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Migraine and Atrial Fibrillation: a Systematic Review

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Abstract

Background: Patients with migraine are at increased risk of stroke. We aim to systematically review the current literature on the association between migraine and atrial fibrillation, which is a relevant risk factor for stroke.

Methods: We searched Pubmed for 'migraine' AND 'atrial fibrillation' and selected original investigations on the association of migraine and atrial fibrillation for our analysis. Articles without original data, such as guidelines, narrative reviews, editorials, and others were excluded.

Results: 109 publications were found. 22 were included and analyzed for this review. The population-based ARIC study showed a significant association of migraine with visual aura and incident atrial fibrillation, but not for migraine without aura, compared to non-headache persons (HR 1.30, 95% CI 95% 1.03-1.62, p=0.02) after multivariable adjustment for vascular risk factors. An even larger population-based study in Denmark confirmed this association (OR 1.25, 95% CI 1.16-1.36). Studies investigating patients with ischemic stroke and migraine are methodologically insufficient and provide contradictory results. Ablation therapy for atrial fibrillation in patients with migraine might reduce migraine-attacks, but transient post-ablation new-onset migraine-like headaches in persons without a history of migraine have also been reported.

Conclusion: Population based studies indicate a significant association of migraine with aura and atrial fibrillation. In practical terms, screening for atrial fibrillation in patients who have a long history of migraine might be reasonable, whereas in patients with stroke or other disorders and migraine extensive screening for atrial fibrillation should be performed like in all patients without migraine.

Key points

Migraine, aura, atrial fibrillation, stroke, cortical spreading depression, cortical spreading depolarization.

Background

Migraine is a common primary headache disorder characterized by recurrent attacks with or without aura.[1] According to the Global Burden of Disease Study 2017, nearly one fifth of the world's population suffer from migraine.[2] A third of migraineurs experience aura, i.e. transient neurologic symptoms or signs typically occurring before or during an attack. Migraine with aura is associated with increased risk of ischemic stroke.[3] Multiple mechanisms have been proposed: higher susceptibility of brain tissue to ischemia because of cortical spreading depression, endothelial dysfunction, and genetic factors.[3] An association between migraine with aura and atrial fibrillation has recently been suggested.[4] Since atrial fibrillation is a risk factor for stroke, it might be a pathophysiological link between migraine with aura and stroke.

A bidirectional relationship between atrial fibrillation and migraine would be possible: On one hand atrial fibrillation might result from autonomic dysfunction during a migraine attack.[5] On the other hand, emboli occurring during atrial fibrillation might induce cortical spreading depression, the pathophysiological basis of migraine aura, without causing overt ischemia.[6] A further confounder might be that vascular risk factors are more prevalent in patients with migraine.[7] To which extent migraine per se and the vascular risk factors increase the risk of atrial fibrillation is not clear.

The aim of this systematic review is to summarize the current knowledge on the relationship between migraine and atrial fibrillation in different populations: general population, patients with stroke, migraine with aura, migraine without aura, during migraine attacks, and after catheter ablation of atrial fibrillation. Further aims were to assess a potential genetic linkage between both conditions and whether searching for atrial fibrillation in patients with migraine and to what extent might be necessary.

Methods:

We searched PubMed for 'migraine' AND 'atrial fibrillation' without year restriction. Last search date is 17.08.2021. Abstracts were independently screened by AS and CJS to assess whether the following inclusion criteria were met: original articles including case reports, written in English, investigating the association between migraine and atrial fibrillation. In the identified articles, the reference lists were screened for relevant titles. Papers without original data, such as guidelines, narrative reviews, reader/author responses and editorials were excluded. In addition, we excluded studies reporting atrial fibrillation after closure of atrial septal disorders since the intervention rather than migraine might have caused atrial fibrillation. All authors independently assessed risk of bias of included studies. The quality of the studies was assessed using criteria proposed by Kuijpers et al.[48] A study scoring more than 10 out of 18 points was considered of "high quality".

Results:

109 articles were identified by searching for 'migraine' and 'atrial fibrillation'. One duplicate was identified. Based on the abstract, 32 articles met inclusion but not exclusion criteria[4, 8-39]. Of these, 11[8-18] were excluded since they reported atrial fibrillation after closure of atrial septal disorders. The remaining 21[4, 19-35, 37-39] plus 1 case series[36] found from reference[26] were included in this review (**Figure 1**). Thirteen[4, 19-22, 26-29, 34, 35, 37, 38] presented original data. Seven[4, 19-22, 37, 38] investigated the association between migraine and atrial fibrillation, four[26-29] the association between migraine after catheter ablation of atrial fibrillation and two[34, 35] the association of genetic determinants for migraine with atrial fibrillation. Of the seven articles on association between migraine and atrial fibrillation[4, 19-22, 37, 38], two were population-based sudies[4, 19], three reported the association between migraine and atrial fibrillation in stroke populations[21, 22, 37], and two reported the association of atrial fibrillation with migraine aura in migraine populations[20, 38]. **Tables 1 and 2** summarize the selected studies as well as the quality assessment. We found nine case-reports[23-25, 30-33, 36, 39]. Four of them reported the occurrence of atrial fibrillation during migraine attacks [23-25, 39], and five reported migraine after ablation therapy for atrial fibrillation[30-33, 36].

