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HEALTH TECHNOLOGY ASSESSMENT:

Patent foramen ovale closure, antiplatelet therapy or anticoagulation therapy alone for management of cryptogenic stroke

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Key messages

Patent foramen ovale (PFO) represents an opening in the heart placing people at risk of ischemic stroke. This report evaluates catether-based PFO closure as an alternative treatment to antiplatelet therapy or anticoagulation for patients with a PFO having suffered a stroke.

Our findings:

- PFO closure plus antiplatelet therapy probably results in a large decrease in ischemic stroke, when compared to antiplatelet therapy alone (8.7% absolute risk reduction, moderate certainty evidence)
- There may be little or no difference in the risk for ischemic stroke when comparing PFO closure to anticoagulation (low certainty evidence)
- Compared to anticoagulation, PFO closure will probably result in fewer cases of major bleeding (2% absolute risk reduction, moderate certainty evidence)
- PFO closure comes with an increased risk of adverse events (3.6%), such as procedure-related complications and atrial fibrillation
- PFO closure is very likely a cost-effective treatment alternative to medical management
- Assuming available capacity, the annual budget impact of national implementation is NOK 34 million
- PFO closure introduces both patient and operator to radiation comparable to other routine procedures
- PFO closure may require additional investments in increased intervention capacity and likely also a need for additional diagnostic investigations in Norwegian hospitals

Title:
Patent foramen ovale closure, antiplatelet therapy or anticoagulation therapy alone for management of cryptogenic stroke

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Health technology assessment
Health technology assessment (HTA) is a multidisciplinary process that summarizes information about the medical, social, economic and ethical issues related to the use of a health technology in a systematic, transparent, unbiased, robust manner. Its aim is to inform the development of safe, effective health policies that are patient focused and that seek to achieve best value.

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Last search for studies:
August 2018

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Executive summary

Background

Some people have an opening in the partition between the anterior ventricles, a patent foramen ovale (PFO). Such an opening is relatively common and most individuals will never notice any ailments. However, in some individuals, a PFO can lead to an ischemic stroke.

If a patient subsequently to an ischemic stroke is carefully examined and no other causes of the stroke are identified, but a PFO is detected, then closing the PFO may be a treatment option to prevent new embolic strokes. Today's treatment is drug prevention with platelet inhibitor or anticoagulation.

Objective

The purpose of this report is to investigate whether PFO closure is an effective and cost-effective alternative to medical treatment.

Method

The commission of this report contained a new systematic overview of the efficacy and safety of PFO closure compared to treatment with platelet inhibitors and anticoagulation. In line with our methods, we conducted a systematic search for other systematic reviews published in 2018. We chose the systematic overview with relevant comparator and which had the most participants and most recent literature search.

We developed a health economic model in dialogue with clinical experts. The model is a Markov model with a lifetime perspective. Included in the model is the effect of measures on the outcomes of ischemic stroke and large bleeding. The model also includes a number of sequelae states defined based on the modified ranking scales (mRS). Input data for the model is based on published literature. Health effects and costs are discounted by 4%. The absolute shortfall for patients with PFO and a previous

ischemic stroke receiving the current treatment is calculated as specified in the guidelines of the Norwegian Medicines Agency.

The Norwegian Radiation and Nuclear Safety Authority have carried out assessment of radiation effects of introduction. Possible organisational consequences are outlined based on assumptions and input from clinical experts. Cardiologists and neurologists in the clinical expert group have added their own paragraphs to the chapter on organisational consequences.

Results

We identified 18 potentially relevant studies, of which 13 were systematic reviews. 11 of these 13 compared PFO closure with medical treatment, but did not distinguish between type of drug in the comparator. Two studies report separate efficacy estimates for comparison with platelet inhibitors and anticoagulation, one of which had a higher number of participants and a recent literature search.

The chosen systematic overview indicates that PFO closure in patients under the age of 60 with stroke reduces the risk of new stroke compared to platelet inhibition (OR: 0.12, 95% CI: 0.04-0.27, moderate quality of documentation). Compared with anticoagulation treatment, the effect of PFO closure on stroke is more uncertain (OR: 0.44. 95% CI: 0.08-3.83, low quality of documentation). However, PFO closure is likely to result in fewer serious bleedings than anticoagulant treatment.

PFO in persons with a previous stroke is calculated to provide an absolute shortfall of 14.8 years in good health (quality adjusted life years, QALYs) compared to the normal population.

PFO closure leads to a large gain in the form of QALYs and cost savings over a lifetime perspective. As an alternative to treatment with platelet inhibitors, PFO closure has been estimated to give a 98% probability tof being cost-effective alternative. Compared to anticoagulation, the health benefits and cost savings are less, but still large compared to other technologies. Compared to anticoagulation, PFO has an estimated probability of 80% to be a cost-effective alternative. The uncertainty in cost-effectiveness is less than the uncertainty in single outcomes of clinical efficacy, as both the effect of fewer ischemic strokes; fewer large bleeds and the effect of minor sequelae are here captured in a single, pooled estimate.

Budget effect per year of PFO closure is likely to be approximately NOK 34 million. The estimate does not include any investment in increased capacity.

PFO closure introduces patient and operator for ionizing radiation compared to medical treatment. The dose levels are comparable to other common cardiac procedures and will be eligible for PFO closure.

A national introduction of PFO closure as a method will lead to the need for training as well as increased capacity for diagnostics and treatment.

Conclusion

Compared to platelet inhibitors, PFO closure is clinically effective in preventing new strokes in patients under the age of 60 with cryptogenic stroke and PFO. Compared to anticoagulation, the effect on the prevention of new stroke is uncertain, however, PFO closure will probably lead to fewer cases of major bleedings.

PFO closure is very likely a cost-effective alternative to drug treatment.

The radiation effects are comparable to other cardiac procedures.

The national introduction of PFO closure will implicate organisational consequences in the form of increased need for training, increased capacity for diagnostics and treatment. Organisational consequences should be considered to be investigated further by the Regional Health Authorities before implementation.

Hovedbudskap

Patent foramen ovale (PFO) er en åpning i hjertet som kan medføre økt risiko for iskemisk slag. I denne rapporten ser vi på kateterbasert lukking av PFO som et behandlingsalternativ til platehemmer eller antikoagulasjon for pasienter med PFO som allerede har gjennomgått et iskemisk slag.

Vi fant at:

- PFO-lukking i kombinasjon med platehemmer fører trolig til en vesentlig reduksjon i iskemiske slag sammenlignet med platehemmer alene (8,7% absolutt risikoreduksjon, evidens av moderat kvalitet)
- Sammenlignet med antikoagulasjon, ser det ut til å være liten eller ingen forskjell i risiko for iskemisk slag (evidens av lav kvalitet)
- Sammenlignet med antikoagulasjon, vil PFO lukking trolig føre til færre tilfeller av alvorlig blødning (2% absolutt risikoreduksjon, evidens av moderat kvalitet)
- PFO-lukking kan øke risiko (3,6%) for uheldige hendelser som prosedyrerelaterte komplikasjoner og atrieflimmer
- PFO-lukking er med stor sannsynlighet et kostnadseffektivt alternativ til medikamentell behandling
- Forutsatt tilstrekkelig kapasitet, kan innføring gi en årlig budsjettvirkning på NOK 34 millioner.
- PFO-lukking utsetter pasient og operatør for stråledoser som er lignende de man ser ved andre vanlige hjerteprosedyrer
- Innføring av PFO-lukking kan medføre behov for økt kapasitet til diagnostikk og behandling

Tittel:
Patent Foramen Ovale lukking, platehemming eller antikoagulasjon for behandling av kryptogent hjerneslag

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Publikasjonstype:
Metodevurdering

En metodevurdering er resultatet av å
- innhente
- kritisk vurdere og
- sammenfatte

relevante forskningsresultater ved hjelp av forhåndsdefinerte og eksplisitte metoder.

Svarer ikke på alt:
- Ingen studier utenfor de eksplisitte inklusjonskriteriene
- Ingen anbefalinger

Hvem står bak denne publikasjonen?
Folkehelseinstituttet har gjennomført oppdraget etter forespørsel fra Bestillerforum RHF.

Når ble litteratursøket utført?
Søk etter studier ble avsluttet august 2018.

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Sammendrag

Innledning

Omlag 25% av befolkningen har en åpning i skilleveggen mellom hjertets forkamre, en såkalt patent foramen ovale (PFO). Et slikt hull er relativt vanlig og de fleste personer vil aldri merke noen plager. Hos noen personer kan imidlertid PFO føre til et iskemisk hjerneslag.

Dersom en person etter å ha hatt et embolisk slag utredes nøye og man ikke finner andre årsaker til slaget, men også finner en PFO, så kan lukking av PFO være et behandlingsalternativ for å forebygge nye emboliske slag. Dagens behandling er medikamentell forebygging med platehemmer eller antikoagulasjon. Formålet med denne rapporten er å undersøke om PFO-lukking er et effektivt og kostnadseffektivt alternativ til medikamentell behandling.

Metode

Bestillingen av denne rapporten inneholdt en ny systematisk oversikt på effekt og sikkerhet av PFO-lukking sammenlignet med behandling med platehemmer og antikoagulasjon. I tråd med våre metoder utførte vi et systematisk litteratursøk etter andre systematiske oversikter publisert i 2018. Vi valgte den systematiske oversikten med relevant komparator og som hadde flest deltagere og nyest litteratursøk.

Helseøkonomisk modell ble utviklet i dialog med kliniske eksperter. Modellen er en Markovmodell med et livstidsperspektiv. Inkludert i modellen er effekt av tiltak på utfallene iskemisk slag og store blødninger. Modellen inkluderer også en rekke sekveletilstander definert ut fra modified ranking skale (mRS). Input-data til modellen er hovedsakelig basert på publisert litteratur. Helseeffekter og kostnader er diskontert med 4%. Absolutt prognosetap for pasienter med PFO og et tidligere iskemisk slag som mottar dagens behandling er beregnet som spesifisert i retningslinjer fra Statens Legemiddelverk.

Vurdering av stråleeffekter ved innføring av PFO-lukking er utført at Direktoratet for strålevern og atomsikkerhet. Mulige organisatoriske konsekvenser er skissert basert på antagelser og innspill fra kliniske eksperter. Kardiologer og nevrologer i klinisk ekspertgruppe har tilført egne avsnitt til kapittelet om organisatoriske konsekvenser.

Resultat

Vi identifiserte 18 potensielt relevante studier, av disse var 13 systematiske oversikter. 11 av disse 13 sammenlignet PFO-lukking med medisinsk behandling, men skilte ikke mellom type legemidler i komparator. To studier rapportere separate effektestimater for sammenligning med platehemmer og antikoagulasjon, av disse hadde en av de to et høyere antall deltagere og også et nyere litteratursøk.

Den valgte systematiske oversikten indikerer at PFO-lukking hos pasienter under 60 år med hjerneslag reduserer risiko for nye hjerneslag, sammenlignet med platehemming (OR: 0.12, 95% KI: 0.04-0.27, moderat kvalitet på dokumentasjonen). Sammenlignet med antikoagulasjonsbehandling er effekten av PFO-lukking på slag mer usikker (OR: 0.44. 95% KI : 0.08-3.83, lav kvalitet på dokumentasjonen). PFO-lukking vil imidlertid trolig føre til færre alvorlige blødninger enn antikoagulasjonsbehandling.

PFO hos personer med et tidligere slag beregnes til å gi et absolutt prognosetap (APT) på 14,8 gode leveår sammenlignet med normalbefolkningen.

PFO-lukking fører til en stor gevinst i form av vunnede gode leveår og også til kostnadsbesparelser over et livstidsperspektiv. Som alternativ til behandling med platehemmere, har PFO-lukking estimert 98% sannsynlighet for å være et kostnadseffektivt alternativ. Sammenlignet med antikoagulasjon, er helsegevinsten og kostnadsbesparelsen mindre, men allikevel stor sammenlignet med andre tiltak. Sammenlignet med antikoagulasjon, har PFO en estimert sannsynlighet på 80% for å være et kostnadseffektivt alternativ. Sikkerheten i estimatet på kostnadseffektivitet er høyere enn sikkerheten på hvert enkelt utfall på klinisk effekt, ettersom man her fanger både effekten av færre ischemiske slag, færre store blødninger og effekten av mindre sekvele i et samleestimat.

Budsjettvirkning per år av PFO-lukking vil trolig bli om lag NOK 34 millioner per år. Estimatet inkluderer ikke en eventuell investering i økt kapasitet.

PFO-lukking introduserer pasient og operatør for ioniserende stråling sammenlignet med medisinsk behandling. Dosenivåene er sammenlignbare med andre vanlige hjerte-prosedyrer og vil være berettiget for PFO-lukking.

En nasjonal innføring av PFO-lukking som metode vil føre til behov for opplæring samt økt kapasitet for diagnostikk og behandling.

Konklusjon

Sammenlignet med platehemmer er PFO-lukking klinisk effektiv til forebygging av nytt slag hos pasienter under 60 år med kryptogent slag og PFO. Sammenlignet med anti-koagulasjon er effekten på forebygging av nytt slag usikkert, PFO-lukking vil imidlertid trolig føre til færre tilfeller av store blødninger.

PFO-lukking er med stor sannsynlighet et kostnadseffektivt alternativ til medikamen-tell behandling. Stråleeffektene er sammenlignbare med andre prosedyrer. Nasjonal innføring av PFO-lukking vil gi organisatoriske virkninger i form av økt behov for opp-læring, økt kapasitet til behandling og diagnostikk. Organisatoriske konsekvenser bør utredes nærmere av de regionale helseforetakene.

Preface

The Norwegian Institute of Public Health takes full responsibility for the content of this report. External expert group and external reviewers hold no responsibility for the content of the report.

The Norwegian Institute of Public Health received a commission from the Commissioning Forum in The National System for Managed Introduction of New Health Technologies within the Specialist Health Service in Norway on the 9th of March 2018 to undertake a full Health Technology Assessment, with emphasis on Health Economics, of PFO closure for the prevention of ischemic stroke. NIPH started the project on the 14th of August 2018.

The project group would like to extend a large thank you to our excellent expert group, internal reviewers and external reviewers who all provided valuable insights and comments to the draft report.

The internal project group consisted of:
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Potential conflicts of interest:

Per Olav Vandvik declares: Per Olav Vandvik is a part-time employee at NIPH as senior researcher. He also holds a position as professor at Faculty of Medicine, University of Oslo. Of particular relevance for this report is his leadership of the MAGIC Evidence Ecosystem Foundation, a non-profit based in Oslo, which also is responsible for The BMJ Rapid Recommendations project. Dr Vandvik declares no conflict of interest for his participation in the systematic review team and in the expert panel who issued a strong recommendation for PFO closure in The BMJ (1). He suggested to Norwegian stroke experts that they could propose a national HTA for this topic and base the work on the linked systematic review informing the recommendations in The BMJ. This is aligned with objectives of NIPH and the New Methods system in order to increase efficiency and gain speed in the face of new technologies that could change practice and national HTA processes.

Specific contributions to the report:

Ida Ormberg wrote sections on risks from radiation. Ulrike Waje-Andreassen, Titto Idicula and Mona Skjelland wrote the first draft of the section «Organisational aspects from a neurological perspective». Elisabeth Leirgul and Kjetil Lunde wrote the first draft of the section «Organisational aspects from a cardiological perspective».

LOGG	
Suggestion submitted for full HTA	25.01.2018
HTA report commissioned	09.03.2018
Start HTA	14.08.2018
Clinical experts contacted first time	08.10.2018
First meeting with clinical expert group	30.10.2018
Report sent to external reviewers	01.02.2019
Report sent to New Methods	29.03.2019
Time	
Number of days from commission to project start	158
Number of days from commission to delivery	385

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Introduction

In this report, we evaluate the clinical effectiveness, safety, cost-effectiveness and organisational consequences of PFO closure in patients with cryptogenic stroke and PFO. This intervention aims to reduce the risk of recurrent stroke.

12 000 Norwegians have a stroke annually and represents an important cause of loss of life expectancy and quality of life (2). Stroke occurs most commonly in the older population, but approximately 20% patients are under the age of 60. Patients with a previous stroke are at increased risk of secondary strokes (3-5). Recurrent strokes are associated with a higher risk of cognitive worsening, drop-out of working life, problems with child care, loss of independence and death (6;7), compared to primary strokes.

Prevention of recurrent stroke aims to target the causes of the primary stroke. The recommended diagnostics for identifying possible aetiologically relevant factors includes blood-samples, ultrasound of the carotid and vertebral arteries, transcranial ultrasound, transthoracic and transoesophageal echocardiography and long-time heart rhythm monitoring. When these tests do not find any clear etiology, the stroke is classified as «cryptogenic». Approximately a third of all ischemic strokes are cryptogenic among young ischemic stroke patients. It is believed that some of the most common causes of cryptogenic strokes are paradoxical embolism (=embolic strokes) due to a right-to left shunt, most often communication between the right and left side of the heart (such as patent foramen ovale), less often located in the lungs or in other place.

Foramen ovale is an opening between the right and the left atrium of the heart, which has an embryological function in allowing the circulation to bypass the immature lungs by direct shunting of oxygen-loaded blood through the foramen ovale to the left heart, whitch then pump this blood to the whole body prior to birth. Normally, this opening

closes at birth, when oxygen exchange via the lungs becomes possible. In approximately 25% of the population, however, the foramen ovale is not completely closed («patent foramen ovale=PFO»). This can allow blood clots that form in veins to bypass the lungs and travel into the systemic circulation, where they can cause a cerebral infarction or damage to other organs.

