Supplementary Material

**Recent progress in patent foramen ovale and related neurological diseases: A narrative review**

**Supplementary Table. Summary of clinical studies on PFO-related neurological diseases**

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| **Clinical research on risk factors of PFO related stroke** | | | | | | | | | | | | | | | |
| **Study** | **Study type** | **Study object** | **Control group** | **Sample size （observation group /** **control group）** | **Average age （observation group /** **control group）** | **Main research results（observation group /** **control group）** | | | | | | **Conclusions** | | | |
| Holda MK, etal.2021(1) | prospective cohort | CS patients with PFO | Non-CS group with PFO | 199（106/93） | 45.611.8/48.114.5 | 1. PFO channel length change（OR=2.50，*P*<0.001） 2. PFO length/height ratio (OR=0.75.*P=*0.015) 3. Septum primum thickness (OR=0.34,*P*=0.013) 4. Septum secundum height(OR=0.91,*P*=0.013) 5. Atrial septal aneurys(OR=3.38,*P*=0.014)   （6）RLS large shunt(OR=2.49,*P*=0.022) | | | | | | The MorPFO score may help to identify high and moderate-risk PFO channels | | | |
| Bayar N, etal.2015(2) | retrospective cohort | CS and TIA patients with PFO | Asymptomatic patients with PFO | 156(64/92) | 43.88.6/37.89.3 | 1. Height of PFO（3.0 vs 2.0,*P*<0.001） 2. Thickness of septum secundum（5.0 vs 3.0,*P*<0.001） 3. Septal excursion distance（7.0 vs 4.0,*P*<0.001） 4. The ratio of length to height of PFO tunnel（3.0 vs 5.0,P<0.001） | | | | | | The long PFO, relatively large interatrial fluidity, thick septum pellucidum, and the presence of ASA may help to identify PFO patients aged ≤55 years | | | |
| Nakayama R, etal.2019(3) | retrospective cohort | CS patients planned for PFO closure | Migraine patients scheduled for PFO closure（Non- CS group） | 107（57/50） | 5014/4218 | （1）PFO tunnel（≥10mm vs <10mm(OR=3.16)）  （2）Hypermobile interatrial septum（OR=7.26）  （3）Eustachian valve or Chiari's network（OR=4.58）  （4）RLS shunt（large vs small，OR=3.87）  （5）PFO angle（≤10°vs ＞10°，OR=5.12） | | | | | | Long-tunnel PFO, the presence of hypermobile interatrial septum, the presence of prominent Eustachian valve or Chiari's network, the large right-to-left shunt during Valsalva maneuver, and low-angle PFO were independently related to CS | | | |
| Cerrato P,  etal.2002(4) | case-control | CS or TIA (including lacunar group and non-lacunar group) | Health control | 253（175/78） | 49.7/53.2 | 1. PFO frequency:31.4% vs 16.6%,P=0.02,N-LAC group vs LAC group=40.6% vs 17.4%,P=0.0005 ;   （2）Frequency of atrial septal aneurys :12% vs 1.3%,P=0.003 | | | | | | PFO and ASA are independent predictors of ischemic cerebrovascular disease, and PFO is independently associated with N-LAC stroke subtype | | | |
| Natanzon A, etal.2003(5) | case-control | CS patients with PFO | Non-CS group with PFO | 78（36/42） | 56.818.3/58.217.6 | （1）RLS shunt（*P*=0.004）  （2）The size of the overlap between septum primum and septum secundum（7.5 vs 9.9,*P*=0.026） | | | | | | Both anatomic and pathophysiologic mechanisms should be considered in determination of the potential clinical significance of a PFO | | | |
| Goel SS, etal.2009(6) | case-control | CS or TIA patients with PFO | Asymptomatic patients with PFO | 116（58/58） | 5416/615 | （1）Proportion of large PFOs(>4 mm) :46% vs 17%，*P*<0.001  （2）Proportion of long tunnels (>1 cm):78% vs 55%，*P*<0.01  （3）Frequency of atrial septal aneurysm:45% vs 21%，*P*<0.005  （4）The frequencies of prominent Eustachian valves and Chiari’s network were not significantly different。 | | | | | | PFOs in patients with cryptogenic CVAs are larger, have longer tunnels, and are more frequently associated with atrial septal aneurysms | | | |
