including stroke, TIA and vascular mortality in only 1 study^[27]. Combining the 5 CCT studies, percutaneous closure of PFO was better than medical treatment in reducing stroke, TIA or the combination of both even if in the presence of significant heterogeneity. However, our confidence in the results of this review is undermined by the poor methodological quality and heterogeneity of the studies included.

Stratification by device type of the overall pooling of study data was attempted but resulted in loss of power and further fragmentation of the evidence base.

The safety profile of the technology was also defined by looking at the serious adverse events reported in the group underwent PFO closure. The only RCT identified^[28], reported 4.7% of serious adverse events considered device- or procedure-related.

6. Recommendations

Given the paucity of high-quality evidence of benefit of using PFO occluding devices for the secondary prevention of cardiovascular events, we recommend that large multicentre, randomised controlled trials be conducted in Europe with particular attention to the risk/benefit ratio. The trials would have to be sufficiently powered and properly randomised before widespread use of any invasive device such as these. A careful design with particular attention to participant selection and outcome quantification at follow-up are ethically necessary before any European patient is subjected to the procedure. The trial design should also include elements for following cost-effectiveness analyses.

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8. Competing interests declaration

The Authors declare that they will not receive either benefits or harms from the publication of this report.

None of the Authors have or have held shares, consultancies or personal relationships with any of the manufacturers of the devices assessed in this report.

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List of acronyms and abbreviations

CI: confidence interval.

CND: Classificazione Nazionale Dispositivi medici – national classification of medical devices.

GMDN: global medical device nomenclature.

HTA: Health technology assessment.

NOS: Newcastle-Ottawa Scale.

PFO: patent foramen ovale.

RDM: general repertory of medical devices.

SSN: Servizio Sanitario Nazionale – the Italian national health service.

TIA: transient ischemic attack.

TOE: transoesophageal echocardiography.

VAT: value added tax.

Appendix 1 – Search strategy

Searches have been performed on 1st February 2013 in the following databases: MEDLINE, Cochrane Library (all databases), Embase.

Free searches have been performed also on the following websites: clinicaltrials.gov, NICE, DARE, AHRQ, ANZHSN, NHMRC, TRIP database, HTA database.

MEDLINE

("Foramen Ovale, Patent"[Mesh] OR (foramen AND ovale AND patent) (title/abstract) OR PFO OR FOP	AND	Device OR devices
--	-----	-------------------

OR

("Foramen Ovale, Patent"[Mesh] OR (foramen AND ovale AND patent) (title/abstract) OR PFO OR FOP	AND	figulla (title/abstract) OR starflex (title/abstract) OR Helex (title/abstract) OR Cardioseal (title/abstract) OR Amplatzer(title/abstract) OR Ultrasept (title/abstract) OR atriasept (title/abstract) OR (Coherex flat stent ef) (title/abstract) OR (cera pfo) (title/abstract) OR Ceraflex (title/abstract) OR (Premere PFO) (title/abstract) OR cardi-o-fix (title/abstract) OR Gore-helex (title/abstract) OR (Gore helix) (title/abstract)
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Results: 105

Filters: adults (> 19 years old), comparative study, trials, RCT, review, systematic review, evaluation study, English, humans.

Cochrane Library (all databases)

("Foramen Ovale, Patent"(ti,ab,kw) OR (foramen AND ovale AND patent) (ti,ab,kw) OR PFO OR FOP	AND	Device OR devices (ti,ab,kw)
--	-----	------------------------------

OR

("Foramen Ovale, Patent"(ti,ab,kw) OR (foramen AND ovale AND patent) (ti,ab,kw) OR PFO OR FOP	AND	Figulla (ti,ab,kw) OR Starflex(ti,ab,kw) OR Helix (ti,ab,kw) OR Cardioseal (ti,ab,kw) OR Amplatzer (ti,ab,kw) OR (closure device) (ti,ab,kw) OR Ultrasept (ti,ab,kw) OR atriasept (ti,ab,kw)) OR (Coherex flat stent ef) (ti,ab,kw) OR (cera pfo) (ti,ab,kw) OR Ceraflex (ti,ab,kw) OR (Premere PFO) (ti,ab,kw) OR cardi-o-fix (ti,ab,kw) OR Gore-helex (ti,ab,kw) (Gore helix) (ti,ab,kw) OR Occluder
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Results: 137

