Chapter 1
Cardio-cerebrovascular Comorbidity

S. Sacco and C. Bushnell

Abstract Migraine, particularly migraine with aura has been associated with an increased risk of vascular events including ischemic and hemorrhagic stroke, myocardial infarction, and angina. Data also indicated that migraineurs, as compared to non-migraineurs, have an increased burden of infarct-like lesions and white matter abnormalities at brain magnetic resonance. There are no tools to identify the migraineurs who will suffer vascular events. Recent onset of the migraine, active migraine, and frequent attacks are features associated with the increased stroke risk; combined oral contraceptives and cigarette smoking may further increase the risk of ischemic stroke in migraineurs. The mechanisms underlying this increased vascular risk are still unclear but experimental studies indicated an increased cellular excitability in migraineurs that may make the brain tissue more susceptible to ischemia. Additionally, clinical data supported an impairment of the vascular function in migraineurs at the systemic level. There is currently no direct evidence to support that a migraine prophylactic treatment can reduce future stroke risk; however, we cannot exclude that migraine prophylaxis, by raising the threshold for spreading depolarization, may lower stroke risk.

1.1 Epidemiological Evidence

Over the past decades numerous data have pointed to an association between migraine and cardiovascular diseases (CVD).

S. Sacco (✉)
Department of Applied Clinical Sciences and Biotechnology, University of L'Aquila, Institute of Neurology, L'Aquila, Italy
e-mail: simona.sacco@yahoo.com

C. Bushnell
Department of Neurology, Wake Forest Baptist Health, Winston Salem, NC, USA
e-mail: cbushnel@wakehealth.edu

M.A. Giamberardino, P. Martelletti (eds.), *Comorbidities in Headache Disorders*, Headache,
DOI 10.1007/978-3-319-41454-6_1

1.1.1 Migraine and Ischemic Stroke

The first study to demonstrate an association between migraine and stroke was a case–control study from the Collaborative Group which included 598 women with stroke aged from 15 to 44 years and a group of hospital and neighbor control participants [13]. The risk of ischemic stroke was increased by twofold in migraineurs who were oral contraceptives nonusers (relative risk [RR] 2.0; 95 % confidence interval [CI] 1.2–3.3) and by sixfold in migraineurs who used oral contraceptives (RR 5.9; 95 % CI 2.9–12.2) [13]. Subsequent studies [1, 8, 10, 12, 18, 26, 49, 50, 55, 58, 63, 90, 93, 101], with few exceptions [29, 102], further supported an increased stroke risk in migraineurs. Most of those studies included young women [10, 12, 13, 18, 49, 50, 55, 63, 90, 93, 101], some included also young men [10, 55, 90], and fewer included older subjects [1, 8, 26, 29, 58, 102]. Comparable studies [8, 10, 12, 13, 18, 26, 29, 49, 55, 58, 63, 90, 101, 102] were pooled in the first meta-analysis by Etminan et al. (Table 1.1) [21]. This meta-analysis indicated that subjects with migraine had a twofold increased risk of ischemic stroke as compared to non-migraineurs [21]. The risk was increased for both migraine aura and without aura [21]. After this meta-analysis, further studies [5, 27, 36–39, 51, 54, 62, 68, 97, 104] and two meta-analyses [91, 94] became available. Some of those studies included only young subjects [54, 62, 68], while most of them included older men and women [5, 27, 97, 104], older women [36, 37, 39, 51], or older men [38]. Data from comparable studies [10, 12, 26, 27, 29, 37, 38, 101, 102] pooled by Schürks et al. indicated that subjects with any migraine had a 1.7-fold increased risk of ischemic stroke (Table 1.1) [91]. The risk was increased for migraine with but not without aura (Table 1.1) [91]. Data from comparable studies [5, 8, 10, 12, 13, 18, 26, 27, 29, 37, 38, 49, 50, 58, 62, 63, 101, 102, 104] pooled by Spector et al. indicated that subjects with any migraine had a twofold increased risk of ischemic stroke (Table 1.1) [94]. The risk was increased for migraine with but not without aura (Table 1.1) [94]. After the publication of those meta-analyses, the American Migraine Prevalence and Prevention study (AMPP), a case–control study including more than 11,300 participants, further supported the increased overall stroke risk in those with migraine (OR 1.5; 95 % CI 1.2–2.1) [7]. The study confirmed that the association was driven by an increased risk mostly in migraineurs with (odds ratio [OR] 2.8; 95 % CI 2.0–3.8) rather than without aura [7]. More recently, the Northern Manhattan Study (NOMAS), a prospective population-based study including 1,292 participants with a mean age of 68 years followed for a mean of 11 years, evaluated the possible association between migraine and cardiovascular events including stroke [61]. The study was unable to demonstrate an association between migraine, either with or without aura, and stroke [61]. Notably, authors found that migraineurs as compared to non-migraineurs had an increased risk of stroke if they were also current smokers (hazard ratio [HR] 3.2; 95 % CI 1.1–8.9) [61]. Gelfand et al., in a further study including 1,566,952 children aged 2–17 years, were unable to demonstrate an association between migraine and ischemic stroke

Table 1.1 Meta-analyses evaluating the association between migraine and cardiovascular events

Outcome/ study	Search limit (year of publication)	Any migraine		Migraine with aura		Migraine without aura	
		Studies (*n*)	Effect estimates (95 % CI)	Studies (*n*)	Effect estimates (95 % CI)	Studies (*n*)	Effect estimates (95 % CI)
Ischemic stroke							
Etminan (2005) [21]	1996–2004	14	2.16 (1.89–2.48)	8	2.28 (1.89–4.39)	7	1.56 (1.03–2.36)
Schürks (2009) [91]	Up to 2009	9	1.73 (1.31–2.29)	8	2.16 (1.53–3.03)	8	1.23 (0.90–1.69)
Spector (2010) [94]	Up to 2009	19	2.04 (1.72–2.43)	8	2.25 (1.53–3.33)	7	1.24 (0.86–1.79)
Hemorrhagic stroke							
Sacco (2013) [84]	Up to 2013	8	1.48 (1.16–1.88)	3	1.62 (0.87–3.03)	3	1.39 (0.74–2.62)
Myocardial infarction							
Schürks (2009) [91]	Up to 2009	5	1.12 (0.95–1.32)	–	–	–	
Sacco (2015) [87]	Up to 2014	7	1..33 (1.08–1.64)	2	2.61 (1.86–3.65)	2	1.14 (0.81–2.45)
Angina							
Sacco (2015) [87, 88]	Up to 2014	5	1.29 (1.17–1.43)	3	2.94 (1.59–5.43)	3	1.45 (1.06–2.00)
Cardiovascular death							
Schürks (2009) [91]	Up to 2009	5	1.03 (0.79–1.34)	–	–	–	
Schürks (2011) [92]	Up to 2011	6	1.09 (0.89–1.32)	–	–	–	
Coronary heart disease mortality							
Schürks (2011) [92]	Up to 2011	3	0.95 (0.57–1.60)	–	–	–	

CI indicates confidence intervals

in this age group [24]. Notably, a post hoc analysis of adolescents (12–17 years) showed a threefold increased risk of ischemic stroke among those with migraine (incidence ratio [IR] 3.4; 95 % CI 1.2–9.5) [24]. A recent additional study by Albieri et al., using administrative coding data, of 49,711 patients hospitalized for

a first stroke, indicated an increase in the risk of ischemic stroke in migraineurs as compared to non-migraineurs (RR 1.1; 95 % CI 1.0–1.1) [1].