| Komar M,etal.2012(7) | case-control | CS patients with PFO | Asymptomatic patients with PFO | 176（88/88） | 36.116.2/35.714.2 | 1. PFO size:3.9 vs 1.3,*P*<0.0001 2. PFO tunnel length:14 vs 12，*P*<0.05 3. Frequency of atrial septal aneurysm:55% vs 15%,*P*<0.0001 4. Proportion of large PFOs:40% vs 2%,*P*<0.0001 | | | | | | PFO in symptomatic patients is larger in size, has a longer tunnel and is more frequently associated with atrial septal aneurysm | | | |
| **Clinical research on PFO closure in PFO related stroke** | | | | | | | | | | | | | | | |
| **Study** | **Study type** | **Study object** | **Interventions**  **（experimental group/control group）** | **Device** | **Sample Size**  **（experimental group/control group）** | **Average age （experimental group/control group）** | **Follow-up time（months）** | | **Minimum duration of postoperative antiplatelet/anticoagulant therapy (months)** | **Effectiveness** | | **Efficacy evaluation tool** | | **Residuals shunt** | **postoperative complications** |
| CLOSURE I 2012(8) | Multi-center RCT | (1)ischemic stroke or TIA with PFO  (2)between 18 and 60 years of age | PFO closure + antiplatelet drugs VS Drugs | STARFlex 100% | 909(447/462) | 46.3±9.6/  45.7±9.1 | 24 | | 24 | **Cumulative incidence of a composite of**  **stroke or TIA or death:**  HR=0.78，*P*=0.37 | | (1)MRI  (2) DWMRI | | NA | AF（5.7%）、bleeding |
| PC 2013(9) | Multi-center RCT | (1)ischemic stroke or TIA or peripheral thromboembolism with PFO  (2)< 60 years of age | PFO closure VS Drugs | Amplatzer 100% | 414（204/210) | 44.3±10.2/  44.6±10.1 | 48.6 | | 6 | **Cumulative incidence of a composite of**  **death, nonfatal stroke, TIA, or peripheral embolism**:  HR=0.63，*P*=0.34 | | (1)MRI or CT  (2)NIH Stroke Scale | | NA | AF（2.9%）、bleeding、myocardial infarction |
| RESPECT 2013-2017(10) | Multi-center RCT | (1)ischemic stroke or TIA with PFO  (2)between 18 and 60 years of age | PFO closure VS Drugs | Amplatzer 100% | 980(499/481) | 45.7±9.7/  46.2±10.0 | 68.28 | | 6 | **Cumulative incidence of a composite of**  **stroke or death:** HR=0.55，*P*=0.046 | | (1)MRI or CT  (2)NIH Stroke Scale  (3)Modified Rankin Scale and the Barthel Index | | NA | AF（0.48/100 patient-years） |
| REDUCE 2017(11) | Multi-center RCT | (1)cryptogenic ischemic stroke with PFO  (2)18 to 59 years of age | PFO closure + antiplatelet drugs VS Drugs | GORE HELEX39%、Cardioform61% | 664(441/223) | 45.4±9.3/  44.8±9.6 | 38 | | NA | **（1）rate of recurrence of stroke：**  HR=0.23,*P*=0.002  **（2）The incidence of new brain infarctions：**RR=0.44,*P*=0.02 | | MRI or CT | | NA | AF(6.6%)、bleeding |
| CLOSE 2017(12) | Multi-center RCT | (1)ischemic stroke with PFO  (2)16 to 60 years of age | PFO closure + antiplatelet drugs VS antiplatelet drugs VS anticoagulant drugs | NA | 663(238/425) | 42.9±10.1/  54±12 | 63.6 | | 3 | **occurrence of fatal or nonfatal stroke：**  HR=0.03，*P*<0.001 | | (1)MRI or CT  (2)modified Rankin Scale and the Barthel Index | | NA | AF(4.6%)、bleeding |
| DEFENSE 2018(13) | Multi-center RCT | ischemic stroke with high risk PFO | PFO closure VS Drugs | Amplatzer 100% | 120(60/60) | 49±15/  54±12 | 24 | | ≥6 | **Cumulative incidence of a composite of stroke,**  **vascular death, or Thrombolysis**  :*P*=0.013 | | MRI | | 1（1.67%） | AF（3.33%）、bleeding |
| Wahl et al, 2012(14) | prospective cohort | CS、TIA | PFO closure VS Drugs | NA | 308(150/158) | 5012/50.713.3 | 180 | | NA | **Cumulative incidence of the composite of stroke, TIA, or peripheral embolism:**  HR=0.43，*P*=0.033 | | NA | | 4（3.9%） | Apparatus embolism、bleeding |
| Kim et al, 2018(15) | prospective cohort | CS、TIA | PFO closure VS Drugs | Amplatzer、GORE HELEX | 158(67/91) | 47.710.8/51.99..9 | 27.8 | | NA | Cumulative incidence of the composite of stroke, TIA：PFO closure VS Drugs=0.0% vs 6.6%,*P*=0.039 | | NA | | NA | NA |
