Supplementary data

Supplementary Appendix 1. Methods

A detailed review of the methodology used can be found in the appendix of the previously published first part of this position paper [1].

In brief, grading of recommendations assessment, development, and evaluation (GRADE) methodology (http://gdt.guidelinedevelopment.org/app/handbook/handbook.html) was used to develop patient-intervention-comparator-outcome (PICO) questions, evaluate the evidence and formulate position statements. However, additional non-PICO questions were developed when there was a lack of clear evidence.

In June 2019, the evidence-synthesis team performed an additional update, beyond the original searches performed for the first part of the manuscript (databases searched: PubMed, Scopus, Google Scholar and ISI).

Evidence was evaluated qualitatively and, where possible, by quantitative methods. Quality of evidence was evaluated by means of the GRADE-PRO GDT online tool (https://gradepro.org) and graded accordingly as high, moderate, low or very low.

Two original meta-analyses were undertaken for the PICO question regarding migraine and for the non-PICO topic regarding arterial desaturation syndromes, because quantitative absolute risk reduction, normally performed with the GRADE method, was not deemed sufficient to formulate position statements.

The process of approval of the final version of this document by the task force, the EAPCI Scientific Documents and Initiatives Committee and by the Scientific Affairs Committee of the European Society of Cardiology was completed on April 14th 2020 and the paper submitted for publication on June 13th 2020.

Formulation of the PICO questions was performed as described in detail in the first part of this document [1]. While initiating the process of writing the first part of this document, the question regarding the treatment of migraine was classified as non-PICO. However, after the 2019 evidence evaluation update, it was clear that new data had been published, rendering it possible to transform it into a PICO question for this second part.

Position statements were formulated by consensus among the members of the task force.

Position statements were expressed evaluating the relevant outcomes in each particular setting. Before the systematic literature reviews, task force members formally defined outcomes for each question, grading their importance for making a decision regarding the position statements. Details regarding the methods used to grade the outcomes and the final grading of outcomes have been provided elsewhere [1].

Tables summarising the position statements indicate the strength of the position statement – strong or conditional (depending on patient values, physician opinion, resources available or setting) according

to the GRADE method. We also indicated the quality of the data: A) data derived from multiple RCTs or meta-analyses; B) data derived from a single RCT or large non-randomised studies; C) consensus of opinion of experts and/or small studies, retrospective studies and registries.

PICO and non-PICO questions underwent the process described above for developing position statements, all of which were finally incorporated into the various sections of the position paper.

PICO and non-PICO questions

1. Should percutaneous closure of a PFO versus diving avoidance be used for secondary prevention of decompression sickness in professional divers?
2. Should percutaneous closure of a PFO versus diving avoidance be used for secondary prevention of decompression sickness in recreational divers?
3. Should percutaneous closure of a PFO versus flying avoidance be used for secondary prevention of decompression sickness or asymptomatic embolisation in airplane pilots?
4. Should percutaneous closure of a PFO versus diving avoidance be used for primary prevention of decompression sickness in professional divers?
5. Should percutaneous closure of a PFO versus diving avoidance be used for primary prevention of decompression sickness in recreational divers?
6. Should percutaneous closure of a PFO versus flying avoidance be used for primary prevention of decompression sickness in airplane pilots?
7. Should percutaneous closure of a PFO versus medical therapy be used for platypnoea-orthodeoxia syndrome?
8. Should percutaneous closure of a PFO + medical therapy versus medical therapy alone be used for migraine? (slightly modified from the question previously adopted in the first part of this position paper) (**PICO QUESTION**)
9. Should percutaneous closure of a PFO versus no therapy be used in patients scheduled for surgery in a sitting position?
10. Should percutaneous closure of a PFO versus medical therapy be used for pregnant women with indications for the secondary prevention of stroke or other left-circulation thromboembolism?

Literature search queries

1. Should percutaneous closure of a PFO versus diving avoidance be used for secondary prevention of decompression sickness in professional divers?
([decompression] or [sickness] or [professional] or [recreational] or [amateur] or [divers] or [diver] or [scuba diving]) and ([pfo] OR [patent foramen ovale]) NOT ([review[pt] OR editorial[pt] OR letter[pt]])
2. Should percutaneous closure of a PFO versus diving avoidance be used for secondary prevention of decompression sickness in recreational divers?
([decompression] or [sickness] or [professional] or [recreational] or [amateur] or [divers] or [diver] or [scuba diving]) and ([pfo] OR [patent foramen ovale]) NOT ([review[pt] OR editorial[pt] OR letter[pt]])
3. Should percutaneous closure of a PFO versus flying avoidance be used for secondary prevention of decompression sickness or asymptomatic embolisation in airplane pilots?
([decompression] or [sickness] or [airplane] or [pilot] or [fighter]) and ([pfo] OR [patent foramen ovale]) NOT ([review[pt] OR editorial[pt] OR letter[pt]])

4. Should percutaneous closure of a PFO versus diving avoidance be used for primary prevention in professional divers?
([decompression] or [sickness] or [airplane] or [pilot] or [fighter]) and ([pfo]OR [patent foramen ovale]) NOT ([review[pt] OR editorial[pt] OR letter[pt]])
5. Should percutaneous closure of a PFO versus diving avoidance be used for primary prevention in recreational divers?
([decompression] or [sickness] or [professional] or [recreational] or [amateur] or [divers] or [diver] or [scuba diving]) and ([pfo] OR [patent foramen ovale]) NOT ([review[pt] OR editorial[pt] OR letter[pt]])
6. Should percutaneous closure of a PFO versus flying avoidance be used for primary prevention in airplane pilots?
([decompression] or [sickness] or [airplane] or [pilot] or [fighter]) and ([pfo]) OR [patent foramen ovale]) NOT ([review[pt] OR editorial[pt] OR letter[pt]])
7. Should percutaneous closure of a PFO vs medical therapy be used for platypnoea-orthodeoxia syndrome?
([platypnoea] OR [orthodeoxia] or [platypnoea-orthodeoxia syndrome]) and ([pfo] OR [patent foramen ovale]) NOT ([review[pt] OR editorial[pt] OR letter[pt]])
8. Should percutaneous closure of a PFO + medical therapy versus medical therapy alone be used for migraine with aura?
(migraine) and ([pfo] OR [patent foramen ovale]) AND ([closure] OR [percutaneous] or [Amplatzer] OR [Watchman] OR [device] OR [Cardioseal/STARFlex] OR [Helex]) NOT ([review[pt] OR editorial[pt] OR letter[pt]])
9. Should percutaneous closure of a PFO versus no therapy be used in patients scheduled for surgery in the sitting position?
([sitting] or [sitting position] or [semi-sitting position]) and ([pfo]OR [patent foramen ovale]) NOT ([review[pt] OR editorial[pt] OR letter[pt]])
10. Should percutaneous closure of a PFO versus medical therapy be used for pregnant women with indications for secondary prevention for left circulation embolism?
([pregnancy] OR [pregnant] OR [postpartum] OR [caesarean]) and ([pfo] OR [patent foramen ovale]) NOT ([review[pt] OR editorial[pt] OR letter[pt]])

Statistical methods, systematic review of evidence, assessment of its quality and meta-analyses

Continuous variables are reported as means (standard deviation) or medians (range). Categorical variables are expressed as n/N (%).

Two original meta-analyses were performed for PICO and non-PICO questions. Statistical pooling was performed according to a random-effects model with generic inverse-variance weighting, computing risk estimates with 95% confidence intervals, using RevMan version 5.3 (The Cochrane Collaboration, The Nordic Cochrane Centre, and Copenhagen, Denmark, http://community.cochrane.org/tools/review-production-tools/revman). Hypothesis testing for superiority was set at the two-tailed 0.05 level. Hypothesis testing for statistical homogeneity was set at the two-tailed 0.10 level and based on the Cochran Q test, with I^2 values of 25%, 50%, and 75% representing, respectively, mild, moderate, and extensive statistical inconsistency.

A systematic review of evidence was performed for each question. PRISMA diagrams were produced to display the selection of the main searches. PRISMA diagrams were not produced for those questions that yielded a low number of publications.

High-quality evidence is generally lacking for PFO-associated syndromes. An evaluation of the quality of evidence was formally performed with the GRADE method for the meta-analyses performed to achieve the aims of this document.

We performed two meta-analyses aimed at assessing: a) the association of right-to-left shunt and decompression sickness, and b) the efficacy of PFO closure on desaturation syndromes. We also performed an original meta-analysis for supporting decisions on the PICO question on the treatment of migraine with PFO.

Supplementary Figure 6, **Supplementary Figure 7** and **Supplementary Table 14**, respectively, display the PRISMA diagrams and the GRADE evaluation of the quality of evidence of the studies included in the meta-analysis assessing the association of right-to-left shunt and decompression sickness. **Supplementary Table 15**, and **Supplementary Table 16** display the studies included in the above-mentioned meta-analysis and in the review of studies involving decompression sickness.

Supplementary Figure 8 and **Supplementary Table 17**, respectively, display the PRISMA diagram and the GRADE evaluation of the quality of evidence of the meta-analysis of the studies assessing the efficacy of PFO closure on desaturation syndromes.

Supplementary Figure 9, **Supplementary Table 6,** and **Supplementary Table 9**, respectively, display the PRISMA diagram, the GRADE evaluation of the quality of evidence of the studies included in the meta-analysis and the characteristics of the studies comparing PFO closure plus medical therapies with medical therapies only for prevention of migraine in patients with migraine and PFO.

The main results of these meta-analyses are displayed in the published text.

Supplementary Appendix 2. Detailed evaluation of specific issues

Decompression sickness pathophysiology and epidemiology

Decompression sickness (DCS) is a complex condition caused by exposure to a hypobaric environment ("decompression"), such as flying at <350 mmHg barometric pressure or >18,000 ft altitude (altitude DCS) or returning to sea level after an ascent from depth (mining or diving). The fall in environmental pressure normally causes a reduction in partial pressure of inspired inert gases (mainly nitrogen), which then diffuse from the tissues where they were dissolved at higher partial pressures and are carried by the blood to the lungs, where they are expired. Even under normal conditions, vascular gas emboli (VGE) frequently form at this stage [124,125], but DCS occurs only if certain local and general conditions are met, where bubbles may be trapped locally, occluding post-capillary venous vessels and/or compressing adjacent tissues and triggering inflammation and thrombosis [126]. If a structural or functional R-T-L shunt is present [127], bubbles can also be arterialised and, according to their size, also trapped in small arteries or arterioles [128–130]. Small emboli may cause subclinical lesions, with still unknown late consequences [5–9].

The calculation of the actual risk of DCS during diving cannot be accurately estimated because accident data mostly stem from private dive insurance records, with clear selection bias, and because of reporting bias due to sometimes evanescent symptoms. Moreover, there are no data on the total number

of dives performed, except for certain isolated dive regions. In fact, while the risk of DCS has been estimated as being from 1 to 3 per 10,000 dives [126,131], an incidence of approximately 1.5% has also been reported [10]. In contrast, the frequency of severe altitude DCS appears to be lower and overall decreasing over time, mainly due to protective systems (e.g., cabin pressurisation), and the compressive effects of descent from altitude. However, in a survey of high-altitude military pilots performing frequent, long sorties (i.e., typically >9 hours per flight at >70,000 ft with <35 mmHg of barometric pressure), approximately 70% reported at least one episode of DCS during their career and, of those, 12.7% were severe enough for them to alter their flight plan or abort the mission [15]. The most recent evaluation of DCS risk per high-altitude flight in U2 aircraft pilots was 0.23%, and the incidence and severity of DCS, including life-threatening and permanent disability, were reported to increase with the number of missions [16,17].

The link between reported DCS events in high-altitude military pilots and PFO has yet to be established; however, the risk of DCS is more than theoretical for altitude greater than 18,000 ft. While altitude DCS is rare for exposures to altitudes between 18,000 ft and 25,000 ft, most cases occur among individuals exposed to altitudes of 25,000 ft or higher. The prevalence of DCS is influenced also by a series of conditions able to increase the risk: repetitive exposures to altitudes above 18,000 ft within a short period of time, rate of ascent to altitude, duration of the exposure to altitudes, physical activity, adequate period of denitrogenation, previous injury, ambient temperature, age, scuba diving before flying.

An intermediate risk could be acknowledged for high performance aircraft military pilots (F 22, Typhoon, etc.). They are exposed at high altitude (cabin pressure equivalent about 25,000 ft, at the ceiling altitude) but for a shorter period of time than U2 pilots. The anti G straining manoeuvre, very similar to a Valsalva manoeuvre, is frequently performed by pilots of aerotactical aircraft and it could increase the risk of DCS due to R-T-L shunt. However, altitude DCS is typically resolved during descent to a lower altitude while breathing 100% oxygen.

The risk for DCS remains negligible for commercial aircraft pilots. In fact, the typical cruising altitude for commercial aircraft is in the range 11,000–12,200 m (36,000–40,000 ft), and the air pressure in the cabin is equivalent to the outside air pressure at 1,800–2,400 m (6,000–8,000 ft) above sea level. The hypobaric environment below 2,500 m (8,200 ft) is usually well tolerated by healthy individuals. The possibility for altitude DCS remains for accidents (malfunctioning of pressurisation, canopy seal, bullets or objects hitting, etc.). However, accidental depressurisation is rare, often slow, and usually it does not affect aircrew health. Rates have decreased dramatically since the 1980s [132].