It is known that the prevalence of PFO is higher in patients who have had a cryptogenic stroke, than in people without stroke at the same age. While this suggests that the condition may play an etiological role in at least some patients, one must also consider the fact that 25% of the population have PFO, and that in many patients, the PFO is an incidental finding that must be interpreted in the context of other possible causes of stroke. Factors that suggest PFO as a cause of the stroke include a large PFO, with a big right-left shunt and the combination of PFO and an atrial septal aneurysm. Factors that suggest other causes than PFO, include any other reason for increased risk of stroke, such as atrial fibrilation. Patient with cryptogenic stroke and PFO are currently mostly treated with antiplatelet drugs (e.g. aspirin, dipyridamole or clopidogrel), according to national clinical practice guidelines (8). Some patients are also likely being treated with anticoagulation therapy (warfarin or direct oral anticoagulation treatment; DOAC).

Closure of PFO through implantation of a closure device via a catheter, is a mode of treatment which has become increasingly available. Such treatment is usually provided by interventional cardiologists. The known risks of PFO closure include procedure related complications as bleeding complications, pericardial effusion, perforation, embolic events, device embolization and atrial fibrillation and in the long run atrial fibrillation, endocarditis and erosion (9).

In August 2017, 3 high quality randomized trials were published in New England Journal of Medicine, comparing PFO closure with medical management with antiplatelet therapy or anticoagulation therapy. These trials, together with a more recent trial published March 2018, hold the potential to change clinical practice. This was reflected in strong recommendations for PFO closure published August 2018 (1), which triggered the request for the health technology assessment reported here. Similar recommendations have been issued in Denmark and Sweden during 2018.

Methods

Clinical Effectiveness

As proposed in the request for this health technology assessment by the Norwegian Stroke Foundation, we aimed to use a recently published systematic review of high quality, rather than duplicating evidence synthesis to assess clinical effectiveness of PFO closure. We were notified that surch a recent systematic review was published (10), linked to the BMJ Rapid Recommendation on PFO closure, August 2018 (1). In order to ensure identification of the most relevant and high-quality systematic review we performed a systematic literature search and selection process, based on the clinical question we formulated, inclusion outlined below.

Study type:	Systematic reviews of randomized trials
Population:	Patients with cryptogenic stroke (cerebral infarction) and patent foramen ovale
Intervention:	Closure of patent foramen ovale with any closure device (with or without antiplatelet therapy)
Comparator:	Antiplatelet therapy (Acetalsalicylic acid, Clopidogrel, etc) Anticoagluation therapy (Warfarin, DOAC)
Outcome:	Recurrent stroke Death Transient ischemic attack Major bleeding Transient atrial fibriliation Persistent atrial fibrilation Pulmonary embolism Systemic embolism Device or procedure related complications
Languages:	Any language

Literature search

Our research librarian (IH) planned and executed all systematic searches in collaboration with the project group. We searched for systematic reviews and meta-analyses, and replicated the search for primary studies conducted by Mir et al (10) for their systematic review in BMJ Open. The search for systematic reviews was limited to articles published in 2018. The complete search strategy, list of databases and websites and explanations are listed in Appendix 1.

Article selection and assessment of included studies

Two persons (AH and GH) independently reviewed all citations generated by the search for systematic reviews, to identify potentially relevant articles based on title and/or abstract. Full text versions were obtained for articles appearing to meet our inclusion criteria or for articles in which sufficient information was not available to make a decision. Two persons independently assessed the relevance of articles according to our list of inclusion criteria. Disagreements were resolved by discussion or by consulting a third party.

The methodological quality of systematic reviews meeting our pre-defined criteria was evaluated using the checklist for systematic reviews (11). All assessments were performed and agreed upon by two persons. Because more than one systematic review was rated as high quality, we chose between them on the basis of number of included studies/participants, and the date of their search for primary studies. The choice was also influenced by the clinical question formulated in the request for a national HTA.

Studies that attempted to disentangle the effects of antiplatelet therapy from the effects of anticoagulation therapy were preferred to studies that joined these two modes of treatment into a single composite comparator group. Network meta-analyses were preferred to meta-analyses containing only direct comparisons.

Data extraction

We extracted data as they were presented in the attached systematic review. When data were presented in several ways, we chose to report data in our preferred order: hazard ratio (HR), risk ratio (RR) and odds ratio (OR) with 95% confidence intervals (CI), or credible interval (CrI) in the case of network meta-analysis. When the included systematic review did not report data for our pre-specified outcomes, we retrieved the original publications to see if the outcomes were reported there.

Assessment of quality of evidence

We made use of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) ratings presented in the attached systematic review. For all outcomes, the systematic review team assessed the certainty of evidence of benefits and harms of PFO closure compared to other treatments. GRADE allows a systematic and transparent critical appraisal of the potential limitations due to risk of bias, inconsistency, imprecision, indirectness and publication bias. We made use of Summary of Findings (SoF) tables from the selected systematic review and associated BMJ Rapid Recommendations, in an Infographic format and in MAGICapp (www.magicapp.org). The SoF-tables provide evidence summaries with relative and absolute effects across all outcomes and associated certainty of evidence.

GRADE gives the following definitions of the different quality of evidence:

- **High:** Further research is very unlikely to change our confidence in the estimate of effect.
- **Moderate:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- **Low:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
- **Very low:** Any estimate of effect is very uncertain.

We presented the external experts with the GRADE SoF-tables and asked them to explicitly report disagreements with assessments made by the systematic review team. In the case of such disagreements, we planned to perform an independent critical appraisal of the identified studies and reported meta-analysis using the GRADE approach.

Health economic evaluation

We performed a model based cost-utility analysis (CUA) (12). The analysis was performed from a healthcare provider perspective, and discounted both costs and effects by an annual rate of 4%. We present main results as incremental cost-effectiveness ratios (ICERs), i.e. additional cost per additional unit of health. We measured costs in Norwegian kroner (NOK) and health effects in "years of good life" (quality-adjusted life years, QALYs).

Model structure

We designed a de novo health economic model in order to compare two alternative courses of action, interventional PFO closure and current treatment, with respect to health effects and costs. The decision analytic model can be viewed as two simulated cohorts (one for each treatment alternative) of patients that we follow for a given length of time, in this case until death. The model registers new ischemic strokes, major bleedings, deaths, functional status and health care utilisation for the patients in these two cohorts.

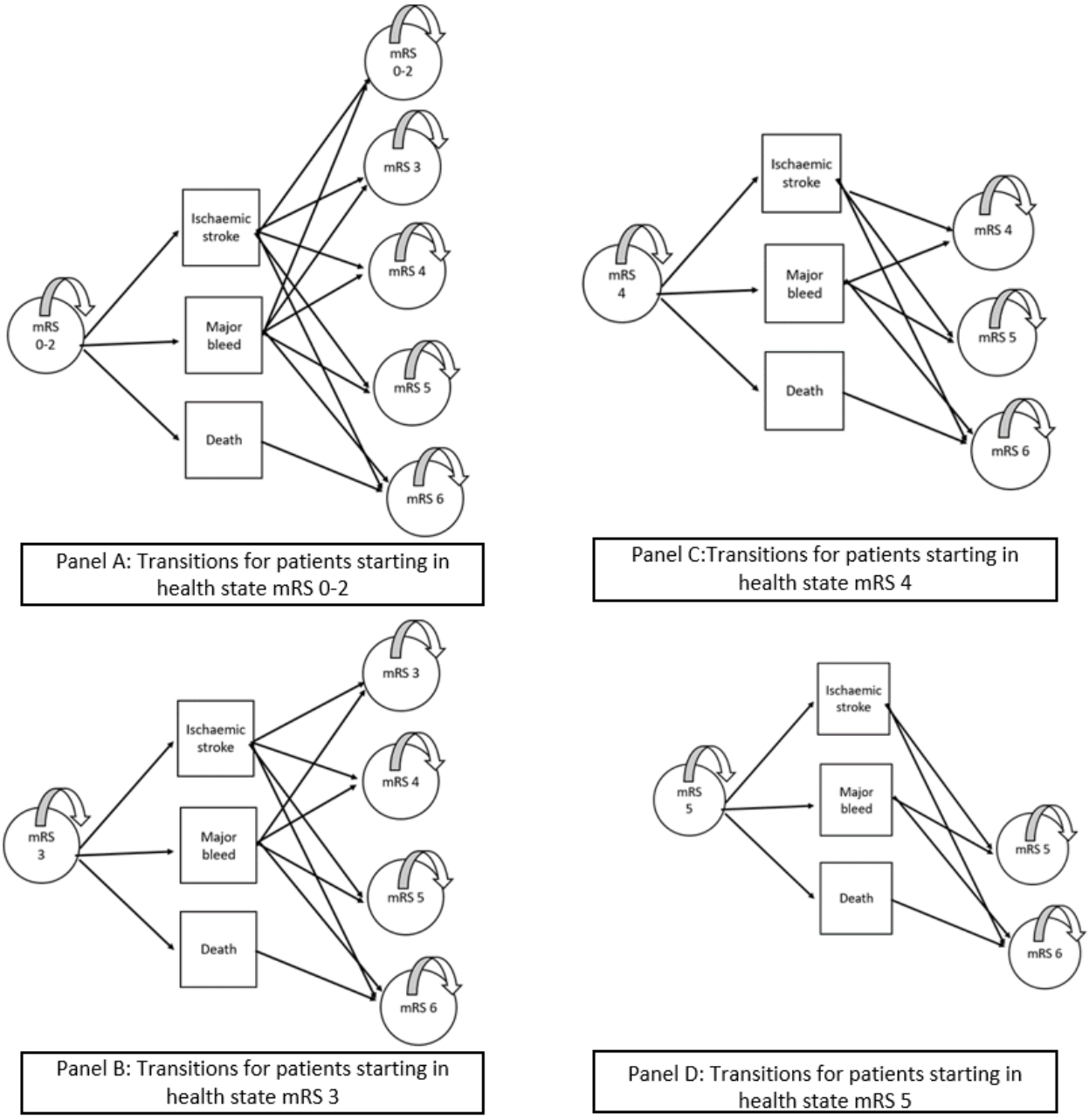
We set up the model as a Markov model with five health states. A specific health state represents a clinical situation that a person can experience for a shorter or a longer time. Health states were in this model defined based on functional status as measured by the modified Ranking Scale (mRS) , we included health states for mRS 0-2, mRS 3, mRS 4, mRS 5 and death (mRS 6). The mRS scale is described below (Table 1):

Table 1: Description of mRS health states (13)

Score	Description
mRS 0	No symptoms
mRS 1	No significant disability: able to carry out all usual activities despite some symptoms
mRS 2	Slight disability: able to look after own affairs without assistance but unable to carry out all previous activities
mRS 3	Moderate disability: requires some help but able to walk unassisted
mRS 4	Moderately severe disability: unable to attend to own bodily needs without assistance and unable to walk unassisted
mRS 5	Severe disability: requires constant nursing care and attention, bedridden, incontinent
mRS 6	Dead

We assigned each health state costs and health effects that accumulate as patients spend time in the specific state. Cost and health effects assigned to different mRS states are described below (Table 4). The model also included new clinical events, such as ischemic stroke, major gastro intestinal bleed and death. Similar to states, events can generate costs and health loss, but new events may also lead to transition to a different state. We illustrate model states, events and possible transitions in Figure 1.

Figure 1: Possible model health states (circles), events (squares) and transitions (arrows) for patients at different levels of disability



Individuals in this evaluation started in mRS state 0-2 (percentage of patients in mRS state 0-1 was approximately 81% and in RS state 2-3 approximately 19% in clinical trials (14)) and were propagated through the model based on transition probabilities estimated from epidemiological and clinical data.

Model parameters

Epidemiology

We based the risk of ischemic stroke on age specific rate of ischemic stroke from the Swedish stroke registry (15), to this rate we applied an increased risk of ischemic stroke connected to the PFO (16) and increased risk of reoccurrence (15) (Table 2). Risk of ischemic stroke caused by PFO was assumed to be higher among younger patients (age below 55) relative to older.

Table 2: Estimated rate of ischemic stroke for patients with PFO and a previous ischemic stroke event

Age in years	Baseline rate of ischemic stroke	Estimated rate of recurrent ischemic stroke with PFO
18	0.0001905	0.0033
45	0.001223	0.0212
55	0.00378	0.0398
65	0.01013	0.1068
75	0.02597	0.2737
85	0.04669	0.4921

For comparison, the estimated rate of ischemic stokes in the control arm of the Mir systematic review (10) was 0.02 for patients with an average age of 45.

Mortality hazards connected to health states are displayed in Table 4. Patients with light disability have a mortality risk similar to the normal population, while patients with severe disability have increased risk of dying. We applied hazards from Slot and colleagues (17) to tables from Statistics Norway. An increased risk of dying was also assigned to patients experiencing an ischemic stroke event or a major bleeding (15;18).

The percentage of patients below the age of 60 experiencing different levels of functional decline following an ischemic stroke were based on information from the Norwe-

gian Stroke Registry (19), c.f. Table 3. Patients with an established functional impairment were assumed not to be able to improve after a new stoke, but would be able to remain at the same functional level or to experience a decline. Possible transitions for persons at different levels of disability are displayed in Figure 1. For example, a person with a functional level mRS 3, could either stay in this health state, or experience a new ischemic stroke. If this person experience a new ischemic stoke, this could lead to increased disability (transition to mRS 4 or transition to mRS 5) or the person could stay at the same level.

Table 3: Modified Ranking Scale (mRS) measured at 3 months after ischemic stroke for patients <65 years old. Numbers from The Norwegian Stroke registry 2015-2017 (19).

	2015	2016	2017	Total 2015-2017
mRS 0-2, n (%)	927 (61.4)	889 (58.4)	985 (61.8)	2801 (60.5)
mRS 3, n (%)	94 (6.2)	70 (4.6)	78 (4.9)	242 (5.2)
mRS 4, n (%)	51 (3.4)	43 (2.8)	49 (3.1)	143 (3.1)
mRS 5, n (%)	3 (0.2)	3 (0.2)	2 (0.1)	8 (0.2)
mRS 6, n (%)	46 (3.0)	44 (2.9)	62 (3.9)	152 (3.3)
Missing data, n (%)	390 (25.8)	473 (31.1)	417 (26.2)	1280 (27.7)
Total, N (%)	1511 (100)	1522 (100)	1593 (100)	4626 (100)

Clinical Efficacy

Current treatment for most patients is antiplatelet therapy. However, since anticoagulation may be considered a better treatment alternative for some patients; we also included this comparison.

In the health economic model, the driving efficacy estimates are risk of ischemic stroke and risk of major bleeding. These are the efficacy estimates generating the difference between the simulated cohorts receiving percutaneous PFO closure and usual care. With different numbers of individuals suffering an ischemic stroke or major bleedings in the two treatment arms, mortality and disability will also be different.

Clinical effect estimates were collected from the systematic review described in the clinical effectiveness section of this report. For the comparison with antiplatelet therapy, the estimates are for the events ischemic stroke and major bleeding, respectively OR= 0.12 (95% CI 0.04 to 0.27) and OR= 0.48 (95% CI 0.20 to 1.12). For the comparison with anticoagulation therapy, the estimates are respectively OR= 0.44 (95% CI 0.08 to 3.83) and OR= 0.26 (95% CI 0.07 to 0.82).

Costs

Costs in health states

Patients with functional decline will use different health and social care resources, e.g. admission to hospital, stays in rehabilitation facilities, home based rehabilitation and other (20).

Cost of ischemic stroke event and sequela health states were based on a Swedish cost study, that linked data from the Swedish stroke registry, Statistics Sweden, the National Board of health and Welfare and the Swedish Social Insurance Agency (21) (Table 4). This study includes data from 42,114 ischemic stroke patients, 17.9% of which were patients below 65 years old.

In order to fit with our purpose of analysing younger patients (below 60) and applying a healthcare perspective as recommended in Norwegian Policy documents (22), information in Supplementary Tables S2 and S4 were combined to generate cost per mRS score for patients below 60 without including cost of work absence. Cost related to work absence constituted 2-34% of cost in the first year and 1-49% in the second year after ischemic stroke, with percentage of total cost clearly largest for the low disability groups (mRS 0-2). Disability costs measured at 12 months were allocated to states and generated as long as a patient spends time at this level of disability, while costs measures at 3 months are assigned as one-time transition costs.

Costs connected to health events

We based cost estimates related to the event major bleed from a previous evaluation of pharmacological anticoagulation treatment (23).

Cost of intervention and comparator

We estimated the total cost of PFO closure to be approximately NOK 113,000 (personal communication Elisabeth Leirgul and Lars Aaberge). Because the device price is confidential, we are not able to present costs disaggregatedly. Based on recommendations for pharmacological antiplatelet treatment and information from the Norwegian Medicines Agency, the annual cost of antiplatelet therapy (acetylsalicylic acid 75 mg per day) is NOK 292 (24). The cost of anticoagulation therapy was based on prices of direct acting oral antagonists (DOACs). Drug cost of one-year treatment with DOAC is estimated to be approximately NOK 9,500.

Health Related Quality of Life

Quality of life multipliers for mRS health states were collected from Samsa et al. 1999 (25), values are displayed in Table 4. We applied multipliers (26) to population values as estimated by Burstøm and colleagues (27). Quality of life decrements connected to the events ischemic stoke and major bleed were based on previous work (23).

Table 4: mRS specific input

Health state	First year cost of ischemic stroke (2017 NOK)	Cost of spending time in mRS health state per subsequent year (2017 NOK)	Death hazard	Quality of life Multiplier	Sources
mRS 0-2	242 657	99 796	1.2	0.7	(17;21;25;28;29)
mRS 3	730 897	580 577	2.58	0.50	(17;21;25;28;29)
mRS 4	940 037	680 624	3.89	0.35	(17;21;25;28;29)
mRS 5	1 532 200	959 164	4.98	0.20	(17;21;25;28;29)
mRS 6 (death)	0	0		0	

One way sensitivity analyses

In order to assess the robustness of the findings to changes in parameters, we performed one-way sensitivity analyses. We present the results as a tornado diagram, where parameters are ranked according to their impact results, with the most important parameter on top and the least influential parameter on the bottom.