| Alushi et al, 2014(16) | prospective cohort | CS、TIA | PFO closure VS Drugs | Amplatzer、Cardia Star | 418(262/156) | 48.513.8/52.313.1 | 70.8 | | 6 | Cumulative incidence of the composite of stroke, TIA：PFO closure VS Drugs=5.7% vs 5.1%,*P>*0.99 | | MRI or CT | | 5（1.9%） | AF、Blood clots in the device、endocarditis |
| Moon et al, 2016(17) | prospective cohort | CS | PFO closure VS Drugs | NA | 164(72/92) | 45.39.8/50.26.7 | 22 | | ≥3 | Cumulative incidence of the composite of stroke, TIA:=2.8% vs 2.2%,*P=*1.000） | | NA | | 8（14.5%） | NA |
| Harrer et al, 2006(18) | prospective cohort | CS | PFO closure VS Drugs | Amplatzer、CardioSEAL、PFOStar | 124(43/81) | 42.515.4/49.514.5 | 32 | | ≥6 | Annual stroke recurrence rates: PFO closure vs Drugs=2.9% vs 2.1%,*P*>0.05） | | MRI or CT | | 0（0.0%） | hematoma |
| Mazzucco et al, 2012(19) | prospective cohort | CS | PFO closure VS Drugs | Amplatzer、BioSTAR | 103(50/52) | 41.611.5/42.69.9 | 27.5 | | ≥6 | There was no difference in the risk of the composite of stroke, TIA | | MRI or CT | | 37% | bleeding |
| Pezzini et al, 2016(20) | prospective cohort | Stroke | PFO closure VS Drugs | Amplazer、CardioSEAL、STARFlex、GORE、BioSTAR、Premere、Figulla、ATRIASEPT | 521(206/315) | 35.37.4/35.76.8 | 36 | | NA | The composite recurrence rate of CS, TIA and peripheral embolism was not statistically significant. | | CT and/or MR angiography | | NA | AF |
| Casaubon et al, 2007(21) | prospective cohort | CS、TIA | PFO closure VS Antithrombotic drugs | CardioSEAL、Amplatzer | 121(60/61) | 46 | 32 | | Anticoagulation for 6 months and long-term antiplatelet | Recurrent rate of stroke: PFO closure group was lower than Antithrombotic drugs ，*P*=0.014） | | MRI or CT | | NA | AF、Thrombus 、hematoma |
| FORI Study, 2011(22) | prospective cohort | CS、TIA(age＜55 years old) | PFO closure VS Antithrombotic drugs | Amplatzer、STAR、Cardioseal/Starflex | 238(121/117) | 43.49.5/40.910.3 | 24 | | NA | Recurrent rate of stroke: PFO closure VS Antithrombotic drugs=0.8% vs 6.8%,*P*=0.018） | | NA | | 20（16.5%） | AF |
| Lee et al, 2010(23) | retrospective cohort | CS | PFO closure VS antiplatelet drugs VS anticoagulant drugs | Amplazer、CardioSEAL、 | 181(22/99/60) | 4112/5313 | 42 | | NA | unadjusted 5-year stroke recurrence-free survival rates were different | | NA | | NA | NA |
| Windecker et al, 2004(24) | retrospective cohort | CS | PFO closureVS Drugs | Amplazer、CardioSEAL、STARFlex | 308(150/158) | 5012/5113 | 27.6 | | NA | Recurrent rate of death, stroke, or TIA: PFO closure VS Drugs =8.5% vs 24.3%，*P*=0.05 | | NA | | 4(27%) | NA |
| Schuchlenz, 2005(25) | retrospective cohort | TIA or Stroke | PFO closure VS Aspirin VS coumadin | CardioSEAL、STARFlex、Amplatze | 280(167/66/47) | 4411/4613/5012 | 31.2 | | NA | Recurrence rate of stroke or TIA: PFO closure VS Aspirin VS coumadin =0.6% vs 5.6% vs 13%,*P*<0.001 | | NA | | NA | retroperitoneal hematomas、device  embolizations、cardiac tamponade |
| Thanopoulos et al, 2006(26) | Case series | CS、TIA | PFO closure VS antiplatelet drugs | Amplatzer | 92(48/44) | 4311/4012 | 24 | | 6~9 | One-year incidence of TIA: PFO closure VS antiplatelet drugs =0% vs 6.8%,*P*=0.001 | | CT and/or MRI | | 4（9%） | NA |
| **Clinical research on drug treatment in PFO related stroke** | | | | | | | | | | | | | | | |
| **Study** | **Study type** | **Study object** | **Interventions**  **（experimental group/control group）** | **Sample Size （experimental group/control group）** | **Average age （experimental group/control group）** | **Follow-up time（months）** | | **Effectiveness** | | | **Efficacy evaluation tool** | | **Safety** | | |
| PICSS study2002(27) | RCT | (1)cryptogenic stroke with PFO  (2)>18 years and <85 years | Warfarin VS Aspirin | 203（97/106） | 57.9±13.3 | 24 | | 1. **year recurrent rates of ischemic stroke or death：** 2. 9.5% vs 17.9%,*P*=0.28 | | | CT or MRI | | 1. **year recurrent rates of ischemic stroke or death：** 2. 9.5% vs 17.9%,*P*=0.28 | | |