The association of migraine and atrial fibrillation in the general population

The prospective Atherosclerosis Risk In Communities study (ARIC) analyzed the association of migraine with visual aura and incident atrial fibrillation[4]. Migraine and visual aura were assessed by trained interviewers using a questionnaire based on ICHD-3 criteria. The migraine-group was divided in two categories: migraine with visual aura and migraine without aura. Of the 11,939 participants included, 1,516 had migraine, 9,405 had no headache and the rest non-migraine headache (not included in the analysis). The average duration of migraine history was 19 years. Atrial fibrillation was found in 15% of the migraine-group and 17% in the non-headache group. Using the non-headache group as the reference, participants with migraine overall (HR 0.82, 95%CI 0.72-0.94) and migraine with visual aura (HR 0.74, 95%CI 0.62-0.87) had a lower risk of incident atrial fibrillation. However, after adjusting for age and sex, migraine with visual aura, but not migraine without aura, was associated with an increased risk of atrial fibrillation compared to the non-headache group (HR 1.39, 95%CI 1.11-1.75, p=0.004). After analyzing separately for sex (male/female) and age (<60/≥60 years), men with migraine with aura (HR 1.89, 95%CI 1.29-2.77, interaction term p=0.009) and patients with migraine with aura who were 60 years and older (HR 1.44, 95%CI 1.08-1.72, interaction term p=0.07) had a higher incidence of atrial fibrillation

compared to the non-headache group. After adjusting for age, sex, hypertension, race, diabetes, hypercholesterolemia, smoking, coronary heart disease, and congestive heart failure, migraine with visual aura was associated with a higher risk of incident atrial fibrillation compared to the non-headache group (HR 1.30, 95% CI 95% 1.03-1.62, p=0.02).
Using migraine without aura as the reference group, migraine with visual aura was associated with incident atrial fibrillation (HR 1.44, 95%CI 1.10-1.88, p=0.0084), which remained significant after adjusting for age, sex, hypertension, race, diabetes, hypercholesterolemia, smoking, coronary heart disease, and congestive heart failure (HR 1.39, 95%CI 1.05-1.83, p=0.0084). The incidence of ischemic stroke in the migraine with aura group was nearly twice that noted in migraine without aura (4.1 vs 2.07/1000 persons-years) and higher than in the non-headache group (4.1 vs 3.02/1000 person-years).

The second population-based study is from Denmark. It used data from the Danish National Patient Registry from January 1995 to November 2013 and included 51,032 migraine patients, and 510,320 matched persons of the general population [19]. Median age at diagnosis of migraine was 35 years (range 22-47), and 71% were women. After adjustment for covariates, migraine was associated with atrial fibrillation or atrial flutter (OR 1.25, 95% CI 1.16-1.36). In the sub-group analysis, migraine with aura had a stronger association with atrial fibrillation than migraine without aura.

According to data presented in the work of Adelborg et al.[19], the number of migraine patients needed to be screened for atrial fibrillation (NNT) to detect one case of atrial fibrillation within the first year of migraine diagnosis, is 499, which however drops down to 30 after 19 years.

The association of migraine and atrial fibrillation in patients with ischemic stroke.
A registry-study investigated the association between migraine and atrial fibrillation in a stroke population (n=1,738 stroke patients, mean age 67.9±14.9 years, 112 of them had migraine without aura and 45 migraine with aura)[21]. Migraine history was assessed by study physicians using the ICHD-3 beta criteria during face-to face interviews with patients and family members. The group of patients with migraine with aura and patients with migraine without aura had less atrial fibrillation than non-migraineurs. After adjustment for demographical and cerebrovascular risk factors, this association did not remain (**Table 2**).

Another retrospective single-center study investigated the association of migraine with and without aura with causes of ischemic stroke in a *young* stroke population (n=339 patients with ischemic stroke aged 18-54 years, 58 of them had migraine with aura, 54 had migraine without aura)[37]. Migraine was diagnosed by a headache specialist using ICHD-3 criteria using face-to-face interviews during the initial hospitalization or at 3-months follow-up. There were no differences in the causes of stroke between migraine without aura patients and non-migraine patients. However, atrial fibrillation was more frequent in migraine with aura patients than in non-migraine patients (10.34% vs 2.2%, OR 5.08; 95%CI 1.24-21.92, p=0.011)[37].