Probabilistic sensitivity analysis

We assigned probability distributions to uncertain parameters following the approach described by Briggs and co-workers (30). We performed probabilistic sensitivity analysis based on Monte Carlo simulation by drawing random numbers from each probability distribution 10,000 times and recalculating the incremental cost-effectiveness ratio (ICER). We plotted the simulated ICERs on the cost-effectiveness plane and calculated probability of the interventions being cost-effective relative to comparator. Based on the same simulation, we also created cost-effectiveness acceptability curves illustrating the sensitivity of findings on cost-effectiveness of assumed equity adjusted estimates of alternative cost.

Organisational aspects

We evaluated the organisational consequences of a national introduction of PFO closure by consulting the clinical expert panel and relevant stakeholders.

Risks from radiation

The section about risks from exposure to radiation was written by the Norwegian Radiation and Nuclear Safety Authority.

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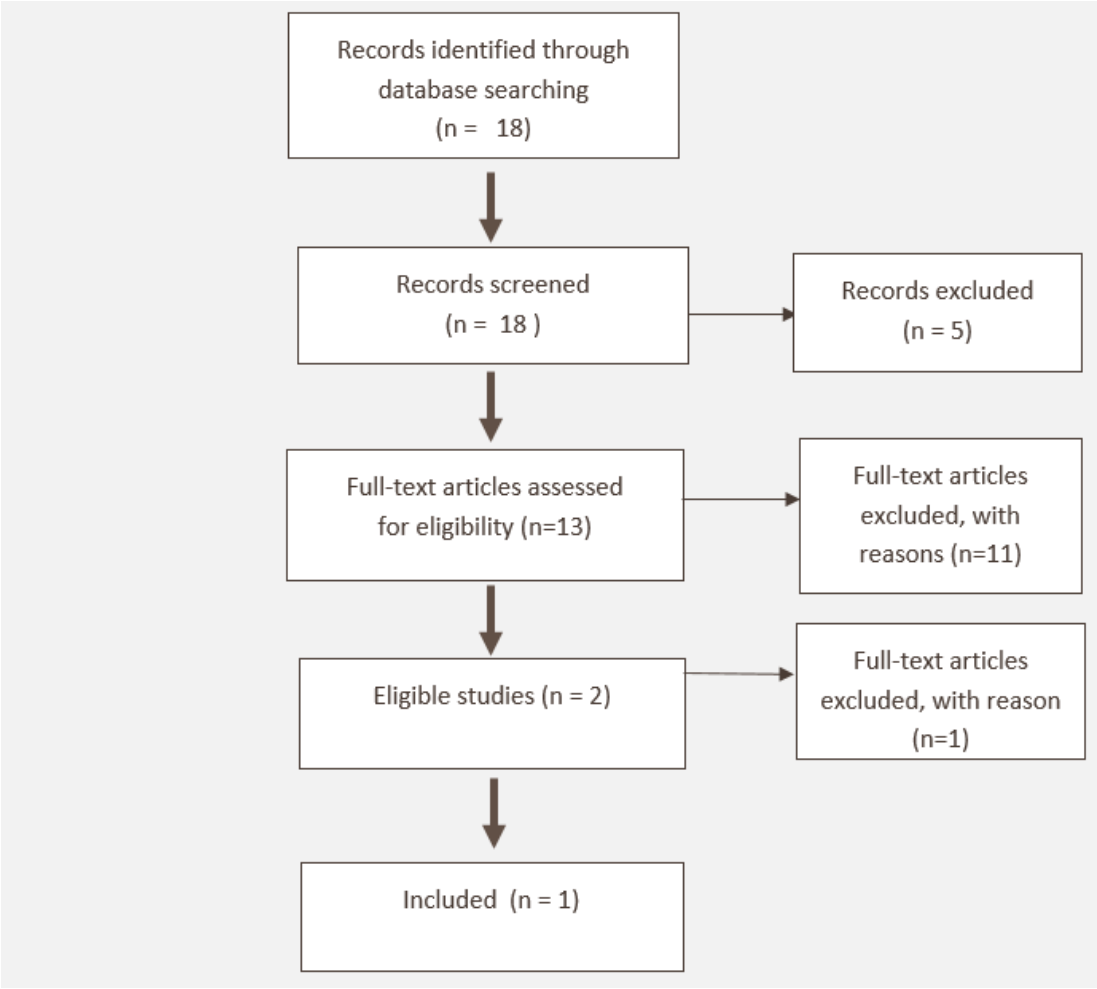
Results

Results of literature search

We identified 18 titles in the systematic literature search for systematic reviews during the period January to August 2018. We reviewed the identified literature and found 13 references to be potentially relevant for our purpose, and full text copies were reviewed. Two systematic reviews with network meta-analyses met our inclusion critera (Figure 2), of which we selected the one with the most appropriate clinical question, design and methods as well as the highest number of participants and the most recent literature search. This selection process is in accordance with our established methods (11). For transparency, we note that the selected review was co-authored by one of the authors of the present report. List of excluded studies and reason for exclusion in Appendix.

Figure 2: Results of literature search



Clinical Effectiveness

Here we report the final evidence summary for both comparisons, followed by detailed results from the literature search, description of the included systematic review and relevant randomised trials as well as some detailed results from a network meta-analysis.

Tables 5 and 6 show the GRADE Summary of Findings for the two comparisons with relative and absolute effects, as well as the certainty in these estimates, across all patient-important outcomes. These SoF-tables are taken from the selected systematic review found to be most credible and informative for our health technology assessment. The external experts agreed on all GRADE assessments made by the systematic review team.

Table 5: PFO closure versus antiplatelet agents

Outcome (time frame)	Antiplatelet therapy	PFO closure	Difference	Certainty in effect (quality of evidence)	Plain text summary
Ischemic stroke (within five years)	100/1000	13/1000	87 fewer per 1000	Moderate (serious imprecision)	PFO closure probably leads to a large decrease in ischemic stroke
Death (within five years)	3/1000	9/1000	6 more per 1000	Moderate (serious imprecision)	There is probably little or no difference in death
Major Bleeding (within five years)	14/100	7/1000	7 fewer per 1000	Moderate (serious imprecision)	There is probably little or no difference in major bleeding
Persistent AF (within one year)	5/1000	23/1000	18 more per 1000	Moderate (serious imprecision)	PFO closure probably increases persistent atrial fibrillation
Device related adverse events (within one year)	0/1000	36/1000	36 more per 1000	High	PFO closure probably increases device related adverse events

Table 6: PFO closure versus anticoagulation agents:

Outcome (time frame)	Anticoagulation theraoy	PFO closure	Difference	Certainty in effect (quality of evidence)	Plain text summary
Ischemic stroke (within five years)	29/1000	13/1000	16 fewer per 1000	Low (very serious imprecision)	There may be little or no difference in ischemic stroke
Death (within five years)	13/1000	9/1000	4 fewer per 1000	Moderate (serious imprecision)	There is probably little or no difference in death
Major Bleeding (within five years)	27/100	7/1000	20 fewer per 1000	Moderate (serious imprecision)	There is probably little or no difference in major bleeding
Persistent AF (within one year)	5/1000	23/1000	18 more per 1000	Moderate (serious imprecision)	PFO closure probably increases persistent atrial fibrillation
Device related adverse events (within one year)	0/1000	36/1000	36 more per 1000	High	PFO closure probably increases device related adverse events

Description of the selected systematic review

The included systematic review by Mir et al. (10), investigated the effects of closure of patent foramen ovale (PFO) in patients with cryptogenic stroke, as compared to medical management with antiplatelet therapy or anticoagulation therapy. The authors conducted the systematic review within the context of a BMJ Rapid Recommendation, with a guideline panel defining which clinical questions to address and that assisted in the interpretation of the evidence (1).

The systematic review and network meta-analysis compared PFO closure +antiplatelet therapy with anti-platelet therapy alone, and with anti-coagulation therapy. We identified two separate comparisons to inform our health technology assessment, as presented below.

Their search for literature was executed on October 16th 2017, with one new study being added later. They aimed to include RCTs addressing the relative impact of PFO closure versus antiplatelet therapy versus anticoagulation in patients with cryptogenic stroke and patent foramen ovale. The authors included 10 RCTs from 8 studies, with a total of 4416 patients. We rated the systematic review to be of high quality, using the «checklist for systematic reviews» (11).

Table 7 provides brief descriptions of the included studies and their characteristics. Some of these studies used a composite comparator group where doctors assigned patients to either anticoagulation or antiplatelet therapy according to clinical judgement, whereas other trials assigned the participants randomly to one of the two options. The participants in the trials are predominantly less than 60 years of age, and a high proportion of participants had a large shunt size. The trials appear to have been conducted in relatively comparable populations, with no obvious causes of between-trial heterogeneity. Note that the CLOSURE 1 trial used the STARFLEX Septal Closure System, an earlier device that is no longer marketed.

The multiprofessional team who conducted the systematic review concluded with moderate certainty evidence for key outcomes such as recurrent stroke, in particular given the risk of bias from lack of blinding as further detailed below. Their assessment was informed by the guideline panel who produced the BMJ Rapid Recommendations. This

panel included experts, without significant conflict of interest but with sufficient clinical, methodological and research-expertise to perform appropriate critical appraisal of the body of evidence identified in the systematic review. The Norwegian external experts separately assessed the GRADE Summary of Findings from the systematic review and agreed on all judgments made concerning relative and absolute effects and the certainty of evidence for all patient-important outcomes.

Table 7: Characteristics of studies in selected Systematic Review (10)

Trial	Intervention Comparator(s)	Study size and duration of follow-up	Patient Characteristics	Comments
PICCS (Homma et al 2002)	Antiplatelet therapy Anticoagulation therapy	N= 601 (approx 1:1) Follow-up: 2 years (fixed)	Age: 59.0 ±12.2 Male (%): 332 (55.2)	Not all patients in this study have cryptogenic stroke
CLOSURE 1 (Furlan et al 2012)	PFO closure + Antiplatelet treatment Medical management	n=909 (approx 1:1) Follow-up: 2 years (fixed)	Age: 50.0 ± 9.4 Male (%): 471 (51.8) PFO shunt size: Moderate or substantial (%): 481 (52.9	STARFLEX Septal Closure System
Shariat et al 2013	Antiplatelet therapy Anticoagulation therapy	N=44 (approx. 1:1) Mean follow-up: 14.6 months	Age: 61.4 ±4.8 Male (%): 28 (63.6)	
PC (Meier et al 2013)	PFO closure + Antiplatelet treatment Medical management	N=414 (approx. 1:1) Max: 5 years Mean follow-up 4.1 years	Age: 44.5 ± 10.1 years Male (%) 206 (49.8) PFO Shunt Size: Small (%):127 (34.4) Medium (%): 162 (43.9) Large (%): 80 (21.7)	Amplatzer PFO Occluder
RESPECT (Saver et al 2013)	PFO closure + Antiplatelet treatment	N= 980 (approx. 1:1) Max: 8 years	Age: 45.9 ± 9.9 years Male (%) 536 (54.7) PFO Shunt size:	Amplatzer PFO Occluder (in 465 of 467 patients)

	Medical management	Median follow-up: 5.9 years	Grade 3: (%): 478 (48.8)	
CLOSE (Mas et al 2017)	PFO closure + Antiplatelet treatment Antiplatelet alone Anticoagulation	N=663 (approx. 1:1:1) Max: 8 years Median follow-up: 5.3 years	Age (%): 43.7 ± 10.2 Male (%): 485 (58.2) PFO with large shunt without atrial septal aneurysm (%): 555(65.5) PFO with large shunt with atrial septal aneurysm (%): 223 (26.7) PFO with mild-to-moderate shunt and atrial septal aneurysm (%): 56 (6.7)	Implantable medical devices approved by intervention cardiology committee
REDUCE (Søndergaard et al 2017)	PFO closure + Antiplatelet treatment Antiplatelet alone	n=664 (approx. 2:1) Max: 5 years Median follow-up: 3.2 years	Age: 45.4 ± 9.3 years Male (%): 399 (60.1) PFO shunt size: Small (%)120 (18.7) Moderate (%) 260 (40.5) Large (%): 261 (40.7)	Helex Septal Occluder or Cardioform Septal Occluder
DEFENSE PFO (Lee et al 2018)	PFO closure + Antiplatelet treatment Medical management	N=120 (approx. 1:1) IQR Max: 4.2 years Median follow-up: 2.8 years	Age: 51.5 ± 13.5 Male (%): 67 (55.9) PFO size, mm: 3.2 ± 1.3	Amplatzer PFO Occluder

Results from primary studies

The systematic review is based on data from direct comparisons in the included primary studies. We present these data as they appear in the original publications. We used the risk of bias evaluations performed by the authors of the systematic review. The authors noted risk of bias due to lack of blinding of medical personnel and patients regarding the placement of a PFO closure device. Also, half of the studies had incomplete data.

The results from the primary studies are shown in Table 8, and are presented as hazards ratios with 95% confidence interval when this was available. Otherwise, risk ratios with 95% confidence intervals were calculated by us derived from information contained in the tables in the original publications. No trials presented data on persistent atrial fibrillation separately from transient atrial fibrillation; these outcomes are therefore presented together as a composite outcome.

Table 8: Individual study results, reported as HR or RR (PFO closure vs medical management) with 95% confidence interval, or as the proportion of intervention group who experienced the adverse outcome.

	CLOSURE 1	PC	RESPECT	CLOSE	REDUCE	DEFENSE PRO
Recurrent stroke	HR=0.90 (0.41 - 1.35)	HR=0.20 (0.02 -1.72)	HR=0.55 (0.31-0.999)	HR=0.03 (0.00-0.26)	HR=0.23 (0.09-0.62)	No events in PFO closure group. 5 events (10.5%) in medication-only group.
All cause mortality	Not reported	HR=5.20 (0.25 - 197.61)	HR=0.61 (0.24-1.57)	No events	2 deaths (0.5% in PFO closure group, no events in antiplatelet group.	Not reported
TIA	HR=0.75 (0.36 -1.55)	HR=0.71 (0.23 - 2.24)	HR=0.64 (0.34-1.20)	HR=0.97 (0.37-2.56)	Not reported	1 event (2%) in medication group, no events in closure group
Major Bleeding	RR=2.43 (0.77- 7.69)	RR=0.34 (0.04 to 3.27)	Not reported	Not reported	RR=0.87 (0.41-2.48)	No events in PFO closure group. 2 events (4.9%) in medication group.
Persistent or Transient Atrial Fibrilation	RR=7.92 (2.40 - 26.21)	RR=3.15 (0.64 - 15.6)	0.4% of procedure group	RR=5.43 (1.22 – 24.24)	RR=14.64 (2.01 – 106.9)	3.3% of procedure group
Device or procedure related complications	3.2% of procedure group	1.5% of procedure group	4.2% of procedure group	5.9% of procedure group	3.9% of procedure group	3.3% of procedure group
Pulmonary Embolism	Not reported	Not reported	RR=3.86 (1.09-13.58)	One event in closure group (0.4%), no events in medication group	RR=1.32 (0.12 to 14.47)	No events
Systemic Embolism	Not reported	Not reported	Not reported	No events	Not reported	Not reported

Results from network meta-analysis

The authors in the included systematic review performed a Bayesian hierarchical fixed-effects network meta-analysis, with non-informative priors. Network meta-analysis combines data from different studies, using both direct and indirect evidence. For the comparison between antiplatelet therapy and PFO closure for the stroke outcome, the analysis was restricted to those trials where patients in the control arm were assigned randomly either to antiplatelet therapy or to anticoagulation therapy, or where they were assigned randomly to medical management and where at least 80% of patients in the control arm received antiplatelet therapy rather than anticoagulation. The PFO closure arm was chosen as the reference group. The report presents data for ischemic stroke, death, major bleeding, persistent atrial fibrillation or flutter, transient or paroxysmal atrial fibrillation or flutter, device or procedure-related adverse events, transient ischemic attack, pulmonary embolism and systemic embolism (See Table 9).

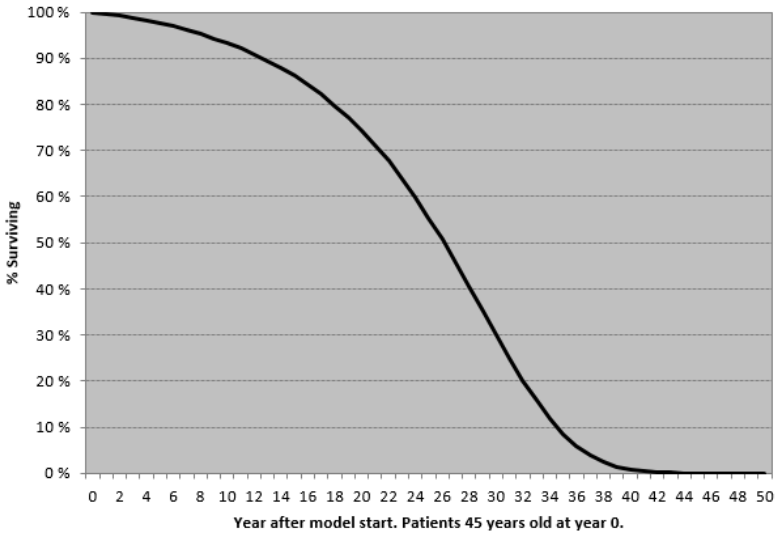
Table 9: Results from network meta-analyses, for PFO closure vs antiplatelet therapy vs anticoagulation therapy

	PFO closure vs antiplatelet therapy	PFO closure vs anticoagulation therapy
Recurrent stroke (OR with 95% CrI)	0.12 (0.04-0.27)	0.44 (0.08-3.83)
All cause mortality (OR with 95% CrI)	3.28 (0.2-174.22)	0.69 (0.02-32.36)
TIA (OR with 95% CrI)	0.82 (0.32-2.11)	1.27 (0.4-4.52)
Major bleeding (OR with 95% CrI)	0.48 (0.2-1.12)	0.26 (0.07-0.82)
Persistent atrial fibrillation or flutter (RR with 95% CI)	4.81 (1.91-12.26)	4.84 (1.91-12.26)
Transient atrial fibrillation or flutter (RR with 95% CI)	3.86 (1.74-8.1)	3.76 (1.74-8.1)
Device or procedure related adverse events (RD with 95% CI)	0.04 (0.02 -0.05)	0.04 (0.02-0.05)
Pulmonary Embolism (OR with 95% CrI)	1.01 (0.09-11.21)	9.09 (3.7-25.0)
Systemic Embolism (OR with 95% CrI)	0.83 (0.13-7.25)	291.0 (0.0-999.0)

Model predictions of survival and ischemic strokes

If we assume no additional mortality connected to the ischemic stroke event or being in a sequela health state, the model predicts a life expectancy of 35 years for 45-year-old patients. When we account for the increased mortality connected to both ischemic stroke events and assign an increased mortality according to disability status as measured by the mRS scale, the predicted life expectancy drops to 27 years in the current treatment group (Figure 3). This means that compared to the general population, the population under evaluation will on average loose eight years of life due to their condition. Figure 3 illustrates the estimated survival curve for the simulated cohort of patients on current treatment.