Training activity for aircrew in a hypobaric chamber is a typical controlled exposure to high altitude (>18,000 ft for a short period of time), that has been carried out for many years now. Reports from training centres show a very low prevalence or absence of DCS [133,134]. Even in these cases of altitude DCS, a clear relationship between index events and PFO presence is still lacking.

Is PFO associated with decompression sickness? Which are the underlying mechanisms?

The incidence of DCS is much lower in both divers and aircrews [27] than the prevalence of PFO in the general population [135]. A higher than normal prevalence of PFO in divers with DCS has been reported, especially with neurological symptoms [12,13,136], inner-ear DCS [11,138,139] and cutaneous DCS [14], particularly cutis marmorata [14,23,139].

A few prospective reports have also revealed a statistically significant association between PFO and white-matter lesions on MRI in military aircraft pilots [140] and in divers [9], but this was not confirmed by another report [141]. Moreover, arterial gas bubbles have been observed more frequently in divers with PFO than in those without PFO [142,143].

The association between risk of DCS and PFO has been estimated in retrospective, case-control studies only, with an OR of approximately 2.5 in a grouped analysis of recreational, military and professional divers [131]. In some studies analysing recreational divers performing provocative diving that requires decompression stops, a fivefold to sixfold risk increase in DCS was reported in divers with versus those without PFO [144,145].

We performed a meta-analysis of four correlation studies comparing the prevalence of R-T-L shunts in patients with and without DCS, and identified an OR of 5.63 (95% CI: 3.14-10.09) for R-T-L shunts in patients with DCS [11–14], albeit with moderate inconsistency between studies (χ^2=25.15, p=0.004; I^2=72%) **(Supplementary Figure 1)**. The observed inconsistencies can be due to false negative results in diagnostic tests for PFO [3,26] (see the previously published section "thrombotic left circulation embolism" [1,2]) and other factors, such as the different types of ascent performed, the size of the PFO [146], and the definition of DCS used [147].

A PFO can play a role in DCS with different, alternative or simultaneous processes of paradoxical gaseous embolisation. Large PFOs with basal R-T-L shunts can also facilitate the process at rest [3,4]. As PFOs may increase their patency over time, this may contribute to the age-dependent vulnerability to DCS observed in some subjects [148]. However, paradoxical embolisation can also occur with smaller PFOs, when a 15-20% rise in right heart pressures, due to the trapping of VGE in the pulmonary arterial vasculature, causes their prolonged opening after 20-30 minutes [149]. This process may be summed to the elevation in right chamber pressures induced by certain common straining manoeuvres or isometric exercises performed by the divers during the decompression phase, such as climbing a vertical ladder while wearing full diving gear [150], or by military high-performance aircraft pilots during antigravity straining manoeuvres.

Is it clinically possible to estimate the probability of a causal relationship between a PFO and decompression sickness?

Studies on PFO-associated DCS remain lacking and considerations can only be based on reports. Therefore, any estimate of the causal role of a PFO should be made on a case-by-case basis.

PFO-associated DCS often has an early onset, occurring even during the ascent phase in cases of a frequently open or large R-T-L shunt, or after 20-30 minutes in cases of small or less frequently open PFO, needing the peak of VGE to cause any increase in right heart pressure. Moreover, symptoms have often been reported to be neurologic (including high-spinal, vestibular, cochlear, visual and cerebellar symptoms), because of the arterialisation of VGE [11–13,136]. More controversial is the link with DCS symptoms caused by lesions in the lower third of the spinal cord, because no clear VGE "pathway" can be proposed [3,12]. Cutis marmorata has been reported to be a sensitive sign of cerebral involvement in PFO-related DCS, especially if it occurs in divers after deeper, repetitive or multi-day diving [14,23,139].

A physical isometric effort or Valsalva (-like) manoeuvre immediately preceding the onset of symptoms is highly suggestive of a causative PFO. The same applies if symptoms occur after low-risk flights, such as those at low cabin altitudes or at high altitudes but for a short time, or dives such as those that are close to the limits of "no-decompression diving" or close to the required mandatory decompression stops, according to the utilised decompression model.

As previously stated, large PFOs also have a higher probability of having a causal role in DCS.

In dive or flight profiles likely causing high bubble loads, the role of intrapulmonary R-T-L shunts should be considered, due to the opening of functional arteriovenous shunts [127].

An association between PFOs and silent brain white-matter lesions on MRI has been suggested, but unreported clinical episodes of DCS might also be the cause of neurological lesions [151-154].

What is the risk (and mechanism) of event recurrence with PFO-associated DCS?

The main issue affecting recurrent DCS is the relationship between dive or flight characteristics and: a) the physiological characteristics that regulate tissue saturation with inert gases and their release; and b) factors that influence the threshold of "VGE tolerance" for DCS occurrence (i.e., the rate of VGE arterialisation and/or VGE trapping in tissues). These factors can both be variable (i.e., functional) or structural (e.g., PFO). Variable factors imply that similar dive/flight profiles can cause different loads of VGE, rendering DCS also possible with profiles classified as low risk if they are present. However, a PFO can also influence the threshold for "VGE tolerance" with a tendency for earlier and more abundant arterialisation during decompression. Therefore, one can assume that, while similar dive/flight profiles may cause different DCS occurrences in different individuals, in the same individual dives or flights with a similar risk profile have a similar risk of DCS [27].

Two studies have shown that, in professional divers who suffer PFO-associated DCS, the size of the PFO is a predictor of recurrence [21,22].

Diagnosis of DCS

The diagnosis of DCS is based on symptoms, the history of a dive or flight, and the apparent absence of other causal factors. Usually the first manifestations start within two hours of the beginning of decompression, but can also present after 1-2 days, especially if further reductions in environmental pressure happen within that time frame [126]. Symptoms of DCS have traditionally been classified as "minor" or "major" (Type I and Type II decompression sickness) **(Supplementary Table 3)**, but these are not directly dependent on the profile of dives or flights. Mild cutaneous, visual or inner ear (vertigo) symptoms may often disappear spontaneously over the course of a few hours or days and should be enquired for. Physical activities or a Valsalva manoeuvre can immediately precede the onset of DCS [26].

Barotrauma of alveoli can lead to arterial embolisation of gas bubbles [155,156] and can mimic DCS, particularly if cerebral or high-spinal symptoms occur within minutes after surfacing from a dive [157]. This can happen: in rapid decompressions (e.g., explosive decompression in aircrews [132,158] and panic ascent without expiring during diving even in very short and shallow dives with compressed gas [159]; or in the presence of airway narrowing or focal stenosis (e.g., by mucous plugs) of pulmonary blebs or bullae during gradual, controlled ascents [155,156,160,161]. Therefore, high-resolution CT

scanning [162] and pulmonary function testing, including bronchial provocation testing, should always be performed [3].

VGE detected by echocardiography in patients with suspected DCS reinforces the diagnosis, because VGE grade is correlated to the risk of DCS [24].

White-matter lesions on MRI are traditionally considered the consequence of cerebral embolisation of decompression bubbles – although this view has recently been challenged [18,19].

Secondary prevention

Secondary prevention should primarily correct those factors that may have caused abnormal VGE production in each particular patient; modifying the patient's lifestyle and "diving hygiene" is often needed (ceasing smoking or alcohol consumption, losing weight; ensuring adequate hydration before and after the dive/flight).

In addition, VGE formation can be prevented by reducing the inert gas saturation of tissues before decompression. Divers commonly use "decompression computers" which allow most recreational dives to be performed at low risk of DCS, especially if the dives are performed within the "no-decompression limit" (NDL). This means that the inert gas saturation (as calculated by the dive computer) at the end of the dive is not yet so high that mandatory "decompression stops" are needed during the ascent phase of the dive. However, there is epidemiological evidence that dives needing decompression stops are at a higher risk of DCS [126]. Consequently, if recommendations for recreational diving generally recommend low-risk "no-decompression dives", this becomes mandatory in secondary prevention. Additional preventive measures include, for divers: reducing the frequency of dives, increasing the surface interval between dives, or using oxygen-enriched air ("nitrox") to reduce the inert gas component of the breathing gas (for the same diving depth, extra safety is achieved if the computer is left on "air setting"); for aircrews: operational limitation on conventional aircraft; for both, controlling temperature during the dive/flight [28,29,36]. In recreational divers, counselling on conservative dive profiles was found to reduce the risk of DCS from 71.6/10,000 dives to 0/10,000 after a 5.3-year evaluation period in subjects with a large PFO and from 41.3/10,000 to 1.4/10,000 dives in those without a PFO [28]. In another study, "no-decompression" recreational diving reduced venous VGE by 50-80%, and arterialisation by 75-100% in divers with a large PFO [29].

Regarding PFO closure, one prospective study in 104 divers with previous DCS uncovered a statistically significant reduction in symptomatic and asymptomatic (as assessed by MRI) DCS recurrence over five years in patients who chose to have their PFO closed, compared to those who did not, yielding a risk of "major DCS" of 0.5/10,000 dives and 35.8/10,000 dives, respectively [5]. It appears that the divers who did not have their PFO closed did not substantially change their diving behaviours. However, the number of subjects was low and there was significant dropout.

Some case reports have been published on divers who suffered recurrent DCS after PFO closure [33–35]. Although a residual shunt was detected in some of these patients, it is possible that, in others, a provocative dive profile caused high VGE loads, resulting in recurrent DCS, even with a successfully closed PFO.

The joint international position paper of underwater medicine societies' statements regarding PFO and diving are the following [30]:

1. Routine screening of divers for the presence of PFO is not recommended
2. Suspect PFO if there were one or more episodes of cerebral, spinal, vestibular or cutaneous DCS
3. PFO testing should be performed using contrast TTE; with provocation manoeuvre and in centres with experience in performing the test
4. When interpreting a positive testing result: consider size and degree of patency (spontaneous or only after provocation manoeuvre) of PFO versus smaller shunts, and the clinical/diving context of DCS. A definite causal relation between the PFO and the DCS episode is not always possible to ascertain.
5. PFO treatment options are
    A. Stop diving
    B. Dive more conservatively
    C. Percutaneous closure
6. When considering these options, careful consideration is needed of the risks and benefits and the clinical considerations that led to the screening
7. Return to unrestricted diving after PFO closure only if:
    A. Closure is confirmed with repeated contrast echo >3 months after procedure
    B. Potent antiplatelet medication is stopped (aspirin is OK)

Is a primary screening or prevention advised?

There are neither prospective observational studies nor randomised controlled clinical trials available in support of routine screening or closure of a PFO for the primary prevention of DCS. Indeed, DCS also remains an infrequent event in individuals with a PFO and there is agreement across diving medicine societies worldwide [30,36] that primary screening for PFO should not be done in recreational divers on a routine basis, because of an unfavourable cost-effectiveness ratio. The same applies for professional divers and conventional altitude pilots, because the risk of DCS in these groups is very low [37], and, even when a R-T-L shunt is present, arterialisation of VGE does not always take place [38].

Some diving medicine societies suggest considering primary screening for PFO in any diver with "high-risk" conditions — such as other congenital heart disease, a family history of atrial septal defects, or a history of migraine with aura or cryptogenic stroke — but little or no evidence supporting this choice is available [30].

Migraine

Migraine can be preceded by an aura with transient visual, verbal, or somatosensory symptoms and can result in significant impairment in daily activities, especially in chronic forms. The most plausible electrophysiological substrate of headaches and aura symptoms is cortical spreading depression (CSD) [61,62].

Is PFO associated with migraine? What are the underlying mechanisms?

The association between PFOs and migraine is supported by a higher prevalence of PFO in migraineurs than in the general population, as observed in several studies [44–47] and, in a meta-analysis, especially in those with auras [48]. Moreover, the high prevalence of migraine attacks in some inherited disorders — like hereditary haemorrhagic telangiectasia — where atrial or pulmonary shunts exist [54,55], stands as indirect evidence of a pathogenic role of a right-to-left shunt. Another source of evidence of the association between PFOs and migraine is the finding of incidental improvement in migraine attacks in patients who undergo percutaneous closure of a PFO for other reasons [52].

However, the association between migraine and PFOs is likely to vary across heterogeneous populations, as other studies have failed to identify such an association [56–60], especially when patients with specific subgroup characteristics were considered [60,69]. A direct link between PFOs and auras rather than headaches has also been hypothesised [46]. In some studies, PFO closure was associated with a dramatic increase in migraine in certain patient subgroups [163,164].

Potential pathophysiological mechanisms include paradoxical cerebral thromboembolism [47,63] which can trigger attacks through focal ischaemia causing a cortical spread depression [61,64–66] and/or the direct passage of metabolites like serotonin or other vasoactive substances to the systemic circulation (also possibly released by platelets activated by shear stress in the PFO), resulting in irritation of the trigeminal nerve and the brain's vascular network [67,68].

Is it clinically possible to estimate the probability of a causal relationship between a PFO and migraine?

