Curr Neurol Neurosci Rep (2015) 15:5
DOI 10.1007/s11910-015-0530-8

HEADACHE (RB HALKER, SECTION EDITOR)

Dissecting the Association Between Migraine and Stroke

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Abstract Migraine is a common disabling neurological disorder resulting from excessive cortical excitation and trigeminovascular afferent sensitization. In addition to aberrant neuronal processing, migraineurs are also at significant risk of vascular disease. Consequently, the impact of migraine extends well beyond the ictal headache and includes a well-documented association with acute ischemic stroke, particularly in young women with a history of migraine with aura. The association between migraine and stroke has been acknowledged for 40 years or more. However, examining the pathobiology of this association has become a more recent and critically important undertaking. The diversity of mechanisms underlying the association between migraine and stroke likely reflects the heterogenous nature of this disorder. Vasospasm, endothelial injury, platelet aggregation and prothrombotic states, cortical spreading depression, carotid dissection, genetic variants, and traditional vascular risk factors have been offered as putative mechanisms involved in migraine-related stroke risk. Assimilating these seemingly divergent pathomechanisms into a cogent understanding of migraine-related stroke will inform future studies and the development of new strategies for the prevention and treatment of migraine and stroke.

Keywords Migraine · Acute ischemic stroke · Migraine genetics · Cortical spreading depression · Endothelial dysfunction

This article is part of the Topical Collection on *Headache*

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Published online: 05 February 2015

Introduction

Migraine is a common neurological condition characterized by recurrent unilateral headaches of moderate to severe intensity lasting 4–72 h in duration. The pain is often pulsatile in quality and associated with nausea, vomiting, and sensitivity to light and sound. Migraines can be heralded by visual aura in addition to other somatosensory, vestibular, motor, and speech-related disturbances [1–4]. Migraine impacts 15 to 20 % of the general adult population, including approximately 17 to 25 % of women and 6 to 10% of men [5–7]. Starting as early as 12 years of age, the highest prevalence of migraine is amongst persons 20 to 50 years of age [6, 8]. The social, economic, and psychological burden of migraine alone can be devastating. In addition to the medical costs related to emergency room visits, indirect costs related to reduced work capacity and disability amplify the economic burden associated with migraine [6, 9, 10].

Comorbid conditions accompanying migraine are worthy of clinical and scientific attention because they contribute to significant disability and death in the migraine population. A number of epidemiologic studies support the observation that migraine is independently associated with acute ischemic stroke. Stroke is a major disabling neurological event with 795,000 new and recurrent cases diagnosed yearly, and is the fourth leading cause of death in the USA [11]. The average age of stroke onset is 60 to 70 years [12, 13]. However, a minority of strokes occur in young individuals less than 45 years of age and with fewer modifiable vascular risk factors (e.g., hypertension, hyperlipidemia, and diabetes mellitus). While this population appears to have fewer identified modifiable risks, the rate of long-term mortality is higher than would be expected [14] and they remain at risk of recurrent stroke [15, 16]. That migraine, particularly migraine with aura, has been identified as a non-modifiable risk factor for stroke in this otherwise relatively healthy younger population

raises important fundamental questions about the cerebrovascular, metabolic, and neurobiological mechanisms underlying this association. The purpose of this article is to review the relationship between migraine and acute ischemic stroke, the potential mechanisms underlying this relationship, therapeutic options, and future research directions.

Migraine and Stroke: Defining the Clinical Problem

The Epidemiology of Migraine-Associated Stroke Risk

Multiple cohort [17–20] and case-control [21–31] studies substantiate an association between migraine and acute ischemic stroke. Migraine is an independent risk factor for acute ischemic stroke. A large cohort study of 63,575 individuals with a documented history of migraine and 76,936 individuals without migraine followed over a 33–35-month period found that those with migraine were at 2.5 times greater risk of developing acute ischemic stroke compared to those without migraine [17].

A consistent association between migraine and stroke has been observed in multiple case-control studies, particularly in the cryptogenic stroke population aged less than 45 years with a gender-based predilection for women (Table 1) [17, 19, 23–28, 32–37]. In a case-control study that included 72 stroke cases and 173 matched controls, migraine in women aged 18–44 years was associated with acute ischemic stroke with an odds ratio (OR) of 3.5 (95 % confidence interval (CI) 1.8–64). The association was greater in the migraine with aura (OR 6.2, 95 % CI 2.1–18.0) group compared to the migraine without aura (OR 3.0, 95 % CI 1.5–5.8) group [25]. The association between migraine with and without aura and stroke was replicated in another case-control study enrolling a similar number of patients [27]. A study enrolling both men and women (308 stroke cases and 591 age- and gender-matched controls) found a significant association between migraine with aura and stroke (OR 8.6, 95 % CI 1.0–75) but not migraine without aura (OR 1.0, 95 % CI 0.5–2.0) [26]. A differential association between stroke and migraine with aura was replicated in a study enrolling a similar number of cases and controls although the effect size in the latter study was more modest as compared to other studies (migraine with aura OR 1.5, 95 % CI 1.1–2.0) [23, 28].

The variability in the strength of association across individual studies may reflect differences in sample size and headache classification. Additionally, there may be differences in patient selection and diagnostic criteria for stroke. Despite these limitations, the consistent association in multiple study populations is compelling. Multiple meta-analyses estimate a pooled adjusted twofold risk of stroke in migraineurs as compared to non-migraineurs [32, 38–39, 40•]. It is important to mention that the strokes migraineurs suffer can have a

Table 1 Case-control studies: the association between migraine and acute ischemic stroke in the young

Study	AIS (*n*)	Ctrl (*n*)	Gender	Age	Migraine						Migraine and other variables			
					All migraine		MwA		MwoA		OCP		Smoking	
					OR	95 % CI	OR	95 % CI	OR	95 % CI	OR	95 % CI	OR	95 % CI
[22]	140	451	Women	15–44	2.0	(1.2–3.3)					5.9	(2.9–12.2)		
[23]	89	178	Both	15–65	1.8	(0.9–3.6)	2.6	(1.1–6.6)	1.3	(0.5–3.6)				
[24]	212	212	Both	18–80	1.3	(0.8–2.3)								
			Women	<45	4.3	(1.2–16.3)							10.2	(1.1–93.3)
[25]	72	173	Women	18–44	3.5	(1.8–6.4)	6.2	(2.1–18.0)	3.0	(1.5–5.8)	13.9	(5.5–35.1)	10.2	(3.5–29.9)
[26]	308	591	Both	15–44	1.3*	(0.7–2.4)	8.6	(1.0–75)	1.0	(0.5–2.0)				
[29]	366	219	Men	16–60	2.12	(1.05–2.95)								
[27]	87	220	Women	20–44	3.54	(1.30–9.61)	3.81	(1.26–11.5)	3.0	(0.66–13.5)	16.9	(2.72–106.0)	7.39	(2.14–25.5)
[21]	86	214	Women	20–44	4.61[a]	(1.27–16.8)								
[30]	626	4054	Women	15–44	3.2[b]	(2.5–4.2)								
[31]	190	1129	Women	15–49	2.33	(1.04–5.21)								
[28]	386	614	Women	15–49			1.5	(1.1–2.0)	1.0	(0.6–1.5)	7.0	(1.3–22.8)[c]		

*$p>0.05$

[a] Migraine for greater than 12 years duration

[b] Includes transient ischemic attack

[c] Combined effect of smoking and oral contraceptive, either alone did not produce a significant effect. OR and CI were not available for smoking alone and oral contraceptive use alone

significant impact on morbidity and mortality [41]. However, in a prospective cohort study of 27,852 women aged >45 years, women with a history of migraine with aura and stroke had a two times greater likelihood of having a modified Rankin Scale score between 0 and 1, suggesting the possibility for good functional outcomes in this population [42].

Influence of Oral Contraceptive Use and Cigarette Smoking

There appears to be a substantial influence of cigarette smoking and oral contraceptive use on the association between migraine and stroke. Multiple studies have demonstrated that smoking produces a greater than multiplicative increase in the association between migraine and stroke. One study published an OR of 10.2 (95 % CI 3.5–29.9) in young women with a history of migraine who smoked cigarettes [25]. A similar study published an OR of 7.39 (95 % CI 2.14–25.5) [27]. Likewise, oral contraceptive use significantly increases the association with stroke in migraineurs. One study published an association between migraine and stroke in young women on oral contraceptives with an OR of 13.9 (95 % CI 5.5–35.1) [25] while a subsequent study published an OR of 16.9 (95 % CI 2.2–106.0) [27]. These data suggest that environmental and modifiable factors may influence the link between migraine and stroke.

Additionally, the greater than multiplicative effect could intimate that oral contraceptive use and smoking amplify the effect of migraine by influencing common downstream targets that are important for stroke pathogenesis. Oral contraceptives can impact the function of the endothelium and production of matrix metalloproteinases [43, 44]. Likewise, cigarette smoking initiates a host of pathological cascades that adversely affect the endothelium, platelet function, and thrombogenicity causing production of reactive oxygen species and cytokines, expression of matrix metalloproteinases, and reduced release of endogenous tissue plasminogen activator [45, 46]. Initially, smoking may impair the vasodilatory properties of nitric oxide, followed by several biochemical and inflammatory reactions that cause physical damage to the endothelial wall [45, 46]. Mirroring some of the same mechanisms, several studies propose migraine-related changes in endothelial function, nitric oxide production, platelet aggregation, and expression of matrix metalloproteinases [47–52]. Therefore, the association between migraine, oral contraceptives, smoking, and stroke risk may reflect a common pathway involving endothelial damage, inflammation, and platelet dysfunction. It is conceivable that these modifiable factors and migraine share common pathobiological processes that interact synergistically to promote atherothrombosis resulting in cardiovascular and cerebrovascular disease. However, whether all or any of these mechanisms can fully explain the amplified influence of smoking and oral contraceptive use on migraine-associated stroke risk requires added investigation.