Notably, data also indicated that migraine may be associated with an increased stroke risk during pregnancy [9, 31, 105]. Data using administrative coding data from the United States Nationwide Inpatient Sample from the Healthcare Cost and Utilization Project of the Agency for Healthcare Research and Quality showed that a diagnosis of migraine was associated with an increased risk of ischemic stroke (OR 30.7; 95 % CI 17.4–34.1) [9].

Because of the low number of events in many of the available studies, we have little information on the frequency of the different types of ischemic stroke in migraineurs. Data from the Stroke Prevention in Young Women (SPYW) Study, a population-based, case–control study including 386 women aged 15–49 years with first ischemic stroke and 614 age- and ethnicity-matched controls, were unable to prove an association between migraine with aura and any of the main ischemic stroke subtypes (large-artery atherosclerosis, cardioembolic, lacunar, undetermined cause) [54]. In contrast, the Oxford Vascular Study (OXVASC), a population-based study including 1,810 participants with transient ischemic attack (TIA) or ischemic stroke, showed that as compared to events with determined etiology, patients with cryptogenic events most often had a history of migraine (OR 1.7; 95 % CI 1.4–2.2). The same association was seen for migraine with aura (OR 1.8; 95 % CI 1.4–2.3) and migraine without aura (OR 2.1; 95 % CI 1.4–3.0) in an analysis stratified by sex and vascular territory [48]. In this study, as expected, the frequency of migraine decreased with age in the overall cohort; however, the frequency of history of migraine did not fall with age in patients with cryptogenic TIA or stroke, such that with an analysis stratified by age, the association of migraine and cryptogenic events was strongest at older ages [48].

More recently, the Italian Project on Stroke in Young Adults (IPSYS) demonstrated that in young patients with ischemic stroke, migraine with aura represented an independent risk factor for overall recurrent vascular events and for recurrent ischemic stroke [69]. In this prospective study, including 1,867 patients with first-ever ischemic stroke aged 18–45 years, migraine with aura emerged as an independent marker of risk of recurrent vascular events (HR 2.0; 95 % CI 1.2–3.4), indicating the striking importance of this condition in young subjects with ischemic stroke.

With regard to functional outcome after ischemic stroke, the analysis of data from the Women's Health Study (WHS) cohort, a prospective study among 27,852 women aged ≥45 years, showed that migraine with aura was only linked with ischemic strokes of good functional outcome [73]. Compared with women without history of migraine and who did not experience a TIA or stroke, women who reported migraine with aura had an increased risk of TIA (RR 1.6; 95 % CI 1.0–2.4) and of non-disabling (modified Rankin Scale score 0–1) stroke (OR 2.3; 95 % CI 1.4–4.0), while the study was unable to demonstrate an association between migraine and the risk of disabling stroke or death [73]. More recently, the study by Albieri et al., further supported that migraine was associated with an increased risk of mild strokes [1].

Beyond the comparisons of migraine with aura rather than without aura, studies provided little knowledge about the other possible characteristics associated with increased stroke risk. Findings from the World Health Organization Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception indicated that migraine of more than 12 years duration (OR 4.6, 95 % CI 1.3–16.8) and migraine with aura with attacks more frequent than 12 times per year (OR 10.4; 95 % CI 2.18–49.4) were associated with an increased risk of ischemic stroke [18]. Data from the SPYW study indicated that women with a higher frequency of migraine with aura (>12 attacks per year) had higher odds of stroke (OR 1.7; 95 % CI 1.1–2.8), in addition to women with recent onset of migraine with aura (OR 8.3; 95 % CI 2.6–25.7). However, lower frequency, longer duration, and any severity of the attacks were not associated with a significant increase in the risk of ischemic stroke [54]. According to data from the WHS cohort, the association between migraine with aura and ischemic stroke appeared J-shaped. Specifically, there were increased risks for less than monthly (HR 1.9; 95 % CI 1.2–3.1) and greater or equal to weekly (HR 4.3; 95 % CI 1.4–13.3) attacks, but not for monthly migraine attacks [40].

Nonetheless, there was consistent evidence that oral contraceptives use substantially increased the risk of ischemic stroke among young women with migraine (Table 1.2) [12, 13, 54, 93, 101]. The meta-analysis by Etminan et al. showed that users of oral contraceptives had an approximately eightfold increase in the risk of ischemic stroke compared to those not using those agents (RR 8.7; 95 % CI 5.1–15.1) [21]. In addition, there is consistent evidence that smoking substantially increases the risk of ischemic stroke among subjects with migraine [12, 39, 54, 61, 101] and that the risk is even higher in smokers who additionally use oral contraceptives (Table 1.2) [12, 54]. With the exception of smoking most studies suggest that the association between migraine and stroke is only apparent among individuals without or with the lowest burden of cardiovascular risk factors [87].

1.1.2 Migraine and Hemorrhagic Stroke

Several studies have also addressed the possible association between migraine and hemorrhagic stroke [1, 8, 11–13, 23, 24, 27, 35, 41, 93]. The pooled analysis of comparable studies [8, 11–13, 27, 35, 41, 93] by Sacco et al. indicated that subjects with any migraine had a 1.5-fold increased risk of hemorrhagic (including intracerebral and subarachnoid hemorrhage) stroke (Table 1.1) [84]. Subgroup analyses showed that female migraineurs had a 1.6-fold increased risk of hemorrhagic stroke as compared with female non-migraineurs (pooled adjusted effect estimate [PAEE] 1.6; 95 % CI 1.2–2.1) as female migraineurs aged less than 45 years (PAEE 1.6; 95 % CI 1.1–2.2) when compared with female non-migraineurs in the same age group [84]. However, solid conclusions could not be made for the different migraine types (with and without aura) because of insufficient data as only three studies [12, 35, 41] collected data on the risk of hemorrhagic stroke according to migraine type (Table 1.1). Two of them [35, 41] showed an association between migraine with

Table 1.2 Risk of stroke in subjects with migraine according to oral contraceptive use and smoking status

	Study population	Outcome	Exposure	OC nonusers	OC users	Not smoking	Smoking	OC+ smoking
Collaborative Group (1975) [13]	Hospital-based case–control study on women with stroke aged 15–44 years	Ischemic stroke	Migraine vs no migraine	Risk estimate (95 % CI)				
Chang (2009) [12]	Hospital-based case–control study on women with stroke aged 20–44 years	Ischemic stroke	Migraine vs no migraine	2.0# (1.2–3.3)	5.9# (2.9–12.2)	–	–	–
Tzourio (1995) [101]	Hospital-based case–control study on women with stroke aged <45 years	Ischemic stroke	Migraine vs no migraine	2.3# (0.7–7.5)	16.9# (2.7–106)	1.6# (0.4–5.9)	7.39# (2.1–25.5)	34.4# (3.3–361)
Schwartz (1998) [93]	Hospital-based case–control study on women with stroke aged 18–44 years	Ischemic stroke	Migraine vs no migraine	3.7# (1.5–9.1)	13.9# (5.5–35.1)	5.8# (2.2–15.3)	10.2# (3.5–29.9)	
MacClellan (2007) [54]	Hospital-based case–control study on women with ischemic stroke aged 15–49 years	Ischemic stroke	Migraine with aura vs no migraine	–	2.1# (1.2–3.7)	–	–	–
Kurth (2008) [39]	Prospective cohort study on women aged ≥45 years participating in a clinical trial	Ischemic stroke	Active migraine with aura vs no migraine	1.5# (1.1–2.1)	–	–	1.5# (1.1–2.3)	[a]7.0# (1.4–22.8) [b]10.0# (1.4–73.7)
Monteith (2015) [61]	Prospective population-based cohort study	Stroke	Migraine vs no migraine	–	–	2.3§ (1.2–4.3)	2.10§ (0.8–5.3)	–
				–	–	0.5§ (0.2–1.3)	3.2§ (1.1–8.9)	–