Embase

("Foramen Ovale, Patent"(EMTREE) OR (foramen AND ovale AND patent) (ab,ti) OR PFO OR FOP	AND	Device OR devices (ab,ti)
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OR

("Foramen Ovale, Patent"(EMTREE) OR (foramen AND ovale AND patent) (ab,ti) OR PFO OR FOP	AND	Figulla (ab,ti) OR Starflex (ab,ti) OR Helex (ab,ti) OR Cardioseal (ab,ti) OR Amplatzer (ab,ti) OR (closure device) (ab,ti) OR Ultrasept (ab,ti) OR atriasept (ab,ti) OR (Coherex flat stent ef) (ab,ti) OR (cera pfo) (ab,ti) OR Ceraflex (ab,ti) OR (Premere PFO)(ab,ti) OR cardi-o-fix (ab,ti) OR Gore-helex (ab,ti) OR (Gore helix) (ab,ti) OR occluder
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Results (excluded duplications from MEDLINE): 67

Appendix 2 – Data extraction sheet

PART 1 **Background Information and Description of study**

Reviewer:

Study unique identifier:

Published: Y/N

Reference: (If applicable)

Period study conducted:

Abstract/Full paper

Country or countries of study:

Number of studies included in this paper:

Funding source (delete non applicable items):

Government ,Pharmaceutical, Private, Unfunded, Unclear

Paper/abstract numbers of other studies with which these data are linked:

Reviewer's assessment of study design (delete non applicable items):

Study Category	Study Design		
Experimental	Parallel RCT	Crossover RCT	Crossover RCT
Non-randomised analytical (specifically designed to assess association)	Retrospective/Prospective Cohort	Case Control	Cross sectional
Non-randomised comparative (not specifically designed to assess association)	Case X Over/Time series	Ecological study	Before and after
Non-comparative	EXCLUDE		

Does the study present data distributed by age group/occupation/health status?

	Age group distribution		
Age group			
Occupation			
Health status			
Gender			
Ethnic group			

Description of study

Methods

Participants

Interventions/Exposure

Outcomes

Effectiveness

Safety

Notes

The authors conclude that

PART 2a
Methodological Quality Assessment
RCT and CCT only

Generation of allocation schedule (delete non applicable items):

- a) random number tables
- b) computer random-number generator
- c) coin tossing
- d) shuffling of allocation cards
- e) any other method which appeared random

Concealment of treatment allocation (delete non applicable items):

- a) there was some form of centralised randomization scheme where details of an enrolled participant were passed to a trial office or a pharmacy to receive the treatment group allocation.
- b) treatment allocation was assigned by means of an on-site computer using a locked file which could be accessed only after inputting the details of the participant.
- c) there were numbered or coded identical looking compounds which were administered sequentially to enrolled participants;
- d) there were opaque envelopes which had been sealed and serially numbered utilised to assign participants to intervention(s)
- e) a mixture of the above approaches including innovative schemes, provided the method appears impervious to allocation bias.
- f) allocation by alternation or date of birth or case record or day of the week or presenting order or enrolment order.

[Concealment methods are described as "adequate" for (a), (b), (c), (d) or (e). Method (f) is regarded as "inadequate".

Exclusion of allocated participants from the analysis of the trial

- a) Did the report mention explicitly the exclusion of allocated participants from the analysis of trial results?
- b) If so did the report mention the reason(s) for exclusion? (if yes, specify)

Measures to implement double blinding

- a) Did the report mention explicitly measures to implement and protect double blinding?
- b) Did the author(s) report on the physical aspect of compound administration - (i.e. appearances, colour, route administration)

PART 2b
Description of interventions and outcomes
 RCT and CCT only

Intervention tested

	Intervention and Composition	Product and Manufacturer	Schedule & Dose and Route	Route of Administration
Arm 1				
Arm 2				
Control				

Notes:

- index intervention goes in the Arm 1 line, Placebo in the last line

Details of Participants

	Enrolled	Assessing	Reasons	Inclusion in Analysis	Notes
Interventive arm 1					
Interventive arm 2					
Controls					

Outcomes List – Effectiveness

Outcome	How defined	Description/Follow-up/Notes

Outcomes List - Safety

Outcome	How defined	Description/Follow-up/Notes

Investigators to be contacted for more information? Yes No

Contact details (principal investigator, fill in only if further contact is necessary):