Migraine-Related Stroke Versus Migrainous Infarction

Migraine-associated stroke can be subdivided into two general categories: migraine-related stroke and migrainous infarction (See Fig. 1a, b). *Migraine-related stroke* is defined as an interictal stroke occurring in a person with a history of migraine. In contrast, *migrainous infarction* is diagnosed in migraineurs that experience prolonged aura lasting >60 min with neuroimaging confirming an acute infarction in the brain region likely responsible for the aura symptoms [53, 54]. One example of migrainous infarction is a prolonged visual aura with concomitant occipital lobe infarction diagnosed on neuroimaging. Migraine-related stroke occurs in ~3 % of the acute ischemic stroke population (~15 % of those with acute ischemic stroke less than 45 years of age). In contrast, migrainous infarction occurs less frequently in ~0.3–0.5 % of those with acute ischemic stroke [35, 55]. It is unclear if there are unique stroke mechanisms underlying these clinical distinctions. In the case of migrainous infarction, it is possible that the stroke occurs during the aura because the electrochemical changes that underlie the aura are directly linked to cerebral ischemia. Conversely, stroke occurring during the interictal period suggests a divergent or indirect epiphenomenon linked to stroke pathogenesis in migraineurs.

Mechanisms Involved in Migraine-Associated Stroke Risk

Although many aspects of the association between migraine and stroke remain unexplained, results from accumulating clinical and preclinical studies are beginning to shed light on potential neuropathologic mechanisms involved in migraine-associated stroke risk. Below, we review the evidence substantiating different proposed mechanisms involved in migraine-associated stroke risk, including vasospasm, endothelial injury, cortical spreading depression, genetic predispositions, and traditional modifiable risk factors (Fig. 2). While these mechanisms differ significantly, migraine is a heterogeneous condition. Therefore, it is not entirely unexpected that there may be multiple mechanisms influencing stroke risk in migraineurs. None of these mechanisms are necessarily exclusive of each other. Therefore, in some migraineurs, it is possible that more than one mechanism exists. Additionally, the individual migraine-associated stroke risk may be biased by unique combinations of these predisposing factors.

Vasospasm

Vasospasm is a diffuse or focal constriction of the blood vessel, limiting blood flow and potentially leading to

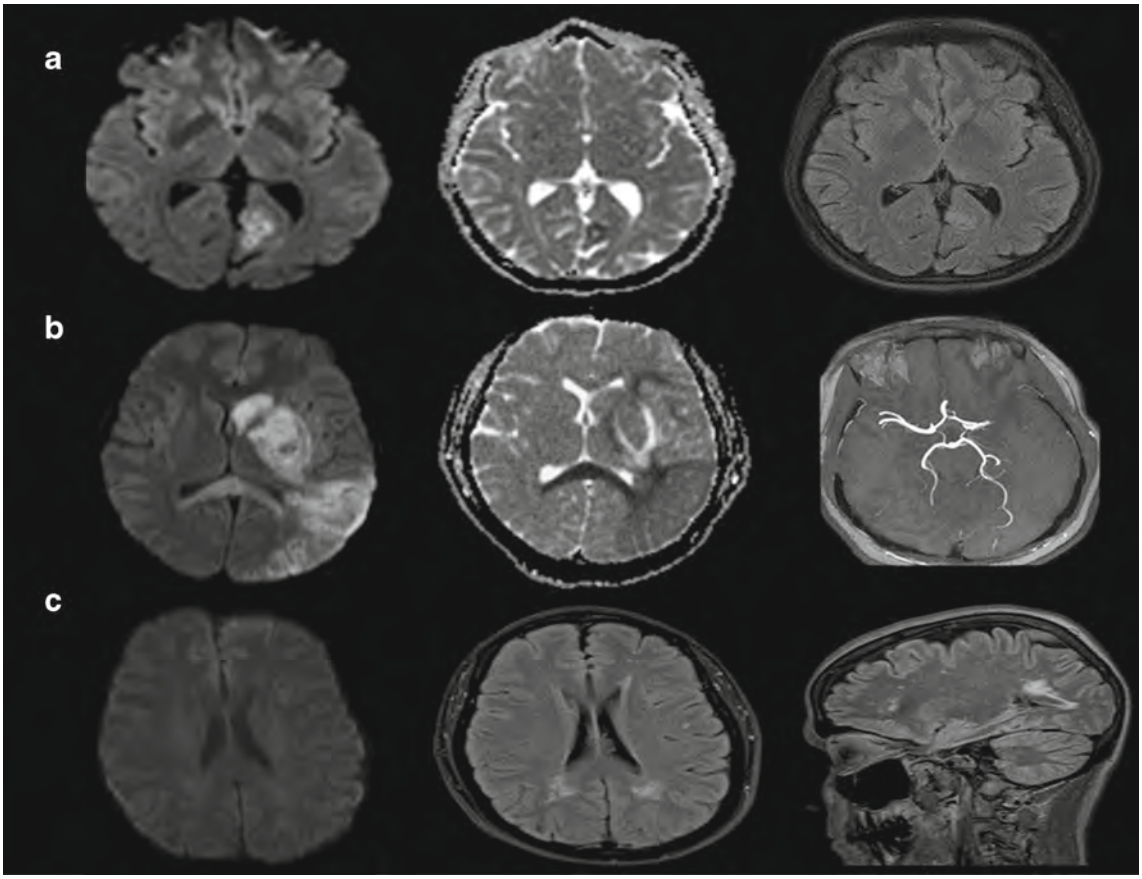

Fig. 1 **a** *Top panel* demonstrates a case of *migrainous infarction* in a 40-year-old woman on oral contraceptive therapy with a history of migraine with visual aura who presented with right hemifield scintillations lasting several hours described as shiny objects, colors, and wavy lines followed by right-sided vision loss. The neurological examination was most notable for a right inferior homonymous quadrantanopia. MR brain demonstrated a 2-cm area of restricted diffusion in the ventral medial left occipital lobe. Topographically, the location of the stroke correlates with the visual aura of her typical and presenting migraine. **b** *Middle panel* demonstrates a case of *migraine-related stroke* in an 18-year-old woman with a history of migraine with aura who presents with right-sided weakness during an interictal period. The neurological examination was notable for mutism, right hemiplegia, left gaze preference, and right homonymous hemianopia. MR brain demonstrated right hemispheric stroke representing multiple vascular distributions involving the caudate, putamen, globus pallidus, parietal lobe, and splenium of the corpus callosum. MR angiogram revealed diminished flow through the left middle and anterior cerebral artery territories. She had a patent foramen ovale with no evidence of lower extremity deep venous thrombosis. Hypercoagulable panel which included protein C, protein S, lupus anticoagulant, antithrombin III mutation, and prothrombin gene mutation was negative or normal. **c** *Bottom panel* demonstrates a case of *migraine-related subcortical white matter disease* in a 54-year-old woman who was evaluated for migraine with prolonged visual aura lasting longer than 60 min. There was no evidence of restricted diffusion, but axial and sagittal MR imaging revealed posterior predominant periventricular white matter hyperintensities

hypoperfusion of the tissue supplied by the affected vessel. Cerebral vasospasm can cause clinically significant brain ischemia and infarction. A small number of case studies report evidence of vasospasm with cerebral angiography and transcranial Doppler insonation of cerebral vessels in migrainous stroke patients [56–61]. Some, but not all, of the regions of vasospasm correspond to the vascular distribution responsible for the observed neurological deficits [62, 63]. Some episodes of vasoconstriction appear to be reversible. In these case descriptions, most patients suffered escalations in their headaches without documented transformation to thunderclap headache, suggesting a potentially different mechanism than has been described with Call-Fleming syndrome or reversible cerebral vasoconstrictive syndrome (RCVS) [64, 65].

Investigators have proposed multiple mechanisms to explain the vasoconstriction observed in migraineurs. Release of local vasoactive chemicals during the aura phase such as endothelin, vasopressin, serotonin, and matrix metalloproteinases [66–69]; sympathetic autonomic dysregulation with release of or withdrawal from vasoactive neurotransmitters [62]; and medication side effect, particularly from the ergot alkaloids [70–72], have been implicated. While vasoconstriction may be a potentially important mechanism in select cases of migraineurs suffering stroke, this phenomenon of vasospasm has been observed in a small proportion of migraine-associated stroke cases and likely does not reflect a unifying mechanism for increased stroke risk in this population.