Risk estimates represent odds ratios# or hazard ratios§

OC indicates oral contraceptives; *CI* indicates confidence interval

[a]Compared with women with migraine with aura who were nonsmokers and non-OC users

[b]Compared with women with no migraine who were nonsmokers and non-OC users

aura and hemorrhagic stroke, while only one showed an association between migraine without aura and hemorrhagic stroke [35]. Regarding hemorrhagic stroke type, available data suggested that the association between migraine and hemorrhagic stroke is driven by an increase of intracerebral but not subarachnoid events [11, 41]. Thereafter, Gaist et al. performed a case–control study using data from 1,797 subjects with intracerebral hemorrhage and 1,340 subjects with subarachnoid hemorrhage and frequency matched controls from a large epidemiological dataset, The Health Improvement Network (THIN) [23]. In this study authors were unable to demonstrate an increased risk of overall hemorrhagic stroke or of intracerebral hemorrhage or subarachnoid hemorrhage in subjects with migraine compared with non-migraineurs. Analysis according to migraine type showed that neither migraine with aura nor migraine without aura were associated with an increased risk of hemorrhagic stroke. Only subjects with a long history (≥20 years) of migraine had an increased risk of intracerebral hemorrhage as compared to control subjects. Gelfand et al., in a further study including 1,566,952 children aged 2–17 years, were unable to demonstrate an association between migraine and hemorrhagic stroke in this age group [24]. Recently, the study by Albieri et al., did not demonstrate an increased risk of hemorrhagic stroke in migraineurs; however, in this study subanalysis by gender suggested an increased risk for hemorrhagic stroke in women migraineurs (RR 1.4; CI 1.1–1.8) as compared to non-migraineurs but no difference by migraine status in men [1]. Notably, data from the Nationwide Inpatient Sample indicated also that, during pregnancy, a diagnosis of migraine was associated with an increased risk of intracerebral (OR 9.1; 95 % CI 3.0–27.8) but not subarachnoid hemorrhage [9].

1.1.3 Migraine and Cardiac Vascular Diseases

Some studies have identified migraine also as a possible risk factor for cardiac vascular events [37, 38, 59], while others were unable to prove this association [27, 98, 104]. The pooled analysis of available data [27, 37, 38, 98, 104] by Schürks et al. did not indicate an increased risk of myocardial infarction in subjects with any migraine versus no migraine (Table 1.1) [91], but subsequently, data has pointed to an association between any migraine with cardiac ischemic disease [107] and between migraine with and without aura and myocardial infarction [7]. A further meta-analysis by Schurks et al., by pooling data from comparable studies [14, 25, 51], showed that the presence of any migraine did not alter the risk of coronary artery disease mortality (Table 1.1) [92]. A more recent meta-analysis by Sacco et al., pooling data from comparable studies [7, 27, 37, 38, 59, 98, 104], indicated a 30 % increase in the risk of myocardial infarction in subjects with migraine as compared to non-migraineurs (Table 1.1) [87]. An analysis stratified according to aura status indicated an increased risk of myocardial infarction in subjects with migraine with aura as compared to non-migraineurs while the meta-analysis was unable to show an increased risk of myocardial infarction in subjects with migraine without

aura (Table 1.1) [87]. This same meta-analysis also indicated that migraineurs as compared with non-migraineurs had an increased risk of angina (Table 1.1) [87]. In the case of angina, the risk was increased in both migraineurs with migraine with and without aura (Table 1.1) [87]. Both for myocardial infarction and angina, the meta-analysis indicated that the overall increased risk was mostly driven by the association in women while the meta-analysis was unable to demonstrate the association in men [87]. Notably, data from the Nationwide Inpatient Sample indicated also that, during pregnancy, a diagnosis of migraine was associated with an increased risk of myocardial infarction (OR 4.9; 95 % CI 1.7–14.2) [9].

Data from the WHS cohort showed that the association with myocardial infarction was evident among women in the highest Framingham risk score group and this pattern of association was driven by a particularly increased risk of myocardial infarction in women with migraine with aura who had high total cholesterol levels [39]. In contrast to the findings for ischemic stroke, this same study reported and association between low migraine frequency (< monthly) and myocardial infarction (HR 2.4; 95 % CI 1.6–3.7) and angina (HR 1.9; 95 % CI 1.3–2.9) among women with active migraine with aura, while the study was unable to demonstrate an association between higher migraine frequency (monthly and ≥ weekly) and those same cardiac end points [40].

1.1.4 Migraine and Vascular Abnormalities at Brain Neuroimaging

Several studies have also indicated that compared to non-migraineurs, migraineurs have a higher burden of asymptomatic white matter brain lesions and, according to some studies, infarct-like lesions on brain magnetic resonance imaging (MRI) [4, 28, 42, 60]. Those lesions may suggest chronic ischemic disease, but their nature still remains elusive because of the lack of neuropathological correlation.

White matter abnormalities in migraineurs have an uncertain pathological significance and may correspond to gliosis, demyelination, and loss of axons; this set of findings has been attributed to microvascular damage. According to a systematic review of studies published up to January 2013, prevalence of white matter abnormalities in migraineurs ranged from 4 to 59 % [4]. A meta-analysis of studies published up to November 2003, of pooled data from 7 studies [16, 22, 30, 67, 74, 77, 109] suggested an increased risk of white matter hyperintensities in migraineurs (OR 3.9; 95 % CI 2.3–6.7) [99]. According to the Cerebral Abnormalities in Migraine an Epidemiological Risk Analysis (CAMERA) study, a population-based study including 134 migraineurs without aura, 161 migraineurs with aura, and 140 controls aged 30–60 years reported that migraine was associated with deep white matter abnormalities in women (OR, 2.1; 95 % CI, 1.0–4.1) [33]. This association was independent of the presence or absence of aura, and the risk increased with attack frequency (highest in those with ≥1 attack per month: OR, 2.6; 95 % CI, 1.2–5.7) [33]. A subsequent analysis from the CAMERA study indicated an

increased risk of infratentorial (mostly pontine) hyperintensities in migraine with and without aura [34]. By contrast, this same study showed that in men, deep white matter abnormalities were not influenced by the presence, subtype, or frequency of migraine. The Epidemiology of Vascular Ageing (EVA) study, a population-based cross-sectional study involving 780 participants, confirmed the association of migraine with white matter abnormalities (OR 1.8; 95 % CI 1.0–2.9) [42]. The association between migraine and white matter hyperintensities was evident only for deep located lesions and migraine with aura (OR 12.4; 95 % CI 1.6–99.4) but not for periventricular lesions and migraine without aura [42]. A meta-analysis by Bashir et al., pooling data from 4 comparable studies [17, 33, 42, 77] published up to January 2013, showed an increased risk of white matter abnormalities in subjects with migraine with aura (PAEE 1.7; 95 % CI 1.1–2.7) and no association with migraine without aura [4]. More recently, data from the NOMAS indicated no association between migraine with or without aura and white matter hyperintensity volume [60]. Recently, an analysis of data from a subset of 506 subjects included in the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) study, a placebo-controlled trial assessing effects by pravastatin on cardiovascular disease, was unable to demonstrate an association between migraine either with and without aura and white matter hyperintensities [2].