Figure 3: Estimated survival curve for patients 45 years old with PFO and previous ischemic stroke receiving current treatment



If we simulate 300 patients 45 years old over a lifetime perspective, the PFO group is estimated to experience 125 new ischemic stokes, while the group treated according to current practice (medical management with antiplatelet treatment) will suffer estimated 261 strokes. This means that the health benefit of introducing interventional PFO closure in addition to antiplatelet therapy is expected to be 136 ischemic strokes prevented over a lifetime perspective per 300 patients treated. This result is a direct consequence of the estimated high efficacy of closure on new ischemic strokes (OR=0.12 95% CI from 0.04 to 0.27).

Estimated disease severity

When we calculate disease severity as absolute shortfall, the severity of disease is dependent on age. Patients, who are 45 year old, have a life expectancy of 30.6 "good life years" (i.e. QALYs) (31). With current treatment, patients 45 years old with a PFO and a previous ischemic stroke have a predicted prognosis of 15.8 QALYs, indicating a potential loss of 14.8 QALYs compared to the normal population. Following the approach described by Magnussen and co-workers (32), an equity adjusted f estimate of opportunity cost NOK 605,000 per QALY is suggested.

Incremental cost-effectiveness estimates

Compared to antiplatelet therapy alone, the addition of PFO closure results in a cost saving of NOK 755 339, and a substantial increase in health, 1.4947 QALYs (Table 10).

Table 10: Base case results for patients aged 45 years old, comparison with antiplatelet treatment. The table shows the absolute costs and QALYs over the lifetime of either alternative, as well as the incremental values and the ICER of adding PFO closure to antiplatelet therapy alone.

Intervention	Costs	Incremental Costs	QALY	Incremental QALY	ICER
Antiplatelet treatment	2 925 387		9.4753		
PFO closure	2 170 048	-755 339	10.9701	1.4947	-505 330

For some patients, the preferred treatment would be anticoagulation. Compared to anticoagulation therapy, PFO closure would generate 0.5958 QALYs, while generating a potential saving of NOK 637 195 (Table 11).

Table 11: Base case results for patients aged 45 years old, comparison with anticoagulation

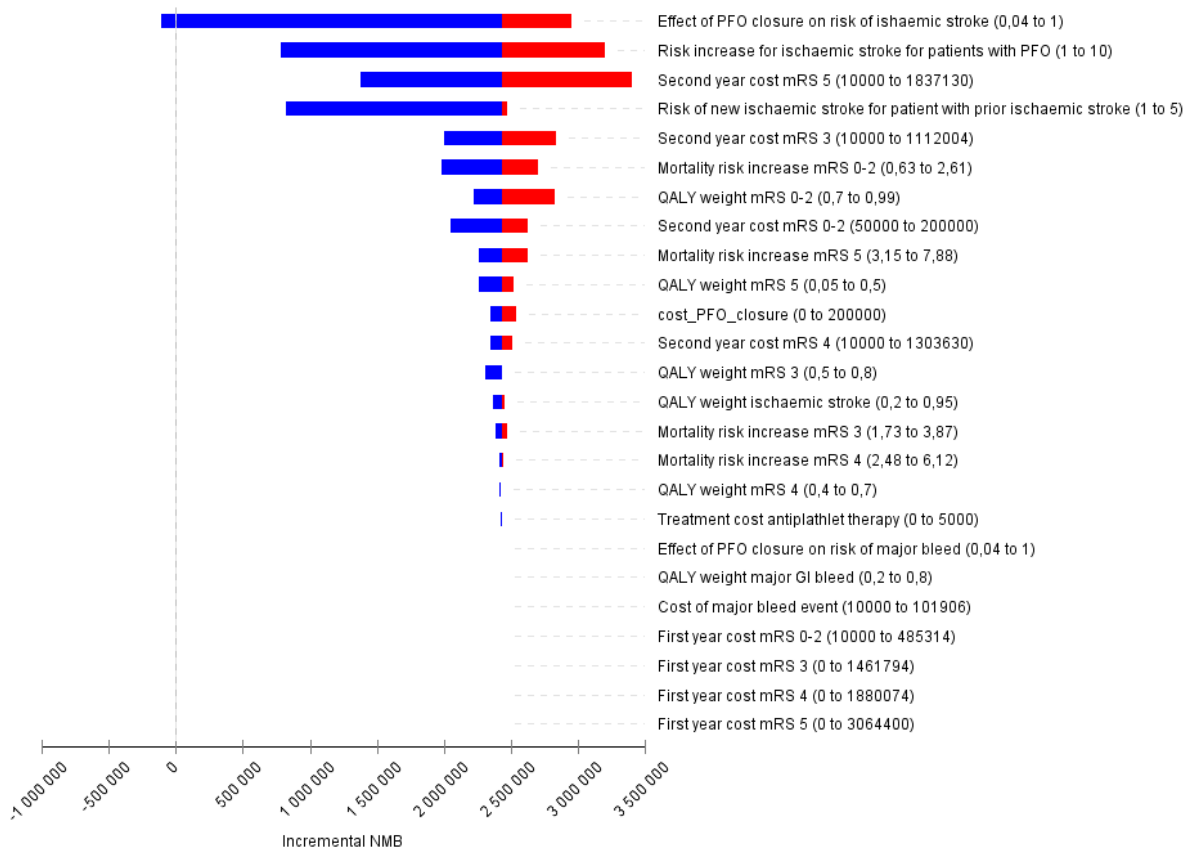
Intervention	Costs	Incremental Costs	QALY	Incremental QALY	ICER
Anticoagulation	3 035 433		9.4862		
PFO closure	2 655 770	-379 663	10.0820	0.5958	-637 195

One way sensitivity analyses

We display the result of the one-way sensitivity analyses in the form of a tornado diagram in Figure 4. As illustrated in the Figure, results are potentially sensitive to reasonable changes for a number of parameters. The most influential parameters are effect of PFO closure on risk of ischemic stroke, risk increase of stroke in the precence of a PFO, second year cost if spending time in the mRS 5 health state and risk of residive stroke.

However, the only change in single parameter that is likely to change the conclusion that PFO closure is a cost-effective alternative to antiplatelet therapy, is if PFO closure is ineffective in reducing the risk of ischemic stroke, this is the only change that will make the incremental net monetary benefits (INMB) cross over to a negative value.

Figure 4: Tornado diagram INMB PFO closure vs. antiplatelet therapy, illustrating the sensitivity of results for reasonable changes in single parameters. Results presented in incremental net monetary benefits (INMB), where all positive values indicate that PFO closure is cost-effective at the defined level of willingness to pay.



Probabilistic sensitivity analysis

Comparison with antiplatelet therapy

Result of the probabilistic sensitivity analysis is displayed in Figure 5. Each dot represents one possible combination from Monte Carlo simulation of incremental cost and effectiveness of PFO closure as compared to antiplatelet therapy. A visual inspection of the plot shows that PFO is likely to generate a larger health gain, while generating cost savings compared to antiplatelet therapy (exact numbers in Table 10).

In exact terms, PFO closure has a probability of 100 % of being more effective (i.e. generating more "good life years") than antiplatelet therapy and a probability of 77% of being less costly. The estimated probability of PFO closure being a cost-effective alternative to treatment with antiplatelet therapy (assuming an equity-adjusted estimate of alternative cost of 605,000 NOK/QALY) is 98%

Figure 5: Incremental cost-effectiveness scatter plot for PFO closure vs. antiplatelet therapy, patients 45 years old.

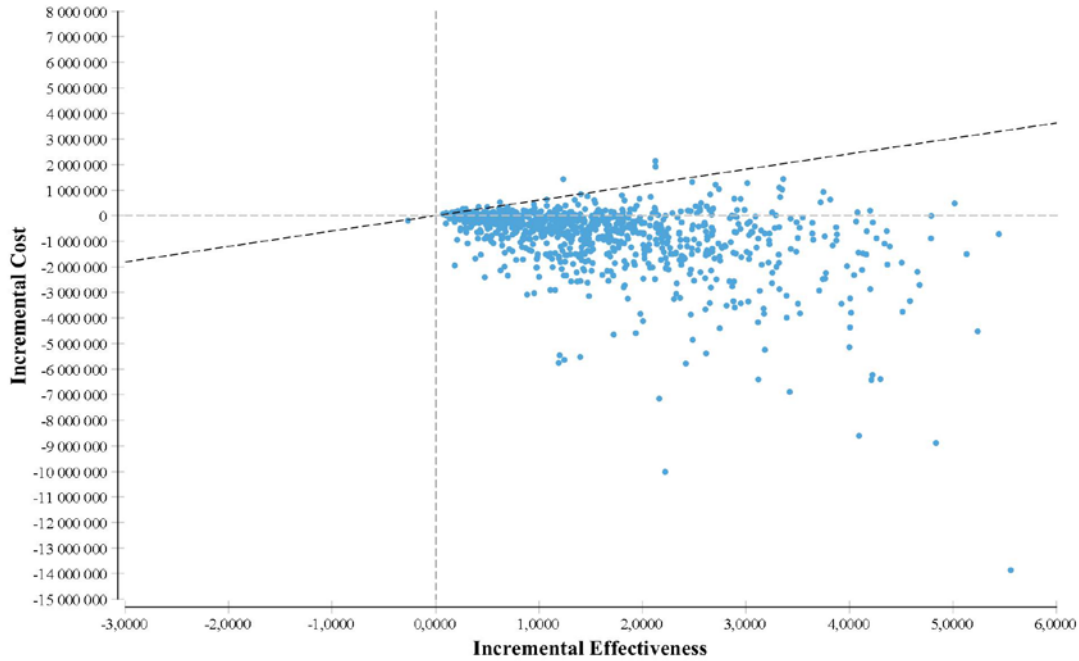


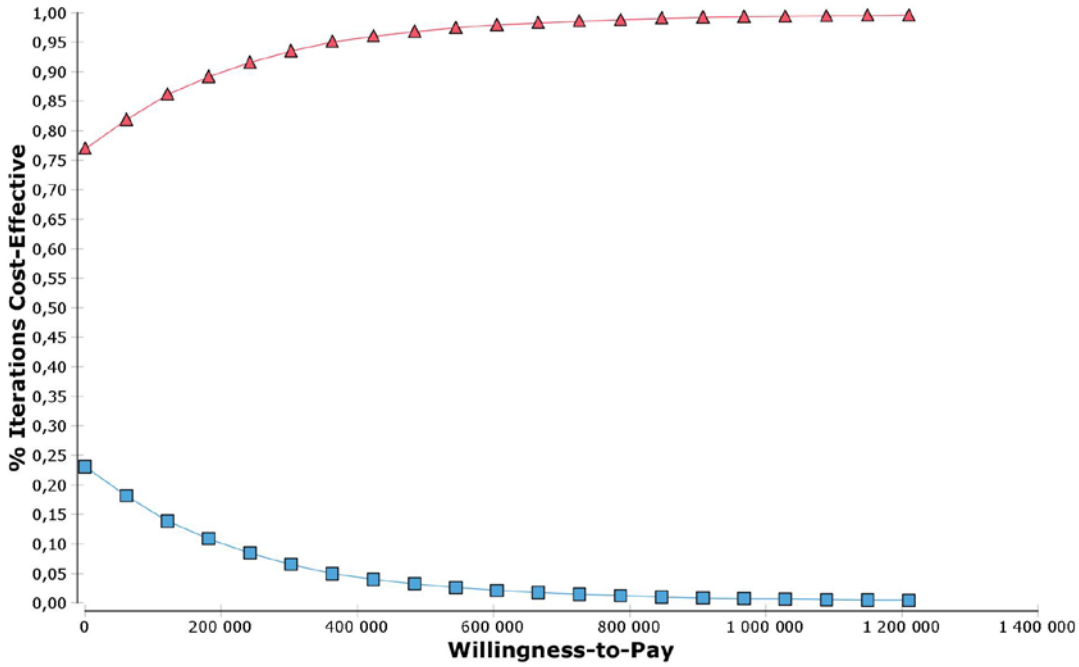
Table 12: Text report for Figure 5

Incremental QALY (IE)	**Incremental cost** (IC)	**Cost-effectiveness**	Frequency	Percentage
IE>0	IC<0	Superior	7690	77 %
IE>0	IC>0	ICER<605000	2094	21 %
IE<0	IC<0	ICER>605000	3	0 %
IE>0	IC>0	ICER>605000	212	2 %
IE<0	IC<0	ICER<605000	0	0 %
IE<0	IC>0	Inferior	1	0 %
Probability that PFO closure is more effective than antiplatelet therapy				100 %
Probability that PFO closure is less costly than antiplatelet therapy				77 %
Probability PFO closure is cost-effective at assumed threshold 605 000				98 %

Cost-effectiveness acceptability curve

The cost-effectiveness acceptability curve (Figure 7) indicates that the conclusion that PFO closure is likely to be cost-effective compared to antiplatelet therapy is insensitive to the assumed equity-adjusted estimate of willingness to pay.

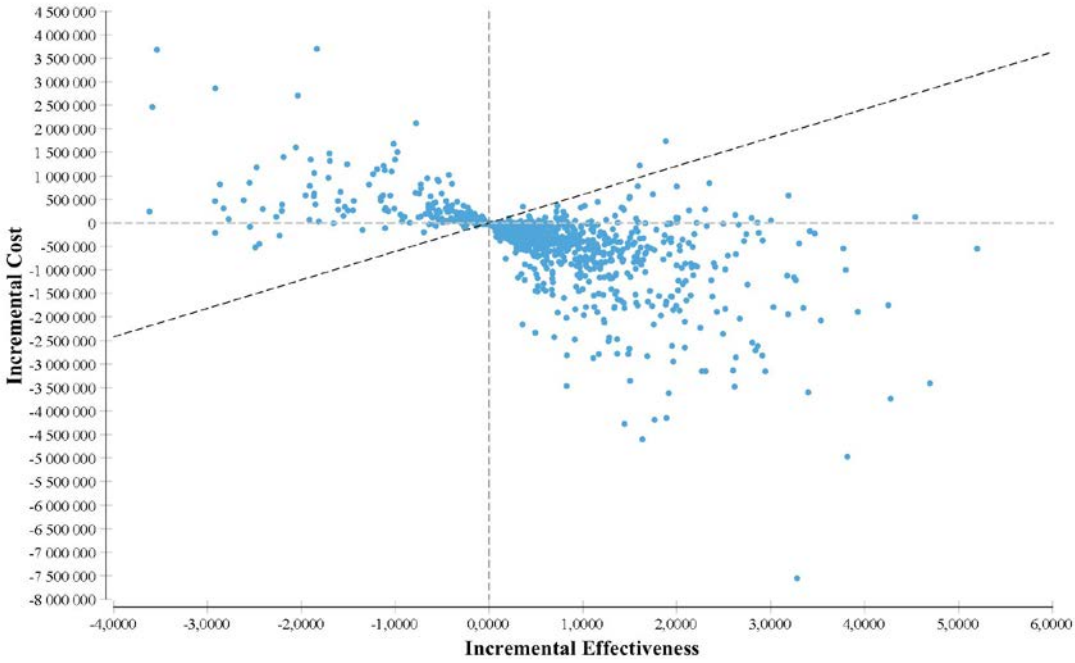
Figure 7: Cost-effectiveness acceptability curve for PFO closure (triangles) vs. antiplatelet therapy (squares)



Comparison with anticoagulation therapy

Results of the probabilistic sensitivity analysis for the comparison of PFO closure vs anticoagulation therapy is shown in Figure 8. As we can see from the plot, there is more uncertainty as to whether or not PFO closure will be more effective, i.e. generate more "good life years", than anticoagulation.

Figure 8: Incremental cost-effectiveness scatter plot for PFO closure vs. anticoagulation therapy, patients 45 years old.