In some studies, the number of bubbles crossing the PFO, detected by c-TCD, has correlated with the severity and frequency of attacks in migraineurs with auras [52,64]. A subpopulation where the association between PFOs and migraine was particularly evident was patients with a previous stroke [47]. Moreover, patients with a history of subclinical brain lesions or a cryptogenic ischaemic event appeared to benefit from PFO closure, in terms of the frequency and severity of migraine attacks, more than patients without cerebrovascular disease [71,72]. Additionally, a trend towards a higher prevalence of right-to-left shunt with larger-size PFOs in subjects with migraine with aura has been reported [60].

In two studies, older age seemed to be associated with an absence of relationship between PFOs and migraine [59,60]; however, other studies did not support an association between the frequency of migraine attacks and PFO characteristics [56–58].

Treatment

Additional insights on the safety and efficacy of percutaneous closure

The MIST trial was published in 2008 as the first double-blind, randomised trial comparing PFO closure versus non-closure in patients with migraine [73]. It evaluated PFO closure with the STARFlex® septal repair implant (NMT Medical Inc., Boston, MA, USA) against a sham intervention in 147 patients (74 assigned to the device group and 73 to the sham procedure). Patients had to be 18 to 60 years of age and have a history of migraine with auras, as defined by the criteria of the International Headache Society, all starting before 50 years of age. They also had to have >5 migraine headache days per month, but at least 7 headache-free days per month; and report having failed at least two classes of

preventative medication because of inefficacy or intolerability, as judged by an investigator. The primary efficacy endpoint was cessation of migraine headache 91 to 180 days after the procedure. No significant difference was observed in the primary endpoint of migraine headache cessation between the implant and sham groups (3 of 74 versus 3 of 73, respectively; p=0.51).

In the main paper, the authors reported that there were 37.7% of patients with a right-to-left shunt attributed to large or moderately large PFO; however, this finding has been a source of dispute because subsequently it was shown that intrapulmonary shunts were erroneously attributed to intracardiac shunts [165]. Furthermore, all the results and how the study was conducted were contested, with two researchers even refusing to sign the final paper [165]. As a consequence, an erratum was published, including a new version of supplements and the paper [166]. The principal investigator of the study was subsequently found guilty of misconduct in this research, including dishonesty, and suspended from the Medical Register [167]. In any case, even considering the published data, the study suffered severe limitations which included an undersized sample, use of a device which is now off the market, and less than optimal primary efficacy after implantation.

The PRIMA trial [74] compared PFO closure with the AMPLATZER™ PFO Occluder (St. Jude Medical, St. Paul, MN, USA) against medical management. This study had a six-year enrolment period and was prematurely stopped by the sponsor at 89% of the foreseen sample size, because of the slow enrolment rate. Ultimately, 107 patients had been randomised 1:1 to percutaneous PFO closure or medical management (53 to device therapy and 54 to medical therapy) with stratification by gender and age, across 20 centres. Of the total, 99% of the patients had migraine with aura. Patients were eligible if their migraine appeared before 50 years of age, if, over a three-month baseline period, they experienced either a minimum of three migraine attacks or five migraine headache days per month with 15 headache days per month and if they had been unresponsive to two commonly applied preventative medications. The primary endpoint was reduction in monthly migraine days during months 9–12 after randomisation compared with the three-month baseline period before randomisation. At six months, 88% of patients in the device therapy arm had the PFO successfully closed, as indicated by transoesophageal echocardiography (TOE).

At one year, a similar number of primary endpoint events was observed in the PFO closure group when compared with the control group (22.9 vs 21.7 days; p=0.17). In the PFO closure group, 38% of patients experienced a 50% or greater reduction in the number of migraine days relative to baseline compared with 15% in the control group (p=0.0189). However, the number of migraine attacks was similar in the PFO closure and control groups (22.1 vs 21.3; p=0.097). Post hoc analysis revealed a greater mean reduction in migraine with aura days per month and in the number of migraine attacks with aura in the PFO closure group versus the control group (22.4 vs 20.6 days; p=0.0141 and 22.0 vs 20.5; p=0.0003, respectively). A complete remission of migraine was observed in 10% of patients, all of these after PFO closure. There were six serious adverse events in the PFO closure group, all without long-term sequelae. Limitations of this study include the lack of blinding, underpowering of the study, lower than anticipated patient retention, and a 12% rate of incomplete closure in the device arm at six months.

The PREMIUM trial [75] compared PFO closure with the AMPLATZER PFO Occluder against medical management with a sham procedure (right heart catheterisation). The study had a seven-year enrolment phase, during which 230 patients were enrolled and randomised: 123 subjects randomised to the active device group and 107 to the control group. Subjects had 6 to 14 days of migraine per month, had failed at least three migraine-preventative medications, and had a significant right-to-left shunt

defined by transcranial Doppler. Sixty-five percent had migraine with aura and 20% had an atrial septal aneurysm. Primary endpoints were responder rate, defined as a 50% reduction in migraine attacks, and adverse events. Secondary endpoints included reduction in migraine days and efficacy in patients with versus without aura.

Adequate closure of the PFO at one year (<30 bubbles in one minute on transcranial Doppler) was obtained in 83% of patients randomised to device therapy. At one year, 78 primary efficacy events and one safety endpoint were adjudicated. The responder rate was similar in the two groups (45/117 in the device group and 33/103 in controls); however, device implantation significantly reduced the number of migraine with aura days ($p<0.01$) and attacks ($p<0.01$), and only after PFO closure did 8.5% of patients experience complete remission of migraine over a one-year time period. Furthermore, on post hoc analysis of trial data, patients with frequent attacks with aura had a statistically significant reduction in the primary outcome relative to controls (49% vs 23%, $p<0.04$). The main limitation of the study was the undersized sample (in the control group the risk was 50% lower than foreseen).

Two trials (MIST II and ESCAPE) were cancelled by their sponsors shortly after the beginning of enrolment.

Arterial desaturation syndromes

In one study, up to 30% of patients with a PFO were discovered to have clinically significant arterial deoxygenation during effort [79], suggesting that this situation might be more frequent than previously hypothesised [168]. Two case-control studies have identified a higher incidence of PFO in patients with obstructive sleep apnoea syndrome (OSAS) than in healthy controls [169,170], while two others revealed a correlation between hypoxaemia and PFO characteristics [169,171]. Among patients with COPD, several studies have shown a higher prevalence of PFO than in normal populations [86,172–175]; however, a correlation with hypoxaemia was not confirmed by all studies [175]. With high-altitude pulmonary oedema (HAPO), linked to hypoxaemia, an association with PFO was hypothesised in even fewer observational studies [176], although the hypoxaemia correlated with PFO characteristics in a small, preliminary observational study [177].

Can PFO be associated with arterial hypoxaemia? What are the underlying mechanisms?

Even though the shunt through a PFO is usually haemodynamically trivial, under certain conditions the right-to-left shunt causes clinically significant arterial deoxygenation by mixing venous and arterial blood. The shunt, and the consequent hypoxaemia, can be transient or persistent, depending upon the underlying mechanisms and anatomical characteristics. The longer the shunt is flowing during the cardiac cycle and the larger the shunt's volume, the more severe the arterial hypoxaemia is. The most important circumstance associated with this is pulmonary arterial hypertension, which may cause right heart chamber pressures to rise, the trans-PFO gradient to increase and, consequently, also the right-to-left shunt grade. However, anatomic factors such as a large Eustachian valve directed towards the PFO and/or deformation of the atria and the septum may cause high localised haemodynamic pressure just around the fossa ovalis, which is capable of generating a significant shunt even in the presence of normal mean right atrial pressure.

Treatment

In platypnoea-orthodeoxia syndrome (POS) due to PFO, the evidence for percutaneous closure is based upon case reports, case series and only two small registries, because of its rarity. Three small series revealed stable relief of symptoms up to five years post closure, with improved standing arterial oxygen saturation in all patients without severe pulmonary hypertension [81–83]. Two larger registries on 128 patients overall confirmed these results with a 6% incidence of procedure-related complications [84,85]. In all these studies, the persistence of dyspnoea at follow-up, mainly exertional, was due to incompletely evaluated underlying pulmonary disease upstream.

For OSAS, PFO closure has been described in case reports [168], all showing improved symptoms and decreased apnoeic episodes, and one case-control observational study involving 40 patients, which showed statistically significant improvements in indices of apnoea and desaturation episodes and a reduction in systemic arterial pressure and increased left ventricular diastolic function [86].

No data are available regarding PFO closure in COPD patients.

For exertional desaturation, only one cohort study with 14 patients has been reported on PFO closure (two surgical), in which statistically significant improvement in oxygen saturation (average increase of 10) and NYHA functional class (by a median of 1.5 classes) was observed after interventional therapy, relative to baseline [79].

For high-altitude pulmonary oedema (HAPO), only two reports describe the prevention of disease by percutaneous closure of PFO [178,179].

Platypnoea-orthodeoxia

Definition of POS

Platypnoea-orthodeoxia syndrome (POS) is a condition characterised by dyspnoea and arterial deoxygenation (SpO_2 <90% or PO_2 <60 mmHg), with or without cyanosis, induced by an upright position, and typically relieved by lying supine [180].

The syndrome is rarely diagnosed and its prevalence in the general population remains unknown [84,181]. Three main pathophysiological processes, in various combinations, may lead to this syndrome: intracardiac shunts (cardiac POS syndrome), pulmonary arteriovenous shunts, and ventilation/perfusion mismatch [182].

The most common aetiologic association is an interatrial right-to-left shunt through a PFO [183], an atrial septal defect (ASD), or a fenestrated atrial septal aneurysm (ASA). Considering the prevalence of PFOs in the adult population (close to 25%), it may be that POS occurs more frequently than has been reported in the literature.

Right-to-left interatrial shunting is usually associated with spontaneous or induced pulmonary hypertension. Right-to-left shunting with normal pulmonary artery pressure is uncommon. In the absence of pulmonary hypertension, other mechanisms might explain a right-to-left interatrial shunt and, consequently, the syndrome: for example, an interatrial pressure gradient, or preferential blood flow streaming from the inferior vena cava into the left atrium, through the PFO, even in the absence of an interatrial pressure gradient.

Even if an interatrial communication (PFO, ASD or fenestrated ASA) is necessary for cardiac POS, a prominent Eustachian valve and right chamber anatomy modification can act as contributing factors. Several mechanical conditions – mainly right diaphragmatic paralysis and ascension [184,185], kyphoscoliosis [186], restrictive lung disease, previous pneumonectomy [187–189], pleural effusion, and an ectasic/aneurysmal ascending aorta [190,191] – may lead to atrial chamber or septal deformity, thereby changing the anatomic relationship between the atrial septum and the inferior vena cava and, thus, facilitating desaturated blood flow redirection through the PFO.

Diagnostic workup of POS

The diagnosis of POS in patients presenting with respiratory symptoms is difficult, so that it is usually a "rule-out diagnosis".

Desaturation is not exacerbated by exercise and is strikingly resistant to the inhalation of high-concentration oxygen.

The history of symptoms can be short; symptoms can emerge acutely, worsen rapidly and be progressive within a few days.

Patients with this syndrome may or may not have a decubitus preference ("trepopnoea").

The initial assessment should be to document the association between dyspnoea and the upright position. Consequently, it is useful to demonstrate an association between oxygen desaturation (via blood gas analysis or pulse oximetry) and the patient being upright, even if 100% oxygen is administered.

Various investigations — including blood analysis, spirometry, pulmonary CT scan, pulmonary CT angiography, and a lung ventilation/perfusion scan — are useful to exclude non-cardiac causes of POS.

The imaging technique initially recommended to investigate intracardiac shunting disease is TTE with colour Doppler or after the intravenous injection of contrast (10 ml of a saline-agitated solution). The examination should be performed with the patient in both a lying and upright position and may allow demonstration of an interatrial communication, the right-to-left shunt (because of the passage of microbubbles to the left atrium in the first three beats after right cavity opacification) and the exclusion of pulmonary hypertension.

The diagnosis of POS due to interatrial communication is very difficult to establish using TTE, because the atrial septum is poorly visualised with TTE.

The simplest examination to determine the diagnosis is c-TOE, taken in the supine and sitting position, showing, either on colour Doppler or after the intravenous injection of contrast (10 ml of a saline-agitated solution), an atrial right-to-left shunt via the PFO, a small ASD, or a fenestrated ASA. In addition, TOE is useful to demonstrate the presence of underlying anatomical causes of the right-to-left shunt, such as a prominent Eustachian valve, deformed aortic root, aneurysmal expansion, or elongation of the ascending aorta.

The diagnosis can be confirmed on contrast TOE with simultaneous monitoring of the peripheral capillary oxygen saturation (SpO_2), which should clearly demonstrate concordance between a postural increase in right-to-left shunting and desaturation.

The gold standard cardiac test remains cardiac catheterisation. However, these measurements are not routinely performed, as a non-invasive workup (echocardiography and peripheral oxygen saturation measurements) is usually sufficient to establish the diagnosis, because patient disability rather than shunt magnitude dictates the decision for interatrial defect closure.