A single-center cohort study evaluated the prevalence of migraine (according to ICHD-2 criteria) in a stroke population[22]. Two hundred twenty nine patients received a questionnaire, of whom 175 (76%) responded. Thirty-six of 175 (20.6%) fulfilled the criteria for definite or probable migraine. Twenty-two (12.5%) had migraine with aura. Patients with migraine were younger (<60 years, 38.9% vs 19.4%). In this cohort, atrial fibrillation was less common in migraineurs compared to those without migraine (OR 0.89, 95%CI 0.11-0.97, p=0.049).

The association of migraine aura and atrial fibrillation in patients with migraine

A large retrospective cross-sectional study explored the prevalence of ischemic stroke and atrial fibrillation in 834,875 migraine patients[38]. 4.9% had migraine with aura, 94.9% migraine without aura, mean age was 33 years. The data collection spanned over 3 ¾ years (**Table 2**). Ischemic stroke and atrial fibrillation occurred more often in migraine with aura patients compared to those with migraine without aura (OR 3.23, 95%CI 3.05-3.42, p<0.001 for stroke and OR 1.4; 95%CI 1.27-1.54, p<0.001 for atrial fibrillation)[38]. Atrial fibrillation was associated with higher stroke risk (OR 1.63; 95%CI 1.42-1.88, p<0.001)[38]. The low prevalence of migraine with aura indicates a selection bias in this study and likely represents a major limitation.

A retrospective cross-sectional analysis used data from the US Nationwide Inpatient Sample database between January 2013 and December 2014. The authors investigated the prevalence of vascular and non-vascular risk factors in migraine patients (n=983,065 hospitalized patients with migraine) compared to non-migraineurs (55,516,723 patients)[20]. The presence or absence of migraine aura was not considered in the analysis. Migraine was negatively associated with atrial

fibrillation (HR 0.57, 95%CI 0.56-0.58, p<0.0001). However, migraine was associated with several cerebrovascular risk factors [20]. The prevalence of migraine was 1.76%, which is much lower than expected in the general population suggesting a strong selection bias.

Atrial fibrillation during migraine attacks

A retrospective study[23] reviewed stroke mimics over 10 years in 1,355 patients. 36 of them were diagnosed with definite migraine with aura according to ICHD 3 criteria. This paper is listed here as a case report since presenting the case of a 88-year old female patient with hemiplegic aura who had atrial fibrillation on ECG during a migraine attack, which resolved the day after.

We found additional three case reports directly linking migraine-headaches with atrial fibrillation[24, 25, 39]. The authors present the case of a 42-year old man with a history of migraine without aura since age 30, which occasionally were associated with vomiting[24]. He had episodes of atrial fibrillation with high ventricular response each time he vomited. Between attacks, the electrocardiogram showed normal sinus rhythm. No other reason for atrial fibrillation was found. The second case report presents a 34-year old man with a 10-year history of migraine without aura[25]. He experienced repeated episodes of atrial fibrillation during migraine attacks with vomiting, but showed sinus rhythm between attacks. Each episode of atrial fibrillation lasted less than 24 hours and responded to verapamil and digoxin, and no other cause of atrial fibrillation was found.

The third case-report presents a 46-year old man with migraine with brainstem aura[39]. A typical migraine attack consisted of clammy feeling, dizziness, rotatory vertigo, and unsteadiness of gait followed by bilateral occipital headache, nausea and vomiting. On multiple occasions, he was admitted to the emergency department in coma with electrocardiographically confirmed atrial fibrillation. Coma lasted 1-4 hours, drowsiness up to 20 hours, followed by headache and reversion to sinus rhythm. Ancillary investigations ruled out other reasons for his attacks and recurrent episodes of atrial fibrillation.

New-onset migraine after ablation therapy of atrial fibrillation

An open-label prospective study included 40 patients with migraine (mean age 64±8, 78% men) and 85 patients without migraine (mean age 61±10, 73% men) to investigate the impact of atrial fibrillation ablation on migraine headache. The follow-up period was 17±5 months[26]. The success

rate of the ablation was similar in both groups (70% in migraine-group vs 73% in non-migraine group). All patients were taking warfarin before the ablation procedure. Eighty eight (70%) patients underwent the procedure without discontinuing warfarin, 37 (30%) had the procedure with warfarin discontinued 3 days before and received enoxaparin 1mg/kg twice daily. The investigators performed a non-contrast head MRI at baseline and 12 hours after the procedure to detect silent or overt brain infarcts.
In the migraine-group (n = 40) headache frequency and severity improved in 38 (95%) and 25 (62.5%) were migraine-free after the procedure during the follow-up. In two patients (5%) both migraine frequency and intensity worsened. In the non-migraine group two patients (2.3%) developed new onset migraine with visual aura within the first week after the ablation.
All 4 patients with new-onset or worsened migraine had warfarin discontinued and showed new silent cerebral infarcts on follow-up imaging.

Another prospective observational study investigated the occurrence of headaches after catheter ablation for atrial fibrillation[27]. The patients were followed at 3 months and yearly thereafter. 48 (2.3%) of 2069 patients developed new onset headaches, 22 (1.1%) definite migraine and 12 (0.6%) probable migraine according to ICHD-II criteria.