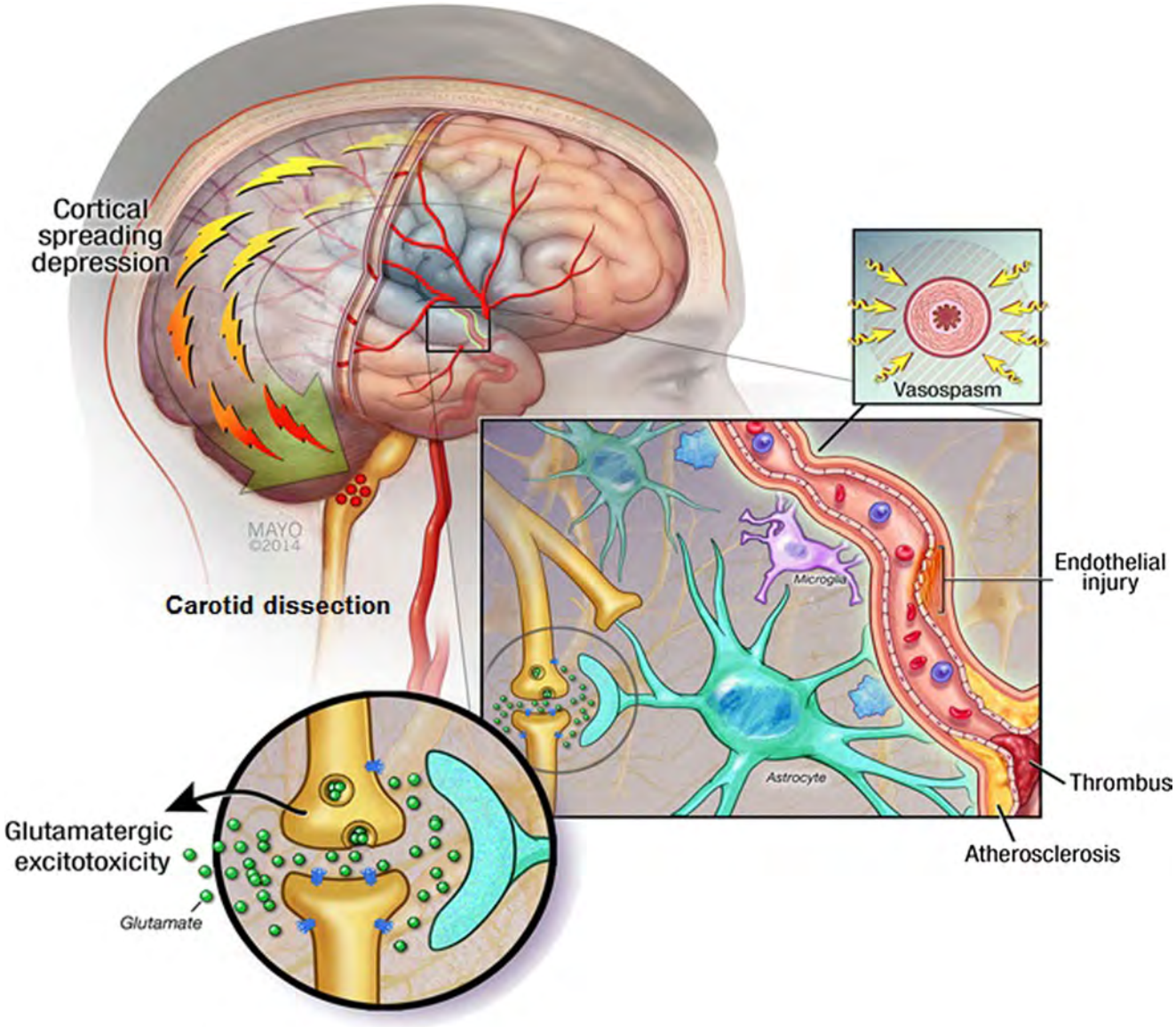

Fig. 2 Multiple mechanisms likely contribute to stroke in migraineurs. Inflammatory, vascular/endothelial, electrical/depolarizing, and coagulable factors have been proffered as putative links between migraine and stroke pathogenesis. This figure depicts major intracranial and extracranial mechanisms that may be involved in migraine-related stroke. Of the extracranial mechanisms, cervical carotid dissection has been associated with migraine and stroke in the young and may reflect an underlying predisposition for endothelial injury in this population. Other vascular mechanisms include cerebral vasospasm which has been reported in various cases, endothelial injury with changes in endothelial repair mechanisms, and atherosclerotic disease. Platelet dysfunction and endothelial injury may be a source of or response to systemic inflammation and lead to increased clot formation. There is an emerging role of cortical spreading depression and depolarizing excitotoxicity as potential mediators of cerebral ischemia and infarction. These mechanisms may be influenced by a combination of environmental exposures and genetic variants

Endothelial Dysfunction

Migraineurs may be vulnerable to endothelial injury. Elucidating the relationship between the endothelium, migraine, and stroke has the potential for generating therapeutic targets that could significantly reduce vascular disease in this population. Additionally, smoking, oral contraceptive use, and migraine appear to amplify the stroke risk in a way that suggests a convergent influence on the vascular endothelium.

Release of Vasoactive and Vaso-Inflammatory Molecules

Endothelin is a vasoactive molecule released by endothelial cells, neurons, and glia. There are three subtypes (endothelin 1, 2, and 3) that bind two receptors (endothelin receptor A [ET-A] and B), of which the ET-A receptor is responsible for the vasoconstrictive properties of endothelin [73]. While there are some conflicting data [74], several studies have found an increase in vasoactive substances like vasopressin

and endothelin 1 during the ictal phase of a migraine attack [66, 75–77]. In addition to their influence on endothelial injury, endothelin release also appears to be involved in spreading depression and neurogenic mechanisms associated with migraine pain [78–80]. Interestingly, increased plasma endothelin 1 and endothelin 3 concentrations have also been found within 72 h of stroke onset in patients without a known history of migraine [81], suggesting a potential link between increased concentrations of endothelin and stroke pathogenesis in the general stroke and migraine population [82]. In animal models, endothelin 1 topically applied to brain tissue not only induces spreading depression but also micro-areas of ischemia and necrosis [78, 83]. While endothelin likely has direct effects on the endothelium, release of endothelins could also be a by-product of endothelial injury related to other pre-existing vascular inflammatory or dysregulatory mechanisms that occur during and between migraine attacks.

In previous studies, markers of endothelial injury are increased in the systemic circulation of patients with small-vessel disease and cerebral leukoaraiosis [84]. These circulating vaso-inflammatory substances have been implicated in the production of or response to endothelial dysfunction [85]. Similar substances are released during the ictal and interictal period in migraineurs [86]. Migraine is associated with increased release of C-reactive protein and interleukins [87–89], tumor necrosis factor alpha [89], vascular endothelial growth factor [49], and adhesion molecules [90]. One retrospective study examining women aged 18 to 50 years with a history of migraine with or without aura found that migraineurs were more likely to have elevated plasma concentrations of C-reactive protein, tissue plasminogen activator antigen, and reduced nitrate and nitrite concentrations in the circulating blood compared to migraine-free controls during the interictal period. This association was strongest in migraine with aura. These data suggest that migraine may predispose to increased clot formation, reduced fibrinolysis, and increased vascular inflammation [91]. von Willebrand factor (VWF) is released by endothelial cells and can activate platelets and lead to platelet aggregation. Migraineurs have increased circulating VWF as compared to controls [92, 93]. Furthermore, in migraineurs with a history of stroke, the increase in VWF appears to be greater than in stroke-free migraineurs [92].

Elevations in matrix metalloproteinases (MMP) have been observed following acute ischemic stroke and after administration of intravenous thrombolytic therapy. MMPs can increase hemorrhagic transformation, brain swelling, and infarct size in the acute stroke setting. Furthermore, inhibiting MMPs has been proposed as a potential stroke therapy [94, 95]. Migraineurs with and without aura have increased plasma MMP-9 concentrations during the headache attack and possibly between headache attacks when compared to non-migraine controls [51, 96]. MMP may be linked to metabolic disturbance in migraineurs as it has been associated with low-density lipoprotein cholesterol levels and hyperinsulinemia in migraineurs [97].

Taken together, these data suggest release of soluble inflammatory molecules may result in increased stroke risk in migraineurs via endothelial injury, tissue necrosis, platelet aggregation, and metabolic dysfunction [86].

Endothelial Repair

The consequences of endothelial injury which predispose to vascular aging and cerebrovascular and cardiovascular disease are counterbalanced by endothelial repair mechanisms. Neo-endothelialization, a process by which endothelial injury is repaired, is in part dependent on endothelial precursor cells (EPC) produced in the bone marrow [97]. Prior data support alterations in the profile of circulating peripheral blood endothelial progenitor and precursor cells (EPCs) in migraineurs as compared to controls [98, 99]. Migraineurs have increased circulating CD-62E+ late EPCs as compared to non-migraine controls which is a marker for endothelial damage [99]. In one study, women who have a history of migraine with aura have increased circulating endothelial microparticles that are CD-62E+ and CD-144+ as compared to controls, suggesting increased endothelial activation [100]. However, in this study, patients with a prior history of stroke were excluded. Therefore, while the data are interesting and suggestive of a plausible relationship, it remains unclear if these mechanisms are truly responsible for the observed increased stroke risk in migraineurs.

Platelet Aggregation

Increased platelet aggregation can lead to thrombus formation in both ischemic stroke and migraine. Migraine patients appear to have increased platelet aggregability as compared to control patients with no history of migraine [101]. Additional studies have identified increases in platelet activating factor during a migraine which may contribute to ictal increases in platelet aggregation and thrombus formation [102].