| Shariat,etal.  2013(28) | Single blind RCT | (1)undetermined causes of stroke with PFO  (2)>18 years | Warfarin VS Aspirin | 44(21/23) | 60.6±4.3/ 63.0±4.7 | 18 | | **The rate of ischemic events or death:**  HR= 0.45; *P* = 0.259 | | | NA | | **The rate of ischemic events or death:**  HR= 0.45; *P* = 0.259 | | |
| NAVIGATE ESUS trial(29) | RCT | (1)ischemic stroke with PFO  (2)>49 years at the time of the stroke | Rivaroxaban VS Aspirin | 7213(3609/3604) | 66.9±9.8/  66.9±9.8 | 11 | | **The first recurrence rate of ischemic or hemorrhagic stroke or systemic embolism：**5.1% vs 4.8%,*P*=0.52 | | | NA | | **The first recurrence rate of ischemic or hemorrhagic stroke or systemic embolism：**5.1% vs 4.8%,*P*=0.52 | | |
| RE-SPECT ESUS2019(30) | Multicenter, double-blind RCT | (1)undetermined source of stroke  (2)>18 years | Dabigatran VS Aspirin | 5390(2695/2695) | 64.5±11.4/ 63.9±11.4 | 19 | | **The recurrence rate of ischemic or hemorrhagic or unspecified type stroke:**  6.6% vs 7.7%,*P*=0.10  **Subgroup analysis: Patients with PFO consistent with the overall trial results** | | | NA | | **The recurrence rate of ischemic or hemorrhagic or unspecified type stroke:**  6.6% vs 7.7%,*P*=0.10  **Subgroup analysis: Patients with PFO consistent with the overall trial results** | | |
| CODICIA study2008(31) | prospective cohort | massive RLS of CS | Warfarin VS  Aspirin | NA | NA | NA | | The rate of recurrent strokes：Warfarin vs Aspirin = 6.6% vs 1.6%，*P*=0.18 | | | NA | | NA | | |
| K Nedeltchev2002(32) | retrospective cohort | TIA or Stroke | vitamin K antagonists  VS Aspirin/ clopidogrel | 159(79/80) | 50.713.5 | 29 | | Has no association between the treatment regimen and the risk for recurrence (p=0.99)，but there was a trend indicating an increased risk for stroke recurrence in Aspirin group | | | CT or MRI | | No bleeding complications were seen | | |
| **Clinical research on the correlation between PFO and** **migraine** | | | | | | | | | | | | | | | |
| **Study** | **Study type** | **Study object** | **Control group** | **Sample size （observation group /** **control group）** | **Average age （observation group /** **control group）** | **Outcome** | **Main research results** | | | | | **Conclusions** | | | |
| Ferrarini 2005(33) | retrospective cohort | migraine with aura | NA | 25 | 38.4 | The presence of PFO | 72% | | | | | the presence of arteriovenous (AV) shunts could represent a trigger for MA attacks as well as for stroke | | | |
| Rundek (NOMAS) 2008(34) | retrospective cohort | migraine | No Migraine | 1101 | 69 | The prevalence of PFO | no significantly difference between groups(14.6% vs 15.0%; P=0.9） | | | | | In this multiethnic, elderly, population-based cohort, PFO detected with transthoracic echocardiography and agitated saline was not associated with self-reported migraine | | | |
| Anzola 1999(35) | cross-sectional study | migraine patients | Non-migraine patients | MA+ 113  MA- 53  Non-migraine patients 25 | 33.7 | The prevalence of PFO | (1)MA（+） vs MA（-）OR=3.13,*P*=0.002;  (2)MA（+） vs control group：OR=3.66,*P*=0.01；  (3)MA（-） vs control group：OR=1.17 | | | | | Patency of the foramen ovale is associated with migraine with aura but not with migraine without aura | | | |
| Dalla Volta 2005(36) | cross-sectional study | migrainous patients | cluster headache(CH) | MA+ 260  MA- 74  CH 38 | 36.7 | The presence of PFO | MA(+) vs MA(-) vs CH=61.9% vs 16.2% vs 36.8% | | | | | There was a link between MA+, CH, and PFO, | | | |
| Domitrz 2007(37) | cross-sectional study | migraine patients | healthy control | MA+ 61  MA- 60  healthy control 65 | 36 | The presence of PFO | 1. MA(+) vs MA(-):*P*=0.0014; 2. MA(+) vs healthy control：*P=*0.0011; 3. MA(-) vs healthy control：*P*=0.087 | | | | | Possible association of migraine with aura and PFO | | | |