PART 2c
Data Extraction and manipulation
 (to be used for dichotomous or continuous outcomes)
 RCT and CCT only

Comparison

Outcomes	N Index Arm	N Comparator

Notes (for statistical use only)

PART 3a
Methodological Quality Assessment
Non-randomised studies only

Newcastle - Ottawa quality assessment scale
Cohort studies

Selection

- 1) Representativeness of the exposed cohort
 - a) truly representative of the average _____ (describe) in the community
 - b) somewhat representative of the average _____ in the community
 - c) selected group of users eg nurses, volunteers
 - d) no description of the derivation of the cohort
- 2) Selection of the non exposed cohort
 - a) drawn from the same community as the exposed cohort
 - b) drawn from a different source
 - c) no description of the derivation of the non exposed cohort
- 3) Ascertainment of exposure
 - a) secure record (eg surgical records)
 - b) structured interview
 - c) written self report
 - d) no description
- 4) Demonstration that outcome of interest was not present at start of study
 - a) yes
 - b) no

Comparability

- 1) Comparability of cohorts on the basis of the design or analysis
 - a) study controls for _____ (select the most important factor)
 - b) study controls for any additional factor (This criteria could be modified to indicate specific control for a second important factor.)

Outcome

- 1) Assessment of outcome
 - a) independent blind assessment
 - b) record linkage
 - c) self report
 - d) no description
- 2) Was follow-up long enough for outcomes to occur
 - a) yes (select an adequate follow up period for outcome of interest)
 - b) no
- 3) Adequacy of follow up of cohorts
 - a) complete follow up - all subjects accounted for
 - b) subjects lost to follow up unlikely to introduce bias - small number lost - > ____ % (select an adequate %) follow up, or description provided of those lost)
 - c) follow up rate < ____% (select an adequate %) and no description of those lost
 - d) no statement

PART 3b
Description of interventions and outcomes
 Non-randomised longitudinal studies only

Intervention used

	Intervention and Composition	Product and Manufacturer	Schedule & Dose and Route	Route of Administration
Arm 1				
Arm 2				
Placebo				

Notes:

- index intervention goes in the Arm 1 line, Placebo in the last line

Details of Participants

	Enrolled	Assessing	Reasons	Inclusion in Analysis	Notes
Group 1					
Group 2					
Comparator					

Outcomes List – Effectiveness

Outcome	How defined (including length of follow-up)	Description/Follow-up/Notes

Outcomes List - Safety

Outcome	How defined (including length of follow-up)	Description/Follow-up/Notes

Investigators to be contacted for more information? Yes No

Contact details (principal investigator, fill in only if further contact is necessary):

PART 3c

Data Extraction and manipulation

(to be used for dichotomous outcomes)

non-randomised longitudinal studies only

Comparison

Outcomes	N Index Group	N Comparator

Notes (for statistical use only)

Appendix 3 – Excluded studies

Table A3.1: Summary of the excluded studies with reason for exclusion.

Reason of exclusion	Number of studies excluded
Protocols or studies on STARFlex*	7
Protocols or ongoing studies	9
Commentaries	3
Non atrial closure	2
Language	1
Etiologic studies	1
Economic studies	1
Correspondence	1
PFO device not specified	1
Total excluded	26

*STARFlex is a PFO device manufactured by NMT Medical Inc. STARFlex received FDA pre-market approval in 2009 but failed to meet clinical endpoints a year later, causing bankrupt for the manufacturer NMT Medical. As STARFlex has been withdrawn from the market, we decided to exclude studies in which all the patients received STARFlex.

Full references of the excluded studies

Studies excluded as protocols or studies on STARFlex (n = 7)

Dowson A, Mullen MJ, Peatfield R, Muir K, Khan AA, Wells C, Lipscombe SL, Rees T, De Giovanni JV, Morrison WL, Hildick-Smith D, Elrington G, Hillis WS, Malik IS, Rickards A. Migraine Intervention With STARFlex Technology (MIST) trial: a prospective, multicenter, double-blind, sham-controlled trial to evaluate the effectiveness of patent foramen ovale closure with STARFlex septal repair implant to resolve refractory migraine headache. Circulation. 2008 Mar 18;117(11):1397-404.