Cervical Carotid Artery Dissection and Migraine

Carotid artery dissection is the most common identifiable cause of stroke in the young. Intramural hematoma formation at the time of arterial dissection can cause hemodynamically significant stenosis or occlusion and result in thromboembolic stroke. A small percentage of carotid dissection occurs on the background of known predisposing factors such as fibromuscular dysplasia, Ehlers-Danlos syndrome, Marfan syndrome, and osteogenesis imperfecta. The remainder appears to be either spontaneous or traumatic with no additional underlying predisposing factors identified [103]. Both

migraine- and dissection-related stroke patients have in common younger age at presentation and relatively fewer traditional vascular risk factors compared to the general stroke population [103]. It is therefore plausible that the influence of migraine on stroke risk in the young could reflect an underlying association between migraine and carotid artery dissection. In one hospital-based case-control study enrolling 99 French subjects between 18 and 65 years of age, spontaneous carotid artery dissection was associated with a history of migraine (OR 3.6, 95 % CI 1.5–8.6) [104]. In the larger Cervical Artery Dissection and Ischemic Stroke Patients (CADISP) population, migraine appeared to be more common in the carotid artery dissection-stroke population as compared to the general stroke population. The association between carotid dissection-related stroke and migraine appeared stronger in migraine without aura (OR 2.09, 95 % CI 1.46–2.99) and in men who have migraine without aura (OR 3.09, 95 % CI 1.79–5.31) [105]. A meta-analysis of five case-control studies examining the relationship between migraine and carotid artery dissection found a twofold increased risk of carotid dissection amongst migraineurs (pooled OR 2.06, 95 % CI 1.33–3.19) as compared to non-migraine controls. There were no statistical differences relative to gender or accompanying aura in this meta-analysis [106•].

Migraine may hasten vascular mechanisms involved in spontaneous carotid dissection [105, 106•]. Similar to migraine, carotid dissection may involve changes in endothelial function. For example, in patients with spontaneous carotid dissection, there are alterations in endothelium-mediated vasodilation likely related to changes in release of or response to nitric oxide [107]. Migraine is also associated with increased levels of elastase, a metalloendopeptidase responsible for enzymatic metabolism of elastin. It is hypothesized that this enzymatic degradation of the extracellular matrix may make the vessel wall particularly susceptible to stress, resulting in cervical artery dissection and stroke [108].

Cortical Spreading Depression

The visual aura accompanying classic migraine occurs in ~20 % of migraineurs. This unique visual perception is described as scintillating colored and arched shapes and zigzag and jagged-edged lines, starting near the center of vision and migrating to the peripheral hemifield [109]. The neurobiological mechanism likely responsible for the visual aura of migraine is cortical spreading depression described initially by Leao—a wave of neuroglial depolarization that travels across the cerebral cortex at a speed of 3–5 mm per minute followed by a wave of intense hyperpolarization. Electrochemical release of ions in the extracellular milieu and dysregulation of sodium potassium ATPase activity can augment cerebral metabolism, oxygenation, and glucose handling during spreading depression [110, 111]. These changes eventually lead to release of glutamate and glutamatergic excitotoxicity. Cortical spreading depression has some similarity to the peri-infarct depolarizations and spreading depressions observed in vulnerable tissue surrounding the core of a cerebral infarct [112]. Furthermore, in experimental studies, mice expressing dominantly inherited migraine gene mutations were more susceptible to ischemic depolarizations [113]. Migraine-related aura may increase oxygen consumption and result in tissue hypoxia [114, 115]. The results of these studies strongly implicate spreading depression in brain ischemia and electrochemical tissue injury which could explain the phenomenon of migrainous infarction.

Genetic Factors

That migraine-associated stroke occurs in the younger population with relatively fewer identifiable stroke risk factors than the older stroke population raises the possibility that the relationship between migraine and stroke risk could in part be explained by genetic predisposing factors. Identification of inherited mutations and risk alleles has advanced our understanding of the interplay between migraine and stroke pathogenic mechanisms.

Inherited Mutations in Familial and Sporadic Migraine

Familial hemiplegic migraine (FHM) is a rare autosomal dominant inherited form of migraine characterized by migraine with aura and transient neurological deficits including unilateral motor weakness or ataxia. Mutations in several genes are associated with familial hemiplegic migraine. Mutations in the *CACNA1A* gene encoding the alpha subunit of voltage-gated P-Q-type calcium channels are responsible for FHM type I, whereas mutations in the *ATP1A2* gene encoding the alpha 2 subunit of neuronal and glial sodium potassium ATPases and mutations in the *SCN1A* gene encoding the alpha subunit of voltage-gated sodium channels are responsible for FHM types 2 and 3, respectively. These forms of FHM share the common phenomenon of cortical hyperexcitability and predisposition for cortical spreading depression [116]. Rodent mouse models expressing mutations associated with FHM have lower thresholds for induction of spreading depression, increased susceptibility to brain ischemia during these depolarizing events (anoxic depolarizations), and expansion of the infarcted core following experimental middle cerebral artery occlusion. These data suggest that mechanisms of cortical excitation responsible for triggering a migraine could also generate unique alterations in cerebral blood flow leading to irreversible tissue damage and cerebral infarction [110]. Additional rare case reports of recurrent strokes in patients with mutations involving FHM-associated genes also raise the clinical suspicion that spreading depression and cortical hyperexcitability are major

contributing factors to brain ischemia not only in migraineurs with familial forms of migraine but perhaps also in those with more common forms of migraine [117].

Other monogenic disorders with migraine and stroke as part of the clinical phenotype include cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) [118]; hereditary endotheliopathy with retinopathy, nephropathy, and stroke (HERNS) [119, 120]; and mitochondrial disorders including mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS). CADASIL is associated with smooth muscle proliferation within small cerebral arteries and arterioles due to mutations in the *NOTCH3* gene resulting in multiple subcortical strokes and migraine. The clinical phenotype of CADASIL suggests that mechanisms involved in the headache of migraine may overlap with those that predispose to blood vessel remodeling and subsequent vasculopathy [116]. MELAS patients can present with episodic headaches and migraine in addition to strokes. The association between migraine-related stroke and mitochondrial dysfunction with MELAS may involve shifts in energy metabolism, glucose, and oxygen handling that favor cerebral ischemia [121].

Polymorphisms in the General Migraine Population May Raise Stroke Risk

While stroke and migraine appear to exist along a continuum in monogenic disorders, identifying risk alleles associated with common migraine and stroke in the general population has been more challenging. A recent genome-wide association study examining 2326 German and Dutch subjects diagnosed with migraine and 4580 matched non-migraine controls identified several single nucleotide polymorphisms associated with migraine [122]. Genetic variants associated with migraine were identified in the monocyte enhancer factor 2D (MEF2D), transforming growth factor β receptor-2 (TGFB2), phosphatase and actin regulator 1 (PHACTR1), astrotactin (ASTN2), transient receptor potential melastatin 8 (TRPM8), and low-density lipoprotein receptor-related protein 1 (LRP1) genes [122]. Of this group, vascular disease has been associated with variants of the TGFBR2 gene and the PHACTR1 gene. Mutations in the TGFBR2 gene have been associated with aortic dissection, making it an attractive candidate gene for the association between migraine and cervical dissection [123], while variants in the PHACTR1 may influence angiogenesis and endothelial function [124, 125]. The LRP1 gene is another putative gene that could link migraine pathogenesis and stroke. LRP1 mediates vesicle and transmembrane transport and synaptic function [126, 127]. LRP1 can influence smooth muscle cell proliferation, vascular inflammatory markers, and atherosclerosis [128–130]. Evidence of LRP involvement in cerebral ischemia has been demonstrated in various animal models. For example, penumbral LRP1 expression increases following experimental middle cerebral artery occlusion (MCAO) and LRP antagonists increase return of function following MCAO in animals [131, 132]. Other GWAS studies confirm the associations between these variants and migraine [133] in addition to identifying other variants associated with migraine [134•].

Population-based case-control studies examining candidate genes have also identified putative migraine-associated variants that could play a role in acute ischemic stroke. Several case-control studies in the younger and older migraine population have demonstrated associations between polymorphisms of the *endothelin receptor* and *endothelin 1* genes and either acute ischemic stroke or migraine [135, 136]. These data support the hypothesis that endothelial dysfunction and vasoconstriction may contribute to migraine and stroke pathogenesis. Dysregulation of the Na^+/K^+ ATPase may be important for rare forms of migraine and for cerebral ischemia [137, 138]. While the role of the *ATP1A2* gene in common migraine requires further elucidation with some reports demonstrating no association between *ATP1A2* gene mutations and classic migraine [139], in one study examining families with clustering of common forms of migraine without signs or symptoms of motor weakness, missense mutations in the *ATP1A2* gene were identified [140]. In a study of young individuals with a history of stroke, variants in the *ATP1A2* gene demonstrated modest associations with acute ischemic stroke [141]. Variants in the *methylenetetrahydrofolate reductase* (*MTHFR*) gene are linked to migraine, and in association studies, these variants appear to explain some of the increased stroke risk in the migraine with aura population. Furthermore, the association between *MTHFR* gene variants, migraine, and stroke appears to be stronger in the population of patients suffering from spontaneous cervical dissection [142, 143]. Additional prothrombotic gene mutations in the *Factor V Leiden* gene and *prothrombin* gene have been associated with migraine in a cohort of Italian patients with acute ischemic stroke [144].