Neurosurgery in the sitting position

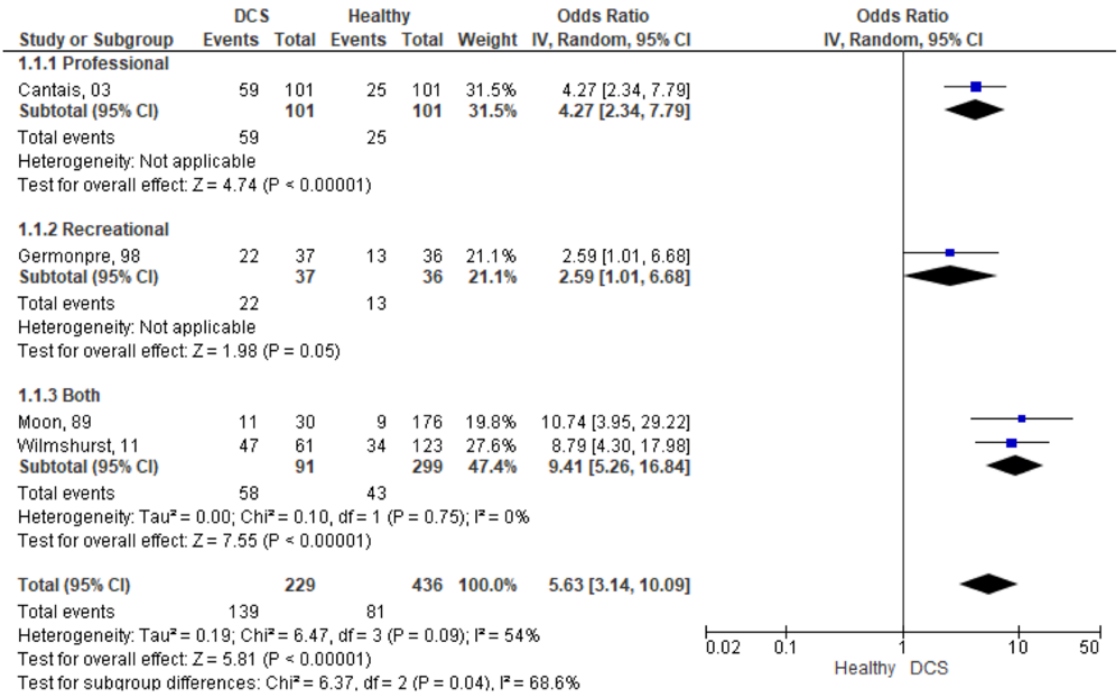
Despite the risks associated with operations conducted in patients in a sitting position, performed to approach the posterior fossa or dorsally located parietal lesions [102], and the dramatic decrease in operations in this position [101], many teams still adopt this strategy as a first choice because of its considerable advantages for patients [105–109].

Among the most dreadful complications associated with this position, venous air embolism after venous incision can occur in up to 50-79% of cases, depending on the sensitivity of the monitoring tool used [93,103,104], with severe immediate and delayed cardiopulmonary and cerebral complications [95–98]. In turn, these can cause paradoxical air embolisms in up to 14% of patients if a PFO is present [112–115]. The lower rate and the wide range (0-14%) in the overall reported incidence of paradoxical air embolism, relative to venous air embolism (VAE) at large, is probably primarily due to selection bias, but also to differences in monitoring tools, incomplete data registration, and heterogeneity within the populations of patients with PFO. For this reason, a PFO remains an absolute contraindication to surgery in the sitting position. Moreover, many surgeons routinely prefer other surgical positions [99,100], even though VAE [93] and hypotension [94] may also occur with patients in a lateral or prone position, and these can also cause serious additional hazards [110,111]. Nonetheless, if surgeons are aware of a PFO's presence, neurosurgical operations can be carried out safely on patients with a PFO in a prone position, provided close monitoring is performed throughout the operation [116,117].

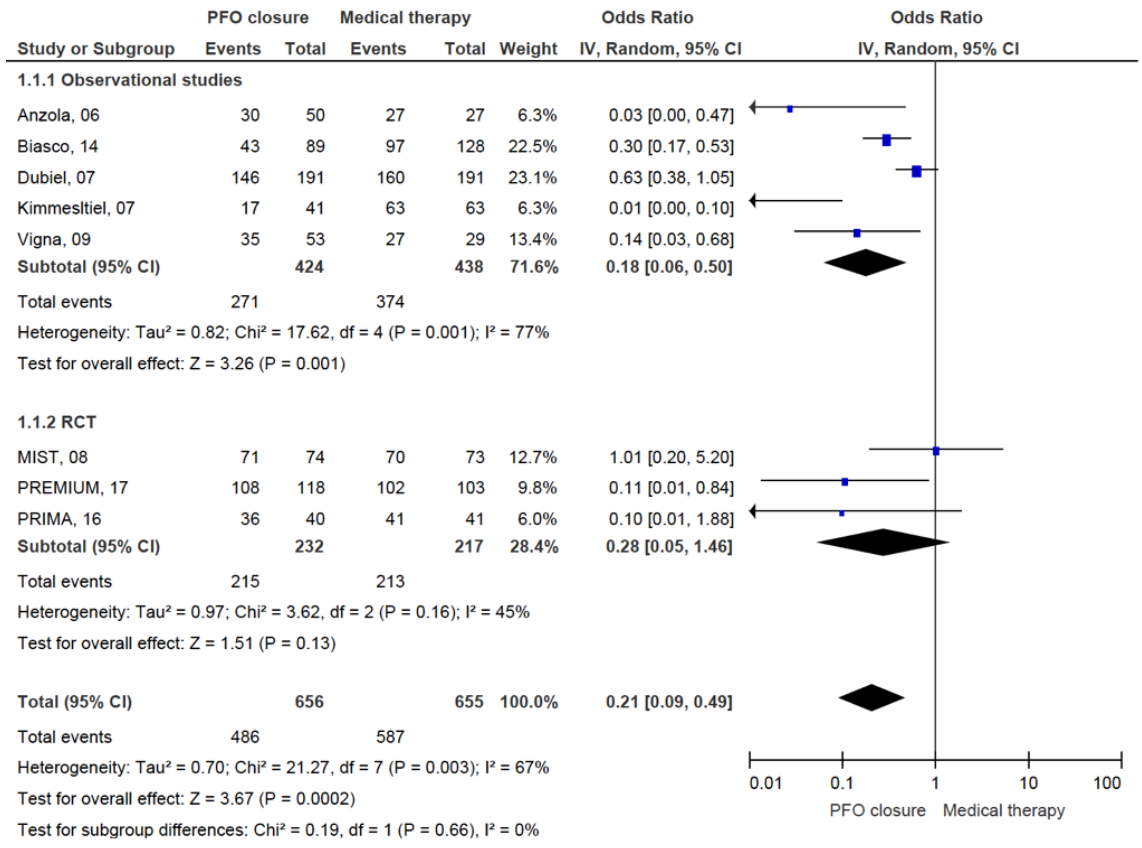
Prevention and treatment

Perioperative monitoring

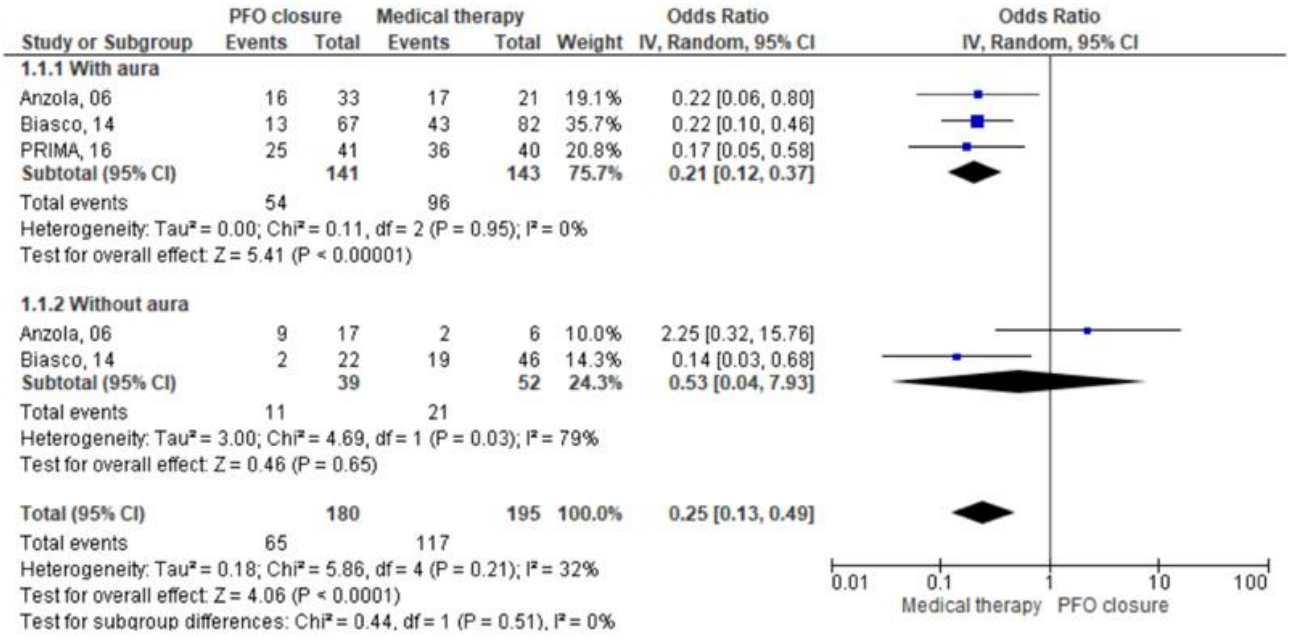
Besides routine monitoring, continuous monitoring of end tidal CO_2 ($ETCO_2$) is used throughout the operation to detect clinically significant VAEs. $ETCO_2$, in combination with TOE, is used as the most sensitive parameter [118]. A sudden drop in the $ETCO_2$ level associated with hypotension is highly suggestive of air embolism [119]. Capnography is also a widely available diagnostic tool. An alternative method is the measurement of expired nitrogen [120].



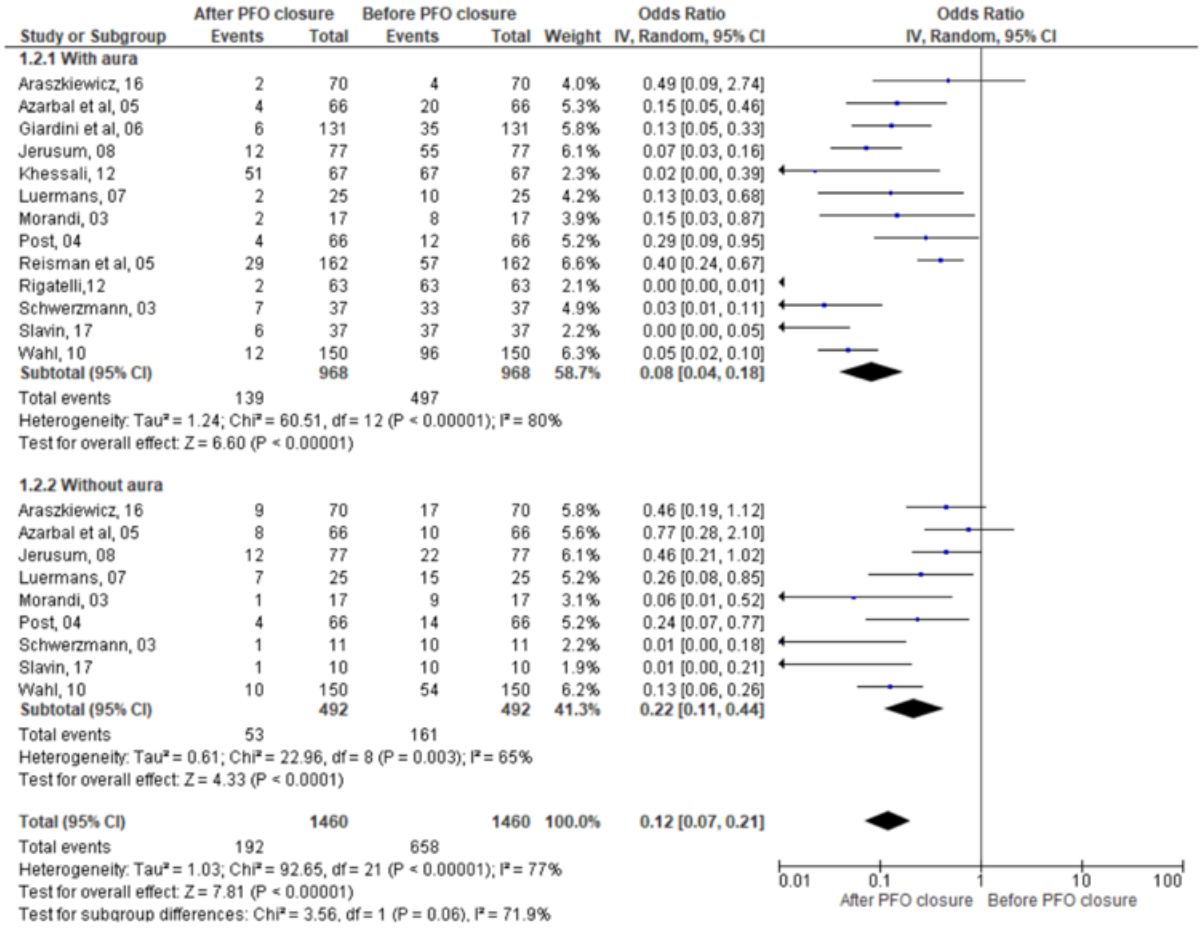
Supplementary Figure 1. Meta-analysis of studies comparing the prevalence of R-T-L shunting in patients with and without DCS.