Dowson AJ, Wilmshurst P, Muir KW, Mullen M, Nightingale S. A prospective, multicentre, randomised, double-blind, placebo-controlled trial to evaluate the efficacy of PFO closure with the STARFlex (R) device to prevent refractory migraine: The MIST trial. Eur J Neurol. 2006(7):22.

Furlan AJ, Reisman M, Massaro J, Mauri L, Adams H, Albers GW, Felberg R, Herrmann H, Kar S, Landzberg M, Raizner A, Wechsler L; CLOSURE I Investigators. Study design of the CLOSURE I Trial: a prospective, multicenter, randomized, controlled trial to evaluate

the safety and efficacy of the STARFlex septal closure system versus best medical therapy in patients with stroke or transient ischemic attack due to presumed paradoxical embolism through a patent foramen ovale. Stroke. 2010 Dec;41(12):2872-83.

Evaluate safety/effectiveness of PFO closure with the STARFlex system to resolve refractory migraine with aura. ClinicalTrialsgov, NCT00330850.

Furlan AJ, Reisman M, Massaro J, Mauri L, Adams H, Albers GW, et al. Study design of the CLOSURE i trial: A prospective, multicenter, randomized, controlled trial to evaluate the safety and efficacy of the STARFlex septal closure system versus best medical therapy in patients with stroke or transient ischemic attack due to presumed paradoxical embolism through a patent foramen ovale. Stroke. 2010;41(12):2872-83.

Dowson AJ, Wilmshurst P, Muir KW, Mullen M, Nightingale S. A Prospective, Multicenter, Randomized, Double Blind, Placebo-Controlled Trial to Evaluate the Efficacy of Patent Foramen Ovale Closure with the STARFlex Septal Repair Implant to Prevent Refractory Migraine Headaches: the MIST Trial. Neurology July 11, 2006 vol. 67 no. 1 185-185-a.

Furlan AJ, Reisman M, Massaro J, Mauri L, Adams H, Albers GW, et al. Closure or medical therapy for cryptogenic stroke with patent foramen ovale. N Engl J Med. 2012 2012 Mar 15;366(11):991-9.

Studies excluded as protocols or ongoing studies (n = 9)

Li J, Liu M, Zhang S, Hao Z, Zhang C, Zhang J. Closure versus medical therapy for preventing recurrent stroke in patients with patent foramen ovale and a history of cryptogenic stroke or transient ischemic attack (Protocol). Cochrane Database of Systematic Reviews 2012, Issue 7. Art. No.: CD009938.

Khattab AA, Windecker S, Juni P, Hildick-Smith D, Dudek D, Andersen HR, et al. Randomized clinical trial comparing percutaneous closure of patent foramen ovale (PFO) using the Amplatzer PFO Occluder with medical treatment in patients with cryptogenic embolism (PC-Trial): rationale and design. Trials. 2011 2011;12:56.

Evaluation of the STARFlex® Septal Closure System in Patients With a Stroke or TIA Due to the Possible Passage of a Clot of Unknown Origin Through a Patent Foramen Ovale (PFO). ClinicalTrialsgov, NCT00201461.

Kasner SE. GORE HELEX Septal Occluder and Antiplatelet Medical Management for Reduction of Recurrent Stroke or Imaging-Confirmed TIA in Patients with Patent Foramen Ovale (PFO) - The Gore REDUCE Study. International Stroke Conference 2011.

Effect of septal closure of atrial PFO on events of migraine with aura: The ESCAPE migraine trial. ClinicalTrials.gov, NCT00267371.

PC-Trial: Patent Foramen Ovale and Cryptogenic Embolism. ClinicalTrials.gov, NCT00166257.

GORE HELEX septal occluder for patent foramen ovale (PFO) closure in stroke patients (Gore REDUCE). ClinicalTrials.gov, NCT00738894.

Patent Foramen Ovale Closure or Anticoagulants Versus Antiplatelet Therapy to Prevent Stroke Recurrence (CLOSE). ClinicalTrials.gov, NCT00562289.

RESPECT PFO Clinical Trial. ClinicalTrials.gov, NCT00465270.

Studies excluded as commentaries (n = 3)

Anzola GP. Can patent foramen ovale closure using the Cardia PFO occluder reduce the occurrence of thromboembolic events? *Nat Clin Pract Cardiovasc Med.* 2006 2006 Apr;3(4):186-7.