| Domitrz 2014(38) | cross-sectional study | migraine patients | healthy control | MA+ 62  MA- 96  healthy control 53 | 3811 | The prevalence of PFO | (1)migraine patients vs healthy control：*P*=0.03; (2)MA vs MO：*P*=0.06; (3)MA vs healthy control:*P*=0.01. | | | | | Do not find any clear connection between PFO and migraine occurrence | | | |
| Guo 2014(39) | cross-sectional study | Chronic migraine（CM） | medication-overuse headache (MOH) | 261(159/102) | 38.25 | The prevalence of RLS | The prevalence of RLS :CM vs MOH=37% vs 31%,*P*=0.49 | | | | | PFO is thus unlikely to have a significant causal role in these chronic headaches | | | |
| Tang, Y. etal2022(40) | cross-sectional study | PFO group | No PFO group | 2640(880/1760) | 50.90 | The prevalence of migraine without aura | The prevalence of migraine without aura : PFO group VS No PFO group =12.83% vs 7.83%,*P*<0.0001 | | | | | a strong association between PFO and migraine  without aura, especially when the shunt is large | | | |
| Garg 2010(41) | case-control | migraine patients | healthy control | 288(144/144) | 41.5 | Presence of PFO | Presence of PFO： (1)migraine VS healthy control =26.4% vs 25.7%,OR=1.04，*P*=0.90；  (2)MA VS MO=26.8% vs 26.1%,OR=1.03，*P*=0.93 | | | | | Had no association between migraine headaches and the presence of PFO | | | |
| Kuper 2013(42) | case-control | migraine patients | healthy control | MA+ 42  MA- 44  healthy control 41 | NA | Prevalence of RLS | Differences did not reach statistical significance between the three groups (p = 0.564) | | | | | a trend towards higher prevalence of RLS with larger shunts in subjects with migraine with aura | | | |
| Schwerzmann 2005(43) | case-control | patients with migraine with aura | healthy control | 186(93/93) | NA | The presence of PFO and moderate-sized or large shunt | 1. The presence of PFO :MA+ VS healthy control=47% vs 17%，*P*<0.001;   (2) The presence of moderate-sized or large shunt :MA+ VS healthy control =38% vs 8%,*P*<0.001 | | | | | Shunt size is larger in migraineurs than controls | | | |
| Tatlidede 2007(44) | case-control | Migraine patients with intra-atrial right to left shunt | healthy control | 80(53/ 27) | NA | The percentages of PFO | MA+ VS MA- VS healthy control =66.7% vs 47.4% vs 22.2% | | | | | There were association between PFO and migraine, especially with aura | | | |
| **Clinical research on PFO closure in PFO related migraine** | | | | | | | | | | | | | | | |
| **Study** | **Study type** | **Study object** | **Interventions**  **（experimental group/control group）** | **Device** | **Sample Size**  **（experimental group/control group）** | **Average age （experimental group/control group）** | **Follow-up time（months）** | | **Maximum duration of postoperative antiplatelet/anticoagulant therapy (months)** | **Effectiveness** | | **Efficacy evaluation tool** | | **Residuals shunt** | **postoperative complications** |
| MIST 2008(45) | Multicenter, double-blind RCT | (1)≥5 headache days/month  (2)failed at least 2 lasses medication  (3)18 to 60 years of age | PFO closure VS sham | STARFlex | 147(74 /73) | 44.3±10.6/  44.6±10.4 | 6 | | NA | Migraine headache cessation:  （3 of 74）vs  （3 of 73），*P*=0.51 | | （1）HIT-6  （2） SF-36v2  （3）MIDAS questionnaire | | 4（5.4%） | pericardial effusion、retroperitoneal bleed |
| PRIMA 2016(46) | Multicenter, open-label RCT | minimum of 3 migraine attacks or 5~15 headache days/month | PFO closure VS Medical management | Amplatzer | 107(53/54) | 44.1±10.7/  42.7±11.0 | 12 | | NA | Reduction in monthly migraine days:  −2.9 days vs. −1.7 days , *P* = 0.17) | | （1）MIDAS questionnaire  （2）SF-36v2  （3）Beck Depression Inventory (BDI) | | NA | AF、bleeding、retroperitoneal haematoma |