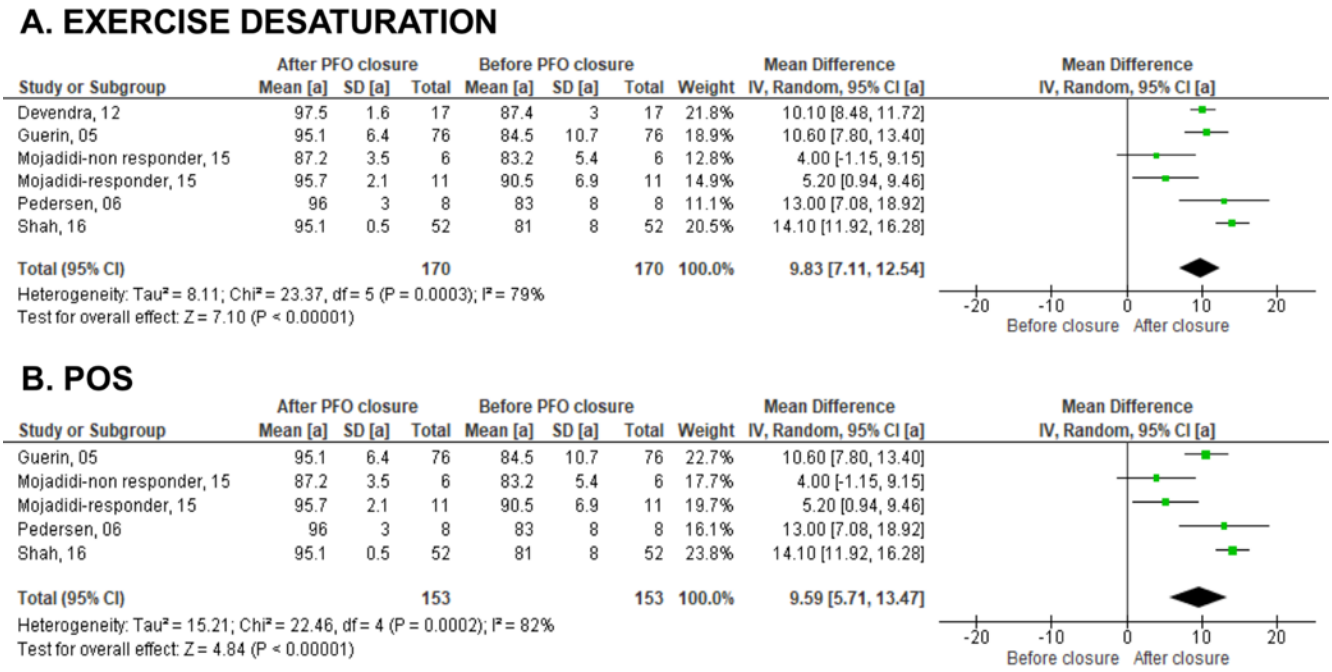
Supplementary Figure 2. Meta-analysis of observational and randomised trials regarding the incidence of persistent migraine comparing closure versus non-closure of PFO in studies with two cohorts.



Supplementary Figure 3. Meta-analysis of observational and randomised trials regarding the incidence of persistent migraine comparing closure versus non-closure of PFO in studies with two cohorts, by aura status.



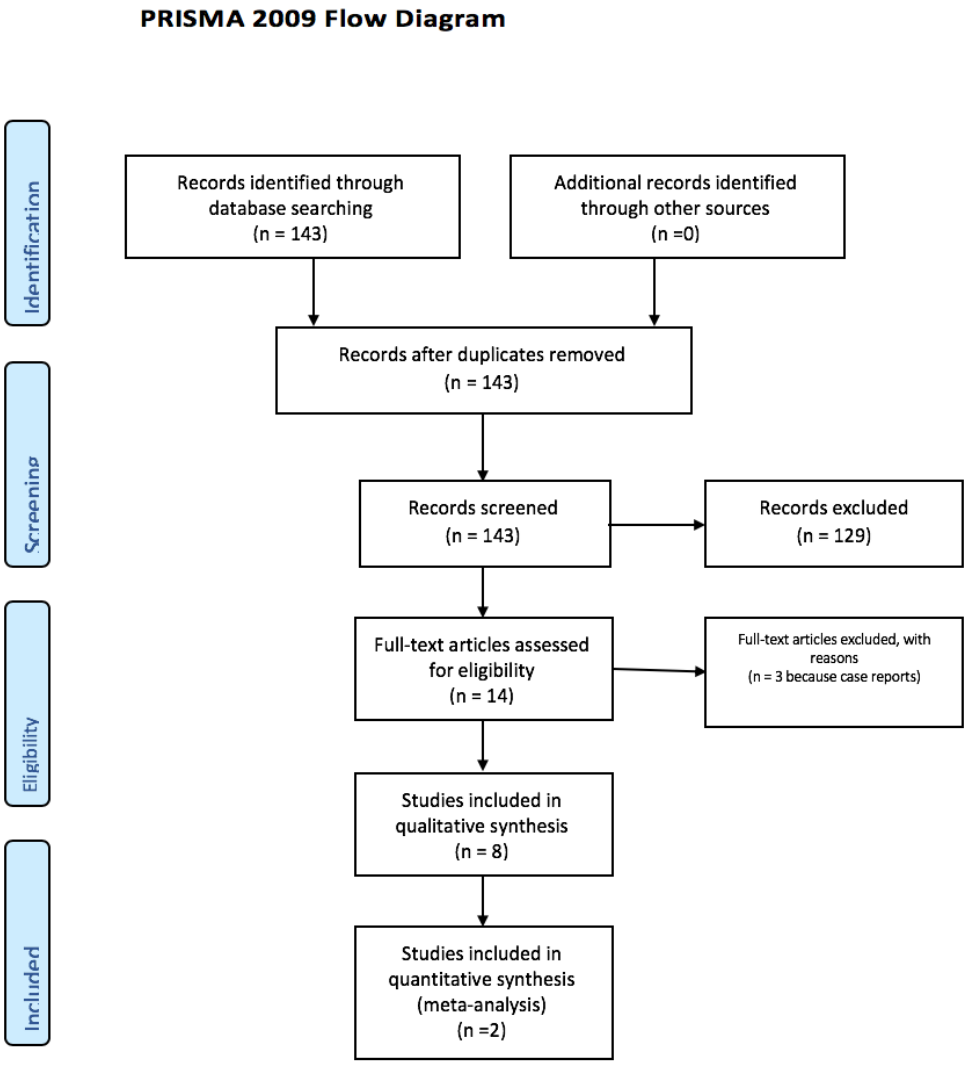
Supplementary Figure 4. Meta-analysis of observational trials assessing persistence of migraine before and after PFO closure, by aura status.



Supplementary Figure 5. Meta-analysis of studies on PFO closure in desaturation syndromes.

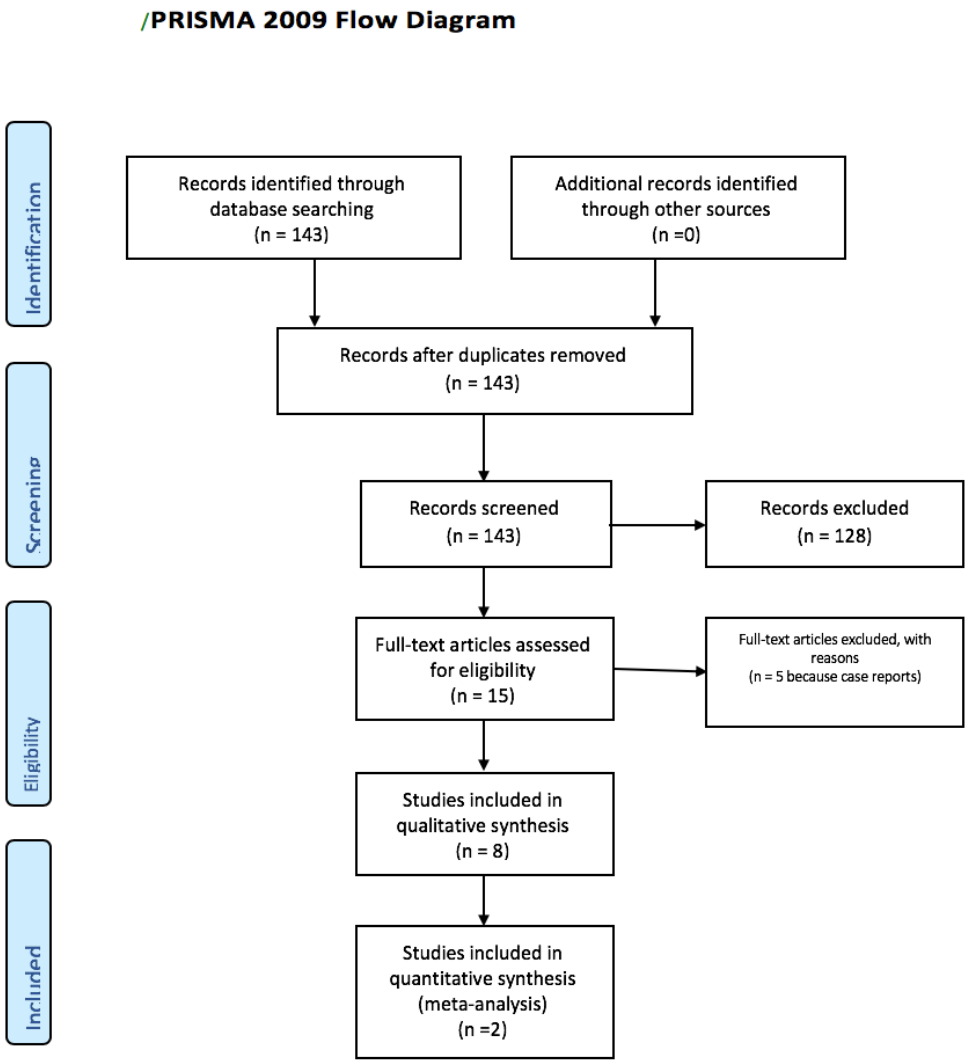
Improvement in blood oxygen saturation after PFO closure.

Supplementary Figure 6.



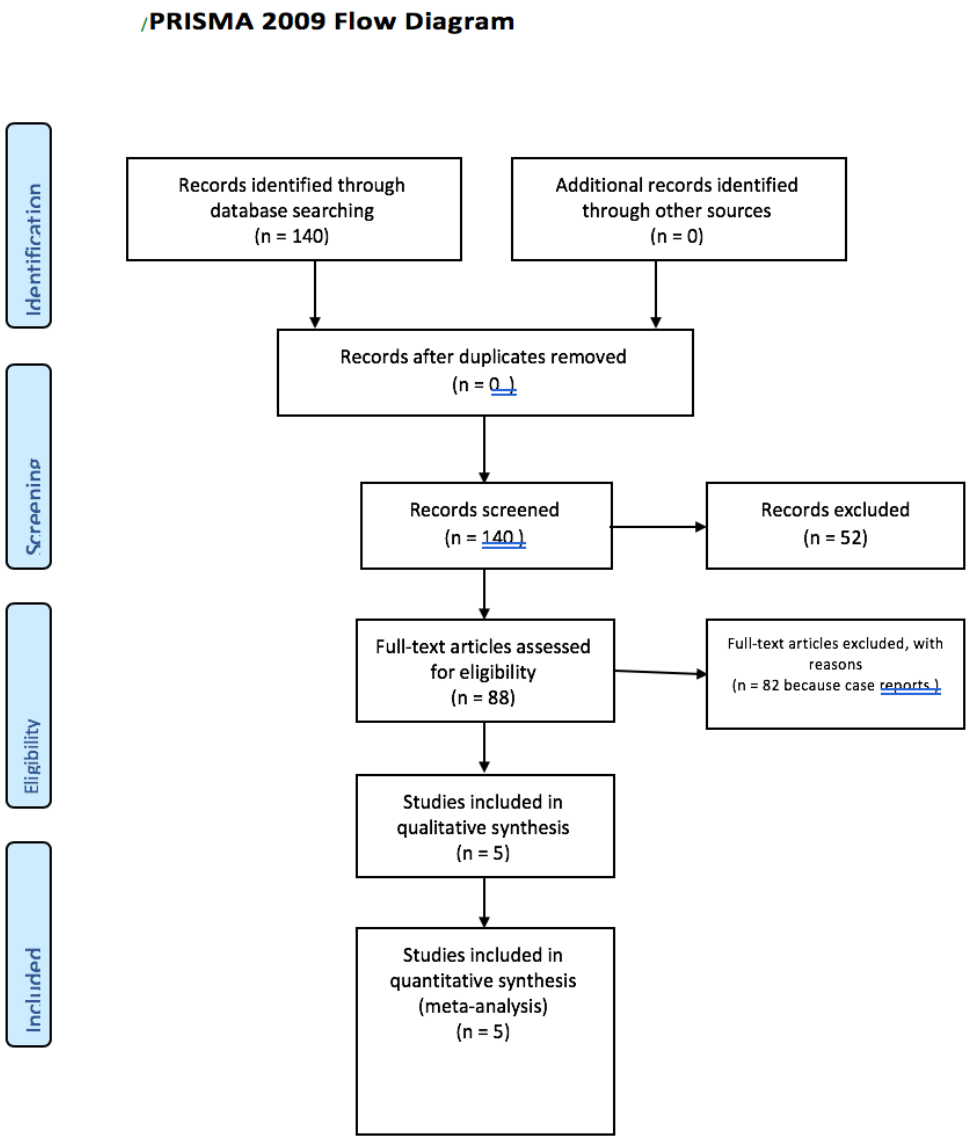
Supplementary Figure 6. PRISMA diagram of decompression sickness studies in recreational divers.