Tabell 13: Text report for Figure 8

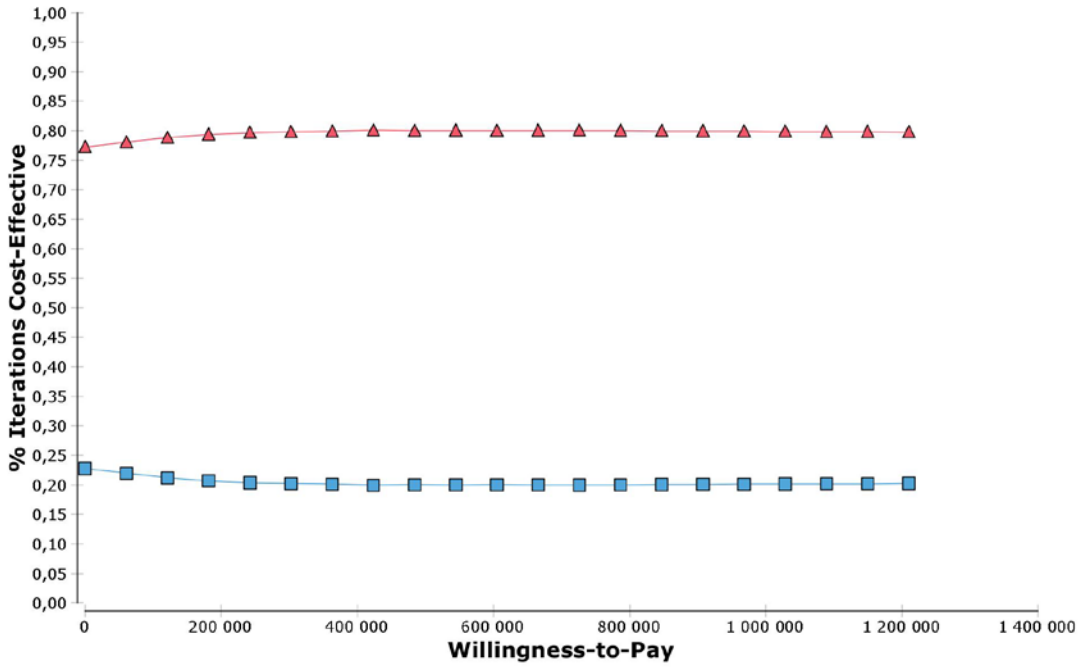
Incremental QALY (IE)	Incremental cost (IC)	Cost-effectiveness	Frequency	Percentage
IE>0	IC<0	Superior	7220	72 %
IE>0	IC>0	ICER<605000	664	7 %
IE<0	IC<0	ICER>605000	113	1 %
IE>0	IC>0	ICER>605000	28	0 %
IE<0	IC<0	ICER<605000	391	4 %
IE<0	IC>0	Inferior	1584	16 %
Probability that PFO closure is more effective than anticoagulation				79 %
Probability that PFO closure is less costly than anticoagulation				77 %
Probability PFO closure cost-effective at assumed threshold 605 000				80 %

In exact terms, our estimates indicate that PFO closure has a probability of 77% of being less costly than anticoagulation, and a probability of 79% of being more effective in terms of QALYs. Probability of being a cost-effective alternative (assuming an equity-adjusted estimate of alternative cost of 605,000 NOK/QALY) is 80%.

Cost-effectiveness acceptability curve

The cost-effectiveness acceptability curve (Figure 9) indicates that the conclusion that PFO closure is likely to be cost-effective compared to anticoagulation is insensitive to the assumed equity-adjusted estimate of willingness to pay.

Figure 9: Cost-effectiveness acceptability curve for PFO closure (triangles) vs. anticoagulation (squares)



Budget impact

If we assume that 300 patients (c.f. section under about organisational aspects) are eligible per year and that cost of PFO closure is NOK 113, 000, budget impact of implementation of the procedure would be NOK 33,900,000 per year. This estimate does not account for potential investments in increased capacity. Considering that approximately 135 of these 300 currently receive PFO closure, the marginal impact of implementation is NOK 18,645,000. The rate of new closures is assumed constant over time, impact per year will thus be the same.

Organisational aspects

Introduction of PFO closure at the national level may entail changes to existing routines, and may require investment in new facilities and new human capital. These consequences may affect both the general, stroke and cardiology units at local hospitals, and the university hospitals which will be conducting the intervention.

If a strong recommendation is issued for PFO closure in patients <60 years with stroke, most patients in this age range will be eligible for PFOclosure. Our deliberations on organisational consequences are built upon this scenario.

From the perspective of the local hospitals, the most important consideration arising from systematic introduction of PFO closure, will be the need to ensure adequate diagnosis (to identify patients with cryptogenic stroke and PFO) and referral for PFO closure. This requires that clinicians refer patients with cryptogenic stroke below 60 years of age to cardiological assessment with transesophageal echocardiography (TEE) to determine the presence and size of a patent foramen ovale and the extent of right-left shunt. Cardiologists then need expertise and capacity to perform TEE with satisfactory quality. Whereas we believe all hospitals, have cardiologists and equipment for TEE, the quality of the TEE procedures in the setting of PFO likely warrants further exploration.

Further testing could be conducted at the local hospitals, including transcranial Doppler (TCD) with bubble test to determine the presence of right-to-left shunt. The diagnostic test accuracy of TCD, using TEE as the reference standard, was considered excellent in a meta-analysis of prospective studies (33). Another study found TCD study feasible in 91% of consecutive patients with TIA or stroke (34). It follows that this test could be introduced at the other university hospitals and local hospitals, pending on local expertise and access to equipment. We have not assessed organisational consequences of the introduction of TCD in more detail as it is not considered necessary, but rather a useful additional test to be considered introduced systematically in Norway, which is outside the scope of our report.

From the perspective of the hospitals at which the PFO closure is conducted, the organisational consequences may be appreciable. Today, this procedure is available only at Oslo University Hospital and Haukeland University Hospital in Bergen. Currently 135 closures are performed each year, but numbers seem to be increasing.

Norway experiences approximately 12,000 incident cases of stroke each year (2), of which 85% are ischemic strokes (35). Approximately 20% of strokes occur in patients aged 60 or younger, and 30% of these are estimated to be cryptogenic. In patients with cryptogenic stroke, with some estimates as high as 50%. With these numbers, one would expect that approximately 300 new patients would become eligible for this treatment each year. In order to meet this demand, increased capabilitites would be required.

There may be a «backlog» of patients who had a cryptogenic stroke before age 60, who may be eligible for PFO closure, but who were not referred at the time of their stroke. The age cut-off is set because PFO is more likely to be aetiologically relevant in young stroke patients; therefore, the key consideration is age at first stroke, not current age. For this reason, a large group of patients with earlier stroke may be eligible. This backlog may result in higher demand in the first few years after national introduction of the PFO procedure, however, it is unlikely that all of the eligible prevalent patients will be referred for closure. If PFO closure is going to be systematically offered to patients previously diagnosed with cryptogenic stroke and PFOclosure the number of procedures will be substantially higher on a temporary basis.

Organisational aspects from a neurological perspective

At the time of this report, few stroke units in Norway utilize transcranial Doppler with bubble test to evaluate young patients (aged 15-60) with acute cerebral infarction. Traditionally, TEE has been considered the “gold standard”, and this method is crucial for verifying the presence of PFO. However, the diagnostics are improved when TEE is complemented by neurological evaluation including transcranial Doppler (33;36;37) .

This requires ultrasound equipment, training of staff and accumulation of competence at the university hospitals and other stroke units that are involved in treating young patients with acute cerebral infarction.

Organisational aspects from a cardiological perspective

With a sensitivity of about 90% and specificity of 90% in studies (33), transesophageal echo (TEE) is considered the gold standard modality for diagnosing PFO. However, the examination is highly dependent on the skill of the operator.

Most local hospitals in Norway have available equipment for echocardiographic assessment including TEE, but the expertise of the cardiologists is varying with regard to examination of the atrial septum and PFO. The sensitivity might be improved by complementing investigations with transcranial Doppler bubble test. Nevertheless, training of cardiologists at local hospitals is necessary to ensure adequate assessment of the atrial septum and other cardiac structures before the decision on treatment.

PFO closure has been performed by interventional cardiologists at OUS Rikshospitalet and Haukeland University Hospital. If new guidelines lead to a substantial increase in referral for PFO closure, it would be reasonable to offer this treatment in all the regional hospitals. This would require training of PFO teams (interventional and imaging cardiologists, and nurses) at St Olav´s University Hospital and possibly at the University Hospital of Northern Norway.

The estimated increase in PFO closure procedures from 125 annually today to 300 annually in Norway may have organisational consequenses. With close to 60 procedures pr million people, more university hospitals with heart surgical service in Norway will have sufficient patient volumes to offer PFO closure on a regular basis. These hospitals all have the necessary facilities for performing these procedures (cath labs, interventional cardiologists, TEE servce etc). However, this patient volume may have an impact on total capacity for patient treatment in cardiological departments as likely will demand more beds, lab capacity and staff. New centers will need training of staff to safely perform these new procedures.

Risks from radiation

PFO closure is a catheter-based transcutaneous procedure to prevent additional ischemic events after cryptogenic stroke. The procedure requires x-ray imaging and can potentially involve high radiation doses. It is therefore necessary to consider the risk related to exposure of both patient and operator. Radiation doses for patients and personnel depend on several factors such as equipment, working technique, experience and competence of personnel, use of protective equipment, complexity of the procedure and equipment for closure. The method for measuring PFO size will also be a relevant factor. The Radiation Protection Regulation (38) has requirements for all medical use of radiation. It is a prerequisite for implementing the method that the hospital meet these requirements.

Stochastic risk for patients

Dose statistics from the last 20 PFO closure procedures at Oslo University hospital and Haukeland university hospital have been collected and are presented in Table 14.

Table 14: Radiation exposure during PFO closure procedures

Hospital	Average patient weight [kg]	Average DAP[Gycm^2]	Median DAP [Gycm^2]	Effective dose [mSv]
A	80	2,37 (0,4-7,2)	2,0	0,5*
B	89	13,75 (2,2-54,0)	10,5	2,7*
PCI**	77	40,7	31,7	8,1*

*Estimate from conversion factor given in Karambatsakidou A. et al (39)

** As a comparison, representative doses from 25 Norwegian coronary laboratories performing percutaneous coronary intervention (PCI) is included (40).

As the table shows, PFO closure results in less exposure than PCI given these data, and the radiation from PFO procedure at both hospitals can be considered to be low in dose. The two hospitals have relatively large difference in DAP-values, which indicate differences in equipment, technique or procedure optimization.

Risk for the patient

Considering the presented dose data there is little risk for deterministic effects. Regular radiation protection routines will be sufficient and detect any incidents involving over exposure. As for x-ray induced cancer, the increased risk of developing cancer compared to the population in general is negligible under these circumstances.

Risk for personnel

Personnel closest to the patient will be exposed to the highest radiation doses, especially cardiologists (REF). Organs most at risk are fingers and eye lenses (usually the left lens is exposed the most). Periodic monitoring of finger and eye lens doses are required. A personal dose meter attached to the left shoulder will give a good indication of the eye lens dose if no safety goggles are used.

It is important that adequate shielding equipment is used and that the personnel have competence to use it properly. Lead aprons and collar should be adapted to the current work situation and be personal. Use of safety goggles will significantly reduce the risk of induction of post capsular opacities and cataracts, if the goggles are ergonomically shaped and suitable for the cardiologist concerned. Lead curtains should be used on the side of the x-ray board, and ceiling mounted screens should be optimally positioned.

Personnel must also comply with regulatory dose limits, as proposed by The International Commission on Radiological Protection (ICRP) (41) and the Radiation protection regulations in Norway (38):

- Skin / hands: 500 mSv (equivalent dose).
- Eye lens: 20 mSv (equivalent dose).
- Whole body dose: 20 mSv (effective dose).

Summary

Percutaneous PFO closure will normally give a moderate radiation dose to the patient and operator. The total dose (investigation, treatment and follow-up) for patients should be documented and evaluated, which is standard procedure in Norwegian hospitals performing such procedures. Any change in PFO closing technique and imaging procedures can affect the patient and personnel doses. This must be taken into account in the risk assessments prior to any relevant change in the procedures.

Discussion

Key findings summary

Key findings of systematic review

Patients diagnosed with cryptogenic (embolic) stroke due to PFO are at high risk of recurrent strokes (e.g. 10% over 5 years) being subsequently treated with currently recommended treatment (i.e. antiplatelet therapy). The selected systematic review included 6 randomized trials comparing PFO closure with medical treatment options, and 2 randomized trials comparing different medical treatment options with each other. In total, there were 3911 participants in these studies. In patients below 60 years PFO closure probably confers an important reduction in ischemic stroke recurrence compared with antiplatelet therapy alone (8%, moderate certainty evidence), but may make no difference compared with anticoagulation (low certainty evidence). PFO closure incurs a risk of persistent atrial fibrillation (2%) and device-related adverse events (3.6%). The most frequent device-related complications reported in the trials were vascular (1%), conduction abnormalities (1%), device dislocation (0.7%) and device thrombosis (0.5%). Compared with alternatives, anticoagulation probably increases major bleeding (2%).

Key findings of health economic evaluation

We find PFO closure to be a cost-effective alternative for secondary stroke prevention in patients with a previous cryptogenic ischemic stroke and diagnosed PFO. Health gains are most pronounced in the antiplatelet comparison, although gains in terms of QALYs are larger for both comparisons than what is usually observed in cost-effectiveness analyses (42). In both comparisons, the base case analysis indicates cost savings over a lifetime perspective.

Strengths and weaknesses

Possible limitations of systematic reviews

The selected review is based only upon randomized controlled trials, which is the optimal study design to inform questions about treatment effects. However the exclusion of non-randomized studies, such as large registry studies, may also result in failing to capture certain important clinical considerations, such as rare adverse events and complications in ordinary clinical practice.

Strengths and weaknesses of health economic evaluation

We have not included costs of informal care; although the effect on family members of functional decline in a loved one following an ischemic stroke may be significant (43). Inclusion of costs of informal care would have made the already very favorable results even stonger.

One simplification made in the health economic model is the assumption that patients are not able to improve their condition. This is a simplification of reality made in this modelling project; in reality, some persons may e.g. improve from mRS 3 to mRS 1. The earlier evaluation of thrombolysis included the possibility for 10% of patient to improve during the first year after a stroke, the 10% improvement probability was based on an expert opinion (44).

One weakness in this economic evaluation relates to the efficacy data on PFO closure as compared to anticoagulation. In the randomized trials, the chosen anticoagulation therapy was in 93% cases warfarin. The most used anticoagulation therapies for incident use is in Norway currently DOACs (45). The Norwegian Institute of Public Health has previously found DOACs to have a favorable profile compared to warfarin (23;46). If we believe that DOACs are more efficacious in preventing strokes while inducing less bleedings than warfarin, differences between PFO closure and DOACs would likely have been smaller, indicating more uncertain health economic results than found in the current analysis.

The cost of antiplatelet therapy is based on the assumption of monotherapy with ASA, a very inexpensive treatment alternative. According to national guidelines and current practice patients having undergone an ischemic stroke are, if they do not have atrial fibrillation, treated with ASA in combination with dipyridamole or with clopidogrel as monotherapy, rather than aspirin. As these are more expensive alternatives than ASA,

the impact on the cost-effectiveness of PFO closure would be to further strengthen the already robust results. As illustrated in the tornado diagram (Figure 4), conclusions are very robust to changes in the cost of antiplatelet therapy.

Strengths of the analysis include strong registry- based input data for mortality rate, rate of ischemic strokes, costs and probability of different mRS states following an ischemic stroke.

Generalisability of findings

Overall completeness and applicability of evidence from the systematic review

The participants in the trials included in the systematic review were primarily younger than 60 years of age, and a large proportion of the participants had moderate or large PFOs or atrial aneurysms. We suggest caution against generalizing study findings to other groups of patients where the magnitude of the effect of PFO closure is expected to be lower (e.g. patients above 60 years of age, smaller PFOs, lower likelihood that the original stroke due to PFO). However, for patients matching inclusion criteria in trials the results should be generalisable, as reflected in the moderate certainty evidence where indirectness was not considered a problem in the GRADE evaluation (1;10).

Generalisability of findings from health economic evaluation

The health economic evaluation is specifically designed for the Norwegian context. Results for comparison with anticoagulation may be different in a Norwegian context than indicated in this analysis, owing to the high uptake of direct-acting oral antagonists (DOACs) (47).

Consistency with other reviews

Consistency of systematic review with other reviews

At least 13 systematic reviews on the effects of PFO closure were published in 2018. These reviews all reach qualitative conclusions, which are broadly consistent with Mir et al. Due to differences in methodological approaches, other systematic reviews differ slightly in their estimates of the magnitude of the effect.

Consistency of health economic evaluation with other studies

Some health economic evaluations of PFO closure have been published in recent years (48-50) (Table 15). Similar to our analysis, these analyses find PFO closure to be a cost-effective alternative compared to medical management. Compared to our analysis, two of the analyses (48;50) differ in terms of finding increased incremental cost. One reasonable explanation for this divergence is the relatively high costs we have included in the mRS health states, making stroke prevention very favorable in terms of reduced cost. Cost estimates included in our analysis are from a very detailed study using real world data (21), this feature should be considered as a strength of this analysis. Variations in QALY gains estimated is within what is expected, considering differences in model structures and data sources.

Table 15: Published cost-effectiveness analyses

Study (reference) (time perspective, discount factor)	**QALY PFO**	**QALY MM***	**Incr. QALY**	**Cost PFO**	**Cost MM***	**Incr. Cost**	**ICER**
Tirshwell **(50)** (20 years, 3.5%)	12.12	10.8	1.32	£8,084	£5,237	£ 2,842	2,158 £/QALY
Hildick-Smith **(48)** (20 years, 3.5%)	11.21	9.93	1.28	£10,936	£9,869	£ 1,067	833 £/QALY
Leppert **(49)** (15 years, 3%)	12.4	12.0	0.4	$29,282	$32,850	$-3,568	-8,920 $/QALY

*MM= medial management

Implication of results on clinical practice

The national guidelines for stroke will likely be updated in 2019, based on the new and potentially practice-changing evidence for PFO closure. This process will allow clinical experts to weigh in on the implications of the new trials on PFO closure, for management of different groups of patients with cryptogenic stroke.