Two studies addressing the impact of migraine on white matter hyperintensities progression over time provided conflicting results [28, 66]. Data from the CAMERA study indicated that, after a mean follow-up of 8.5 years, migraine was associated with white matter hyperintensities progression (OR 2.1; 95 % CI 1.0–4.1) [66]. In contrast, data from the Atherosclerosis Risk in Communities (ARIC) cohort study involving 1,028 participants who received 2 magnetic resonance imaging 8–12 years apart was unable to demonstrate any difference in white matter hyperintensity progression over the time between individuals with and without migraine [28]. The available studies did not support the hypothesis that migraineurs with white matter abnormalities are at risk of cognitive impairment [42, 66, 73].

Infarct-like lesions appear as small infarcts on brain magnetic resonance imaging mostly in the absence of a clinical history of stroke. Their exact nature still remains elusive and they might be of a different nature rather than ischemic. Data from the CAMERA study indicated that migraine with aura was associated with an increased risk of posterior circulation (mostly cerebellar) infarcts (OR 13.7; 95 % CI 1.7–112), while the study was unable to demonstrate an association between migraine without aura and posterior circulation infarcts [33, 34]. Another population-based study in Reykjavik involving 4,689 participants indicated that subjects with migraine with aura had an increased risk of late-life infarct-like lesions (OR 1.4; 95 % CI 1.1–1.8) that specifically reflected an association with cerebellar lesions in women (OR 1.9; 95 % CI, 1.4–2.6) [89]. Migraine without aura and non-migraine headache were not associated with an increased risk. Data from the EVA study further supported an increased risk of infarct-like lesions in subjects with migraine with aura (OR 3.4; 95 % CI 1.2–9.3) [42]. However, in contrast to other studies, the results of the EVA study indicated that most of the infarcts were located outside of the cerebellum or the brain stem [42]. Data from the NOMAS indicated that those

reporting migraine overall had double the odds of infarct-like lesions (OR 2.1; 95 % CI 1.0–4.2) when compared with those reporting no migraine [60]. Recently, data from the PROSPER study showed no association between migraine either with or without aura and infarct-like lesions [2]. With regard to migraine progression, data from the CAMERA study also indicated that migraine was not associated with the progression of infarct-like lesions over time [66].

Recently, an analysis of data from the PROSPER study evaluated the possible association between migraine with cerebral microbleeds [2]. These authors were unable to demonstrate overall an association between overall migraine and cerebral microbleeds. However, analysis stratified by migraine type and microbleeds location (lobar, basal ganglia, infratentorial) indicated an association between migraine without aura with infratentorial microbleeds (OR 3.3; 95 % CI 1.0–11.0) [2].

1.2 Monogenic Diseases with Migraine and Stroke

Several monogenic diseases have been recognized that include both migraine and cerebrovascular disease in the disease spectrum, and this represents further evidence of shared mechanisms between the two conditions [81]. Those diseases are represented by cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), mitochondrial encephalopathy lactic acidosis with stroke-like episodes (MELAS), autosomal dominant retinal vasculopathy with cerebral leukodystrophy (AD-RVCL), and hereditary infantile hemiparesis, retinal arteriolar tortuosity and leukoencephalopathy (HIHRATL).

CADASIL is due to a mutation of the Notch3 gene on chromosome 19. It is characterized by migraine with or without aura, mood disturbances, TIA, or strokes (usually lacunar infarcts) and progressive cognitive decline; other less common clinical features are epilepsy, acute reversible encephalopathy, and myopathy. Migraine is very common in CADASIL and it is often the presenting symptom [103]. Subjects may have typical attacks of migraine with aura but atypical auras are particularly common [80].

MELAS is due to a mutation at position 3243 of the mitochondrial genome [95]. It is characterized by seizures, encephalopathy, stroke-like episodes, migraine mostly associated with vomiting and aura, short stature, cognitive impairment, depression, cardiomyopathy, cardiac conduction defects, and diabetes mellitus.

AD-RVCL is due to TREX1 mutation on chromosome 3 and is characterized by systemic microvasculopathy with adult-onset retinal vasculopathy and cerebrovascular disease variably associated with migraine, mainly without aura [32].

HIHRATL is due to a mutation in the COL4A1 gene on chromosome 13 [45]; the disease has some similarities with CADASIL and is characterized by features of cerebral small-vessel disease, including subcortical hemorrhagic and ischemic lacunar strokes and leukoaraiosis. Patients usually suffer also from migraine mostly with aura, seizures, infantile hemiparesis, developmental delay, neuropsychological abnormalities, and ocular, renal, and cardiac involvement.

1.3 Mechanisms Linking Migraine to Cardiovascular Diseases

The mechanisms underlying the relationship between migraine and cardiovascular events are still unclear and several hypotheses have been raised and extensively revised and discussed [6, 43, 56, 78, 79, 83, 86]. Current hypotheses mostly try to link vascular events in migraineurs to those mechanisms that usually cause the same vascular events in non-migraineurs subjects. Hypothesized mechanisms include the role of confounders such as pharmacological agents used to treat migraine (non-steroidal anti-inflammatory drugs, triptans, and ergotamine) or anxiety and depression; antiphospholipid antibodies and prothrombotic factors, including prothrombin factor, factor V of Leiden, elevations in von Willebrand factor antigen and activity, decreased platelet hemostasis time, clotting time, and collagen-induced thrombus formation time; MTHFR and ACE D/I polymorphisms; cervical arterial dissection; and patent foramen ovale. However, since none of those factors can entirely explain the cardiovascular risk of migraineurs, alternative hypotheses should also be considered and among them peculiar migraine-specific mechanisms.

Migraine headache depends on the activation and sensitization of the trigeminovascular pain pathway, while cortical spreading depression is considered the neurophysiologic correlate of migrainous aura [70]. The origin of the cortical spreading depression in human migraineurs remains unclear, but in animal models, cortical spreading depression has been triggered by ischemic phenomena, such as through infusions of endothelin-1, a powerful vasoconstrictor [19]. Other mechanisms include microembolization of the carotid circulation using tiny plastic spheres, cholesterol crystals, and microbubbles, following large reduction of local blood flow [64]. Cortical spreading depression may predispose to brain lesions by hypoperfusion (spreading oligemia), by activating a cascade of inflammatory events, and by a failure of neurovascular coupling to provide a sufficient increase in blood flow for the raised energy use in cortical spreading depression [3, 6, 43, 46]. The genetic mouse models expressing migraine mutations (e.g., familial hemiplegic migraine 1 and CADASIL) show a faster onset of ischemia-triggered spreading depolarization; an increased frequency of ischemic depolarization; enlarged infarcts with worse neurological outcomes (which could be prevented by anti-excitatory treatment); and more severe spreading of depolarization-induced oligemia [20]. As a result, the minimum critical level of blood flow required for tissue survival is elevated and infarction occurs, even in mildly ischemic tissues. Considering the above reported evidences, some authors have proposed that as cortical spreading depression may occur as a consequence of subclinical ischemia, thus aura may represent a variant of TIA [56]. The suggestion that a common alteration may cause both migraine and stroke is further supported by the existence of the above-reported monogenic diseases that are associated with both conditions. These conditions might serve as models to study migraine-vascular disease mechanisms [81, 108].