| PREMIUM 2017(47) | Double-blind RCT | (1)6 to 14 headache days/month  (2)failed at least 3 lasses medication  (3)severity RLS | PFO closure VS Medical management | Amplatzer | 230(123/107) | 42.8±10.3/  43.7±10.2 | 12 | | NA | Responder rate,:  38.5% vs 32.0% | | （1）MIDAS questionnaire  （2）Beck Depression Inventory (BDI) | | 22(18%) | AF |
| Xing, 2016(48) | NRCT | substantial or severe migraineurs with a right-to-left shunt (RLS) (grade II–IV) | Transcatheter closure group VS control group | cardio - fix | 241(125/116) | 39.0± 12.9  38.3 ± 12.2 | 12 | | 6 | HIT-6 score(49.1 vs 57.5,*P*<0.001) | | HIT-6 | | 18(14.4%) | Pericardial tamponade |
| Jesurum,2008(49) | prospective cohort | patients with presumed paradoxical embolism and  Migraine Aura who underwent PFO closure | PFO closure | Amplatzer、Cardioseal、 | 77（55/22） | 47±12/46±10 | 18 | | 6 | Migraineurs with aura were 4.5 times more likely to experience migraine relief than  migraineurs without aura(*P*=0.02) | | NA | | 23(34%) | NA |
| Luermans,2008(50) | prospective cohort | Migraine patients underwent a percutaneous closure | Before-after control | Amplatzer、Cardioseal、Cardiastar、Helex | 92 | 51.6±12.3 | 6 | | 6 | prevalence of migraine in this group decreased from 28.6% to 10.7% (P = 0.001) | | Headache questionnaire | | NA | inguinal haematoma |
| Rigatelli  et al.2012(51) | prospective cohort | with severe, disabling, medication-refractory migraine and documented PFO underwent transcatheter PFO closure | Before-after control | Amplatzer、Premere、Biostar | 80 | 38.9±5.8 | 24~76 | | NA | (1)87.5% patients reported improved migraine symptomatology;(2)96.8% migraine with aura patients were definitively cured | | MIDAS | | NA | NA |
| Vigna 2009(52) | prospective cohort | moderate/severe migraine with PFO | PFO closure group vs Control group | Amplatzer/Cardia/  CardioSEAL/STARFlex | 82(53/29) | 42.0± 10  43 ± 11 | 16±7 | | 6 | Migraine disappeared in 34% of the closure group patients and 7% of  controls (p= 0.007) | | NA | | 3 (6%) | NA |
| Azarbal et al., 2005(53) | prospective cohort | Migraine patients | Migraine patients | CardioSEAL、Amplatzer | 89 | 49± 13 | 12 | | NA | MHA disappeared  completely in 75% of patients with MHA and aura and in 31% of patients with MHA  without aura. | | MIDAS | | 12(13.5%) | NA |
| Kimmelstiel 2007(54) | prospective cohort | Migraine patients | PFO closure VS Open  PFO VS No PFO | Amplatzer | PFO closure:41  Open PFO:63  No PFO:65 | 54  62  63 | NA | | NA | PFO closure reduced migraine MIDAS scores compared with the other two groups（*P*<0.001;*P*=0.035） | | MIDAS | | NA | NA |
| Dubiel,2008  (55) | retrospective cohort | patients with presumed paradoxical embolism underwent percutaneous transcatheter closure | Before-after control | Amplatzer、SEAL、STARFlex | 46 | 44±13.5 | 39.6±23.9 | | 6 | number of accompanying symptoms were significantly reduced (P<0.000) | | Self-made questionnaire | | 1（2.2%） | NA |
| Eyal.  et al.2020(56) | retrospective cohort | Migraine patients underwent transcatheter PFO closure | Before-after control | Amplatzer、CardioSEAL | 110 | 32.7±11.5 | 38.4 | | 6 | 87.0% of symptoms were significantly relieved and 48% were completely eliminated. | | Headache questionnaire | | 26% | NA |
| Biasco 2014(57) | retrospective cohort | Migraine with PFO | PFO closure VS medical treatment | Amplatzer/Cardia/  Others | 217(89/128) | 46.4 ± 12.7  47.1 ± 12.3 | 12 | | 6 | 1. MIDAS score decreased:*P*=0.204 2. number of patients reported a perceived   clinical benefit or the disappearance of migraine（*P*<0.001） | | MIDAS | | 16 (24%) | endocarditis |
| He, 2019(58) | retrospective cohort | migraineurs with RLS | PFO closure group VS non-PFO closure group | NA | 192(91/101) | 37.1± 12.8  39.2± 12. 1 | 60 | | NA | HIT-6 scores:  36 vs 52,*P*<0.001 | | HIT-6 | | NA | NA |