Need for further research

For the comparison of PFO closure vs anticoagulation the evidence only permits low certainty for the critical outcome of stroke recurrence, due to serious imprecision and indirectness. Further trials could lead to increased certainty and precision around the use of anticoagulation in particular, but also for clarifying the effectiveness of PFO closure in older patients and in patients with smaller PFOs. In addition to randomized trials on anticoagulation, follow-up studies, using observational data (e.g. large registry-based cohort studies) should further clarify the safety profile of PFO closure when performed in usual clinical practice, and add information on potential rare adverse events.

We have indicated some possible organisational consequences of national implementation of PFO closure. However, we would recommend that the regional hospital authorities carefully assess these challenges to ensure that patients across Norway receive equal access to high quality and safe PFO closure.

Conclusion

After combining data from eight trials on this topic, the systematic review by Mir et al, concluded that there is moderate certainty evidence for an important protective effect of PFO closure on risk of ischemic stroke, when compared to antiplatelet therapy alone. It is possible that some of this protective effect can be achieved with anticoagulation therapy. When using anticoagulation therapy as the comparator, the evidence for the effectiveness of PFO closure on risk of ischemic stroke only reaches low certainty. There is however, moderate evidence that PFO closure reduces risk of major bleedings compared to anticoagulation. PFO closure may based on this, be preferable to anticoagulation therapy for some patients.

Findings are likely to be specific to those groups of patients in whom the likelihood is high that the primary stroke was due to paradoxical embolism. This primarily includes younger stroke patients (<60 years). Further research is needed to clarify the extent to which other patient groups would benefit from PFO closure and to obtain higher certainty evidence on use of anticoagulation as an alternative to PFO closure.

We conclude that PFO closure is very likely to be a cost-effective alternative compared to medical management for stroke prevention in patients with cryptogenic ischemic stroke in a Norwegian setting. Conclusion is robust to changes in input data and consistent with findings in the published literature. PFO closure likely carries an acceptable risk from radiation. Introduction of PFO closure will have organisational consequences. Regional Health Authorities should further explore organisational aspects before implementation.

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Appendices

Search strategy

Literature search: ID2018_003 Patent foramen ovale (PFO)-closure

Search date: 2018.08.27
Year of publication: 2018
Study type: Systematic review, meta-analysis, health technology assessment
Searched by: Ingrid Harboe, research librarian
Peer review: Elisabet Hafstad, research librarian

Name of database	**Search result**
Cochrane Library: CDSR Reviews, CDSR Protocols	2
Centre for Reviews and Dissemination (CRD): Database of Abstracts of Reviews of Effects; Health Technology Assessments (HTA) Database	0
*__Embase__	62
**__MEDLINE__	17
Epistemonikos	38
PubMed (pubmednotmedline/aheadofprint)	45
SBU	0
Total	**173**
BMJ search result (Hassan's search)	186
Total hits exclusive BMJ search result	**18**
	Ongoing projects
PROSPERO*** (unique hits registered 2014-2018)	**7**
POP database	(1 NICE, 2011)

Annotation:
*Embase [code: oemezd]
**Ovid MEDLINE(R) [code: ppez]
***PROSPERO International prospective register of systematic reviews

Search strategies:

Databases: Embase 1974 to 2018 September 6, Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to September 06, 2018

Hits: 79

#	Searches	Results
1	cerebrovascular disease/ or basal ganglion hemorrhage/ or brain ischemia/ or brain vasospasm/ or experimental cerebral ischemia/ or hypoxic ischemic encephalopathy/ or transient ischemic attack/ or carotid artery disease/ or carotid artery thrombosis/ or cerebral artery disease/ or thromboembolism/ or arterial thromboembolism/ or embolism/ or thrombogenicity/ or thrombophilia/ or thrombosis/ or venous thromboembolism/ or cerebrovascular accident/ or cardioembolic stroke/ or experimental stroke/ or lacunar stroke/	826545
2	(isch?emi$ adj6 (stroke$ or apoplex$ or cerebral vasc$ or cerebrovasc$ or cva or attack$)).tw.	164948
3	((brain or cerebr$ or cerebell$ or vertebrobasil$ or hemispher$ or intracran$ or intracerebral or infratentorial or supratentorial or middle cerebr$ or mca$ or anterior circulation) adj5 (isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus$ or hypoxi$)).tw.	244309
4	((transient adj3 attack$) or TIA or TIAs).tw.	45047
5	paradoxical embolism/	2529
6	heart atrium/ and (embolism/ or thromboembolism/)	867
7	((atria or atrium or paradoxic$ or crossed) adj5 (embolism$ or thromboembolism$)).tw.	3913
8	(cryptogen* adj5 stroke).tw.	3623
9	or/1-8 [Annotation: population part 1: stroke or cryptogenic stroke]	964475
10	heart septum defect/ or heart atrium septum defect/ or patent foramen ovale/	33897
11	heart septum/ or interatrial septum/ or heart foramen ovale/	11251
12	(patent foramen oval? or PFO).tw.	12830
13	(atrial sept$ adj5 defect$).tw.	21514
14	((right to left or R-L or venous to arterial or venous-arterial or V-A) adj3 shunt).tw.	5204
15	or/10-14 [Annotation: population part 2: PFO]	62288
16	9 and 15	10643

17	"prostheses and orthoses"/ or septal occluder/ or atrial septal occluder/ or endoprosthesis/ or cardiac implant/	22233
18	heart surgery/ or minimally invasive cardiac surgery/ or interventional cardiovascular procedure/ or cardiovascular procedure/ or cardiovascular therapeutic device/ or wound closure/	101544
19	(close or closure or occlu*).tw.	1250939
20	(cardioseal or gore helex or amplatzer or starflex or cardia or intrasept or premere).tw.	21544
21	su.fs. [surgery]	3675360
22	or/17-21	4817821
23	16 and 22	5600
24	limit 23 to yr="2018 -Current" [Annotation: since last review search]	352
25	limit 24 to ("reviews (maximizes specificity)") use oemezd	61
26	24 and (Systematic Review/ or Meta Analysis/ or Biomedical Technology Assessment/ or (systematic* review* or meta-analys* or technology assessment*).tw.) use oemezd)	69
27	25 or 26 use oemezd [Annotiation: Embase SR or meta-analysis - Stroke and PFO and closure 2018]	91
28	cerebrovascular disorders/ or basal ganglia cerebrovascular disease/ or exp brain ischemia/ or carotid artery diseases/ or carotid artery thrombosis/ or intracranial arterial diseases/ or cerebral arterial diseases/ or exp "intracranial embolism and thrombosis"/ or exp stroke/	917343
29	(isch?emi$ adj6 (stroke$ or apoplex$ or cerebral vasc$ or cerebrovasc$ or cva or attack$)).tw.	164948
30	((brain or cerebr$ or cerebell$ or vertebrobasil$ or hemispher$ or intracran$ or intracerebral or infratentorial or supratentorial or middle cerebr$ or mca$ or anterior circulation) adj5 (isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus$ or hypoxi$)).tw.	244309
31	((transient adj3 attack$) or TIA or TIAs).tw.	45047
32	Embolism, Paradoxical/	1785
33	heart atria/ and (embolism/ or thromboembolism/)	850
34	((atria or atrium or paradoxic$ or crossed) adj5 (embolism$ or thromboembolism$)).tw.	3913
35	(cryptogen* adj5 stroke).tw.	3623

36	or/28-35 [Annotation: population part 1: stroke or cryptogenic stroke]	1033919
37	heart septal defects, atrial/ or foramen ovale, patent/	19360
38	heart septum/ or atrial septum/ or foramen ovale/	11971
39	(patent foramen oval? or PFO).tw.	12830
40	(atrial sept$ adj5 defect$).tw.	21514
41	((right to left or R-L or venous to arterial or venous-arterial or V-A) adj3 shunt).tw.	5204
42	or/37-41 [Annotation: population part 2: PFO]	54440
43	36 and 42	10386
44	"prostheses and implants"/ or septal occluder device/	58044
45	Wound Closure Techniques/	14938
46	(close or closure or occlu*).tw.	1250939
47	(cardioseal or gore helex or amplatzer or starflex or cardia or intrasept or premere).tw.	21544
48	su.fs. [surgery]	3675360
49	or/44-48	4777289
50	43 and 49	5412
51	limit 50 to yr="2018 -Current" [Annotation: since last review search]	361
52	limit 51 to ("reviews (maximizes specificity)") use ppez	31
53	51 and (Technology Assessment, Biomedical/ or (systematic* review* or meta-analys* or technology assessment*).tw.) use ppez	50
54	52 or 53 use ppez [Annotiation: MEDLINE SR or meta-analysis - Stroke and PFO and closure 2018]	106
55	27 or 54 [Embase or MEDLINE]	110
56	remove duplicates from 55	79
57	56 use oemezd [Embase]	62
58	56 use ppez [MEDLINE]	17

Database: Cochrane Library
Hits: 2

ID	Search	Hits
#1	[mh ^"cerebrovascular disorders"] or [mh ^"basal ganglia cerebrovascular disease"] or [mh "brain ischemia"] or [mh ^"carotid artery diseases"] or [mh ^"carotid artery thrombosis"] or [mh ^"intracranial arterial diseases"] or [mh ^"cerebral arterial diseases"] or [mh "intracranial embolism and thrombosis"] or [mh stroke]	10358
#2	(isch*emi* near/5 (stroke* or apoplex* or cerebral vasc* or cerebrovasc* or cva or attack*)):ti,ab	10735
#3	((brain or cerebr* or cerebell* or vertebrobasil* or hemispher* or intracran* or intracerebral or infratentorial or supratentorial or middle next cerebr* or mca* or anterior next circulation) near/5 (isch*emi* or infarct* or thrombo* or emboli* or hypoxi*)):ti,ab	6619
#4	((transient near/3 attack*) or TIA or TIAs):ti,ab	2308
#5	MeSH descriptor: [Embolism, Paradoxical] this term only	10
#6	[mh ^"heart atria"] and ([mh ^embolism] or [mh ^thromboembolism])	9
#7	((atria or atrium or paradoxic* or crossed) near/5 (embolism* or thromboembolism*)):ti,ab	36
#8	(cryptogen* near/5 stroke):ti,ab	155
#9	{OR #1-#8}	21430
#10	[mh ^"heart septal defects, atrial"] or [mh ^"foramen ovale, patent"]	155
#11	[mh ^"heart septum"] or [mh ^"atrial septum"] or [mh ^"foramen ovale"]	112
#12	(patent next foramen next oval* or PFO):ti,ab	267
#13	(atrial sept* near/5 defect*):ti,ab	174
#14	(("right to left" or R-L or venous to arterial or venous-arterial or V-A) near/3 shunt)	440
#15	{OR #10-#14}	959
#16	#9 AND #15	180
#17	[mh ^"prostheses and implants"] or [mh ^"septal occluder device"]	620
#18	MeSH descriptor: [Wound Closure Techniques] this term only	123
#19	(close or closure or occlu*):ti,ab	27099
#20	(cardioseal or gore helex or amplatzer or starflex or cardia or intrasept or premere):ti,ab	408
#21	MeSH descriptor: [mh /SU] explode all trees and with qualifier(s)	53424
#22	(51-#21)	77451
#23	#16 AND #22	108
#24	#23 with Cochrane Library publication date between Jan 2018 and Dec 2018, in Cochrane Reviews and Cochrane Protocols	2

Annotation:
Line #1: *[mh ^"cerebrovascular disorders"]* - MeSH heading without term explosion
Line #2: *[mh stroke]* - MeSH heading, with term explosion

Line #2: *near/5* - allows for up to four words between two search terms within one sentence
Line #21: *[mh /SUJ]* explode all trees and with qualifier *Surgery*

Database: Centre for Reviews and Dissemination
Hits: 0 (none)

Line	Search	Hits
1	MeSH DESCRIPTOR Foramen Ovale, Patent EXPLODE ALL TREES	32
2	(patent foramen ovale)	37
3	#1 OR #2	42
3	(close or closure or occlu*)	1835
4	#3 AND #4	37
5	#4 IN DARE, NHSEED, HTA FROM 2018 TO 2018	0

Database: Epistemonikos
Hits: 38
Search: (title:(((foramen AND ovale AND patent) AND (closure OR occlu*) AND (stroke OR "brain infarction" OR TIA OR (transient AND attack*)))) OR abstract:(((foramen AND ovale AND patent) AND (closure OR occlu*) AND (stroke OR "brain infarction" OR TIA OR (transient AND attack*))))) AND publication type Systematic Review

Database: PubMed:
Hits: 45
Search (((((foramen[Title/Abstract] AND ovale[Title/Abstract] AND patent)[Title/Abstract] AND (closure[Title/Abstract] OR occlu*)[Title/Abstract] AND (stroke[Title/Abstract] OR "brain infarction"[Title/Abstract] OR TIA[Title/Abstract] OR (transient[Title/Abstract] AND attack*)))[Title/Abstract]))) AND (((systematic* review*[Title/Abstract] OR meta-analys*[Title/Abstract])) AND ("2018/01/01"[PDat] : "2018/12/31"[PDat])) Sort by: Best Match Filters: Publication date from 2018/01/01 to 2018/12/31

Source: Google scholar
Hits: 2
Search: allintitle: patent foramen ovale close OR closure OR occlusion "systematic review "

Database: PROSPERO ongoing systematic reviews
Hits: 9
Search: patent foramen ovale closure

Search update Hassan PFO August 2018

MEDLINE 38

EMBASE 194

Central 49

Subtotal 281

-Dupes/

already seen -95

Total 186

Database: OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Search Strategy:

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1 cerebrovascular disorders/ or basal ganglia cerebrovascular disease/ or exp brain ischemia/ or carotid artery diseases/ or carotid artery thrombosis/ or intracranial arterial diseases/ or cerebral arterial diseases/ or exp "intracranial embolism and thrombosis"/ or exp stroke/ (230969)

2 (isch?emi$ adj6 (stroke$ or apoplex$ or cerebral vasc$ or cerebrovasc$ or cva or attack$)).tw. (62559)

3 ((brain or cerebr$ or cerebell$ or vertebrobasil$ or hemispher$ or intracran$ or intracerebral or infratentorial or supratentorial or middle cerebr$ or mca$ or anterior circulation) adj5 (isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus$ or hypoxi$)).tw. (103913)

4 (TIA or TIAs).mp. (8172)

5 Embolism, Paradoxical/ (900)

6 heart atria/ and (embolism/ or thromboembolism/) (597)

7 ((paradoxic$ or crossed) adj5 embolism$).tw. (1566)

8 (cryptogenic adj5 stroke).tw. (1228)

9 or/1-8 (286727)

Annotation: population part 1: stroke or cryptogenic stroke

10 heart septal defects, atrial/ or foramen ovale, patent/ (13816)

11 heart septum/ or atrial septum/ or foramen ovale/ (9613)

12 (patent foramen ovale or PFO).tw. (5135)

13 (atrial sept$ adj5 defect$).tw. (9704)

14 ((right to left or R-L or venous to arterial or venous-arterial or V-A) adj3 shunt).tw. (2154)

15 or/10-14 (29151)

Annotation: population part 2: PFO

16 9 and 15 (3481)

Annotation: population Stroke and PFO

17 limit 16 to yr="2012 -Current" (1189)

Annotation: since last review

18 limit 17 to ("therapy (maximizes sensitivity)" or "therapy (maximizes specificity)" or "therapy (best balance of sensitivity and specificity)") (479)

19 randomized controlled trial.pt. (466775)

20 controlled clinical trial.pt. (92580)

21 randomized.ab. (419272)

22 placebo.ab. (191052)

23 drug therapy.fs. (2039777)

24 randomly.ab. (295548)

25 trial.ab. (436583)

26 groups.ab. (1824057)

27 or/19-26 (4261802)

28 exp animals/ not humans.sh. (4486684)

29 27 not 28 (3684280)

30 17 and 29 (308)

31 18 or 30 (537)

Annotation: Population stroke and PFO limit to since 2012 and RCTs

32 "prostheses and implants"/ or septal occluder device/ (45797)

33 Wound Closure Techniques/ (1146)

34 (close or closure or septal occluder).tw. (376846)

35 (cardioseal or gore helex or amplatzer or starflex or cardia or intrasept or premere).tw. (9117)

36 su.fs. (1844743)

37 or/32-36 (2191630)

Annotation: Septal occluder device as per Liu 2015 CDSR

38 exp Anticoagulants/ (203901)

39 anticoagulant$.tw. (54749)

40 (acenocoumarol$ or dicoumarol$ or ethyl biscoumacetate$ or phenprocoumon$ or warfarin$ or ancrod$ or citric acid$ or coumarin$ or chromonar$ or coumestro$ or esculi$ or ochratoxin$ or umbelliferone$ or dermatan?sul$ or dextran$ or edetic acid$ or enoxaparin$ or gabexate$ or heparin$ or lmwh$ or nadroparin$ or pentosan sulfuric polyester$ or phenindione$ or protein c or protein s or tedelparin$).tw. (186773)

41 (argatroban or tinzaparin or parnaparin or reviparin or danaparoid or lomoparan or org 10172 or mesoglycan or polysaccharide sulphate$ or sp54 or sp-54 or md805 or md-805 or cy222 or cy-222 or cy216 or cy-216).tw. (2806)

42 (Marevan or Fragmin$ or Fraxiparin$ or Klexane).tw. (607)

43 exp Pipecolic acids/ae, tu (3497)

44 exp Vitamin K/ai (2478)

45 Vitamin K antagonist$.tw. (4748)

46 exp Antithrombins/ae, pd, de, tu (6816)

47 exp Blood coagulation factors/ai, de (16182)

48 exp Blood coagulation/de (18624)

49 (anticoagulat$ or antithromb$).tw. (66451)

50 or/38-49 (365054)

Annotation: anticoagulants as per Berge 2002 CDSR

51 Factor Xa Inhibitors/ (3684)

52 Dabigatran/ (2458)

53 Rivaroxaban/ (2239)

54 (dabigatran or rivaroxaban or apixaban or edoxaban).mp. (7426)

55 anti-factor Xa.mp. (883)