However, in migraineurs the risk of vascular events is increased even outside the brain. Even if it cannot be excluded that different mechanisms may be of importance

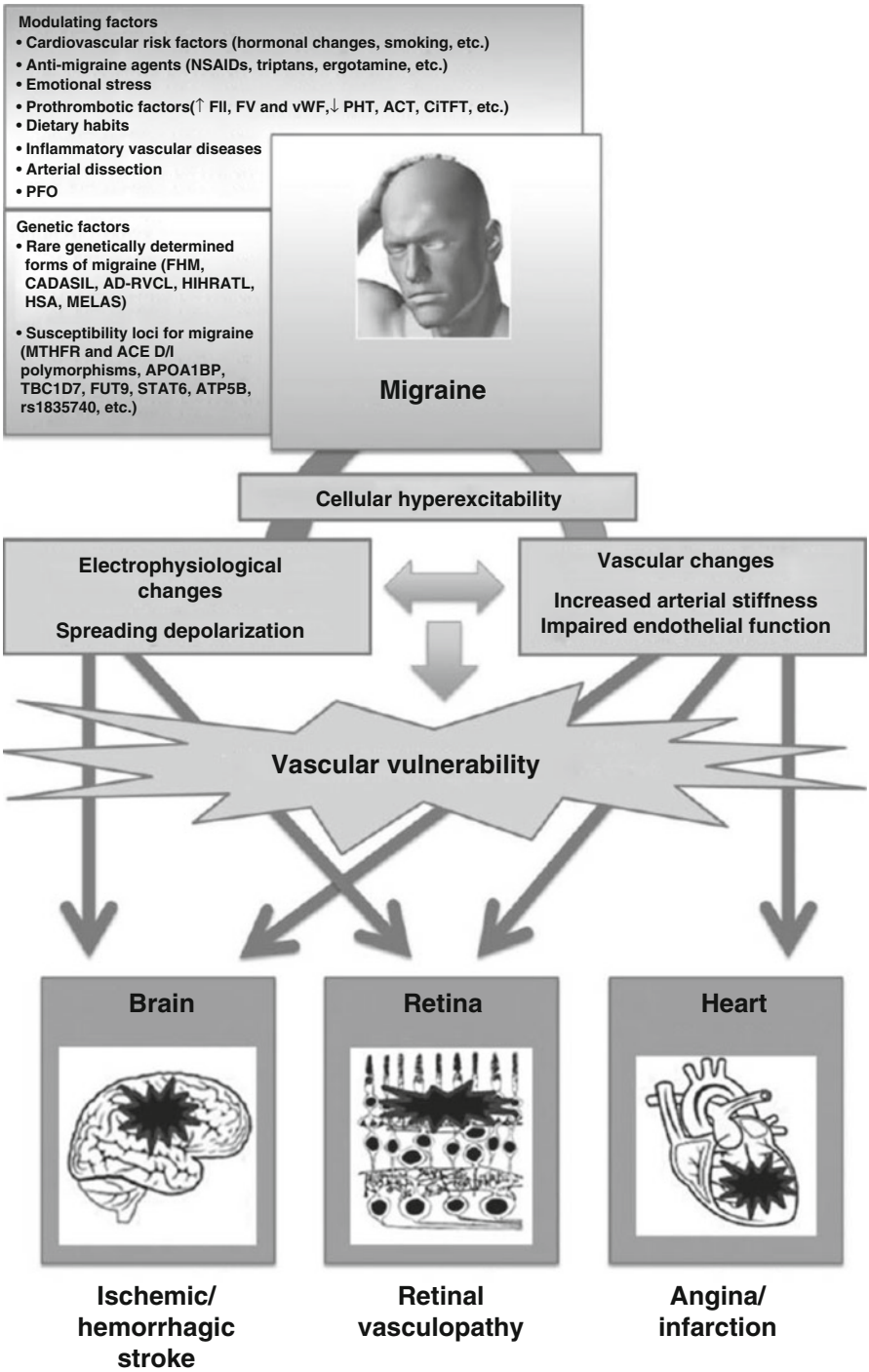
in cardiac and cerebral events, this possibility is unlikely and consequently the search for a cause for the association between migraine and vascular events should look at a general level. Electrophysiological changes could be present not only within the brain but also in other tissues (e.g., heart), and a complementary hypothesis may rely on a systemic peculiar vascular vulnerability of migraineurs that may contribute to the pathogenesis of migraine and over time, to the development of vascular events (Fig. 1.1) [71]. Numerous data suggest that in migraineurs the vascular system is impaired at a systemic level since migraineurs showed an alteration of arterial function (greater stiffness or impaired compliance of the arterial system) and according to some studies also of the endothelial function (altered flow-mediated dilation, reduced number of endothelial progenitor cells) compared to non-migraineurs [85]. Additionally, alteration of circulating factors linked to vascular dysfunction has been found in migraineurs [47, 52, 65, 76]. However, while in the general population markers of endothelial and arterial impairment represent precursors of atherothrombotic disease, evidence suggests that in migraine this may not be the case [96].

Recently, Mawet et al. investigated the hypothesis that a history of migraine predisposes to faster acute cerebral infarct growth [57]. They performed a case–control study of subjects with acute stroke (45 migraineurs and 27 controls), including chart documentation of migraine status and brain magnetic resonance imaging within 72 h of the stroke. In this study, migraine, particularly migraine with aura, more frequently showed the no-mismatch pattern with diffusion and perfusion magnetic resonance. This suggests accelerated loss of viable tissue at risk, as shown in the migraine mouse model [100].

1.4 Implications for Clinicians

While the evidence that links migraine to cardiovascular disease is robust, the overall increase in absolute risk of cardiovascular disease in migraineurs is rather small. Unfortunately, at the moment there are no reliable features that may indicate which subjects, across the overall migraine population, are at the highest risk of vascular events. The role that comorbid conventional vascular risk factors have on the risk

Fig. 1.1 Vascular vulnerability in migraine. *ACE* angiotensin-converting enzyme, *ACT* activated clotting time, *AD-RVCL* autosomal dominant retinal vasculopathy with cerebral leukodystrophy, *C-iTFT* collagen-induced thrombus formation time, *CADASIL* cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, *F II* prothrombin factor, *F V* Leiden factor, *FHM* familial hemiplegic migraine, *HIHRATL* hereditary infantile hemiparesis, retinal arteriolar tortuosity, and leukoencephalopathy, *HSA* hereditary systemic angiopathy, *MELAS* mitochondrial encephalopathy with lactic acidosis and stroke-like episodes, *MTHFR* methylenetetrahydrofolate reductase, *NSAIDs* nonsteroidal anti-inflammatory drugs, *PFO* patent foramen ovale, *PHT* platelet hemostasis time, *vWF* von Willebrand factor (From Ripa et al. [72])