Another prospective observational study (n=87, 13 of whom had a re-intervention) reported new-onset migraine or new aura in 7 patients (8%) after catheter ablation for atrial fibrillation after 3 months. However, the questionnaire used in this study was not validated for migraine[28].

A study of 571 patients who underwent atrial trans-septal punctures during catheter ablation for cardiac arrhythmias found isolated aura in three patients, (0.5%)[29]. All auras occurred in the first 7 days after the procedure.

Five case reports on new onset migraine with aura or isolated aura after ablation therapy of atrial fibrillation were found[30-33, 36]. In four, migraine attacks with or without aura subsided within 1-6 weeks after the procedure[30-32, 36]. In the fifth case, an 80-year old woman, migraine attacks persisted, but she had a history of previous peri-menstrual migraine[33].

Genetic association of migraine and atrial fibrillation

A genome-wide association study (GWAS) (n=59,674 migraine cases, n=316,078 controls of European ancestry) investigated the impact of 44 single-nucleotide polymorphism associated with migraine on coronary heart disease, myocardial infarction, self-reported or physician-assessed angina pectoris, and atrial fibrillation[34]. Mendelian randomization estimates showed a protective effect of the polymorphisms on coronary artery disease (OR 0.86, 95%CI 0.76-0.96, p=0.003), myocardial infarction (OR 0.86, 95%CI 0.74-0.97, p=0.01), and angina (OR 0.86, 95%CI 0.75-0.99, p=0.04). There was no association on atrial fibrillation (OR 1.0, 95%CI 0.95-1.05, p=0.88).

Another GWAS (n=425,196 UK Biobank participants) aimed to construct a genetic risk score based on 300 coronary artery disease associated variants, representing 240 gene loci. The score was associated with heart failure (OR 1.25, 95% CI 1.22-1.29), atrial fibrillation (OR 1.08, 95% CI 1.05 to 1.10), and premature death (OR 1.04, 95%CI 1.02-1.06). The score had an inverse association with migraine headache (OR 0.94, 95%CI 0.93-0.96)[35].

Discussion

Two large and, according to Kuijpers et al.[48], high-quality prospective population based studies, the ARIC study and a Danish study, show a significant association of migraine with aura and atrial fibrillation in otherwise healthy persons, while the association of migraine without aura and atrial fibrillation is still uncertain. In absolute numbers the annual incidence of atrial fibrillation in patients with migraine is quite small, however, over the years substantial. In patients with additional disease to migraine the current knowledge of the interaction of migraine and atrial fibrillation is scarce. For clinical practice it is inconclusive.

In the ARIC study[4], migraine with visual aura was associated with atrial fibrillation. Incidence of ischemic stroke was higher in patients with migraine with aura compared to patients with migraine without aura or no headache. However, a direct causality between higher incidence of atrial fibrillation and ischemic stroke in patients with migraine with aura could not be ascertained. There are limitations of this study. For instance, the method to identify migraine excluded a substantial number of patients with migraine like patients with bilateral headache, patients with other than visual aura or headache attacks for less than one year. The importance of paradoxical emboli through a patent foramen ovale as a potential cause of ischemic stroke or long-term heart-rhythm monitoring was not recognized yet at the time of the ARIC study. Therefore, many strokes related to paroxysmal atrial fibrillation or patent foramen ovale may have been missed in the ARIC study[46].

The Danish population-based study used data of the Danish National Patient Registry (DNPR). Baseline and clinical follow-up data were collected prospectively for patients with migraine and were matched with controls without migraine. The strength of the Danish study, in addition to the prospective data collection, is the large number of patients and matched controls. However, like in the ARIC study, paroxysmal atrial fibrillation may have been missed and the validity of such a registry for identifying migraine and migraine types reliably is unknown[4].

Why is atrial fibrillation associated with migraine with aura? A likely explanation is that patients suffering from migraine with aura have more vascular risk factors compared to patients with migraine without aura[7]. Vascular risk factors may induce structural heart abnormalities, which may cause atrial fibrillation. Therefore, vascular risk factors in patients suffering from migraine

with aura must be actively sought and treated. This may be important for patients with frequent migraine attacks, since their vascular risk might be especially high[47].