Traditional Modifiable Stroke Risk Factors and Migraine

Migraineurs appear to have both unique and traditional risk factors for stroke. Several studies support a more systemic increased risk of vascular disease in migraineurs as compared to controls and highlight an increased propensity for developing an unfavorable vascular profile. In the Genetic Epidemiology of Migraine Study examining 620 migraineurs and 5135 non-migraine controls, migraineurs were more likely to have traditional risk factors for stroke, including an increased history of smoking, a threatening lipid profile, elevated blood pressure, and increased risk of heart disease [145, 146]. In a similar study, migraineurs were more likely to have a history of myocardial infarction, peripheral vascular disease, and diabetes as compared to non-migraine controls [147]. Despite

these data, migraineurs tend to have lower incidence of diabetes, hyperlipidemia, and hypertension identified at the time of stroke compared with stroke patients that have no history of migraine [144]. Therefore, the higher incidence of traditional risk factors in migraineurs as compared to non-migraine controls does not entirely explain the association between migraine and stroke. These data would seem to suggest that while migraineurs have an increased risk of vascular disease as compared to non-migraine controls, other unique and non-traditional risk factors are likely also playing a significant role in migraine-associated stroke risk [144]. These data also underscore the importance of a comprehensive approach in treating migraine that targets identifying unique risk factors in migraineurs as well as modifying traditional risk factors that may accompany migraine.

Clinical Implications and Treatment

The relationship between migraine and stroke leaves a number of challenging questions—some of which have evidence-based answers while others remain unanswered. Interesting and as yet unanswered questions are how this relationship impacts migraine and stroke treatment and if other migraine-related phenomena like subclinical white matter lesions and late-life migraine accompaniments are predictors of stroke risk.

White Matter Lesions and Subclinical Infarctions

In the Cerebral Abnormalities in Migraine and Epidemiological Risk Analysis (CAMERA) cross-sectional study, migraine was associated with subclinical white matter lesions [148]. Migraineurs have an increased risk of posterior circulation silent infarctions. This association was stronger with increased migraine frequency and migraine aura, suggesting overlapping cerebrovascular mechanisms are involved in headache initiation and brain ischemia (See Fig. 1c) [148, 149]. The increased risk of white matter lesions was not associated with triptan use. It is possible that transient changes in cerebral blood flow related to the migraine attack may predispose to these white matter lesions. Mechanisms predisposing to white matter lesions in migraineurs mirror those proposed for increased risk of stroke including vasoconstriction, microemboli, and endothelial dysfunction [149]. Moreover, the existence of white matter lesions and silent infarctions may exist on a continuum with acute ischemic stroke in migraineurs. However, it remains unclear whether or not migraineurs with white matter lesions or subcortical infarcts are at increased risk of stroke as compared to migraineurs without these white matter lesions [150].

Late-Life Migraine Accompaniments

C. Miller Fisher described transient neurological deficits that resemble migrainous phenomena without accompanying headaches in individuals over 45 years old. These events were termed late-life migraine accompaniments. These patients typically did not have a prior history of migraine or headache disorder [151]. However, headache accompanied these events in 40–50 % of cases [151, 152]. The deficits can affect vision, speech, and somatosensory processing and typically "build up" or "migrate." The event can last from 20 to 60 min with complete resolution following the event. In the Framingham study population, visual migrainous symptoms were identified in less than 2 % of the population sampled with an average age greater than 45. In this study population, patients with late-life visual migraine accompaniments did not appear to be at a greater risk of stroke as compared to those with transient ischemic attacks. Approximately 10 % of those with visual migrainous symptoms developed stroke. In contrast, one third of those identified as having transient ischemic attack developed stroke [153]. Because of the atypical nature of late-life migrainous accompaniments, this diagnosis is one of exclusion. However, in an older individual with marching paresthesias or scintillating scotomas that resemble that of migraine aura with otherwise normal electroencephalography and parenchymal and vascular imaging, late-life migraine accompaniments can be entertained as part of the differential diagnosis. It remains unclear if there are similar pathobiological mechanisms between late-life migraine accompaniments in older individuals and migraine with aura in younger individuals [151].

Migraine Therapies and Risk of Stroke

Triptans are serotonin 1B/1D receptor agonists that are used as abortive treatments for migraine. Both triptans and the less selective and older dihydroergotamine medications cause vasoconstriction. While the vascular effects of these drugs do not appear to be of prime importance for aborting a migraine, there is a perceived risk of increasing stroke and myocardial infarction because of blood vessel constriction. However, in large studies examining incidence rates of stroke, myocardial infarction, and death amongst 63,575 migraineurs with and without a history of triptan use as compared to 77,239 non-migraine controls, triptan use was not associated with an increased risk of stroke, myocardial infarction, or mortality [17]. In a similar study examining 130,411 migraineurs and the same number of non-migraine controls, ergot alkaloid use but not triptan use was associated with an increased risk of stroke [18]. Taken together, these data support that triptans are safe for use in migraineurs and do not appear to increase the risk of myocardial infarction, stroke, or death despite their proposed vasoconstrictive properties. The risk of stroke with

triptan use is therefore a relative one with data accumulating against an association between triptan use and stroke in migraineurs. The ergot alkaloids on the other hand appear to be associated with a modest increased risk of stroke in the migraine population (relative risk 1.49, 95 % CI 0.93–2.41) [18]. It remains unclear if prophylactic medications that reduce risk of spreading depression can decrease stroke risk in migraine with aura sufferers.

Predictors of Stroke in Migraineurs and Stroke Prevention

There are few studies examining predictors of stroke or stroke recurrence in migraineurs. Smoking and oral contraceptive use appear to have great influences on stroke risk in this population. Therefore, counseling patients on smoking cessation and careful use of oral contraceptive medications is important. While prothrombotic states have been linked to migraine, it is unclear if migraineurs would benefit from antithrombotic therapy as a means of primary stroke prevention. Additional studies have linked right-to-left intra-atrial shunt with migraine and stroke [144]. However, to date, there is no evidence that shunt closure reduces the risk of recurrent stroke in the cryptogenic stroke population or in migraine-related stroke [53, 154]. Given our current definitions of migrainous infarction and the results of multiple epidemiological studies, it is a reasonable estimate that migraineurs with prolonged aura, new neurological deficits or new aura symptoms (transformed migraine), smoking or oral contraceptive use, and other prothrombotic states may be at increased risk of stroke. Based on the current landscape of knowledge, it is reasonable to employ aggressive modifiable risk factor reduction in migraine-related stroke cases for secondary stroke prevention which is the same goal for the general stroke population. This may include blood pressure and blood glucose control, low-density lipoprotein level lowering, antiplatelet medication administration, smoking cessation, healthy nutritional habits, and exercise [155•]. However, the ambition of ongoing research may focus on how identifying unique mechanisms involved in migraine-related stroke can translate into more targeted stroke preventative strategies and treatments in this population.

Conclusions

Future approaches to migraine-related stroke will likely center on understanding the particular mechanisms involved in stroke pathogenesis and preventative and treatment strategies. Putative goals of therapy may include reducing the risk of spreading depression, protecting against endothelial injury, and reducing platelet aggregation. It is unknown if reducing headache frequency or aura frequency with prophylactic agents can reduce stroke risk. Genetic studies on migraine and stroke may provide additional targets for novel drug therapies and raise the hopes of developing screening tools for migraineurs with increased stroke risk. Currently, the treatment of stroke in migraineurs, similar to stroke in non-migraineurs, should continue to involve augmenting traditional modifiable risks.

Acknowledgments The authors thank Margaret Alice McKinney, Medical Illustrator, Creative Media, Mayo Clinic Rochester, for providing the illustration.

Compliance with Ethics Guidelines

Conflict of Interest Andrea M. Harriott and Kevin M. Barrett declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- Of importance

1. The international classification of headache disorders, 3rd edition (beta version). Cephalalgia. 2013;33:629–808.
2. Manzoni GC, Farina S, Lanfranchi M, Solari A. Classic migraine—clinical findings in 164 patients. Eur Neurol. 1985;24:163–9.
3. Jensen K, Tfelt-Hansen P, Lauritzen M, Olesen J. Classic migraine. A prospective recording of symptoms. Acta Neurol Scand. 1986;73:359–62.
4. Vincent MB, Hadjikhani N. Migraine aura and related phenomena: beyond scotomata and scintillations. Cephalalgia. 2007;27:1368–77.
5. Smitherman TA, Burch R, Sheikh H, Loder E. The prevalence, impact, and treatment of migraine and severe headaches in the United States: a review of statistics from national surveillance studies. Headache. 2013;53:427–36.
6. Stewart WF, Lipton RB, Celentano DD, Reed ML. Prevalence of migraine headache in the United States. Relation to age, income, race, and other sociodemographic factors. JAMA. 1992;267:64–9.
7. Victor TW, Hu X, Campbell JC, Buse DC, Lipton RB. Migraine prevalence by age and sex in the United States: a life-span study. Cephalalgia. 2010;30:1065–72.
8. Lipton RB, Stewart WF, Scher AI. Epidemiology and economic impact of migraine. Curr Med Res Opin. 2001;17 Suppl 1:s4–s12.
9. Stewart WF, Roy J, Lipton RB. Migraine prevalence, socioeconomic status, and social causation. Neurology. 2013;81:948–55.
10. Stewart WF, Wood GC, Manack A, Varon SF, Buse DC, Lipton RB. Employment and work impact of chronic migraine and episodic migraine. J Occup Environ Med. 2010;52:8–14.
11. Furie KL, Kasner SE, Adams RJ, et al. Guidelines for the prevention of stroke in patients with stroke or transient ischemic attack: a guideline for healthcare professionals from the American Heart