Modulating factors
• Cardiovascular risk factors (hormonal changes, smoking, etc.)
• Anti-migraine agents (NSAIDs, triptans, ergotamine, etc.)
• Emotional stress
• Prothrombotic factors(↑ FII, FV and vWF,↓ PHT, ACT, CiTFT, etc.)
• Dietary habits
• Inflammatory vascular diseases
• Arterial dissection
• PFO
Genetic factors
• Rare genetically determined forms of migraine (FHM, CADASIL, AD-RVCL, HIHRATL, HSA, MELAS)
• Susceptibility loci for migraine (MTHFR and ACE D/I polymorphisms, APOA1BP, TBC1D7, FUT9, STAT6, ATP5B, rs1835740, etc.)
Migraine
Cellular hyperexcitability
Electrophysiological changes
Spreading depolarization
Vascular changes
Increased arterial stiffness
Impaired endothelial function
Vascular vulnerability
Brain
Retina
Heart
Ischemic/ hemorrhagic stroke
Retinal vasculopathy
Angina/ infarction

of cardiovascular events in migraineurs is controversial. While according to some studies the risk of ischemic stroke in migraineurs is magnified in the presence of some acknowledged vascular risk factors, according to other studies the risk is higher in those subjects not having comorbid vascular risk factors [88]. Data indicated that cigarette smoking is associated with three- to ninefold increased risk of ischemic stroke in migraineurs and oral contraceptive use with a four- to eightfold increased risk [12, 21, 101, 102]. The combination of smoking and oral contraceptive use in women is associated with a tenfold increase in the risk with respect to the presence of migraine alone [12]. According to those data, subjects with migraine with aura should be strongly advised to quit smoking and prescription of combined oral contraceptives deserves special caution [83]. Since migraine without aura is not a definite risk factor for stroke, no specific restrictions are warranted in women with this condition, especially in the absence of comorbidities. Oral contraceptive use should be carefully discussed in women with migraine with aura since they may contribute to an unacceptable increased vascular risk in particular if women smoke. Their prescription should be contraindicated in women with migraine with aura and other comorbid vascular risk factors or congenital or acquired thrombophilia [83].

So far, no drugs are currently recommended for the vascular prevention in migraineurs. Patients with migraine should not be prescribed aspirin or other antithrombotics for cardiovascular prevention unless other (i.e., non-migraine) clear indications are present. The same should be applied to migraineurs showing evidence of white matter hyperintensities or infarct-like lesions at brain magnetic resonance. Since patent foramen ovale has not been reliably associated with migraine nor with ischemic stroke in migraineurs [15], no specific strategies should be adopted in the presence of patent foramen ovale even in association with white matter hyperintensities and infarct-like lesions unless in some isolated cases showing proven additional markers of high vascular risk (e.g., thrombophilia). In general, the acute treatment and the secondary prevention measures of a patient with stroke who has a history of migraine do not differ from those of other stroke patients [44], regardless of the implications that migraineurs have a shorter therapeutic window during the course of an acute stroke [57, 100].

There is currently no direct evidence that a migraine prophylactic treatment can reduce future stroke risk [82]; however, we cannot exclude that migraine prophylaxis, by raising the threshold for spreading depolarization, may lower stroke risk [100]. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers that in some preliminary studies have shown some efficacy in migraine prevention have been also associated with reduction of cardiovascular risk independently of their blood pressure-lowering effect [71]. However, further evidence is needed to support their role as migraine preventive treatment in the absence of high blood pressure values and to demonstrate any possible benefit on the cardiovascular risk of migraineurs. On the contrary, β-blockers (propranolol, metoprolol, atenolol, bisoprolol) that are commonly used as migraine prophylactic agents have not been reliably associated with vascular preventive effects independently of blood pressure lowering.

Ergot alkaloids and triptans, two effective migraine acute treatments, may raise concerns regarding cardiovascular safety because of their vasoconstrictive effect. Data suggest that intense use of ergotamines is associated with a more than twofold increased risk of serious ischemic events; the risk may be even higher in subjects with comorbid cardiovascular disease [75, 104, 106]. Conversely, in the case of triptans, available studies and the resulting overall effect size estimate did not indicate an increased occurrence of cardiovascular events among intense users [53, 75, 104, 106]. Becker et al. found more than a twofold increased risk of stroke among migraineurs recently exposed to triptans and found more than a twofold increased risk for triptan users compared to unexposed migraineurs [5]. In addition, the fact that the migraine-stroke association is limited to migraine with aura argues against a strong influence of migraine treatment in stroke occurrence as patients with migraine with and without aura are similarly treated. In patients with a documented history of cardiovascular disease, use of ergot derivatives and triptans for acute migraine attacks is contraindicated as well as in patients with uncontrolled high blood pressure.

1.5 Gaps and Future Research

Currently, the evidence linking migraine with aura with stroke and other vascular events is so consistent that we can reliably consider this condition as a risk factor for vascular disease [7, 21, 91, 94]. In contrast, for migraine without aura data indicated only a trend toward an association that only in some studies reached the statistical significance [7, 21, 91, 94]. This may indicate that the risk of cerebrovascular disease for migraineurs without aura may be absent, but more likely it is just lower than the risk for migraineurs with aura; this possibility should be tested in larger studies.

Because most studies included women and young migraineurs, the role of age and gender needs to be better clarified in order to determine if migraine with aura can be considered a risk factor for vascular events in men and in older migraineurs. Some data indicated that recent onset migraine, active migraine with aura, and frequent attacks are associated with increased vascular risk [38, 40, 54], but this evidence needs to be further supported by additional studies. Additionally, most of the studies which showed an increased risk of stroke in migraineurs using oral contraceptives are not generalizable to newer drugs with new generation, low-dose estrogens compared with new formulations, or to progesterone-only contraceptives.

Migraine is a very common condition in the general population but only a limited number of subjects with migraine experience a vascular event. So far, we have no reliable features to identify those migraineurs at particularly increased risk, and future studies should establish laboratory, imaging, or other instrumental markers that can be reliably linked to future vascular event occurrence in migraineurs.

So far, cellular hyperexcitability, the postulated mechanism that links migraine to the increased vascular risk, has been demonstrated only in the mouse model [20]

and not in humans, whereas future studies will have to prove this mechanism even in human subjects. Additionally, studies should also try to explain why migraineurs have an increased risk of vascular events even outside the brain and the reasons for the impairment of the vascular function at a systemic level in migraineurs.

Currently, we do not know if migraine is a modifiable vascular risk factor. While we can suppose that migraine preventive drugs may reduce cellular hyperexcitability, we do not know if this may be associated with a reduced vascular risk. Studies involving mouse models of migraine are needed to provide some evidence about this possibility in the near future.