Further mechanisms linking migraine with aura and atrial fibrillation have to be discussed. For instance, could migraine-attacks induce atrial fibrillation, or vice versa?[4, 19] Within the brain cortical spreading depolarization occurs during migraine aura. When spreading neuronal excitation followed by depression hits the insular cortex, cardiovascular autonomic control will become impaired.[41] Autonomic dysfunction has been shown to be involved in both migraine[5] and atrial fibrillation[40], and both sympathetic hyperfunction and concomitant parasympathetic hypofunction have been reported in migraine attacks[5]. Furthermore, various electrocardiographic changes such as sinus bradycardia, premature ventricular contraction, non-specific ST-T changes, and right bundle branch block have been described during migraine attacks [5]. In addition, QTc-interval and P-dispersion can be increased during migraine attacks compared to pain-free periods, which is considered as a predictive marker for atrial fibrillation in electrocardiography and could indicate atrial and ventricular repolarization abnormalities caused by autonomic dysfunction[5]. Nevertheless, evidence of atrial fibrillation during migraine attack is scarce and mostly anecdotal[23-25, 39]. It further should be emphasized, that the occurrence of atrial fibrillation during migraine attacks would not explain permanent atrial fibrillation between the attacks.

Because of the association of migraine with aura and atrial fibrillation and because atrial fibrillation is a treatable risk for stroke the practical question arises whether routine screening for atrial fibrillation should be recommended. The long-term incidence of atrial fibrillation becomes substantial in patients with migraine[4, 19]. Thus, it might be reasonable to screen for atrial fibrillation in patients who have a long history of migraine. However, even in developed health care systems, such screening might not be feasible from a logistic perspective.
The most devastating complication of atrial fibrillation is ischemic stroke. While some studies reported a higher prevalence of atrial fibrillation in migraine patients who suffered an ischemic stroke[37, 38], others have not[21, 22]. This conflicting result might be due to a selection bias leading to heterogeneous study populations. Also, the quality of the studies varies, with some being of high[21, 22] and others of low[37, 38] quality according to Kuijpers et al.[48]. Nevertheless, in all stroke patients with migraine, atrial fibrillation needs to be searched for like in other stroke patients according to guidelines. Further research is necessary to better understand if migraineurs should be screened for

atrial fibrillation even in the absence of stroke. Also, because of the association of migraine with patent foramen ovale, a search for patent foramen ovale, as a mediator for stroke risk in patients suffering from migraine, must be performed.

Since microemboli might induce cortical spreading depression[6], atrial fibrillation could theoretically induce migraine auras. Consistently, coumarin treatment in patients with migraine has been previously shown to reduce migraine attacks independent of comorbid atrial fibrillation[42,43]. However, this would suggest repeated emboli in the occipital lobes in migraine without leaving traces of ischemia in MRI, which is an unlikely clinical scenario.

One practical question is whether catheter ablation to treat atrial fibrillation could induce or change the intensity and frequency of migraine attacks. As outlined above cortical spreading depolarization during migraine attacks can cause autonomic dysfunction and atrial fibrillation. The question is therefore if improvement of autonomic dysfunction after catheter ablation for treatment of atrial fibrillation could also stabilize autonomic function and thus improve migraine. The hypothesis is that catheter ablation stimulates postganglionic efferent parasympathetic fibers and decreases efferent sympathetic activity[26]. Since sympathetic hyperfunction and parasympathetic hypofunction has been observed in migraine, catheter ablation for atrial fibrillation would reverse the autonomic balance, leading to fewer migraine-attacks[26]. Study results on this topic are contradictory and probably also confounded by anticoagulation therapy. A prospective high quality study found improvement of migraine headache after ablation for atrial fibrillation[26]. However, few patients in this study experienced a worsening of headaches after discontinuation of Warfarin. As pointed out above, coumarin treatment has been previously shown to reduce migraine attacks[42,43], highlighting a possible role of pro-thrombotic pathways in the pathophysiology of migraine, while another study did not confirm this beneficial effect with acenocoumarol[44]. In contrast, three prospective series and case reports showed new-onset post-procedural migraine in up to 8 percent of patients without a history of migraine.[29, 27, 28, 30-33, 33, 36] Micro-emboli have been reported to induce cortical spreading depression without overt ischemia[6]. Therefore, ablation-induced migraine with aura might be a consequence of the intervention, e.g. by iatrogenic cardiac emboli, and subside as soon as the iatrogenic wound has healed. However, whether migraine-aura will change after ablation therapy for atrial fibrillation has yet to be investigated systematically. In this respect, the results from studies on patients with migraine,

atrial fibrillation and ablation therapy cannot be generalized, since they are based on a highly selected patient population.

In two GWAS studies no common genetic factors were found between migraine and atrial fibrillation[35, 35]. This is unexpected, especially because of positive association of migraine and atrial fibrillation in the population-based clinical studies[4, 19]. A possible explanation are confounders, which were not identified[34].

The main limitation of our analysis is the low number of eligible articles of patients with additional disease to migraine and atrial fibrillation, as well as the low quality of certain studies. This impairs statistical conclusions or a meta-analysis of the results. However, this underscores that further research is needed to understand the complex interaction of those two highly prevalent and potentially devastating conditions.