Supplementary Figure 7 -



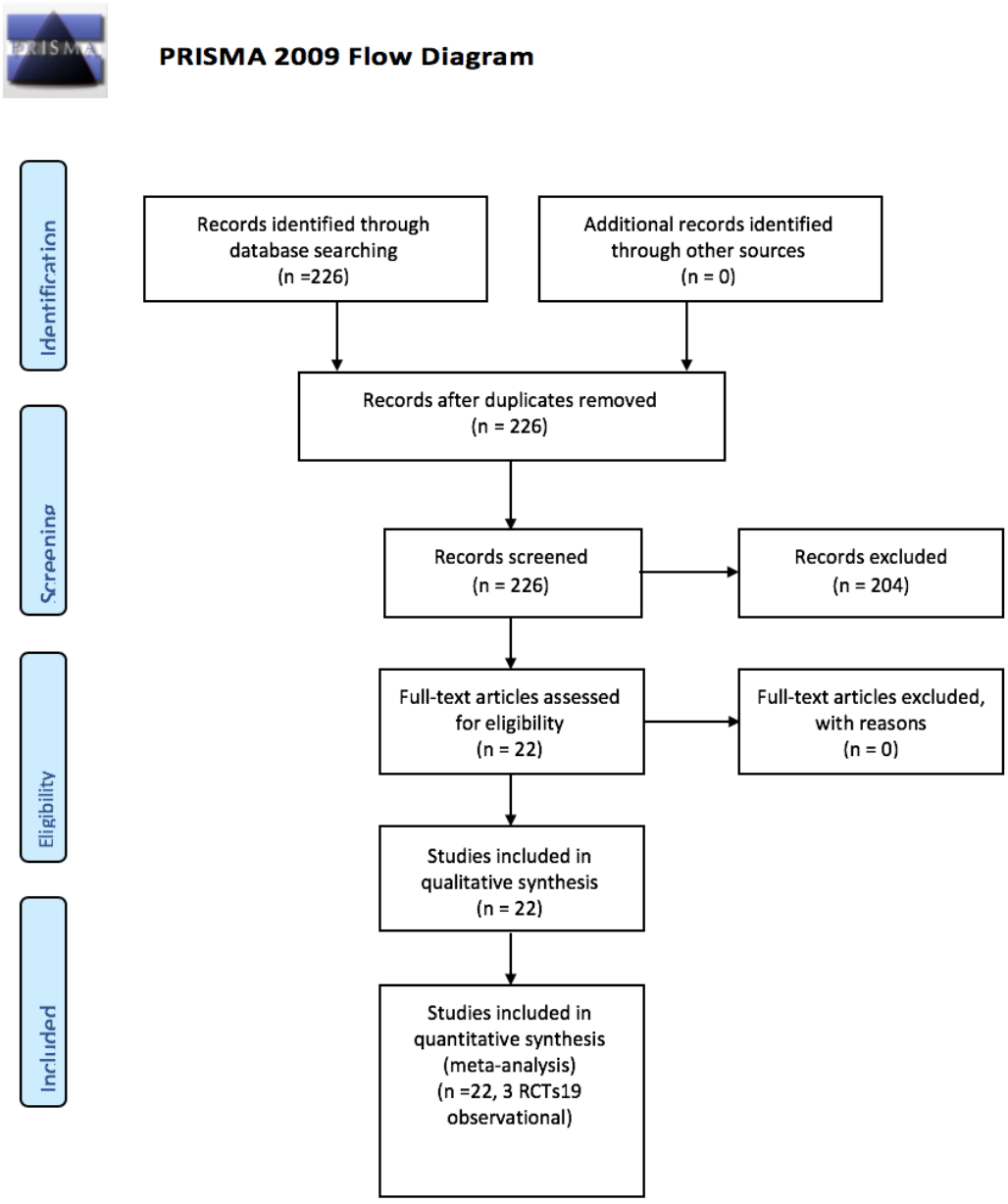
Supplementary Figure 7. PRISMA diagram of decompression sickness studies in professional divers.

Supplementary Figure 8.



Supplementary Figure 8. PRISMA diagram of decompression sickness studies in desaturation syndromes.

Supplementary Figure 9



Supplementary Figure 9. PRISMA diagram of migraine studies**.**

Supplementary Table 1. Characteristics for the evaluation of a probable causal link between a PFO and DCS.

Characteristics	Level of evidence
• Large size of the PFO [24,25]:	C
• Early onset of DCS during or after the ascent (with a large PFO)	C
• Onset of DCS 20-30 minutes after the ascent (with a small PFO)	C
• Neurological (high-spinal, vestibular, cochlear, visual and cerebellar) symptoms [15-17,26]	C
• Cutis marmorata (in divers, after deep and/or repetitive dives) [18]	C
• History of any isometric effort shortly before DCS onset	C
• DCS onset after/during low-risk flights (low cabin altitude or high cabin altitude for a short time)	C
• DCS after/during low-risk dives, close to no-decompression limits	C
• Dives or flights causing low bubble loads [27]:	C

Supplementary Table 2. Summary of statements on DCS and PFO.

APPROACH TO DECOMPRESSION SICKNESS

Position Statements	Strength of the statement	Level of evidence
A secondary prevention work-up should be initiated only if a DCS diagnosis is probable or if uncertainty regarding DCS is unacceptable for the individual risk profile or patient's preference.	Strong	C
Individual risk stratification should consider clinical, anatomical and functional neuroimaging and dive/flight profile data	Strong	C
In the same patient, the dive/flight profile relative to individual characteristics is the main determinant of DCS	Strong	C
In cases of DCS during low-risk activities or activities with a high but non-modifiable risk, PFO screening must be considered part of the diagnostic work-up	Strong	C
Decision making should be considering estimations of the patient's: a) Probability that the PFO has a causal role in the clinical picture b) Risk of recurrence (flight/diving habits and/or needs)	Strong	C
The probability of simultaneous or alternative intrapulmonary shunts and/or of pulmonary overpressure syndrome should always be considered	Strong	C
Shared decision making should be documented, accompanied by open, individualised, informed consent	Strong	C

SECONDARY PREVENTION OF DECOMPRESSION SICKNESS

Position Statements	Strength of the statement	Level of evidence
Regardless of the presence of a PFO, secondary prevention should primarily be aimed at suppressing VGE production, up to possible permanent cessation of the activity (Supplementary Table 4).	Strong	C
PFO closure can be offered to those patients having suffered from DCS: a) with a high probability of causal PFO; b) when cessation of diving/flying is not an option; or c1) when it is not possible to achieve an effective behavioural change to prevent the production of venous gas emboli; or c2) when the risk of further DCS, despite conservative limitations, is deemed unacceptable by the patient after consultation with an experienced dive or aerospace physician.	Strong	C
Prior to consideration of PFO closure, patients should be informed that this procedure is expected to reduce the risk of paradoxical VGE but will have no effect on VGE or pulmonary shunts.	Strong	C
In cases involving professional divers or pilots, offering PFO closure should be balanced against the possible consequences of PFO closure on work activities, according to local and international regulations.	Strong	C
In patients who have undergone PFO closure, documentation of complete closure of the PFO on follow-up is necessary for the patient to resume unrestricted diving.	Strong	C

PRIMARY PREVENTION OF DECOMPRESSION SICKNESS

Position Statements	Strength of the statement	Level of evidence
Primary screening for PFO is not indicated on a routine basis in divers and/or aircrews.	Strong	C
When PFO is an incidental finding, no restrictions on conventional altitude flights are advisable for any person.	Strong	C

When PFO is an incidental finding in a recreational diver, the individual should be counselled by an experienced diving physician, according to the context, size of shunt, and the individual's compliance/preferences.	Strong	C
Primary PFO screening can be proposed to professional divers performing working activities with non-modifiable high-risk characteristics for DCS	Conditional	C
Military pilots assigned to frequent and prolonged flight activity at <280 mmHg barometric pressure or >25.000 ft can undergo PFO screening according to local regulations	Conditional	C
In an individual at very high risk for DCS for professional reasons, possible primary closure of the PFO must be evaluated in conjunction with the individual and an experienced diving or aerospace physician, considering job characteristics, individual clinical features, local/international work regulations, and patient's preference.	Strong	C

Supplementary Table 3. Classification of DCS (modified from Germonpré et al [23]**).**

	Type I DCS	Type II DCS
Classification	Non-systemic, peripheral, "minor"	Systemic, serious
Symptoms and signs	Pain – Joint and tendon pain Lymphatic – Localised lymphatic congestion Cutaneous symptoms – Itching – Rash – Localised cyanosis – Cutis marmorata	Cerebral–cerebellar – Altered consciousness – Visual disturbances – Auditory, vestibular symptoms Spinal – Paralysis, paresis – Bladder or bowel dysfunction – Sensory disturbances Pulmonary – Dyspnoea, cough – Desaturation Circulatory – Shock

Supplementary Table 4. Primary measures for secondary prevention of DCS.

Measures
• Lifestyle and behavioural changes (stop smoking, stop alcohol consumption, lose weight, ensure adequate hydration) • Provide temperature control during dive or flight • **For divers** - Conservative diving profile [28]: No-decompression dives [29,30] and reducing the frequency of dives • **For aircrews** - flying with operational limitation on conventional aircraft • Breathing high concentrations of oxygen before the ascent (pre-breathing with 100% oxygen before and during the flight in aircrews and, in divers, oxygen-enriched gas mixes for underwater breathing using the "air" setting decompression profile on the computer)

Supplementary Table 5. Summary of statements on migraine and PFO.

Position Statements	Strength of the statement	Level of evidence
The association between migraine and PFO is supported by observational data, but it is variable across subpopulations and therefore in the clinical setting may be incidental	Strong	B
The clinical, anatomical and imaging characteristics of different subpopulations of patients with PFO-associated migraine have not been sufficiently assessed.	Strong	C
According to literature, factors that may suggest a pathogenic role of PFO in migraine are the presence of 1) an aura and 2) previous stroke; while older age and small shunts through the PFO would suggest a less likely causative relationship between a PFO and migraine.	Conditional	C

Supplementary Table 6. GRADE evaluation of the certitude of effects - studies on PFO closure for migraine prevention.

Certainty assessment						
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**
RCT						
449 (3 RCTs)	Serious[a]	Serious[b]	Not serious	Serious[c]	Not serious	⊕⊕◯◯ LOW
OBSERVATIONAL STUDIES						
1460 (22 observational studies)	Serious[d,e]	serious[b]	Not serious	Serius[c]	Serious[f]	⊕◯◯◯ VERY LOW

a. Due to different selection criteria among the studies, including high risk patients in 1/3 studies.
b. Due to different methods to assess migraine severity
c. Due to: 1) Different methods to assess migraine severity and b) heterogenous or not defined medical therapy for migraine
d. Risk of inclusion of "palliative" procedures
e. No data about medical therapy
f. Due to tendency to publish positive results

Supplementary Table 7. Summary of the PICO question on migraine treatment

In patients with migraine and PFO, should percutaneous closure of PFO vs. medical therapy be used for reduction of migraine?

TYPE OF STATEMENT

Strong statement against the intervention	**Conditional statement against the intervention**	Conditional statement for either the intervention or the comparison	Conditional statement for the intervention	Strong statement for the intervention
○	●	○	○	○

CONCLUSIONS

Statement

The position of our societies is that available data do not allow us to support interventional therapy as an alternative or as adjunct to medical therapy in patients with migraine, but new randomized studies should indeed be performed.
However, outside of specific trials, it is acceptable to propose percutaneous closure of a PFO, after an in-depth individual multidisciplinary evaluation, on a compassionate-use basis in the extreme cases of carefully selected patients suffering from migraine with aura and/or cerebrovascular disease who have a poor quality of life despite optimal medical therapy prescribed by migraine specialists. In this case, the role of the patient should be pro-active, keeping in highest regard his/her values and preferences regarding outcomes and therapeutic trade-offs, and informing him/her about the uncertainties of their condition and available evidence.
Moreover, patients with migraine and previous cerebrovascular accident should be evaluated according the previously published position statements for systemic thromboembolism and treated for the prevention of this condition.