| Wahl  et al.2010(59) | retrospective cohort | patients undergoing percutaneous PFO closure | Before-after control | Amplatzer | 150 | 51.6±11 | 60 | | 6 | 1. mean headache frequency:(from 233/month to 13/month; p<0.001),; 2. The prevalence of any migraine headaches (from 100% to 66%; p<0.001) 3. the number of patients taking any migraine medication (from 90% to 50%; p<0.001) | | A structured questionnaire about Headache | | 14（9%） | NA |
| Rigatelli  et al.2010(60) | case-control | Migraine with PFO | PFO closure VS Medical therapy | Amplatzer、Premere | 86(40/46) | 38.9±5.8  40.0±3.7 | 29.2±14.8 | | NA | Mean MIDAS scores（8.3 vs 7.8,*P*<0.03） | | MIDAS | | NA | NA |
| **Clinical research on drug treatment in PFO related migraine** | | | | | | | | | | | | | | | |
| **Study** | **Study type** | **Study object** | **Interventions**  **（experimental group/control group）** | **Sample Size （experimental group/control group）** | **Average age （experimental group/control group）** | **Follow-up time（months）** | | **Effectiveness** | | | **Efficacy evaluation tool** | | **Safety** | | |
| Guo Y, et al.2020(61) | Single arm trial | drug-refractory migraineurs with PFO | Clopidogrel（Before-after control） | 30 | NA | 3、6 | | （1）Headache Frequencies lower (*P*=0.003)（2）Headache attack durations lower(*P*=0.0049)  （3）VAS scores decreased(*P*<0.001)  （4）MIDASscores decreased(*P*=0.001) | | | VAS scores 、MIDAS scores | | **NA** | | |
| TRACTOR study.2018(62) | Single arm trial | MHA patients with PFO | Ticagrelor（single arm） | 40 | 36.3 ± 14.5 | 72 | | MHA responder rate：43% | | | NA | | Mild facial edema、Shortness of breath, transient | | |
| Sommer, R. J. etal.2018(63) | retrospective study | MHA/PFO patients | prasugrel、Clopidogrel（single arm） | 136 | 37.9 ± 14.6 | NA | | MHA responder rate：59% | | | NA | | mild bleeding、Cutaneous bruising | | |
| Spencer etal,2014(64) | retrospective study | Women with severe migraine and documented RLS | Clopidogrel（single arm） | 15 | 32.3 ± 11.9 | 11.9 | | MHA responder rate：87% | | | NA | | allergy | | |
| **Clinical research on correlation between PFO and other neurological diseases** | | | | | | | | | | | | | | | |
| **Study** | **Study type** | **Study object** | **Control group** | **Sample size （observation group /** **control group）** | **Average age observation group /** **control group）** | **Outcome** | **Main research results** | | | | | **Conclusions** | | | |
| [Manolo Beelke](https://pubmed.ncbi.nlm.nih.gov/?term=Beelke+M&cauthor_id=14592325).etal 2003 (65) | case-control | OSA patients | Healthy control group | 167（78/89） | 53.0±12.0  48.0±9.0 | the prevalence of PFO | Case group vs control group=27% vs 15%，*P*＜0.05 | | | | | The prevalence of PFO in OSAS was significantly higher than that in normal control group | | | |
| [HShanoudy](https://pubmed.ncbi.nlm.nih.gov/?term=Shanoudy+H&cauthor_id=9440574).  etal (1998)(66) | case-control | OSA patients | Healthy control group | 72（48/24） | NA | the prevalence of PFO | Case group vs control group=69% VS 17%，*P*＜0.0001 | | | | | The prevalence of PFO is increased in OSA patients | | | |
| Xiaonan Li,etal(67) | case-control | OSA patients with PFO | PFO without OSA group 、Healthy control group | 171(48/61/62) | 53.17±9.69  48.62±13.15  43.77±13.54 | sleep quality  polysomnography | 1. Compared with the control group   poor sleep quality (P<0.001) 、efficiency (P<0.010), a decrease in the proportion of REM sleep, and a decrease in N3 sleep (P<0.050) and prolonged N2 sleep (P < 0.010). Lower nighttime minimum SpO2 and higher oxygen saturation index (p < 0.50)   1. Compared with the simple PFO group,   sleep latency (p < 0.001) was prolonged; wake after sleep onset (p < 0.001) and arousal times (p = 0.031) were increased; and sleep micro-arousal index (p = 0.037), periodic leg movement index (p = 0.024), and apnea hypopnea index (p < 0.001) were higher in the PFO with OSA group | | | | | Patients with PFO and OSA have poor sleep quality with changes in sleep stage and high occurrence rate of sleep disorders. | | | |