Conclusion

Two high-quality prospective population based cohort studies show an association of migraine with aura and atrial fibrillation (level IV evidence, i.e. evidence derived from prospective cohort studies). Studies investigating this association in patients with ischemic stroke and migraine are methodologically of heterogeneous quality and provide contradictory results. Patients with migraine and atrial fibrillation have fewer migraine-attacks after ablation therapy for atrial fibrillation, but transient post-ablation migraine-like headaches have also been reported.
In practical terms, screening for atrial fibrillation in patients who have a long history of migraine might be reasonable, whereas in patients with stroke and migraine extensive screening should be performed like in all patients without migraine.

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Table 1

Summary of studies of atrial fibrillation and migraine in prospective population-based cohorts. Quality assessed according to Kuijpers et al.[48].

Authors	Study type	Number of participants	Study aim	Study years	Results	Comments	Quality [48]
Sen et al.[4]	longitudinal, community based cohort study	11,939 of whom 436 with MA 1,090 with MO 1,018 with non-migraine headache 9,405 no headache	to test the association of migraine with visual aura and atrial fibrillation	1993-2013	migraine with visual aura is associated with atrial fibrillation compared to no headache, OR 1.3, 95% CI 1.03-1.62	Advantages: prospective design; population-based; large number of participants; long follow-up period; low percentage of drop-outs (18%). Disadvantages: exclusion of patients with bilateral headaches; exclusion of patients with other than visual aura, lack of assessment of PFO (potential confounder for stroke), lack of long-term heart-rhythm monitoring, identification of atrial fibrillation using ECGs, death certificates and discharge codes only might have resulted in an underestimation of the	High (14/18 points)

						frequency of atrial fibrillation.	
Adelborg et al.[19]	nationwide, community based cohort study	51,032 with migraine 510,320 participants from general population, matched for age, sex, and calendar year	to examine the risk of myocardial infarction, ischemic and hemorrhagic stroke, peripheral artery disease, venous thromboembolism, atrial fibrillation or atrial flutter, and heart failure in patients with a first time diagnosis of migraine compared with the general population	1995-2013	migraine is associated with atrial fibrillation or atrial flutter, OR 1.25, 95% CI 1.16-1.36	Advantages: prospective data collection; population-based; large number of participtans; long follow-up period. Disadvantages: Information on presence of migraine aura was available only in 59% of migraine cohort; the validity of identifying migraine with the Danish registry is unknown; it is not reported how many patients completed the follow-up.	High (11/18 points)

Table 2

Studies of atrial fibrillation and migraine in patients with migraine, stroke or catheter ablation for atrial fibrillation and genetic studies of atrial fibrillation and migraine. Quality assessed according to Kuijpers et al.[48].

Author	Study type	Patients and controls	Question, purpose	Study years	Findings	Comments	Quality [48]
Patel et al.[20]	retrospective cross-sectional analysis	983,065 with migraine	to evaluate the association of vascular and non-vascular diseases with migraine	2013-2014	atrial fibrillation is not associated with migraine	Advantages: large sample size. Disadvantages: retrospective study design; low prevalence of migraine in this study (1.74%) suggesting a strong selection bias.	Low (7/18 points)
Kuybu et al.[38]	cohort-study, retrospective	834,875 with migraine, 4.9% of whom had migraine with aura	to assess the prevalence of atrial fibrillation and ischemic stroke in patients with migraine	2012-2015	ischemic stroke occurred more frequently in migraine with aura patients compared to those with migraine without aura (3.7% vs 1.2%, $p<0.001$). The odds of having atrial fibrillation	Advantages: large sample size. Disadvantages: retrospective study design; lower prevalence of migraine with aura compared to the general population suggesting a selection bias	Low (6/18 points)

					was significantly higher in patients with migraine with aura (OR 1.4; 95% CI [1.27-1.54], p<0.001)		
Gollion et al.[37]	single-centre retrospective	339 patients with ischemic stroke aged 18-54 years, 58 of whom had migraine with aura, 54 had migraine without aura	to explore the causes of ischemic stroke in migraineurs in a young population treated for ischemic stroke	2017-2019	atrial fibrillation was significantly more frequent in migraine with aura patients than in non-migraine patients (10.34% vs 2.2%, OR 5.08; 95%CI [1.24-21.92], p=0.011)	Advantages: migraine diagnosis was made by a headache specialist. Disadvantages: retrospective study design; small sample size.	Low (9/18 points)
De Giuli et al.[21]	single-centre longitudinal cohort study	1,738 with ischemic stroke or TIA, of whom	to explore the association between atrial	2015-2018	no association between atrial fibrillation and	Advantages: large sample size; prospective design; diagnosis made using face-to-face	High (13/18 points)

		1,581 with no migraine, 112 with MO, 45 with MA	fibrillation and migraine, to evaluate whether it varies according to migraine subtype and to evaluate whether specific structural heart abnormalities may be predictive markers of migraine in stroke patients		history of migraine or its pathogenic subtypes	interviews with patients or family members Disadvantages: allowing patients with transient ischemic attack might have introduced a bias (TIA vs TIA mimics).	
Lantz et al.[22]	single-centre, questionnaire based cohort study	175 with ischemic stroke, 36 of whom with migraine	to assess the prevalence of migraine in a stroke population	2009, 6 months	no association between atrial fibrillation and migraine	Advantages: prospective data collection Disadvantages: retrospective study design; questionnaires was filled by patients alone within a time frame of 6 months after stroke diagnosis	High (13/18 points)