Association/American Stroke Association. Stroke. 2011;42:227–76.
12. Kissela BM, Khoury JC, Alwell K, et al. Age at stroke: temporal trends in stroke incidence in a large, biracial population. Neurology. 2012;79:1781–7.
13. Tissue plasminogen activator for acute ischemic stroke. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. N Engl J Med. 1995;333:1581–1587.
14. Rutten-Jacobs LC, Arntz RM, Maaijwee NA, et al. Long-term mortality after stroke among adults aged 18 to 50 years. JAMA. 2013;309:1136–44.
15. Rutten-Jacobs LC, Maaijwee NA, Arntz RM, et al. Long-term risk of recurrent vascular events after young stroke: The FUTURE study. Ann Neurol. 2013;74:592–601.
16. Putaala J, Haapaniemi E, Metso AJ, et al. Recurrent ischemic events in young adults after first-ever ischemic stroke. Ann Neurol. 2010;68:661–71.
17. Hall GC, Brown MM, Mo J, MacRae KD. Triptans in migraine: the risks of stroke, cardiovascular disease, and death in practice. Neurology. 2004;62:563–8.
18. Velentgas P, Cole JA, Mo J, Sikes CR, Walker AM. Severe vascular events in migraine patients. Headache. 2004;44:642–51.
19. Kurth T, Slomke MA, Kase CS, et al. Migraine, headache, and the risk of stroke in women: a prospective study. Neurology. 2005;64:1020–6.
20. Kurth T, Gaziano JM, Cook NR, Logroscino G, Diener HC, Buring JE. Migraine and risk of cardiovascular disease in women. JAMA. 2006;296:283–91.
21. Donaghy M, Chang CL, Poulter N. Duration, frequency, recency, and type of migraine and the risk of ischaemic stroke in women of childbearing age. J Neurol Neurosurg Psychiatry. 2002;73:747–50.
22. Oral contraceptives and stroke in young women. Associated risk factors. JAMA. 1975;231:718–722.
23. Henrich JB, Horwitz RI. A controlled study of ischemic stroke risk in migraine patients. J Clin Epidemiol. 1989;42:773–80.
24. Tzourio C, Iglesias S, Hubert JB, et al. Migraine and risk of ischaemic stroke: a case-control study. BMJ. 1993;307:289–92.
25. Tzourio C, Tehindrazanarivelo A, Iglesias S, et al. Case-control study of migraine and risk of ischaemic stroke in young women. BMJ. 1995;310:830–3.
26. Carolei A, Marini C, De Matteis G. History of migraine and risk of cerebral ischaemia in young adults. The Italian National Research Council Study Group on Stroke in the Young. Lancet. 1996;347:1503–6.
27. Chang CL, Donaghy M, Poulter N. Migraine and stroke in young women: case-control study. The World Health Organisation Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. BMJ. 1999;318:13–8.
28. MacClellan LR, Giles W, Cole J, et al. Probable migraine with visual aura and risk of ischemic stroke: the stroke prevention in young women study. Stroke. 2007;38:2438–45.
29. Haapaniemi H, Hillbom M, Juvela S. Lifestyle-associated risk factors for acute brain infarction among persons of working age. Stroke. 1997;28:26–30.
30. Lidegaard O, Kreiner S. Contraceptives and cerebral thrombosis: a five-year national case-control study. Contraception. 2002;65:197–205.
31. Nightingale AL, Farmer RD. Ischemic stroke in young women: a nested case-control study using the UK General Practice Research Database. Stroke. 2004;35:1574–8.
32. Schurks M, Rist PM, Bigal ME, Buring JE, Lipton RB, Kurth T. Migraine and cardiovascular disease: systematic review and meta-analysis. BMJ. 2009;339:b3914.
33. Merikangas KR, Fenton BT, Cheng SH, Stolar MJ, Risch N. Association between migraine and stroke in a large-scale epidemiological study of the United States. Arch Neurol. 1997;54:362–8.
34. Kittner SJ, Stern BJ, Wozniak M, et al. Cerebral infarction in young adults: the Baltimore-Washington Cooperative Young Stroke Study. Neurology. 1998;50:890–4.
35. Sochurkova D, Moreau T, Lemesle M, Menassa M, Giroud M, Dumas R. Migraine history and migraine-induced stroke in the Dijon stroke registry. Neuroepidemiology. 1999;18:85–91.
36. Marini C, Carolei A, Roberts RS, et al. Focal cerebral ischemia in young adults: a collaborative case-control study. Nat Res Counc Study Group Neuroepidemiology. 1993;12:70–81.
37. Welch KM, Levine SR. Migraine-related stroke in the context of the International Headache Society classification of head pain. Arch Neurol. 1990;47:458–62.
38. Etminan M, Takkouche B, Isorna FC, Samii A. Risk of ischaemic stroke in people with migraine: systematic review and meta-analysis of observational studies. BMJ. 2005;330:63.
39. Cole JW, Kittner SJ. Meta-analysis of results from case control and cohort studies finds that migraine is associated with approximately twice the risk of ischaemic stroke. Evid Based Med. 2010;15:193–4.
40.• Spector JT, Kahn SR, Jones MR, Jayakumar M, Dalal D, Nazarian S. Migraine headache and ischemic stroke risk: an updated meta-analysis. Am J Med. 2010;123:612–24. *The authors provide a review and meta-analysis of 13 case control and 8 cohort studies examining the association between migraine and stroke. The results summarize the current observations that migraine is associated with a doubled risk of acute ischemic stroke.*
41. Gudmundsson LS, Scher AI, Aspelund T, et al. Migraine with aura and risk of cardiovascular and all cause mortality in men and women: prospective cohort study. BMJ. 2010;341:c3966.
42. Rist PM, Buring JE, Kase CS, Schurks M, Kurth T. Migraine and functional outcome from ischemic cerebral events in women. Circulation. 2010;122:2551–7.
43. Lizarelli PM, Martins WP, Vieira CS, et al. Both a combined oral contraceptive and depot medroxyprogesterone acetate impair endothelial function in young women. Contraception. 2009;79:35–40.
44. Mueck AO, Seeger H, Wallwiener D. Medroxyprogesterone acetate versus norethisterone: effect on estradiol-induced changes of markers for endothelial function and atherosclerotic plaque characteristics in human female coronary endothelial cell cultures. Menopause. 2002;9:273–81.
45. Csordas A, Bernhard D. The biology behind the atherothrombotic effects of cigarette smoke. Nat Rev Cardiol. 2013;10:219–30.
46. Messner B, Bernhard D. Smoking and cardiovascular disease: mechanisms of endothelial dysfunction and early atherogenesis. Arterioscler Thromb Vasc Biol. 2014;34:509–15.
47. Danese E, Montagnana M, Lippi G. Platelets and migraine. Thromb Res. 2014;134:17–22.
48. Uzar E, Evliyaoglu O, Toprak G, et al. Increased asymmetric dimethylarginine and nitric oxide levels in patients with migraine. J Headache Pain. 2011;12:239–43.
49. Rodriguez-Osorio X, Sobrino T, Brea D, Martinez F, Castillo J, Leira R. Endothelial progenitor cells: a new key for endothelial dysfunction in migraine. Neurology. 2012;79:474–9.
50. Busija DW, Bari F, Domoki F, Horiguchi T, Shimizu K. Mechanisms involved in the cerebrovascular dilator effects of cortical spreading depression. Prog Neurobiol. 2008;86:379–95.
51. Imamura K, Takeshima T, Fusayasu E, Nakashima K. Increased plasma matrix metalloproteinase-9 levels in migraineurs. Headache. 2008;48:135–9.
52. Gao HM, Li L, Zhang KL, Chen XH, Tian SQ, Zhang ZL. Impact of migraine attacks on the blood-brain barrier. Chin Med J (Engl). 2010;123:2559–61.