56 (factor Xa adj2 (antag* or inhibit*)).mp. (5293)

57 novel oral anticoagulant*.mp. (1079)

58 noac.mp. (942)

59 noacs.mp. (1244)

60 pradax.mp. (9)

61 pradaxa.mp. (129)

62 BIBR-953.mp. (9)

63 BIBR-953ZW.mp. (2)

64 xarelto.mp. (117)

65 BAY 59-7939.mp. (28)

66 BMS-562247.mp. (7)

67 eliquis.mp. (48)

68 lixiana.mp. (14)

69 DU-176.mp. (2)

70 DU-176b.mp. (26)

71 non-vitamin K.mp. (976)

72 or/51-71 (12209)

73 direct oral anticoagulant*.mp. (1556)

74 DOAC.mp. (633)

75 DOACs.mp. (776)

76 TSOAC.mp. (24)

77 TSOACs.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (36)

78 oral anticoagulant.mp. (4766)

79 (new or novel or direct or direct-acting or target-specific or targeted or non-vitamin K).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (3905470)

80 78 and 79 (2003)

81 72 or 73 or 74 or 75 or 80 (13484)

Annotation: NOACs or DOACs from 2016 Canadian Cardiac Society GL search RC

82 exp Platelet aggregation inhibitors/ (101727)

83 (antiplatelet$ or anti-platelet$ or antiaggreg$ or anti-aggreg$ or (platelet$ adj5 inhibit$) or (thrombocyt$ adj5 inhibit$)).tw. (49721)

84 (alprostadil$ or aspirin$ or dipyridamol$ or disintegrin$ or epoprostenol$ or iloprost$ or ketanserin$ or ketorolac tromethamine$ or milrinone$ or mopidamol$ or pentoxifyllin$ or procainamide$ or ticlopidine$ or thiophen$ or trapidil$).tw. (82822)

85 (acetyl salicylic acid$ or acetyl?salicylic acid or clopidogrel$ or picotamide$ or ligustrazine$ or levamisol$ or suloctidil$ or ozagrel$ or oky046 or oky-046 or defibrotide$ or cilostazol or satigrel or sarpolgrelate or kbt3022 or kbt-3022 or isbogrel or cv4151 or cv-4151 or triflusal).tw. (27102)

86 (Dispril or Albyl$ or Ticlid$ or Persantin$ or Plavix).tw. (670)

87 exp Platelet glycoprotein gpiib-iiia complex/ai, de (3288)

88 (((glycoprotein iib$ or gp iib$) adj5 (antagonist$ or inhibitor$)) or GR144053 or GR-144053 or abciximab$ or tirofiban$ or eftifibatid$).tw. (5236)

89 (ReoPro or Integrilin$ or Aggrastat).tw. (451)

90 exp Platelet activation/de (25889)

91 exp Blood platelets/de (19033)

92 or/82-91 (195586)

Annotation: antiplatelets as per Berge 2002 CDSR

93 37 or 50 or 81 or 92 (2680704)

Annotation: Intervention block

94 31 and 93 (409)

95 limit 94 to ed=20171016-20181231 (38)

Database: Embase <1974 to 2018 August 13>

Search Strategy:

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1 cerebrovascular disease/ or brain infarction/ or brain steminfarction/ or cerebelluminfarction/ or exp brain ischemia/ or carotid artery disease/ or exp carotid artery obstruction/ or cerebral artery disease/ or exp cerebrovascular accident/ or exp occlusive cerebrovascular disease/ or stroke patient/ (384115)

2 (isch?emi$ adj6 (stroke$ or apoplex$ or cerebral vasc$ or cerebrovasc$ or cva or attack$)).tw. (97188)

3 ((brain or cerebr$ or cerebell$ or vertebrobasil$ or hemispher$ or intracran$ or intracerebral or infratentorial or supratentorial or middle cerebr$ or mca$ or anterior circulation) adj5 (isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus$ or hypoxi$)).tw. (138407)

4 tia.mp. or tias.tw. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (16742)

5 paradoxical embolism/ (1555)

6 exp heart atrium/ and (embolism/ or thromboembolism/) (2405)

7 ((paradoxic$ or crossed) adj5 embolism$).tw. (1986)

8 (cryptogenic adj5 stroke).tw. (2218)

9 or/1-8 (434930)

10 heart atrium septum defect/ or patent foramen ovale/ or heart septum defect/ or heart right left shunt/ (33045)

11 heart atrium septum/ or heart foramen ovale/ (4384)

12 (patent foramen ovale or PFO).tw. (7367)

13 ((atrial or atrium) adj3 sept$ adj3 defect$).tw. (12425)

14 ((right to left or R-L or venous to arterial or venous-arterial or V-A) adj3 shunt).tw. (3144)

15 or/10-14 (40661)

16 9 and 15 (6266)

Annotation: condition section as per Liu 2015 CDSB

17 atrial septal occluder/ or septal occluder/ or endoprosthesis/ or cardiac implant/ (9206)

18 heart surgery/ or minimally invasive cardiac surgery/ or interventional cardiovascular procedure/ or cardiovascular procedure/ or cardiovascular therapeutic device/ or wound closure/ (91300)

19 (close or closure or septal occluder).tw. (436892)

20 (cardioseal or gore helex or amplatzer or starflex or cardia or intrasept or premere).tw. (12483)

21 su.fs. (1772947)

22 or/17-21 (2224270)

Annotation: septal occluder device as per Liu 2015 CDSR

23 exp anticoagulant therapy/ or anticoagulant*.mp. or exp anticoagulant agent/ (590546)

24 (acenocoumarol$ or dicoumarol$ or ethyl biscoumacetate$ or phenprocoumon$ orwarfarin$ or ancrod$ or citric acid$ or coumarin$ or chromonar$ or coumestro$ or esculi$ or ochratoxin$ or umbelliferone$ or dermatan?sul$ or dextran$ or edetic acid$ or enoxaparin$ or gabexate$ or heparin$ or lmwh$ or nadroparin$ or pentosan sulfuric polyester$ or phenindione$ or protein c or protein s or tedelparin$).tw. (205198)

25 (argatroban or tinzaparin or parnaparin or reviparin or danaparoid or lomoparan or org 10172 or mesoglycan or polysaccharide sulphate$ or sp54 or sp-54 or md805 or md-805 or cy222 or cy-222 or cy216 or cy-216).tw. (4576)

26 (Marevan or Fragmin$ or Fraxiparin$ or Klexane).tw. (3077)

27 pipecolic acid derivative/ae, dt [Adverse Drug Reaction, Drug Therapy] (76)

28 (Vitamin K adj3 (antagonist$ or inhibit$)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (8050)

29 exp antithrombin/ae, it, dt, pd [Adverse Drug Reaction, Drug Interaction, Drug Therapy, Pharmacology] (1451)

30 (anticoagulat$ or antithromb$).tw. (95439)

31 or/23-30 (713336)

32 exp antithrombocytic agent/ (303720)

33 (antiplatelet$ or anti-platelet$ or antiaggreg$ or anti-aggreg$ or (platelet$ adj5 inhibit$) or (thrombocyt$ adj5 inhibit$)).tw. (70972)

34 (alprostadil$ or aspirin$ or dipyridamol$ or disintegrin$ or epoprostenol$ or iloprost$ or ketanserin$ or ketorolac tromethamine$ or milrinone$ or mopidamol$ or pentoxifyllin$ or procainamide$ or ticlopidine$ or thiophen$ or trapidil$).tw. (151202)

35 (acetyl salicylic acid$ or acetyl?salicylic acid or clopidogrel$ or picotamide$ or ligustrazine$ or levamisol$ or suloctidil$ or ozagrel$ or oky046 or oky-046 or defibrotide$ or cilostazol or satigrel or sarpolgrelate or kbt3022 or kbt-3022 or isbogrel or cv4151 or cv-4151 or triflusal).tw. (40886)

36 (Dispril or Albyl$ or Ticlid$ or Persantin$ or Plavix).tw. (5097)

37 exp fibrinogen receptor antagonist/ae, it, dt [Adverse Drug Reaction, Drug Interaction, Drug Therapy] (12542)

38 (((glycoprotein iib$ or gp iib$) adj5 (antagonist$ or inhibitor$)) or GR144053 or GR-144053 or abciximab$ or tirofiban$ or eftifibatid$).tw. (7497)

39 (ReoPro or Integrilin$ or Aggrastat).tw. (2799)

40 thrombocyte activation/ (24169)

41 thrombocyte/ (92146)

42 or/32-41 (456524)

43 31 or 42 (845913)

Annotation: anti coag or antiplatelet as per Berge 2001 CDSR

44 Dabigatran/ (9357)

45 Rivaroxaban/ (10856)

46 (dabigatran or rivaroxaban or apixaban or edoxaban).mp. (17604)

47 anti-factor Xa.mp. (1121)

48 (factor Xa adj2 (antag* or inhibit*)).mp. (4294)

49 novel oral anticoagulant*.mp. (1787)

50 noac.mp. (1980)

51 noacs.mp. (2215)

52 pradax.mp. (39)

53 pradaxa.mp. (920)

54 BIBR-953.mp. (49)

55 BIBR-953ZW.mp. (4)

56 xarelto.mp. (858)

57 BAY 59-7939.mp. (119)

58 BMS-562247.mp. (52)

59 eliquis.mp. (424)

60 lixiana.mp. (70)

61 DU-176.mp. (18)

62 DU-176b.mp. (194)

63 non-vitamin K.mp. (1164)

64 direct oral anticoagulant*.mp. (2050)

65 DOAC.mp. (983)

66 DOACs.mp. (1100)

67 TSOAC.mp. (60)

68 TSOACs.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (75)

69 ((new or novel or direct or direct-acting or target-specific or targeted or non-vitamin K) adj3 oral anticoagulant*).mp. (7522)

70 (Factor Xa Inhibitors/ or (factor Xa adj2 (antag* or inhibit*)).mp.) and oral.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (3183)

71 or/44-70 (23667)

72 blood clotting factor 10a inhibitor/ or antistasin/ or apixaban/ or betrixaban/ or darexaban/ or edoxaban/ or eribaxaban/ or fidexaban/ or fondaparinux/ or idrabiotaparinux/ or idraparinux/ or letaxaban/ or otamixaban/ or razaxaban/ or rivaroxaban/ or tanogitran/ (19836)

73 oral.mp. or oral drug administration/ (1376085)

74 72 and 73 (10416)

75 71 or 74 (24711)

Annotation: NOAC/DOAC

76 22 or 31 or 42 or 75 (2983556)

77 16 and 76 (3943)

78 limit 77 to yr="2012 -Current" (1957)

79 limit 78 to ("therapy (maximizes sensitivity)" or "therapy (maximizes specificity)" or "therapy (best balance of sensitivity and specificity)") (673)

80 randomized controlled trial/ (484743)

81 ((treatment or control) adj3 group*).ab. (715481)

82 (allocat* adj5 group*).ab. (26099)

83 ((clinical or control*) adj3 trial).ti,ab,kw. (322114)

84 or/80-83 (1269458)

85 78 and 84 (97)

86 79 or 85 (696)

87 limit 86 to em=201736-201852 (194)

Search Name: 2017-10-16 Hassan PFO

Date Run: 14/08/2018 18:40:17

Comment:

ID Search Hits

#1 MeSH descriptor: [Stroke] explode all trees 7664

#2 MeSH descriptor: [Cerebrovascular Disorders] explode all trees 12578

#3 (isch*emi* near/6 (stroke* or apoplex* or cerebral next vasc* or cerebrovasc* or cva or attack*)) 10995

#4 ((brain or cerebr* or cerebell* or vertebrobasil* or hemispher* or intracran* or intracerebral or infratentorial or supratentorial or middle next cerebr* or mca* or "anterior circulation") near/5 (isch*emi* or infarct* or thrombo* or emboli* or occlus* or hypoxi*)) 12242

#5 (tia or tias) 1326

#6 MeSH descriptor: [Embolism, Paradoxical] explode all trees 10

#7 ((paradoxic* or crossed) near/5 embolism*) 45

#8 (cryptogenic near/5 stroke) 154

#9 MeSH descriptor: [Heart Atria] explode all trees 562

#10 MeSH descriptor: [Embolism and Thrombosis] explode all trees 6406

#11 #9 and #10 47

#12 atria* near/3 (emboli* or thromboemboli*) 262

#13 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #11 or #12 25850

#14 MeSH descriptor: [Heart Septal Defects, Atrial] explode all trees 155

#15 "patent foramen ovale" or PFO 286

#16 atrialsept* near/5 defect* 1

#17 (("right to left" or "R-L" or "venous to arterial" or "venous-arterial" or "V-A") near/3 shunt) 2

#18 #14 or #15 or #16 or #17 371

#19 #13 and #18 with Publication year from 2017 to 2018 (in Central) 43

Excluded studies

Study	Reason for Exclusion
Alnasser S, Lee D, Austin PC, Labos C, Osten M, Lightfoot DT, et al. **Long Term Outcomes among Adults Post Transcatheter Atrial Septal Defect Closure: Systematic Review and Meta-Analysis**. International Journal of Cardiology 2018.	Includes observational data. Not limited to PFO, also considers other atrial septal defects.

Alushi B, Lauten A, Cassese S, Colleran R, Schupke S, Rai H, et al. **Patent Foramen Ovale Closure Versus Medical Therapy for Prevention of Recurrent Cryptogenic Embolism: Updated Meta-Analysis of Randomized Clinical Trials**. Clinical Research in Cardiology 2018;107(9):788-98.	Composite comparator group (antiplatelet therapy and anticoagulation therapy analyzed as a single, composite exposure)
Alvarez C, Siddiqui WJ, Aggarwal S, Hasni SF, Hankins S, Eisen H. **Reduced Stroke after Transcatheter Patent Foramen Ovale Closure–a Systematic Review and Meta-Analysis**. The American Journal of the Medical Sciences. **Abstract:** Background	Composite comparator group (antiplatelet therapy and anticoagulation therapy analyzed as a single, composite exposure)
Anonymous. **Correction: Patent Foramen Ovale Closure, Antiplatelet Therapy or Anticoagulation in Patients with Patent Foramen Ovale and Cryptogenic Stroke: A Systematic Review and Network Meta-Analysis Incorporating Complementary External Evidence.[Erratum for Bmj Open. 2018 Jul 25;8(7):E023761; Pmid: 30049703]**. BMJ Open 2018;8(8):e023761corr1. **Abstract:** Mir H, Siemieniuk RAC, Ge LC, et al. Patent foramen ovale closure, antiplatelet therapy	Correction notice, not an article.
Elbadawi A, Barssoum K, Abuzaid AS, Rezq A, Biniwale N, Alotaki E, et al. **Meta-Analysis of Randomized Trials on Percutaneous Patent Foramen Ovale Closure for Prevention of Migraine**. Acta cardiologica 2018:1-6.	Not relevant to our outcomes

Fiorelli EM, Carandini T, Gagliardi D, Bozzano V, Bonzi M, Tobaldini E, et al. **Secondary Prevention of Cryptogenic Stroke in Patients with Patent Foramen Ovale: A Systematic Review and Meta-Analysis**. Internal & Emergency Medicine 2018;21:21.	Composite comparator group (antiplatelet therapy and anticoagulation therapy analyzed as a single, composite exposure)
Fortuni F, Crimi G, Leonardi S, Angelini F, Raisaro A, Lanzarini LF, et al. **Closure of Patent Foramen Ovale or Medical Therapy Alone for Secondary Prevention of Cryptogenic Cerebrovascular Events**. J Cardiovasc Med (Hagerstown) 2018;19(7):373-81.	Composite comparator group (antiplatelet therapy and anticoagulation therapy analyzed as a single, composite exposure)
Giacoppo D, Caronna N, Frangieh AH, Michel J, Ando G, Tarantini G, et al. **Long-Term Effectiveness and Safety of Transcatheter Closure of Patent Foramen Ovale Compared with Antithrombotic Therapy: A Meta-Analysis of 6 Randomised Clinical Trials and 3560 Patients with Reconstructed Time-to-Event Data**. EuroIntervention 2018;12:12.	Composite comparator group (antiplatelet therapy and anticoagulation therapy analyzed as a single, composite exposure)
Kheiri B, Abdalla A, Osman M, Ahmed S, Hassan M, Bachuwa G. **Patent Foramen Ovale Closure Versus Medical Therapy after Cryptogenic Stroke: An Updated Meta-Analysis of All Randomized Clinical Trials**. Cardiology Journal 2018;07:07.	Composite comparator group (antiplatelet therapy and anticoagulation therapy analyzed as a single, composite exposure)
Leppert MH, Poisson SN, Carroll JD, Thaler DE, Kim CH, Orjuela KD, et al. **Cost-Effectiveness of Patent Foramen Ovale Closure Versus Medical Therapy for Secondary Stroke Prevention**. Stroke 2018;49(6):1443-50.	Only health economic evaluation
Lindgren A, Vergouwen MDI, van der Schaaf I, Algra A, Wermer M, Clarke MJ, et al. **Endovascular Coiling Versus Neurosurgical Clipping for People with Aneurysmal Subarachnoid**	Not relevant

Haemorrhage. Cochrane Database of Systematic Reviews 2018;(8).	
Pickett CA, Villines TC, Resar JR, Hulten EA. **Cost-effectiveness and Clinical Efficacy of Patent Foramen Ovale Closure as Compared to Medical Therapy in Cryptogenic Stroke Patients: A Detailed Cost Analysis and Meta-Analysis of Randomized Controlled Trials**. International Journal of Cardiology 2018;21:21.	Composite comparator group (antiplatelet therapy and anticoagulation therapy analyzed as a single, composite exposure)
Sa M, Oliveira Neto LAP, Nascimento G, Vieira E, Martins GL, Rodrigues KC, et al. **Closure of Patent Foramen Ovale Versus Medical Therapy after Cryptogenic Stroke: Meta-Analysis of Five Randomized Controlled Trials with 3440 Patients**. Brazilian Journal of Cardiovascular Surgery 2018;33(1):89-98.	Composite comparator group (antiplatelet therapy and anticoagulation therapy analyzed as a single, composite exposure)
Saber H, Palla M, Kazemlou S, Azarpazhooh MR, Seraji-Bozorgzad N, Behrouz R. **Network Meta-Analysis of Patent Foramen Ovale Management Strategies in Cryptogenic Stroke**. Neurology 2018;91(1):e1-e7.	Smaller sample size and older search than Mir et al.
Saraswat A, Singh K, Jayasinghe R. **Patent Foramen Ovale Closure Compared to Medical Therapy for Prevention of Stroke Recurrence in Cryptogenic Stroke Population: Systematic Review and Meta-Analysis**. Heart, Lung and Circulation 2018;27:S465.	Not systematic review. Retrospective observational analysis
Soomro A, Munir AB, Khan T, Teslova V, Duvvuri S, Kliger C, et al. **Are Percutaneous Patent Foramen Ovale Closure Devices Effective? A Meta-Analysis Assessing Their Long Term Outcomes**. Catheterization and Cardiovascular Interventions 2018;91 (Supplement 2):S196-S7.	Composite comparator group (antiplatelet therapy and anticoagulation therapy analyzed as a single, composite exposure)

Tsivgoulis G, Katsanos AH, Mavridis D, Frogoudaki A, Vrettou AR, Ikonomidis I, et al. **Percutaneous Patent Foramen Ovale Closure for Secondary Stroke Prevention: Network Meta-Analysis**. Neurology 2018;91(1):e8-e18.	No comparison betweenantiplatelet therapy and anticoagulation therapy

List of ongoing trials

International PFO Consortium: Secondary Stroke Prevention In Patients With Patent Foramen Ovale: International PFO Consortium

Prosjektplan for kostnadseffektivitet, effekt og sikkerhet av kirurgisk lukking av patent foramen ovale (PFO) sammenlignet med medisinsk behandling for pasienter med kryptogent iskemisk slag

Prosjektnummer / aktivitetsnummer / bestillingsnummer:	**ID2018_003**
Plan utarbeidet:	20.01.2019

Kort tittel PFO

Kort ingress
Vi vil undersøke kostnadseffektivitet, effekt og sikkerhet av lukking av patent foramen ovale (PFO) til forebygging av nye iskemiske slag hos pasienter med tidligere kryptogent iskemisk slag.