Justification

Overall justification
The last comprehensive meta-analysis of 3 RCTs and 22 observational studies in 1909 patients showed a statistically-significant advantage of PFO closure vs. medical therapy for improving migraine **(Supplementary Appendix 2 – Supplementary Figures 2, 3 and 4, Supplementary Tables 6, 8 and 9)**. However, the certainty of these effects was very low, given that this evidence is only driven by observational studies and not by RCTs, which were all negative for the primary hypothesis. Nonetheless, two out of three RCTs showed superiority for some secondary outcome measures with PFO closure over medical therapy. Moreover, the benefit of percutaneous closure was clear in patients with aura or, in a previous meta-analysis that incorporated a smaller number of patients, in those with cerebrovascular disease. The data supporting therapeutic efficacy in some subgroups underscores the heterogeneity of this population and the need to better characterise key features. Therefore, the weakness of the evidence accrued so far should still be considered only hypothesis-generating for future specifically targeted randomised studies.

Nonetheless, given the invalidating nature of the disease, the signal towards a benefit of PFO closure in patients with aura and cerebrovascular disease, the low incidence of undesirable effects with percutaneous closure, and the frequent preference of patients for therapies which have the potential to improve their poor quality of life regardless of the risks and side effects, percutaneous PFO closure may be proposed on a compassionate-use basis in patients with aura or cerebrovascular disease who are poor responders to maximal drug therapy, after a carefully-shared decision-making process involving migraine specialists and cardiologists and which must be tailored to the patient's personal values and preferences.

Detailed justification
Problem
Migraine is a frequent and incapacitating disease in the population, despite medical treatments. Patients suffering from migraine, in the majority of cases, prefer any therapy which is effective, regardless of its risks and side effects. Therefore, the therapy of migraine is a priority and all potential solutions should be considered to relieve life-impairing pain.
Desirable effects
The 3 RCTs individually did not show any superiority of percutaneous closure of PFO over medical therapy at reducing the primary endpoint of the studies in disparate patient populations. The results of our meta-analysis of RCTs are also neutral.
However, in the PRIMA and PREMIUM trials, statistically-significant improvements in the number and duration of attacks were reported (secondary endpoints - see **Supplementary Appendix 2**), showing that a benefit could be achieved, albeit not in the primary outcome[74,75]. These findings were confirmed by a previously published meta-analysis [77]. Furthermore, in our meta-analysis of observational trials, we identified a statistically significant reduction in migraine with PFO closure vs medical therapy **(Supplementary Appendix 2 – Supplementary Table 8 and Supplementary Figures 2, 3 and 4)**.
Undesirable effects

The undesirable effects of both PFO closure and medical therapy have been inconsistently reported across studies. However, in our meta-analysis of RCTs, their incidence was low and most adverse effects were transient (0.5-1.1%).

Certainty of evidence

The certainty of evidence is severely questioned, since the main evidence stems from non-randomized studies or secondary endpoints of RCTs, with all inherent limitations of this kind of analyses. Moreover, several limitations of RCTs also make their interpretation problematic: e.g., ubiquitous under-sized studies, wide confidence intervals, high incidence of incomplete PFO closures, disparate selection criteria, and different PFO closure devices. Specifically, in our meta-analysis, the certainty of the evidence was judged severely **(Supplementary Tables 6 and 8).**

Further adequately structured studies are, therefore, necessary to improve the certainty of evidence.

Values

No specific studies addressing values and preferences of patients have been performed for PFO-associated migraine. However, in patients with migraine at large, studies have shown that patients do have preferences in therapies, and they tend to prioritize the effectiveness of therapy for migraine over side effects and safety [192-196].

Balance of effects

In our meta-analysis, the incidence of undesirable effects was similar with drug and interventional therapy; therefore, in subjects in whom PFO closure is effective at improving migraine, the balance is in favor of interventional therapy.

Acceptability

No conclusions can be drawn on cost-effectiveness.

Feasibility

PFO closure is a widely standardised procedure worldwide.

Subgroup considerations

In our meta-analysis, only patients with aura experienced a statistically-significant improvement in migraine **(Supplementary Table 8 – Supplementary Figure 3)**. This is in keeping with a previously published meta-analysis [77]

Moreover, in a previously published meta-analysis considering observational studies and one RCT only, patients with cerebrovascular disease were reported to have a statistically-significant improvement in migraine with PFO closure versus medical therapy [72].

The evidence of therapeutic efficacy in subgroups underscores the heterogeneity of this population and the need to better characterise key features.

Implementation considerations

No cost-effectiveness studies have been performed in this field.

Monitoring and evaluation

PFO closure may be proposed to patients only on a compassionate-use basis and after a thorough neurological evaluation and documented assessment of different medical therapies prescribed by migraine specialists. The cardiologist and neurologist must come to the conclusion that current therapy is insufficiently effective to allow for a good quality of life. Patients should be actively involved at all stages of management and their contribution to choices should be documented. Local registries providing prospective evaluations of outcomes are strongly encouraged.

Research priorities

- To identify high risk-phenotypes for a causal PFO, encompassing different clusters of clinical, anatomical and biological characteristics in prospective observational trials (systems and precision approaches)
- To design adequately dimensioned RCTs comparing PFO closure to medical therapy in specific high-risk subgroups (e.g., patients with migraine with aura and/or documented cerebrovascular disease).
- To perform new, cost-effectiveness analyses based on contemporary practices
- To obtain quantitative and qualitative data on patient preferences and values in the setting of migraine with PFO, and to involve patients in the design and choice of outcomes in the studies, particularly including in the outcomes the evaluation of post-critical quality of life after migraine attacks
- To design prospective registries to evaluate practices and outcomes in the real world

Supplementary Table 8. Detailed PICO question for therapy of migraine.

PICO QUESTION

Should percutaneous closure of PFO plus medical therapy vs medical therapy alone be used for reducing migraine?	
POPULATION:	Patients with migraine
INTERVENTION:	Percutaneous closure of PFO plus medical therapy
COMPARISON:	Medical therapy alone

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Migraine is a common neurological disorder which affects approximately 4-9% of men and 15-17% of women between 20 and 64 years of age [39] and is often disabling despite medical therapy [40]. It is estimated that 1–4% of the population meet criteria for chronic migraine [41,42]. In the general population, it is estimated that the prevalence of migraine with aura ranges from 1.2 to 37% in men and from 2.6 to 10.8% in women [43].	

Desirable effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ○ Large ● Varies ○ Don't know	Currently, data are available on 1,909 patients in 22 non-randomised comparisons, 3 randomised studies, one study-level meta-analysis including all RCTs, one study-level meta-analysis of observational trials and one RCT (MIST), and one study-level meta-analysis of eight observational trials, mostly retrospective studies **(Supplementary Table 2, Supplementary Table 4, Supplementary Figure 2-Supplementary Figure 4).** All RCTs (MIST, PRIMA and PREMIUM trials) failed individually to show a greater efficacy for primary endpoints with PFO closure plus medical therapy versus medical therapy alone **(Supplementary Appendix 2)** [73–75]. Our updated study-level meta-analysis of observational and randomised case-control trials overall showed superiority of PFO closure over medical therapy for migraine incidence (odds ratio [OR] = 0.27 [95% CI: 0.11-0.66]), with severe heterogeneity across studies (χ^2=25.15, p=0.004; I^2=72%). However, the superior efficacy of PFO closure was driven by observational studies, whereas RCTs, enrolling only 414 patients, showed similar effects of interventional and medical therapies (OR = 0.86 [95% CI: 0.09-8.23]) **(Supplementary Figure 2-Supplementary Figure 4)**. Considering subgroups, relative to medical therapy, our meta-analyses showed significant improvement in migraine with PFO closure only in patients with aura (OR = 0.21 [95% CI: 0.12-0.37]) **(Supplementary Figure 3)**. Our additional analysis of before and after observational studies showed an overall improvement in migraine status with PFO closure (OR = 0.12 [95% CI: 0.07-0.21]) **(Supplementary Figure 4)**. Similarly, in the previously published meta-analysis of RCTs only [77], no statistically significant difference in complete resolution of migraine attacks (OR 3.67, 95% CI: 0.66–20.41) or in responder rate (OR 1.92, 95% CI: 0.76–4.85) was observed overall between PFO closure and control groups. However, a statistically significant higher reduction in the frequency and duration of monthly migraine attacks was observed in the PFO closure versus control group (standardised mean difference [SMD] 0.25; 95% CI: 0.06–0.43; p 0.01 and SMD 0.30; 95% CI: 0.08–0.53; p 0.01, respectively). Moreover, on subgroup analysis, a reduction in migraine attacks in the PFO closure versus control group was reported in patients with a majority of episodes accompanied by an aura (SMD 0.86; 95% CI: 0.07–1.65; p 0.03). The other two previous meta-analyses, including a	

	smaller number of observational trials and one RCT, showed similar results, especially in patients with previous cerebral ischaemic injury or migraine with aura [72,76].	

Undesirable effects
How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know	Undesirable effects of percutaneous closure vs medical therapy have been scarcely and inconsistently reported in both RCTs and, especially, observational trials. In RCTs, the incidence of adverse effects related to the PFO closure procedure or to the device ranged from 0.5% to 1.1%. In our meta-analysis, incidence rates for undesirable procedure- or device-related adverse events in RCTs were similar with PFO closure vs medical therapy only (OR: 4.13, 95%CI: 0.34-49.53).	

Certainty of evidence
What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ● Low ○ Moderate ○ High ○ No included studies	The benefit for patients with unspecified migraine overall derives only from observational studies and, regarding specific measures, from meta-analyses of secondary endpoints in RCTs. The benefit regarding patients with aura derives from only one RCT, influencing the results of the available meta-analyses, and from observational studies. The overall certainty of evidence is furthermore questioned by the judgement on individual studies, both for observational and RCTs **(Supplementary Table 2, Supplementary Table 4)**. All individual RCTs were underpowered **(Supplementary Appendix 2 and Supplementary Table 2)** and meta-analyses should be interpreted accordingly. Moreover, individual RCTs have low internal and external **validity (Supplementary Appendix 2 and Supplementary Table 2, Supplementary Table 4)** and the validity of one of the RCTs was severely criticised by some of the study's own authors. Indeed, event rates were low and confidence intervals wide. Moreover, innumerable data from meta-analyses and randomised and observational studies (see text) show that substantial heterogeneity exists in the populations studied. The potential variability is high due to 1) heterogeneity of disease (aura vs no aura) 2) heterogeneity and/or lack of any assessment of medical therapy for migraine 3) heterogeneity in the assessment of migraine Hence, more precise phenotyping with multidimensional data is warranted for future randomised trials. New research is needed to impact current estimates.	

Values
Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or	No specific studies assessing the priority of outcomes from patients suffering from PFO-associated migraine are available. In a study of 510 subjects with migraine, the impact of any therapy on the post-headache phase was a key determinant of patient preferences regarding treatment [192]. Unfortunately, none of the studies on PFO-associated migraine considered this aspect. However, as migraine is a chronic, disabling disease, it is no surprise that three studies showed, in patients suffering from migraine at large, that the efficacy of headache treatment is more important to them than the treatment's safety or route of administration [193–195]. Indeed, patients often even prefer device therapy (neurostimulation) to drug therapy when it is more effective [193]. Moreover, even though one of these studies also showed that patients are often satisfied with available drug prevention [194], in a recent study, migraineurs were more likely to fill the	

variability	prescription and adhere to the new therapy when their preferred dosing regimen was available [196]. Therefore, even though individual assessment of preferences is paramount, there is probably no important uncertainty or variability in how much patients value the main outcome of migraine improvement.	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ● Probably favours the intervention ○ Favours the intervention ○ Varies ○ Don't know	The available data suggest that the intervention may potentially better benefit select patients with aura and/or cerebrovascular disease, with a similar incidence of adverse events to medical therapy. Adverse events associated with a percutaneous procedure and/or the device were mostly mild and transient, whereas adverse events related to life-long medical therapy can be persistent. However, given the high uncertainty of results, more adequately designed studies are necessary to confirm these findings.	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ● Don't know	No cost-effectiveness evaluation comparing different medical therapies versus percutaneous closure of PFO has been performed in migraineurs.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	PFO closure is a well-established technique performed at many interventional centres across the globe.	

Supplementary Table 9. Characteristics of the studies on PFO closure for migraine.