References

1. Albieri V, Olsen TS, Andersen KK . Risk of stroke in migraineurs using triptans. Associations with age, sex, stroke severity and subtype. EBioMedicine in press. 2016. http://dx.doi.org/10.1016/j.ebiom.2016.02.039.
2. Arkink EB, Terwindt GM, de Craen AJ, Konishi J, van der Grond J, van Buchem MA, Ferrari MD, Kruit MC, PROSPER Study Group. Infratentorial microbleeds: another sign of microangiopathy in migraine. Stroke. 2015;46:1987–9.
3. Attwell D, Buchan AM, Charpak S, Lauritzen M, Macvicar BA, Newman EA. Glial and neuronal control of brain blood flow. Nature. 2010;468:232–43.
4. Bashir A, Lipton RB, Ashina S, Ashina M. Migraine and structural changes in the brain. A systematic review and meta-analysis. Neurology. 2013;81:1260–8.
5. Becker C, Brobert GP, Almqvist PM, Johansson S, Jick SS, Meier CR. Migraine and the risk of stroke, TIA, or death in the UK (CME). Headache. 2007;47:1374–84.
6. Bigal ME, Kurth T, Hu H, Santanello N, Lipton RB. Migraine and cardiovascular disease: possible mechanisms of interaction. Neurology. 2009;72:1864–71.
7. Bigal ME, Kurth T, Santanello N, Buse D, Golden W, Robbins M, Lipton RB. Migraine and cardiovascular disease: a population-based study. Neurology. 2010;74:628–35.
8. Buring JE, Hebert P, Romero J, Kittross A, Cook N, Manson J, Peto R, Hennekens C. Migraine and subsequent risk of stroke in the Physicians' Health Study. Arch Neurol. 1995;52:129–34.
9. Bushnell CD, Jamison M, James AH. Migraines during pregnancy linked to stroke and vascular diseases: US population based case–control study. BMJ. 2009;338:b664.
10. 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.
11. Carter KN, Anderson N, Jamrozik K, Hankey G, Anderson CS, Australasian Co-operative Research on Subarachnoid Haemorrhage Study (ACROSS) Group. Migraine and risk of subarachnoid haemorrhage: a population-based case–control study. J Clin Neurosci. 2005;12:534–7.
12. Chang CL, Donaghy M, Poulter N. Migraine and stroke in young women: case–control study. The World Health Organization Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. BMJ. 1999;318:13–8.
13. Collaborative Group for the Study of Stroke in Young Women. Oral contraceptives and stroke in young women: associated risk factors. JAMA. 1975;231:718–22.
14. Cook NR, Bensenor IM, Lotufo PA, Lee IM, Skerrett PJ, Chown MJ, Ajani UA, Manson JE, Buring JE. Migraine and coronary heart disease in women and men. Headache. 2002;42:715–27.

15. Davis D, Gregson J, Willeit P, Stephan B, Al-Shahi Salman R, Brayne C. Patent foramen ovale, ischemic stroke and migraine: systematic review and stratified meta-analysis of association studies. Neuroepidemiology. 2013;40:56–67.
16. de Benedittis G, Lorenzetti A, Sina C, Bernasconi V. Magnetic resonance imaging in migraine and tension-type headache. Headache. 1995;35:264–8.
17. Degirmenci B, Yaman M, Haktanir A, Albayrak R, Acar M. Cerebral and cerebellar ADC values during a migraine attack. Neuroradiology. 2007;49:419–26.
18. Donaghy M, Chang CL, Poulter N, on behalf of the European Collaborators of The World Health Organisation Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. 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.
19. Dreier JP, Kleeberg J, Petzold G, Priller J, Windmüller O, Orzechowski HD, Lindauer U, Heinemann U, Einhäupl KM, Dirnagl U. Endothelin-1 potently induces Leão's cortical spreading depression in vivo in the rat: a model for an endothelial trigger of migrainous aura? Brain. 2002;125:102–12.
20. Eikermann-Haerter K. Spreading depolarization may link migraine and stroke. Headache. 2014;54:1146–57.
21. 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.
22. Fazekas F, Koch M, Schmidt R, Offenbacher H, Payer F, Freidl W, Lechner H. The prevalence of cerebral damage varies with migraine type: a MRI study. Headache. 1992;32: 287–91.
23. Gaist D, González-Pérez A, Ashina M, Rodríguez LA. Migraine and risk of hemorrhagic stroke: a study based on data from general practice. J Headache Pain. 2014;15:74.
24. Gelfand AA, Fullerton HJ, Jacobson A, Sidney S, Goadsby PJ, Kurth T, Pressman A. Is migraine a risk factor for pediatric stroke? Cephalalgia. 2015;35:1252–60.
25. Gudmundsson LS, Scher AI, Aspelund T, Eliasson JH, Johannsson M, Thorgeirsson G, Launer L, Gudnason V. Migraine with aura and risk of cardiovascular and all cause mortality in men and women: prospective cohort study. BMJ. 2010;341:c3966.
26. Haapaniemi H, Hillbom M, Juvela S. Lifestyle-associated risk factors for acute brain infarction among persons of working age. Stroke. 1997;28:26–30.
27. Hall GC, Brown MM, Mo J, MacRae KD. Triptans in migraine: the risks of stroke, cardiovascular disease, and death in practice. Neurology. 2002;62:563–8.
28. Hamedani AG, Rose KM, Peterlin BL, Mosley TH, Coker LH, Jack CR, Knopman DS, Alonso A, Gottesman RF. Migraine and white matter hyperintensities. The ARIC MRI study. Neurology. 2013;81:1308–13.
29. Henrich JB, Horwitz RI. A controlled study of ischemic stroke risk in migraine patients. J Clin Epidemiol. 1989;42:773–80.
30. Igarashi H, Sakai F, Kan S, Okada J, Tazaki Y. Magnetic resonance imaging of the brain in patients with migraine. Cephalalgia. 1991;11:69–74.
31. James AH, Bushnell CD, Jamison MG, Myers ER. Incidence and risk factors for stroke in pregnancy and the puerperium. Obstet Gynecol. 2005;106:509–16.
32. Kavanagh D, Spitzer D, Kothari PH, Shaikh A, Liszewski MK, Richards A, Atkinson JP. New roles for the major human 3'–5' exonuclease TREX1 in human disease. Cell Cycle. 2008;7:1718–25.
33. Kruit MC, van Buchem MA, Hofman PA, Bakkers JT, Terwindt GM, Ferrari MD, Launer LJ. Migraine as a risk factor for subclinical brain lesions. JAMA. 2004;291:427–34.
34. 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.
35. Kuo CY, Yen MF, Chen LS, Fann CY, Chiu YH, Chen HH, Pan SL. Increased risk of hemorrhagic stroke in patients with migraine: a population-based cohort study. PLoS One. 2013;8:e55253.