| HONĚK J,  etal(68) | case-control | Divers with a history of DCS | Healthy control group | 489（36/453） | 36.4±7.7  35.5±9.1 | the frequency of PFO | Case group vs Control group=97.2% vs 35.5%,*P*＜0.001, PFO grade 3 was a major risk factor for unprovoked DCS | | | | | a high-grade PFO was a major risk factor for unprovoked DCS in recreational scuba divers | | | |
| **Clinical research on PFO closure in other neurological diseases** | | | | | | | | | | | | | | | |
| **Study** | **Study type** | **Study object** | **Interventions**  **（experimental group/control group）** | **Device** | **Sample size** | **Average age (experimental group/control group）** | **Follow-up time（months）** | | **Maximum duration of postoperative antiplatelet/anticoagulant therapy (months)** | **Effectiveness** | | | | **Efficacy evaluation tool** | **postoperative complications** |
| Rimoldi,S. F.2015(69) | NRCT | OSAS | PFO closure VS non-PFO | Amplatzer | 40 | 54±12/54±9 | 3 | | NA | （1）oxygen desaturation index:-7.6 16.6 vs 7.6 17.0 events/h, P=0.01  （2）apnea and hypopnea index:-7.9 10.4 vs 4.7 13.1events/h， P=0.0009  （3）the propotion of patients with severe OSA decreased:79% vs 21%，P=0.007 | | | | Electroencephalograms、  electrooculograms 、electromyograms、  finger pulse oximetry | NA |
| PCOSAstudy.  2017(70) | prospective cohort | OSAS+ Moderate RLS shunts | Comparison before and after PFO closure | GORE | 26 | 51.6 | 6 | | 6 | 1. Epworth Sleepiness Scale score（13 vs 6,P<0.001） 2. Sleep Apnea Quality of Life Index(3.4 vs 4.4,P<0.001) 3. there were no statistically significant in oxygen desaturation index、Apnea Hypopnea Index and 6MWT | | | | (1) 6MWT  (2) ESS  (3)SF-36  (4) Sleep apnoea quality of life index  (5) Functional outcome of sleep questionnaire | NA |
| Shaikh ZF2013(71) | case series | OSAS+PFO | Comparison before and after PFO closure | NA | 6 | 54 | 12 | | NA | There was no significant difference between preoperative and preoperative changes in oxygen-desaturation index（P=0.92）、percentage of nocturnal arterial oxygen saturation < 90%(P=0.35) | | | | (1) 6MWT  (2) ESS  (3) HIT6  (4) SF-36v2 | Palpitations、hematochezia |
| Billinger  et al.2011(72) | prospective cohort | diver with a history of severe decompression | PFO closure VS PFO no closure VS no PFO | Amplatzer | 104 | NA | 63.6 | | NA | DCI events :PFO closure vs PFO not closure(P=0.045) | | | | MRI | NA |
| Anderson  et al.2019(73) | prospective cohort | Adult diver with PFO | PFO closure groupVS Conservative group | NA | 77 | 45.5/52 | 60~72 | | NA | The incidence of DCS decreased significantly after intervention, and the effect was more obvious in patients with larger PFO, while there was no change in conservative group | | | | NA | Bleeding, AF, palpitations, premature atrial and ventricular contractions |
| Honek  et al.2022(74) | prospective and retrospective cohort | Professional divers (including RLS Grade 1-3 and no PFO) | PFO closure VS PFO not closure | Amplatzer/ Occlutech | 829 | 35.4±10 | 78 | | NA | DCS incidence   1. PFO closure in low-grade group vs control group: HR= 3.965; *P* = 0.169; 2. PFO closure in the high-grade group vs control group :HR=26.170; *P* < 0.0001 | | | | NA | bleeding |
| Koopsen  et al.2018(75) | retrospective cohort | Decompression disease of unknown origin | PFO/ASD closed VS PFO/ASD not closed VS PFO/ASD absent | Amplatzer/  Occlutech | 62 | 38.3 | 81.6 | | NA | There was no recurrence of severe DCS in the PFO closure group | | | | NA | NA |

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