Kort beskrivelse/sammendrag
Hos personer med uforklart iskemisk slag, er årsaken noen ganger hull i hjertet (patent foramen ovale; PFO). Lukking av hullet kan være mer effektivt til forebygging av nye iskemiske slag enn medikamentell behandling. Prosjektet skal undersøke kostnadseffektivitet, effekt, sikkerhet og organisatoriske konsekvenser av metoden.

English:
Short title: PFO

Long title: Cost effectiveness, efficacy and safety of PFO closure as compared to medical management for patients with cryptogenic ischaemic stroke

Short ingress: For patients with a cryptogenic ischaemic stroke, we will assess cost effectiveness, efficacy and safety of surgical PFO closure for prevention of new ischaemic strokes.

Short description: In patients with an unexplained ischaemic stroke, the underlying cause is sometimes a hole in the heart (patent foramen ovale; PFO). Closure of PFO may be more effective in preventing new ischaemic strokes than medical management. This project will assess the cost-effectiveness, effectiveness and organisational consequences of this method.

Prosjektkategori og oppdragsgiver

Produkt (programområde):	Helseøkonomisk evaluering Fullstendig metodevurdering
Tematisk område:	Evaluering av tiltak Helseøkonomisk evaluering Kardiovaskulære sykdommer Nevrologiske sykdommer
Oppdragsgiver: (med navn på kontaktperson for eksterne prosjekter):	Bestillerforum RHF
Prosjektledelse og medarbeidere	
Prosjektleder:	Gunhild Hagen
Prosjektansvarlige (gruppeleder):	Øyvind Melien
Interne medarbeidere:	Anders Huitfeldt Per Olav Vandvik Ingrid Harboe Frankie Achille (innleid)
Eksterne medarbeidere:	Elisabeth Leirgul, Helse Bergen HF Ulrike Waje-Andreassen, Helse Bergen HF Mona Skjelland, OUS HF Titto Idicula, St. Olavs Hospital HF Ketil Lunde, OUS HF Stina Jordal, Helse Bergen HF Ida Wendelbo Ormberg, Statens strålevern
Plan for erstatning ved prosjektdeltakeres fravær:	Oppnevnes av Øyvind Melien

Oppdraget
Beskriv konkret oppdragsbeskrivelse fra oppdragsgiver/forslagsstiller/bestiller.
Bestillingstekst: «Fullstendig metodevurdering, med hovedvekt på helseøkonomi, gjennomføres ved Folkehelseinstituttet for patent foramen ovale (PFO)-lukning ved kryptogent slag.«

Mål
Hovedmål: å evaluere kostnadseffektivitet av PFO lukning i en norsk setting.
Delmål:

a. Gjennomføre en systematisk litteraturgjennomgang på effekt og sikkerhet av PFO-lukking. Hvis mulig, legge BMJ rapid recommendations eller annen systematisk litteraturoversikt til grunn (primært utfallsmål iskemisk slag)
b. Utvikle helseøkonomisk modell
c. Beregne sykdommens alvorlighet (gode leveår, målt i QALY, tapt ved fravær av tiltaket)
d. Bidra til utvikling av beslutningsgrunnlag tilpasset behovet til Beslutningsforum for nye metoder.
e. Teste ut nytt presentasjonsformat for metodevurderingsrapport

Bakgrunn
12 000 nordmenn rammes av hjerneslag hvert år, hvilket utgjør en av de mest betydelige årsakene til tap av forventet levealder og livskvalitet. Pasienter med hjerneslag har økt risiko for sekundære slag: Rundt en femtedel får et nytt slag innen 5 år. Sekundære slag er assosiert med høyere risiko for død, og høyere risiko for alvorlig nevrologisk sekvele, sammenlignet med primære slag.

Forebygging av sekundære slag vil ofte rette seg mot årsakene til det primære slaget. Pasientene blir som regel utredet med ultralyd av halskar, hjerne og hjerte, og hjerterytmemonitorering, med tanke på å finne etiologiske faktorer som kan behandles. Når disse undersøkelsene ikke finner noen klar patologi som kan forklare slaget, blir slaget klassifisert som «kryptogent». Det antas at ca. en tredjedel av slag er kryptogene; de antatt hyppigste gjenværende årsakene etter at en standardutredning har utelukket vanlige årsaker, er blant annet paradoksal emboli på grunn av åpning mellom hjertets venstre og høyre side, paroksysmal atrieflimmer, hjerteklaffsykdommer og aneurisme i hjerteatriet.

Foramen ovale er en åpning mellom hjertets høyre og venstre forkammer, som spiller en embryologisk rolle ved å tillate blodomløpet å forbigå det lille kretsløpet i fosterlivet. Normalt sett vil denne åpningen lukke seg ved fødsel, når oksygenutveksling gjen-

nom lungene blir mulig. Hos ca. 25% av befolkningen blir foramen ovale ikke fullstendig lukket («patent foramen ovale (PFO)»). Dette kan føre til at blodpropper som danner seg i vener kan bevege seg opp gjennom hjertet, og i stedet for å forårsake lungemboli, flytte seg til det store kretsløpet og forårsake hjerneslag.

Det er kjent at forekomsten av PFO er høyere blant pasienter som har hatt et kryptogent slag, enn blant pasienter uten slag i samme alder. Dette tyder på at tilstanden kan spille en viktig etiologisk rolle. Likevel må man være oppmerksom på at 25% av befolkningen har PFO, og at dette ofte kan være et incidentalt funn som må sees i sammenheng med andre mulige årsaker. Faktorer som taler i retning av at PFO var årsak til slaget, er blant annet størrelse på åpningen, og hvorvidt pasienten har aneurysme i forkammerskilleveggen. Faktorer som taler mot at PFO var årsak til slaget, er høyere risiko for andre årsaker til kryptogent slag, slik som atrieflimmer. Disse andre årsakene øker som regel med alder.

Pasienter med kryptogent slag og PFO blir nå ofte behandlet enten med platehemmere eller med antikoagulasjonsbehandling hvis platehemmere er kontraindisert. Lukning av patent foramen ovale gjennom kateterstyrt implantering av et lukningsapparat, er en ny behandlingsform som er blitt tilgjengelig de siste årene. Slik behandling kan utføres av radiologer eller intervensjonskardiologer.

Flere randomiserte studier er gjort de siste årene for å sammenligne kateterstyrt lukning av PFO med platehemming og antikoagulasjon.

Metoder og arbeidsform

En systematisk oversikt fra 2018 (1) ligger inne i bestillingen, bestillingen forutsetter bruk av denne.

Systematisk litteratursøk for å identifisere alle systematiske litteraturoversikter (systematic review, meta-analysis, health technology assessment) publisert i 2018 på effekt og sikkerhet av PFO lukking. Søket blir begrenset til 2018 ettersom en systematisk oversikt fra 2018 ligger inne i bestillingen. Søk i Cochrane Library, Centre for Reviews and Dissemination (CRD), Database of Abstracts of Reviews of Effects; Health Technology Assessments, Embase, MEDLINE, Epistemonikos, PubMed og SBU .

Utvelgelse av SR basert på egnethet og dato for litteratursøk. Bruke SR fra Mir et al. hvis det ikke finnes annen SR med nyere litteratursøk som også er mer egnet. Vi vil vektlegge om analyser er utført separat for sammenligning med platehemmer og med antikoagulasjon.

Utvikle helseøkonomisk modell (2) etter innspill fra kliniske eksperter. Deler av modellstrukturen forventes å være lignende tidligere prosjekter i Kunnskapssenteret/FHI (3-5). Noen helseøkonomiske evalueringer av PFO lukking finnes publisert (6-10). Kommentere mulige organisatoriske konsekvenser etter innspill fra kliniske eksperter. Utarbeide prototype for formidling av resultater.

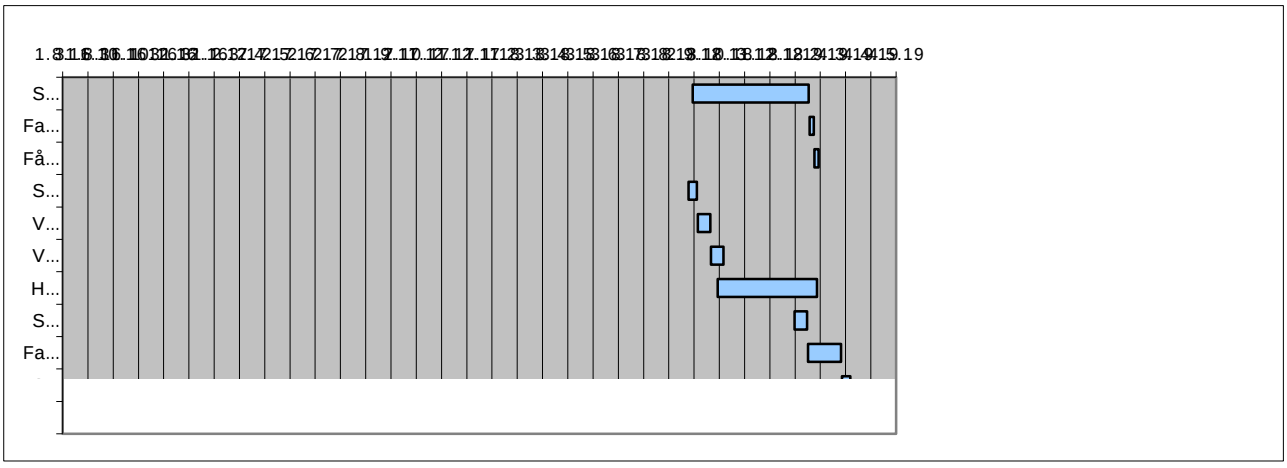
Aktiviteter, milepæler og tidsplan

Gantt-diagram, vedlegg til prosjektplanen

Oppgavene og kalendertiden er kun eksempler og skal endres.

Skriv kun i de gule feltene.

Oppgave	Ansvarlig	Startdato	Kalender-tid i dager	Sluttdato	Reelt tidsforbruk i mnd-verk (overføres budsjettet)
Skrive prosjektplan	GH	01.09.2018	140	19.01.2019	
Fagfellevurdering av prosjektplan	GH	20.01.2019	5	25.01.2019	
Få godkjent prosjektplan	GH	26.01.2019	5	31.01.2019	
Søke etter litteratur	IH	27.08.2018	10	06.09.2018	
Velge ut studier	AH+GH	07.09.2018	15	22.09.2018	
Vurdere studienes metodiske kvalitet	AH+GH	23.09.2018	15	08.10.2018	
Helseøkonomisk modell og analyse	GH	01.10.2018	120	01.01.2019	
Skrive utkast rapport	GH+AH	02.01.2019	15	17.01.2019	
Fagfellevurdering av rappport	GH+POV	18.01.2019	40	27.02.2019	
Skrive ferdig rapport	GH+POV	28.02.2019	10	10.03.2019	
Godkjenne og publisere	GH	11.03.2019	5	16.03.2019	



Oppstartsdato (for FHI.no):
01.09.2018

Sluttdato
Sluttdato (dato for publisering): 16.03.2019

Publikasjon/formidling

– *Sluttprodukt er en fullstendig metodevurdering*
– *Målgruppe for produktet er Beslutningsforum for Nye Metoder*
– *Offentliggjøring to uker etter oversendelse til bestiller*
– *Produktet formidles*
– *Gjeldende rutine er at rapporter normalt sett ikke trykkes opp, men distribueres elektronisk. Oppdragsgiver bør tas med på råd og vurdere opplagets størrelse. Hvis publikasjonen skal trykkes, må utgiften til dette tas med i budsjettet.*
– *Angi om det skal det skrives artikler.*
Planlegger formidling gjennom skriving av artikkel

Risikoanalyse
Hvert elements risikofaktor er produktet av sannsynlighet og konsekvens. Vurderingen angis med graderingene liten, middels og stor.

RISIKOELEMENT	SANNSYNLIGHET	KONSEKVENS	RISIKOFAKTOR
Liten prosjekt-gruppe	Stor	Vanskeligjør rask fremdrift	

Tiltak for å begrense risikoelementenes sannsynlighet og konsekvens:
– Ingen tilgjengelige tiltak grunnet ressurssituasjon

Referanser/litteratur

1. Mir H, Siemieniuk RAC, Ge LC, Foroutan F, Fralick M, Syed T, et al. Patent foramen ovale closure, antiplatelet therapy or anticoagulation in patients with patent foramen ovale and cryptogenic stroke: a systematic review and network meta-analysis incorporating complementary external evidence. BMJ open 2018;8(7):e023761.
2. Petrou S, Gray A. Economic evaluation using decision analytical modelling: design, conduct, analysis, and reporting. BMJ (Clinical research ed) 2011;342:d1766.
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5. Stoinska-Schneider A, Robberstad B, Fure B. NIPH Systematic Reviews: Executive Summaries. In: Mechanical Thrombectomy for Acute Ischemic Stroke, Part 2 Health Economic Evaluation. Oslo, Norway: Knowledge Centre for the Health Services at The Norwegian Institute of Public Health (NIPH)

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6. Hildick-Smith D, Turner M, Shaw L, Nakum M, B OH, Evans RM, et al. Evaluating the cost-effectiveness of percutaneous closure of a patent foramen ovale versus medical management in patients with a cryptogenic stroke: from the UK payer perspective. Journal of medical economics 2018:1-18.
7. Leppert MH, Poisson SN, Carroll JD, Thaler DE, Kim CH, Orjuela KD, et al. Cost-Effectiveness of Patent Foramen Ovale Closure Versus Medical Therapy for Secondary Stroke Prevention. Stroke 2018;49(6):1443-50.
8. Pickett CA, Villines TC, Ferguson MA, Hulten EA. Cost effectiveness of percutaneous closure versus medical therapy for cryptogenic stroke in patients with a patent foramen ovale. The American journal of cardiology 2014;114(10):1584-9.
9. Pickett CA, Villines TC, Resar JR, Hulten EA. Cost effectiveness and clinical efficacy of patent foramen ovale closure as compared to medical therapy in cryptogenic stroke patients: A detailed cost analysis and meta-analysis of randomized controlled trials. International journal of cardiology 2018;273:74-9.
10. Tirschwell DL, Turner M, Thaler D, Choulerton J, Marks D, Carroll J, et al. Cost-effectiveness of percutaneous patent foramen ovale closure as secondary stroke prevention. Journal of medical economics 2018;21(7):656-65.

Indeksering for hjemmesiden

PFO
Patent foramen ovale
Slagforebygging
Iskemisk slag
Slag
Fullstendig metodevurdering
Helseøkonomi
Helseøkonomisk evaluering

Relaterte prosjekter/publikasjoner/studier

1. Wisloff T, Ringerike T, Hagen G, Reikvam A, Klemp M. NIPH Systematic Reviews. In: Efficacy and Cost-Effectiveness of New Oral Anticoagulants Compared to Warfarin for the Prevention of Stroke in Patients with Atrial Fibrillation. Oslo, Norway: Knowledge Centre for the Health Services at The Norwegian Institute of Public Health (NIPH)
   Copyright (c)2013 by The Norwegian Institute of Public Health (NIPH). 2013.

2. Stoinska-Schneider A, Robberstad B, Fure B. NIPH Systematic Reviews: Executive Summaries. In: Mechanical Thrombectomy for Acute Ischemic Stroke, Part 2 Health Economic Evaluation. Oslo, Norway: Knowledge Centre for the Health Services at The Norwegian Institute of Public Health (NIPH)

3. https://nyemetoder.no/metoder/slagambulanse-

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