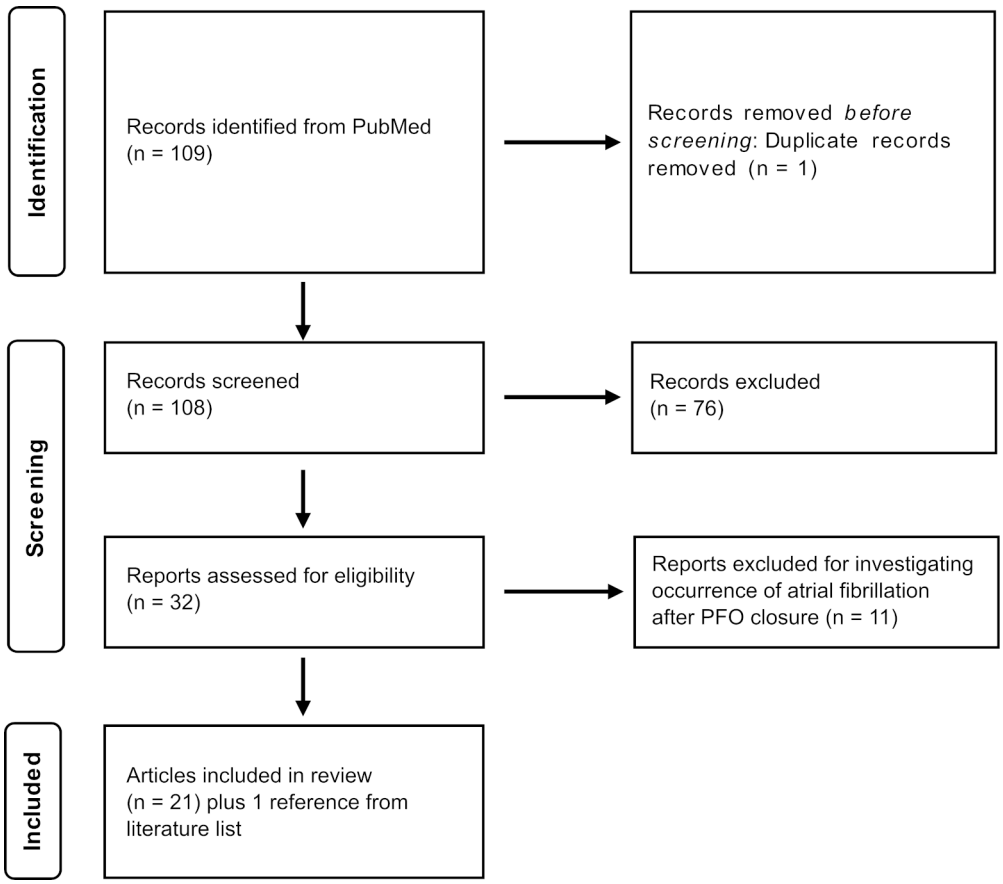
						(recall bias); small sample size.	
Mohanty et al.[26]	single-centre, prospective, cohort study	125, of whom 40 with migraine, 85 without migraine	to examine the influence of catheter ablation for atrial fibrillation and periprocedural anticoagulation regimen on trajectory of migraine in patients with atrial fibrillation with or without migraine history	2011-2013	after ablation therapy 38 of 40 patients reported a significant improvement of migraine-headache; 2 of 85 reported new migraine with visual aura	Advantages: prospective study design; analysis of impact of peri-interventional medication on post-ablation migraine severity. Disadvantages: small sample size; whether migraine aura improved after ablation has not been assessed.	High (13/18 points)
Noheria et al.[27]	single-centre, prospective,	2,069 patients with catheter-ablation	to assess the prevalence of	2001-2008	22 (1.1%) had new-onset	Advantages: large sample size, prospectively performed	Low (7/18 points)

	questionnaire-based cohort study	for atrial fibrillation	new-onset migraine after catheter-ablation for atrial fibrillation		definite migraine, of whom 19 (86%) had a complete resolution of migraine at 1-2 year follow-up; 12 (0.6%) had new-onset probable migraine	follow-up. Disadvantages: the presence of migraine was self-reported using questionnaires; participation rate is not reported.	
Chilukuri et al.[29]	single-centre, prospective	571 patients with catheter-ablation for atrial fibrillation	to assess the incidence of new-onset isolated migraine aura after transseptal catheterization for cardiac arrhythmia	3 years	3 of 571 patients had new onset isolated migraine-aura	Advantages: prospective design; long follow-up period. Disadvantages: patients with migraine symptoms were identified based on their complaining symptom during follow-up; the whole patient population has not been screened for new migraine aura (risk of missing incident migraine cases).	Low (1/18 points)