Carroll JD. Migraine Intervention With STARFlex Technology trial: a controversial trial of migraine and patent foramen ovale closure. *Circulation.* 2008 Mar 18;117(11):1358-60.

NMT Medical announces preliminary results of CLOSURE 1 PFO/stroke trial. <http://www.snl.com/irweblinkx/file.aspx?IID=4148066&FID=9712903>.

Studies excluded as not reporting on atrial closure (n = 2)

Deuling JH, Vermeulen RP, Anthonio RA, van den Heuvel AF, Jaarsma T, Jessurun G, et al. Closure of the femoral artery after cardiac catheterization: a comparison of Angio-Seal, StarClose, and manual compression. *Catheter Cardiovasc Interv.* 2008 2008 Mar 1;71(4):518-23.

Fathi AR, Eshtehardi P, Meier B. Patent foramen ovale and neurosurgery in sitting position: a systematic review. *Br J Anaesth.* 2009 May;102(5):588-96.

Studies excluded as economic studies (n = 1)

Arias AM, Masson WM, Bluro IM, Oberti PF, Falconi ML, Pizarro R, Krauss JG, Cagide AM. Cost-effectiveness analysis of alternative strategies for the management of patients with cryptogenic stroke and patent foramen ovale. *Revista Argentina de Cardiologia* 2011; 79(4): 337-343.

Studies excluded for language restrictions (n = 1)

Dellborg M, Eriksson P, Ladenvall P, Mirzada N, Runmarker B, Jivegard L, Strandell A, Svanberg T, Eriksson M. Kateterburen slutning av persisterande foramen ovale. (PFO). [Percutaneous transcatheter closure of patent foramen ovale] Gothenburg: The Regional Health Technology Assessment Centre (HTA-centrum). HTA-rapport 2010:31. 2010.

Studies excluded as etiologic studies (n = 1)

Patent foramen ovale in cryptogenic stroke study-PICSS. *Stroke Trials Registry*, Internet Stroke Center: www.strokecenter.org/trials/

Studies excluded as correspondence (n = 1)

Dowson A, Mullen MJ, Peatfield R, Muir K, Khan AA, Wells C, Lipscombe SL, Rees T, De Giovanni JV, Morrison WL, Hildick-Smith D, Elrington G, Hillis WS, Malik IS, Rickards A. Migraine Intervention With STARFlex Technology (MIST) trial: a prospective, multicenter, double-blind, sham-controlled trial to evaluate the effectiveness of patent foramen ovale closure with STARFlex septal repair implant to resolve refractory migraine headache. Erratum in: *Circulation*. 2009 Sep 1;120(9):e71-2.

Studies excluded as the PFO device used was not specified (n = 1)

Anzola GP, Frisoni GB, Morandi E, Casilli F, Onorato E. Shunt-associated migraine responds favorably to atrial septal repair: a case-control study. *Stroke*. 2006 Feb;37(2):430-4.

Appendix 4 – Quality assessment

Table A4.1. Quality assessment of included clinical trials

Author	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Carrol 2013	Unclear risk No clear description was reported	Unclear risk No clear description was reported	High risk the use of device could not permit blinding	Low risk The independent clinical events committee member that adjudicated end-point events were unaware of the identities of the patients, the treatment assignments, and the site at which the patients were enrolled. An independent data and safety monitoring board, whose members were unaware of the site at which the patients were enrolled, adjudicated reported adverse events and assessed the severity, expectedness, and relatedness of the event to the device, procedure, delivery system, and study protocol.	Low risk	Low risk Outcomes in the protocol were considered in the final publication	

<p>Casabaun 2007</p>	<p>High risk the study is a controlled clinical trial: <i>Specific management for secondary stroke prevention was decided upon by the treating neurologist and patient after consideration of ease of treatment and anticipated compliance.</i></p>	<p>High risk the study is a controlled clinical trial: <i>Specific management for secondary stroke prevention was decided upon by the treating neurologist and patient after consideration of ease of treatment and anticipated compliance.</i></p>	<p>High risk the use of device could not permit blinding</p>	<p>Unclear risk No statement of blinding was given.</p>	<p>Low risk Follow-up data was collected for all 121 patients.</p>	<p>Low risk</p>	
<p>Harrer 2006</p>	<p>High risk The study is a controlled clinical trial: <i>Quote: Since randomized controlled trials are still ongoing, decision to either close the PFO or use medical therapy was made with patient consent.</i></p>	<p>High risk The study is a controlled clinical trial: <i>Quote: Since randomized controlled trials are still ongoing, decision to either close the PFO or use medical therapy was made with patient consent.</i></p>	<p>High risk the use of device cannot permit blinding</p>	<p>Unclear risk No statement of blinding was given.</p>	<p>Low risk Follow-up data was collected for all 121 patients.</p>	<p>Unclear risk</p>	