53. Meier B, Kalesan B, Mattle HP, et al. Percutaneous closure of patent foramen ovale in cryptogenic embolism. N Engl J Med. 2013;368:1083–91.
54. Arboix A, Massons J, Garcia-Eroles L, Oliveres M, Balcells M, Targa C. Migrainous cerebral infarction in the Sagrat Cor Hospital of Barcelona stroke registry. Cephalalgia. 2003;23:389–94.
55. Milhaud D, Bogousslavsky J, van Melle G, Liot P. Ischemic stroke and active migraine. Neurology. 2001;57:1805–11.
56. Tsai CF, Chen CC, Wang SC, Yip PK. Reversible vasospasm in migrainous infarction: a transcranial Doppler follow-up study. J Ultrasound Med. 2010;29:481–4.
57. Marshall N, Maclaurin WA, Koulouris G. MRA captures vasospasm in fatal migrainous infarction. Headache. 2007;47:280–3.
58. Gomez CR, Gomez SM, Puricelli MS, Malik MM. Transcranial Doppler in reversible migrainous vasospasm causing cerebellar infarction: report of a case. Angiology. 1991;42:152–6.
59. Spierings EL. Angiographic changes suggestive of vasospasm in migraine complicated by stroke. Headache. 1990;30:727–8.
60. Sanin LC, Mathew NT. Severe diffuse intracranial vasospasm as a cause of extensive migrainous cerebral infarction. Cephalalgia. 1993;13:289–92.
61. Stone GM, Burns RJ. Cerebral infarction caused by vasospasm. Med J Aust. 1982;1:556–9.
62. Solomon S, Lipton RB, Harris PY. Arterial stenosis in migraine: spasm or arteriopathy? Headache. 1990;30:52–61.
63. Masuzawa T, Shinoda S, Furuse M, Nakahara N, Abe F, Sato F. Cerebral angiographic changes on serial examination of a patient with migraine. Neuroradiology. 1983;24:277–81.
64. Call GK, Fleming MC, Sealfon S, Levine H, Kistler JP, Fisher CM. Reversible cerebral segmental vasoconstriction. Stroke. 1988;19:1159–70.
65. Calabrese LH, Dodick DW, Schwedt TJ, Singhal AB. Narrative review: reversible cerebral vasoconstriction syndromes. Ann Intern Med. 2007;146:34–44.
66. Hampton KK, Esack A, Peatfield RC, Grant PJ. Elevation of plasma vasopressin in spontaneous migraine. Cephalalgia. 1991;11: 249–50.
67. Tietjen EG. Migraine and ischaemic heart disease and stroke: potential mechanisms and treatment implications. Cephalalgia. 2007;27:981–7.
68. Baggott CD, Aagaard-Kienitz B. Cerebral vasospasm. Neurosurg Clin N Am. 2014;25:497–528.
69. Saengjaroentham C, Supornsilpchai W, Ji-Au W, Srikiatkhachorn A, Maneesri-le Grand S. Serotonin depletion can enhance the cerebrovascular responses induced by cortical spreading depression via the nitric oxide pathway. Int J Neurosci. 2014.
70. Heckmann JG, Tomandl B, Kraus B, Gerlach R, Neundorfer B. A case of diffuse cerebral vasospasm—possibly ergotamine-associated? Cerebrovasc Dis. 2000;10:417–8.
71. Silberstein SD. The pharmacology of ergotamine and dihydroergotamine. Headache. 1997;37 Suppl 1:S15–25.
72. Humphrey PP. How it started. Cephalalgia. 2001;21 Suppl 1:2–5.
73. Chabrier PE. The role of endothelin in the vessel wall. Baillieres Clin Haematol. 1993;6:577–91.
74. Nattero G, Mengozzi G, Inconis T, Paradisi L. Nitric oxide, endothelin-1, and transcranial Doppler in migraine. Findings in interictal conditions and during migraine attack. Headache. 1996;36:307–11.
75. Farkkila M, Palo J, Saijonmaa O, Fyhrquist F. Raised plasma endothelin during acute migraine attack. Cephalalgia. 1992;12: 383–4. *discussion 340*.
76. Kallela M, Farkkila M, Saijonmaa O, Fyhrquist F. Endothelin in migraine patients. Cephalalgia. 1998;18:329–32.
77. Hasselblatt M, Kohler J, Volles E, Ehrenreich H. Simultaneous monitoring of endothelin-1 and vasopressin plasma levels in migraine. Neuroreport. 1999;10:423–5.
78. Dreier JP, Kleeberg J, Alam M, et al. Endothelin-1-induced spreading depression in rats is associated with a microarea of selective neuronal necrosis. Exp Biol Med (Maywood). 2007;232:204–13.
79. Dreier JP, Kleeberg J, Petzold G, et al. Endothelin-1 potently induces Leao's cortical spreading depression in vivo in the rat: a model for an endothelial trigger of migrainous aura? Brain. 2002;125:102–12.
80. Cardell LO, Uddman R, Edvinsson L. Endothelins: a role in cerebrovascular disease? Cephalalgia. 1994;14:259–65.
81. Ziv I, Fleminger G, Djaldetti R, Achiron A, Melamed E, Sokolovsky M. Increased plasma endothelin-1 in acute ischemic stroke. Stroke. 1992;23:1014–6.
82. Salom JB, Torregrosa G, Alborch E. Endothelins and the cerebral circulation. Cerebrovasc Brain Metab Rev. 1995;7:131–52.
83. Petzold GC, Einhaupl KM, Dirnagl U, Dreier JP. Ischemia triggered by spreading neuronal activation is induced by endothelin-1 and hemoglobin in the subarachnoid space. Ann Neurol. 2003;54: 591–8.
84. Hassan A, Hunt BJ, O'Sullivan M, et al. Markers of endothelial dysfunction in lacunar infarction and ischaemic leukoaraiosis. Brain. 2003;126:424–32.
85. Kelleher RJ, Soiza RL. Evidence of endothelial dysfunction in the development of Alzheimer's disease: is Alzheimer's a vascular disorder? Am J Cardiovasc Dis. 2013;3:197–226.
86. Hamed SA. The vascular risk associations with migraine: relation to migraine susceptibility and progression. Atherosclerosis. 2009;205:15–22.
87. Munno I, Marinaro M, Bassi A, Cassiano MA, Causarano V, Centonze V. Immunological aspects in migraine: increase of IL-10 plasma levels during attack. Headache. 2001;41:764–7.
88. Munno I, Centonze V, Marinaro M, et al. Cytokines and migraine: increase of IL-5 and IL-4 plasma levels. Headache. 1998;38:465–7.
89. Perini F, D'Andrea G, Galloni E, et al. Plasma cytokine levels in migraineurs and controls. Headache. 2005;45:926–31.
90. Sarchielli P, Alberti A, Baldi A, et al. Proinflammatory cytokines, adhesion molecules, and lymphocyte integrin expression in the internal jugular blood of migraine patients without aura assessed ictally. Headache. 2006;46:200–7.
91. Tietjen GE, Herial NA, White L, Utley C, Kosmyna JM, Khuder SA. Migraine and biomarkers of endothelial activation in young women. Stroke. 2009;40:2977–82.
92. Tietjen GE, Al-Qasmi MM, Athanas K, Dafer RM, Khuder SA. Increased von Willebrand factor in migraine. Neurology. 2001;57: 334–6.
93. Cesar JM, Garcia-Avello A, Vecino AM, Sastre JL, Alvarez-Cermeno JC. Increased levels of plasma von Willebrand factor in migraine crisis. Acta Neurol Scand. 1995;91:412–3.
94. Morancho A, Rosell A, Garcia-Bonilla L, Montaner J. Metalloproteinase and stroke infarct size: role for anti-inflammatory treatment? Ann N Y Acad Sci. 2010;1207:123–33.
95. Chaturvedi M, Kaczmarek L. Mmp-9 inhibition: a therapeutic strategy in ischemic stroke. Mol Neurobiol. 2014;49:563–73.
96. Leira R, Sobrino T, Rodriguez-Yanez M, Blanco M, Arias S, Castillo J. Mmp-9 immunoreactivity in acute migraine. Headache. 2007;47:698–702.
97. Bernecker C, Pailer S, Kieslinger P, et al. Increased matrix metalloproteinase activity is associated with migraine and migraine-related metabolic dysfunctions. Eur J Neurol. 2011;18:571–6.
98. Lee ST, Chu K, Jung KH, et al. Decreased number and function of endothelial progenitor cells in patients with migraine. Neurology. 2008;70:1510–7.
99. Oterino A, Toriello M, Palacio E, et al. Analysis of endothelial precursor cells in chronic migraine: a case-control study. Cephalalgia. 2013;33:236–44.