Jordaens et al.[28]	single-centre, prospective	87 patients with catheter-ablation for atrial fibrillation	to assess the incidence of new-onset migraine with aura after transseptal catheterization for atrial fibrillation	3 months	a prevalence of 8% of new migraine and/or new aura was found	Advantages: prospective study design. Disadvantages: the questionnaire used was not validated for migraine; small sample size.	Low (6/18 points)
Daghlas et al.[34]	case-control, genome wide association study	59,674 migraine patients, 316,078 controls	to investigate the genetically instrumented susceptibility for migraine and atrial fibrillation	N/A	protective effect of migraine liability on CAD (OR 0.86, 95%CI 0.76–0.96, p= 0.003), myocardial infarction (OR 0.86, 95%CI 0.74–0.96, p = 0.01) and angina pectoris (OR0.86, 95%CI 0.75–0.99,	Advantages: large sample size, mendelian randomization approach, which is less affected by confounders. Disadvantages: a sex-specific analysis was not possible.	Low (8/18 points)

					p=0.04); no association between migraine liability and AF (OR 1.00, 95%CI 0.95–1.05, p= 0.88).		
Ntalla et al.[35]	Longitudinal biobank study	425’196 biobank study participants	to explore the genetic relationship between coronary artery disease to cardiovascular and non-cardiovascular co-morbidity based on a genetic score using 300 coronary artery disease associated variants,	N/A	The score was associated with heart failure (OR 1.25, 95% CI 1.22-1.29), atrial fibrillation (OR 1.08, 95% CI 1.05 to 1.10), and premature death (OR 1.04, 95%CI 1.02-1.06). The score had an inverse association with	Advantages: very large sample size. Disadvantages: underpowered for certain diagnoses; no information on lipid profile available.	Low (9/18 points)

			representing 240 gene loci		migraine headache (OR 0.94, 95%CI 0.93-0.96).		



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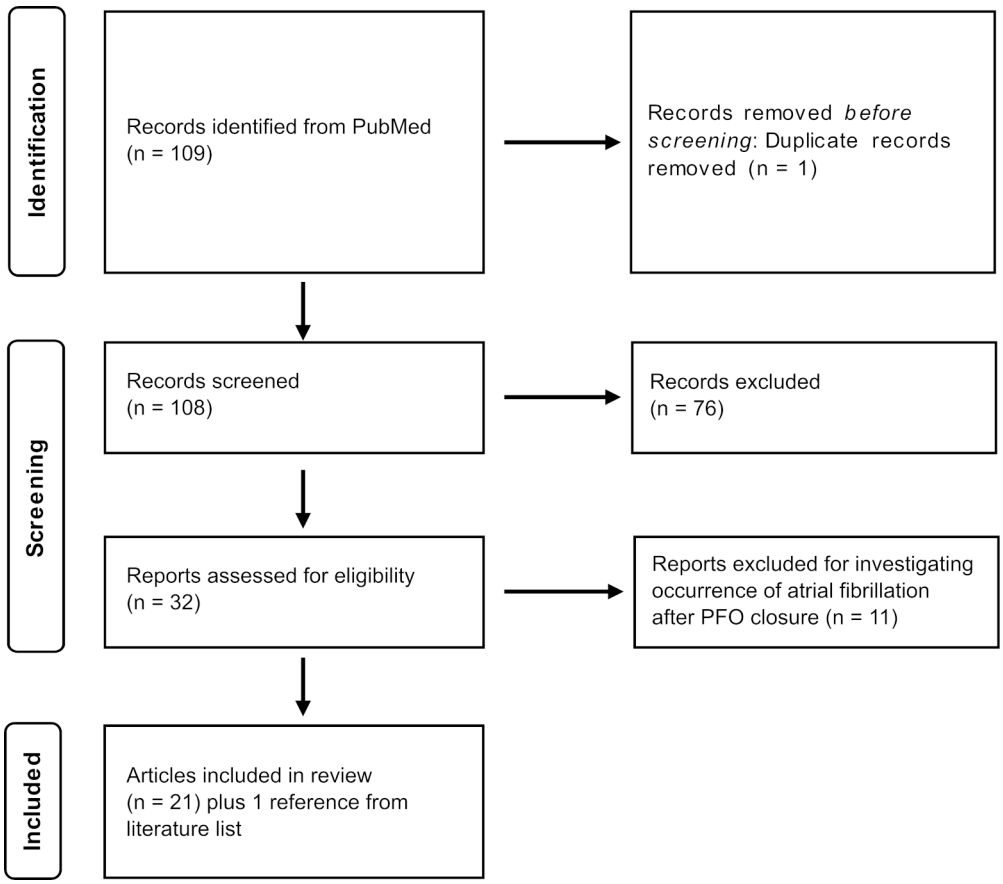

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