First author	Design	FUP (years)	Endpoint	Migraine	Drugs	Multivariate analysis
Anzola [197]	Prospective	1	Migraine score	Improvement of migraine score	NA	NA
Araszkiewicz [198]	Prospective	1.5	No. of patients with migraine	Reduction from 30% to 15.7% after the procedure	NA	NA
Azarbal [199]	Prospective	0.4	No. of patients with migraine	Reduction from 42% to 31% after the procedure	NA	NA
Biasco [200]	Retrospective	0.5	No. of patients with migraine	Improvement of migraine score	NA	NA
Dubiel [201]	Retrospective	2	No. of patients with migraine	Improvement of migraine score	NA	NA
Giardini [202]	Retrospective	1.7	No. of patients with migraine	Reduction from 100% to 17% after the procedure		
Jesurum [203]	Retrospective	2	No. of patients with migraine	Reduction from 71% to 44% after the procedure	NA	No improvement at multivariate analysis
Khessali [46]	Prospective	1	No. of patients with migraine	Reduction from 100% to: - 52% for those with visual aura - 75% for aura not related to migraine - 80% in aura without migraine	NA	NA
Kimmelstiel [204]	Prospective	1	Patients with migraine and migraine score	Reduction from 100% to 17% and reduction in score	NA	NA

Luermans [205]	Retrospective	2	Patients with migraine and migraine score	Reduction of severity of migraine	NA	NA
Milev [206]	Retrospective	2	Patients with migraine	Reduction of severity of migraine	NA	NA
Morandi [207]	Prospective	0.5	Patients with migraine	Reduction from 100% to 29%	NA	NA
Post [208]	Retrospective	0.3	Patients with migraine	Reduction from 39.4% to 15.1%	NA	NA
Reisman [209]	Prospective	0.9	Patients with migraine	Reduction from 100% to 44%	NA	NA
Rigatelli [210]	Prospective	1	MIDAS score	100% reported an improvement of MIDAS score Aura disappeared in all of the patients	NA	NA
Schwerzmann [211]	Retrospective	1	Number of migraine attacks	Relative reduction of 54% in those with aura and of 62% in those without	NA	NA
Trabattoni [212]	Prospective	1	No. of patients with migraine	Reduction from 100% to 54%	NA	NA
Vigna [71]	Prospective	1	No. of patients with migraine	Reduction from 100% to 66%	NA	NA
Wahl [213]	Prospective	1	No. of patients with migraine	Reduction from 100% to 34%	Reduction of patients assuming drugs	NA
Dowson [73]	RCT	0.3-0.6	Migraine headache cessation	No significant reduction of patients with migraine. Reduction in PFO closure of days of migraine	NA	-
Tobis [75]	RCT	1	50% reduction in attacks	No difference in primary endpoint. PFO significantly reduced headache days and complete remission		

First author	Design	FUP (years)	Endpoint	Migraine	Drugs	Multivariate analysis
Elbadawi [77]	Meta-analysis	0.5	Reduction in migraine attacks/months (NNT of 13 assuming a reduction of 1.9 as expected outcome)	PFO closure reduced migraine attacks/months (NNT of 13 assuming a reduction of 1.9 as expected outcome) without leading to migraine resolution	NA	
Kheiri [214]	Meta-analysis	0.5	Reduction in migraine attacks/months	PFO closure reduced migraine attacks and its length	NA	
Shi [76]	Meta-analysis	1	Elimination or significant improvement of migraine symptoms after PFO closure	Reduction in migraine attacks more evident in migraine with aura	NA	
Butera [72]	Meta-analysis	1	Cured or significantly improved migraine	46% with complete resolution, 83% with at least partial		

Supplementary Table 10. Diseases in which PFO can contribute to arterial hypoxaemia and its clinical consequences.

DISEASE	SHUNT CAUSES	CLINICAL CONSEQUENCES	PFO PATHOGENIC ROLE
Platypnoea-orthodeoxia syndrome (POS)	- Pulmonary hypertension (ventilation/perfusion mismatch) [182] - Preferential blood flow towards the PFO from the inferior vena cava (through prominent Eustachian valve or deformation of atrial structures, due to cardiac valve disease, or diaphragmatic, pulmonary, vertebral column, or aortic disease [184-191]	- Upright position dyspnoea relieved by lying supine	VERY FREQUENT [80]
Obstructive sleep apnoea syndrome (OSAS)	- Intermittent and then persistent pulmonary hypertension due to apnoea with hypoxaemia and hypercapnia causing vasocontriction - Fluctuations in intrathoracic pressure during apnoea	- Exacerbation of hypoxaemia during apnoeic episodes [169-171] - More OSAS-related symptoms and at an earlier stage than in those without a PFO [169]	POSSIBLE
Chronic obstructive pulmonary disease (COPD)	- Pulmonary hypertension due to chronic ventilation-perfusion mismatch [172]	- No clinical effect [174] - Transient oxygen desaturation [172] - Arterial oxygen saturation lower than expected given the clinical picture [175] - Lower exercise tolerance [175]	DEBATED
Exercise desaturation	- Pulmonary hypertension	- Reduced exercise tolerance	UNDER INVESTIGATION
High-altitude pulmonary oedema (HAPO)	- Pulmonay hypertension due to hypoxia [177]	- Aggravation of hypoxaemia and pulmonary oedema	UNDER INVESTIGATION

Supplementary Table 11 - Summary of statements on arterial deoxygenation and PFO

Position Statements	Strength of the statement	Level of evidence
PFO has the potential to generate clinically significant right-to-left shunts, often only aggravating pre-existing arterial oxygen desaturation	Strong	C
Assessing the role of a PFO in hypoxaemia should be done only if an interdisciplinary, comprehensive evaluation of all possible factors causing hypoxaemia fails to fully explain the clinical picture	Strong	C
A catheterisation lab assessment of left atrial SaO_2 (including each pulmonary vein), pulmonary pressures and a balloon occlusion test should be performed when the role of PFO is not straightforward.	Strong	C
Pulmonary causes of hypoxaemia (particularly pulmonary embolism, intrapulmonary shunts and severe pulmonary hypertension) should be ruled out before considering PFO closure.	Strong	C
In patients with PFO-related platypnoea-orthodeoxia syndrome and without severe pulmonary hypertension, percutaneous closure of the PFO is a first-line treatment	Strong	C
Percutaneous closure of a PFO can be proposed to patients with any desaturation syndrome in which, despite best conventional treatment, the PFO has been demonstrated to unequivocally and critically contribute to the arterial desaturation and symptoms	Conditional	C
RESEARCH AGENDA: - To assess the incidence of significant PFO-related arterial hypoxaemia in the different syndromes - To identify high-risk phenotypes for clinically significant PFO-related arterial desaturation encompassing different clusters of clinical, anatomical and biological characteristics in prospective observational trials (systems and precision approaches) - To design adequately dimensioned observational studies and RCTs comparing PFO closure vs medical therapy only, in different syndromes - To obtain quantitative and qualitative data on patient preferences and values	Strong	C

Supplementary Table 12. Position statements on pregnancy and the pre-operative management of patients.

Position Statements	Strength of the statement	Level of evidence
PREGNANCY, DELIVERY AND THE PUERPERIUM		
Outside of research, in unselected healthy, asymptomatic women planning a pregnancy or during a normal pregnancy, PFO should not be systematically screened for.	Strong	C
Outside of research, in women with a known PFO but otherwise without coagulation diseases, no primary prevention for thrombotic systemic embolism should be foreseen.	Strong	C
Secondary prevention of PFO-related thrombotic systemic emboli in women of child-bearing age or during pregnancy should be done according the statements published in the first part of this document [1,2] taking into due consideration the risk of irradiation during pregnancy in cases of percutaneous PFO closure.	Conditional	C
RESEARCH AGENDA: - To assess a possible link between PFO and thrombotic systemic embolism in pregnancy, delivery and puerperium - Epidemiological, systems and precision medicine research to identify possible phenotypes at high risk of thrombotic systemic embolism during pregnancy, delivery and the puerperium	Strong	C
PRE-OPERATIVE EVALUATION FOR NON-CARDIAC SURGERY		
Outside of research, in unselected healthy, asymptomatic patients, PFO should not be systematically screened for during preoperative evaluations for non-cardiac surgery	Strong	C
In asymptomatic patients with a known PFO, there is insufficient data to render decisions regarding any form of primary prevention, pharmaceutical or interventional, for thrombotic systemic embolism	Strong	C
Patients at high risk of perioperative thrombosis should be managed according to existing guidelines on the topic, irrespective of the presence of a PFO	Strong	C
RESEARCH AGENDA: - To prospectively assess the incidence of PFO-related perioperative thrombotic systemic embolism - To identify high-risk phenotypes for PFO-related thrombotic systemic embolism encompassing different clusters of clinical, anatomical and biological characteristics in prospective observational trials (systems and precision approaches) - To design adequately dimensioned observational studies and RCTs comparing PFO closure vs medical therapy only, to prevent perioperative thrombotic systemic embolism	Strong	C

Supplementary Table 13. Position statements regarding neurosurgery in the sitting position.

Position Statements	Strength of the statement	Level of evidence
All patients scheduled for neurosurgery in the sitting position should routinely undergo screening for a PFO prior to surgery	Strong	C
In patients with a PFO, neurosurgery in the sitting position is contraindicated; but neurosurgery in a horizontal surgical position also needs to be monitored closely.	Strong	C
In select patients with a PFO in whom the neurosurgical operation can be delayed 1-12 months (preferably 6-12) and: a) the sitting position is mandatory or b) a previous attempt at surgery in a prone or lateral position led to a venous air embolism, PFO closure is reasonable, followed by neurosurgery at a later date after assessing completeness of closure	Conditional	C
RESEARCH AGENDA: - To assess the efficacy and safety of percutaneous closure of a PFO to prevent cerebral air emboli during neurosurgery in the sitting position, both observational and randomised controlled studies are needed.	Strong	C

Supplementary Table 14. GRADE evaluation of certitude of effects – DCS.

A. Professional divers

Certainty assessment							Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	
Nuovo esito							
10 [a,b,c]	Observational studies	Serious [a]	Not serious	Not serious	Very serious [b]	Dose response gradient	⨁◯◯◯ VERY LOW

6 case-control, 1 cohort study, 3 case reports

CI: confidence interval

Explanations

a. High risk of adjudication bias
b. No multivariate analysis and no sample size calculation
c. There is a (imperfect) dose-response relation between deep diving and generation of nitrogen emboli after the dive; based on Doppler studies (Nishi, Eftedal) there is also a (imperfect) relation between numbers/grade of nitrogen bubbles and risk of DCS.

B. Recreational divers

Certainty assessment							Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	
Nuovo esito							
11	Observational studies	Serious [a]	Not serious	Not serious	Serious [b]	None	⨁◯◯◯ VERY LOW

CI: confidence interval

Explanations

a. High risk of blinding and of adjudication of events
b. Few studies with multivariate analysis and no sample size calculation

Supplementary Table 15. Studies on DCS in recreational divers.

First author	Sample size	Incidence of PFO	Design	Causal association	Follow up data
Billinger [215]	106 scuba divers	48 (29%)	Retrospective	**NN**	NN
Gempp [21]	47 divers	24 recurrent cases of DCS	Prospective	Large right to left shunts are associated with repeated episodes	NN
Honek [29]	532 divers	46 (8.4%)	Prospective	A significant reduction of DCS risk was observed after recommendation of conservative profile for the whole group as well as for the subgroups with or without a r/l shunt.	NN
Liou [145]	75 divers	39 (52)	Retrospective	Major DCS was observed significantly more commonly in divers with PFO than in those without	NN
Moon [13]	30 divers (26 sport + 4 professional) and 176 controls	NN	Prospective	Higher incidence of DCS in controls	
Pearman [33]	105 divers with PFO closure	105/105	Retrospective	2/105 had AF. 2/105 residual shunt	NN
Torti [144]	230	63 (27)	Retrospective	PFO increases of 5 risk of DCS	NN
Wilmshurst [14] *	60 divers (57 recreational + 3 professionals)		Retrospective	Higher incidence of RtoL shunt in divers with DCS	NN

*included in quantitative analysis

Supplementary Table 16. Studies on DCS in professional divers.

First author	Sample size	Incidence of PFO	Design	Causal association	Follow-up data
Cantais [11] *	202 (101 DCS, 101 control)	N	Prospective	Major right to left shunt is associated with DCS	NN
Cartoni [22]	66 (41 with DCS, 25 without)	35/66 (53%)	Retrospective	PFO with right-to-left shunting at rest is associated with decompression illness	NN
Germonpre [12]*	74 (37 divers with DCS vs 37 divers without)	22/37 (60%) divers with DCS and 13/37 (36%) divers without	Prospective	Higher incidence of PFOs in divers with DCS compared with those without	NN
Honek [31]	47 divers	47/47	Prospective	PFO closure reduced arterial bubbles	NN
Klingmann [28]	27 divers	4 with PFO closure	Retrospective	A highly significant reduction of DCS risk was observed after recommendation of conservative profile for the whole group as well as for the subgroups with or without a r/l shunt.	NN
Wilmshurst [146]	200 divers	200/200	Retrospective	Larger atrial defect in divers experiencing DCS	NN
Pearman [33]	105 divers with PFO closure	105/105	Retrospective	2/105 had AF. 2/105 residual shunt	NN
Walsh [32]	7 divers with DS	1/7	Retrospective	NN	NN
* included in quantitative analysis					

Supplementary Table 17. GRADE evaluation of certitude of effects – desaturation syndromes.

Certainty assessment							Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	
Nuovo esito							
5	Observational studies	Serious [a]	Not serious	Not serious	Serious [b]	None	⨁◯◯◯ VERY LOW

CI: confidence interval

Explanations

a. High risk of adjudication of outcomes
b. No sample size calculation

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