100. Liman TG, Bachelier-Walenta K, Neeb L, et al. Circulating endothelial microparticles in female migraineurs with aura. Cephalalgia. 2014.
101. Couch JR, Hassanein RS. Platelet aggregability in migraine. Neurology. 1977;27:843–8.
102. Sarchielli P, Alberti A, Coppola F, et al. Platelet-activating factor (PAF) in internal jugular venous blood of migraine without aura patients assessed during migraine attacks. Cephalalgia. 2004;24:623–30.
103. Patel RR, Adam R, Maldjian C, Lincoln CM, Yuen A, Arneja A. Cervical carotid artery dissection: current review of diagnosis and treatment. Cardiol Rev. 2012;20:145–52.
104. Tzourio C, Benslamia L, Guillon B, et al. Migraine and the risk of cervical artery dissection: a case-control study. Neurology. 2002;59:435–7.
105. Metso TM, Tatlisumak T, Debette S, et al. Migraine in cervical artery dissection and ischemic stroke patients. Neurology. 2012;78:1221–8.
106.• Rist PM, Diener HC, Kurth T, Schurks M. Migraine, migraine aura, and cervical artery dissection: a systematic review and meta-analysis. Cephalalgia. 2011;31:886–96. *The authors performed a meta-analysis that included 5 case-control studies demonstrating an association between migraine and cervical artery dissection which may explain in part the association between migraine and stroke risk.*
107. Lucas C, Lecroart JL, Gautier C, et al. Impairment of endothelial function in patients with spontaneous cervical artery dissection: evidence for a general arterial wall disease. Cerebrovasc Dis. 2004;17:170–4.
108. Tzourio C, El Amrani M, Robert L, Alperovitch A. Serum elastase activity is elevated in migraine. Ann Neurol. 2000;47:648–51.
109. Hadjikhani N, Sanchez Del Rio M, Wu O, et al. Mechanisms of migraine aura revealed by functional MRI in human visual cortex. Proc Natl Acad Sci U S A. 2001;98:4687–92.
110. Eikermann-Haerter K. Spreading depolarization may link migraine and stroke. Headache. 2014;54:1146–57.
111. Hashemi P, Bhatia R, Nakamura H, et al. Persisting depletion of brain glucose following cortical spreading depression, despite apparent hyperaemia: evidence for risk of an adverse effect of Leao's spreading depression. J Cereb Blood Flow Metab. 2009;29:166–75.
112. Dohmen C, Sakowitz OW, Fabricius M, et al. Spreading depolarizations occur in human ischemic stroke with high incidence. Ann Neurol. 2008;63:720–8.
113. Eikermann-Haerter K, Lee JH, Yuzawa I, et al. Migraine mutations increase stroke vulnerability by facilitating ischemic depolarizations. Circulation. 2012;125:335–45.
114. Piilgaard H, Lauritzen M. Persistent increase in oxygen consumption and impaired neurovascular coupling after spreading depression in rat neocortex. J Cereb Blood Flow Metab. 2009;29:1517–27.
115. Takano T, Tian GF, Peng W, et al. Cortical spreading depression causes and coincides with tissue hypoxia. Nat Neurosci. 2007;10:754–62.
116. Stam AH, van den Maagdenberg AM, Haan J, Terwindt GM, Ferrari MD. Genetics of migraine: an update with special attention to genetic comorbidity. Curr Opin Neurol. 2008;21:288–93.
117. Knierim E, Leisle L, Wagner C, et al. Recurrent stroke due to a novel voltage sensor mutation in Cav2.1 responds to verapamil. Stroke. 2011;42:e14–7.
118. Chabriat H, Vahedi K, Iba-Zizen MT, et al. Clinical spectrum of CADASIL: a study of 7 families. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. Lancet. 1995;346:934–9.
119. Jen J, Cohen AH, Yue Q, et al. Hereditary endotheliopathy with retinopathy, nephropathy, and stroke (HERNS). Neurology. 1997;49:1322–30.
120. Ophoff RA, DeYoung J, Service SK, et al. Hereditary vascular retinopathy, cerebroretinal vasculopathy, and hereditary endotheliopathy with retinopathy, nephropathy, and stroke map to a single locus on chromosome 3p21.1-p21.3. Am J Hum Genet. 2001;69:447–53.
121. Goodfellow JA, Dani K, Stewart W, et al. Mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes: an important cause of stroke in young people. Postgrad Med J. 2012;88:326–34.
122. Freilinger T, Anttila V, de Vries B, et al. Genome-wide association analysis identifies susceptibility loci for migraine without aura. Nat Genet. 2012;44:777–82.
123. Law C, Bunyan D, Castle B, et al. Clinical features in a family with an R460H mutation in transforming growth factor beta receptor 2 gene. J Med Genet. 2006;43:908–16.
124. Allain B, Jarray R, Borriello L, et al. Neuropilin-1 regulates a new VEGF-induced gene, Phactr-1, which controls tubulogenesis and modulates lamellipodial dynamics in human endothelial cells. Cell Signal. 2012;24:214–23.
125. Jarray R, Allain B, Borriello L, et al. Depletion of the novel protein PHACTR-1 from human endothelial cells abolishes tube formation and induces cell death receptor apoptosis. Biochimie. 2011;93:1668–75.
126. Fuentealba RA, Liu Q, Kanekiyo T, Zhang J, Bu G. Low density lipoprotein receptor-related protein 1 promotes anti-apoptotic signaling in neurons by activating Akt survival pathway. J Biol Chem. 2009;284:34045–53.
127. Liu Q, Trotter J, Zhang J, et al. Neuronal LRP1 knockout in adult mice leads to impaired brain lipid metabolism and progressive, age-dependent synapse loss and neurodegeneration. J Neurosci. 2010;30:17068–78.
128. Lillis AP, Van Duyn LB, Murphy-Ullrich JE, Strickland DK. LDL receptor-related protein 1: unique tissue-specific functions revealed by selective gene knockout studies. Physiol Rev. 2008;88:887–918.
129. Muratoglu SC, Belgrave S, Hampton B, et al. LRP1 protects the vasculature by regulating levels of connective tissue growth factor and HtrA1. Arterioscler Thromb Vasc Biol. 2013;33:2137–46.
130. Hopkins PN. Molecular biology of atherosclerosis. Physiol Rev. 2013;93:1317–542.
131. Gutierrez-Fernandez M, Rodriguez-Frutos B, Fuentes B, et al. CDP-choline treatment induces brain plasticity markers expression in experimental animal stroke. Neurochem Int. 2012;60:310–7.
132. Polavarapu R, Gongora MC, Yi H, et al. Tissue-type plasminogen activator-mediated shedding of astrocytic low-density lipoprotein receptor-related protein increases the permeability of the neurovascular unit. Blood. 2007;109:3270–8.
133. Chasman DI, Schurks M, Anttila V, et al. Genome-wide association study reveals three susceptibility loci for common migraine in the general population. Nat Genet. 2011;43:695–8.
134.• Anttila V, Winsvold BS, Gormley P, et al. Genome-wide meta-analysis identifies new susceptibility loci for migraine. Nat Genet. 2013;45:912–7. *The authors identify several genetic susceptibility loci associated with migraine. The identification of these loci may provide putative variants that may link migraine and stroke.*
135. MacClellan LR, Howard TD, Cole JW, et al. Relation of candidate genes that encode for endothelial function to migraine and stroke: the Stroke Prevention in Young Women study. Stroke. 2009;40:e550–7.
136. Tzourio C, El Amrani M, Poirier O, Nicaud V, Bousser MG, Alperovitch A. Association between migraine and endothelin type

A receptor (ETA −231 A/G) gene polymorphism. Neurology. 2001;56:1273–7.
137. Weigand KM, Swarts HG, Russel FG, Koenderink JB. Biochemical characterization of sporadic/familial hemiplegic migraine mutations. Biochim Biophys Acta. 1838;2014:1693–700.
138. Yang GY, Chen SF, Kinouchi H, Chan PH, Weinstein PR. Edema, cation content, and ATPase activity after middle cerebral artery occlusion in rats. Stroke. 1992;23:1331–6.
139. Kirchmann M, Thomsen LL, Olesen J. The CACNA1A and ATP1A2 genes are not involved in dominantly inherited migraine with aura. Am J Med Genet B Neuropsychiatr Genet. 2006;141B: 250–6.
140. Todt U, Dichgans M, Jurkat-Rott K, et al. Rare missense variants in ATP1A2 in families with clustering of common forms of migraine. Hum Mutat. 2005;26:315–21.
141. Harriott AM, Dueker N, Cheng YC, et al. Polymorphisms in migraine-associated gene, and ischemic stroke risk in a biracial population: the genetics of early onset stroke study. Springerplus. 2013;2:46.
142. Pezzini A, Grassi M, Del Zotto E, et al. Migraine mediates the influence of C677T MTHFR genotypes on ischemic stroke risk with a stroke-subtype effect. Stroke. 2007;38:3145–51.
143. Schurks M, Rist PM, Kurth T. MTHFR 677C>T and ACE D/I polymorphisms in migraine: a systematic review and meta-analysis. Headache. 2010;50:588–99.
144. Pezzini A, Grassi M, Lodigiani C, et al. Predictors of migraine subtypes in young adults with ischemic stroke: the Italian project on stroke in young adults. Stroke. 2011;42:17–21.
145. Scher AI, Terwindt GM, Picavet HS, Verschuren WM, Ferrari MD, Launer LJ. Cardiovascular risk factors and migraine: the GEM population-based study. Neurology. 2005;64:614–20.
146. Sinclair AJ, Matharu M. Migraine, cerebrovascular disease and the metabolic syndrome. Ann Indian Acad Neurol. 2012;15: S72–7.
147. Bigal ME, Kurth T, Santanello N, et al. Migraine and cardiovascular disease: a population-based study. Neurology. 2010;74:628–35.
148. Kruit MC, Launer LJ, Ferrari MD, van Buchem MA. Infarcts in the posterior circulation territory in migraine. The population-based MRI CAMERA study. Brain. 2005;128:2068–77.
149. Kruit MC, van Buchem MA, Hofman PA, et al. Migraine as a risk factor for subclinical brain lesions. JAMA. 2004;291:427–34.
150. Hougaard A, Amin FM, Ashina M. Migraine and structural abnormalities in the brain. Curr Opin Neurol. 2014;27:309–14.
151. Fisher CM. Late-life migraine accompaniments—further experience. Stroke. 1986;17:1033–42.
152. Fisher CM. Late-life migraine accompaniments as a cause of unexplained transient ischemic attacks. Can J Neurol Sci. 1980;7:9–17.
153. Wijman CA, Wolf PA, Kase CS, Kelly-Hayes M, Beiser AS. Migrainous visual accompaniments are not rare in late life: the Framingham Study. Stroke. 1998;29:1539–43.
154. Carroll JD, Saver JL, Thaler DE, et al. Closure of patent foramen ovale versus medical therapy after cryptogenic stroke. N Engl J Med. 2013;368:1092–100.
155.• Kernan WN, Ovbiagele B, Black HR, et al. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2014;45: 2160–236. *The goals for secondary stroke prevention in migraineurs should be the same as those for the general stroke population until unique modifiable risks and treatment options are discovered. The authors review the guidelines for secondary stroke prevention in the general stroke population*.