<p>Schuchlenz 2005</p>	<p>High risk</p> <p>The study is a CCT. Patients were also informed that the therapeutic approach was empirical and that there was insufficient evidence to strongly support one therapy over another. The final treatment decision was left to the patients and their referring physician.</p>	<p>High risk</p> <p>The study is a CCT. Patients were also informed that the therapeutic approach to their condition was empirical and that there was insufficient evidence to strongly support one therapy over another. The final treatment decision was left to the patients and their referring physician.</p>	<p>High risk</p> <p>the use of device cannot permit blinding</p>	<p>Unclear risk</p> <p>No statement of blinding was given.</p>	<p>Unclear risk</p>	<p>Low risk</p> <p>Adverse events related to percutaneous closure were reported: <i>Thirteen patients (8%) had severe complications related to PFO closure. There were 4 retroperitoneal hematomas, 2 device embolizations, and 1 cardiac tamponade requiring surgery and 3 failed implantations. + 3 late complications</i> One device was removed surgically because of a thrombus</p>	<p>High risk</p> <p>Relevant basic prognostic factors were statistically different among the treatment groups: mean age, TIA, and stroke, current smoking, patent foramen ovale size (> =4mm) and mean-patent foramen ovale size.</p>
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<p>Thanopoulos 2006</p>	<p>High risk</p> <p>The study is a CCT: The control group consisted of 44 patients who had declined catheter treatment and received long-term treatment with clopidrogel (75 mg/day) and aspirin (325 mg/day).</p>	<p>High risk</p> <p>The study is a CCT: The control group consisted of 44 patients who had declined catheter treatment and received long-term treatment with clopidrogel (75 mg/day) and aspirin (325 mg/day)</p>	<p>High risk</p> <p>the use of device cannot permit blinding</p>	<p>Unclear risk</p> <p>No statement of blinding was given.</p>	<p>Low risk</p> <p>All patients had completed a 2-year follow-up.</p>	<p>Low risk</p> <p>Data on adverse effects were clearly reported: Immediate complete closure (CC) was observed in 44/48 (91%) patients. Four (9%) patients had a minimal residual shunt immediately after the procedure. Five (11%) patients developed transient atrial arrhythmias during the procedure.</p>	<p>High risk</p> <p>The two groups were not balanced in terms of hypertension, smoking and the presence of multiple events (p<0.05)</p>
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<p>Windecker 2004</p>	<p>High risk</p> <p>The study is a CCT: <i>After excluding patients without a PFO or with a concurrent etiology for the cerebrovascular event, 308 patients were classified as having suffered a cryptogenic stroke presumably related to PFO. Percutaneous PFO closure was performed in 150 patients, whereas 158 patients were treated medically. The individual treatment decision was based on patient and physician preference.</i></p>	<p>High risk</p> <p>The study is a CCT: <i>Percutaneous PFO closure was performed in 150 patients, whereas 158 patients were treated medically. The individual treatment decision was based on patient and physician preference.</i></p>	<p>High risk</p> <p>the use of device cannot permit blinding</p>	<p>Unclear risk</p> <p>No statement of blinding was given.</p>	<p>Low risk</p> <p>2 patients in the medical treatment group and 3 patients in the percutaneous PFO closure group were lost to follow-up</p>	<p>Low risk</p>	<p>High risk</p> <p>Unbalanced baseline characteristics: <i>Patients who underwent percutaneous PFO closure were more likely to have suffered more than one cerebrovascular event before inclusion in the study (p 0.03; risk ratio [RR] 1.68; 95% confidence interval [CI] 1.04 to 2.71) and had a larger right-to-left shunt at baseline (p 0.001; RR 2.01; 95% CI 1.38 to 3.07).</i></p>
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