36. Kurth T, Slomke MA, Kase CS, Cook NR, Lee IM, Gaziano JM, Diener HC, Buring JE. Migraine, headache, and the risk of stroke in women: a prospective study. Neurology. 2005;64:1020–6.
37. 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.
38. Kurth T, Gaziano JM, Cook NR, Bubes V, Logroscino G, Diener HC, Buring JE. Migraine and risk of cardiovascular disease in men. Arch Intern Med. 2007;167:795–801.
39. Kurth T, Schürks M, Logroscino G, Gaziano JM, Buring JE. Migraine, vascular risk, and cardiovascular events in women: prospective cohort study. BMJ. 2008;337:a636.
40. Kurth T, Schürks M, Logroscino G, Buring JE. Migraine frequency and risk of cardiovascular disease in women. Neurology. 2009;73:581–8.
41. Kurth T, Kase CS, Schürks M, Tzourio C, Buring JE. Migraine and risk of hemorrhagic stroke in women: prospective cohort study. BMJ. 2010;341:c3659.
42. Kurth T, Mohamed S, Maillard P, Zhu YC, Chabriat H, Mazoyer B, Bousser MG, Dufouil C, Tzourio C. Headache, migraine, and structural brain lesions and function: population based epidemiology of vascular ageing-MRI study. BMJ. 2011;342:c7357.
43. Kurth T, Chabriat H, Bousser MG. Migraine and stroke: a complex association with clinical implications. Lancet Neurol. 2012;11:92–100.
44. Kurth T, Diener HC. Migraine and stroke: perspectives for stroke physicians. Stroke. 2012;43:3421–6.
45. Lanfranconi S, Markus HS. COL4A1 mutations as a monogenic cause of cerebral small vessel disease. A systematic review. Stroke. 2010;41:e513–8.
46. Lauritzen M, Skyhoj Olsen T, Lassen NA, Paulson OB. Changes in regional cerebral blood flow during the course of classic migraine attacks. Ann Neurol. 1983;13:633–41.
47. Lee ST, Chu K, Jung KH, Kim DH, Kim EH, Choe VN, Kim JH, Im WS, Kang L, Park JE, Park HJ, Park HK, Song EC, Lee SK, Kim M, Roh JK. Decreased number and function of endothelial progenitor cells in patients with migraine. Neurology. 2008;70:1510–7.
48. Li L, Schulz UG, Kuker W, Rothwell PM, Oxford Vascular Study. Age-specific association of migraine with cryptogenic TIA and stroke: population-based study. Neurology. 2015;85:1444–51.
49. Lidegaard O. Oral contraceptives, pregnancy and the risk of cerebral thromboembolism: the influence of diabetes, hypertension, migraine and previous thrombotic disease. Br J Obstet Gynaecol. 1995;102:153–9.
50. Lidegaard O, Kreiner S. Contraceptives and cerebral thrombosis: a five year national case–control study. Contraception. 2002;65:197–205.
51. Liew G, Wang JJ, Mitchell P. Migraine and coronary heart disease mortality: a prospective cohort study. Cephalalgia. 2007;27:368–71.
52. Liman TG, Neeb L, Rosinski J, Wellwood I, Reuter U, Doehner W, Heuschmann PU, Endres M. Peripheral endothelial function and arterial stiffness in women with migraine with aura: a case–control study. Cephalalgia. 2012;32:459–66.
53. Lugardon S, Roussel H, Sciortino V, Montastruc JL, Lapeyre-Mestre M. Triptan use and risk of cardiovascular events: a nested-case–control study from the French health system database. Eur J Clin Pharmacol. 2007;63:801–7.
54. MacClellan LR, Giles W, Cole J, Wozniak M, Stern B, Mitchell BD, Kittner SJ. Probable migraine with visual aura and risk of ischemic stroke: the Stroke Prevention in Young Women Study. Stroke. 2007;38:2438–45.
55. Marini C, Carolei A, Roberts RS, Prencipe M, Gandolfo C, Inzitari D, Landi G, De Zanche L, Scoditti U, Fieschi C. Focal cerebral ischemia in young adults: a collaborative case–control study. Neuroepidemiology. 1993;12:70–81.
56. Mawet J, Kurth T, Ayata C. Migraine and stroke: in search of shared mechanisms. Cephalalgia. 2015;35:165–81.
57. Mawet J, Eikermann-Haerter K, Park KY, Helenius J, Daneshmand A, Pearlman L, Avery R, Negro A, Velioglu M, Arsava EM, Ay H, Ayata C. Sensitivity to acute cerebral ischemic injury in migraineurs: a retrospective case–control study. Neurology. 2015;85:1945–9.

58. 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.
59. Mitchell P, Wang JJ, Currie J, Cumming RG, Smith W. Prevalence and vascular associations with migraine in older Australians. Aust N Z J Med. 1998;28:627–32.
60. Monteith T, Gardener H, Rundek T, Dong C, Yoshita M, Elkind M, DeCarli C, Sacco RL, Wright CB. Migraine, white matter hyperintensities, and subclinical brain infarction in a diverse community. The Northern Manhattan Study. Stroke. 2014;45:1830–2.
61. Monteith TS, Gardener H, Rundek T, Elkind MSV, Sacco RL. Migraine and risk of stroke in older adults. Northern Manhattan Study. Neurology. 2015;85:1–7.
62. Naess H, Nyland HI, Thomassen L, Aarseth J, Myhr KM. Etiology of and risk factors for cerebral infarction in young adults in western Norway: a population-based case–control study. Eur J Neurol. 2004;11:25–30.
63. 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.
64. Nozari A, Dilekoz E, Sukhotinsky I, Stein T, Eikermann-Haerter K, Liu C, Wang Y, Frosch MP, Waeber C, Ayata C, Moskowitz MA. Microemboli may link spreading depression, migraine aura, and patent foramen ovale. Ann Neurol. 2010;67:221–9.
65. Oterino A, Toriello M, Palacio E, Quintanilla VG, Ruiz-Lavilla N, Montes S, Vega MS, Martinez-Nieto R, Castillo J, Pascual J. Analysis of endothelial precursor cells in chronic migraine: a case–control study. Cephalalgia. 2013;33:236–44.
66. Palm-Meinders IH, Koppen H, Terwindt GM, Launer LJ, Konishi J, Moonen JM, Bakkers JT, Hofman PA, van Lew B, Middelkoop HA, van Buchem MA, Ferrari MD, Kruit MC. Structural brain changes in migraine. JAMA. 2012;308:1889–97.
67. Pavese N, Canapicchi R, Nuti A, Bibbiani F, Lucetti C, Collavoli P, Bonuccelli U. White matter MRI hyperintensities in a hundred and twenty-nine consecutive migraine patients. Cephalalgia. 1994;14:342–5.
68. Pezzini A, Grassi M, Del Zotto E, Giossi A, Monastero R, Dalla Volta G, Archetti S, Zavarise P, Camarda C, Gasparotti R, Magoni M, Camarda R, Padovani A. Migraine mediates the influence of C677T MTHFR genotypes on ischemic stroke risk with a stroke-subtype effect. Stroke. 2007;38:3145–51.
69. Pezzini A, Grassi M, Lodigiani C, Patella R, Gandolfo C, Zini A, Delodovici ML, Paciaroni M, Del Sette M, Toriello A, Musolino R, Calabrò RS, Bovi P, Adami A, Silvestrelli G, Sessa M, Cavallini A, Marcheselli S, Bonifati DM, Checcarelli N, Tancredi L, Chiti A, Del Zotto E, Spalloni A, Giossi A, Volonghi I, Costa P, Giacalone G, Ferrazzi P, Poli L, Morotti A, Rasura M, Simone AM, Gamba M, Cerrato P, Micieli G, Melis M, Massucco D, De Giuli V, Iacoviello L, Padovani A, on behalf of the Italian Project on Stroke in Young Adults (IPSYS) Investigators. Predictors of long-term recurrent vascular events after ischemic stroke at young age: the Italian project on stroke in young adults. Circulation. 2014;129:1668–76.
70. Pietrobon D, Moskowitz MA. Pathophysiology of migraine. Annu Rev Physiol. 2013;75:365–91.
71. Ripa P, Ornello R, Pistoia F, Carolei A, Sacco S. The renin-angiotensin system: a possible contributor to migraine pathogenesis and prophylaxis. Expert Rev Neurother. 2014;14:1043–55.
72. Ripa P, Ornello R, Pistoia F, Carolei A, Sacco S. Spreading depolarization may link migraine, stroke, and other cardiovascular disease. Headache. 2015;55:180–2.
73. Rist PM, Buring JE, Kase CS, Schürks M, Kurth T. Migraine and functional outcome from ischemic cerebral events in women. Circulation. 2010;122:2551–7.
74. Robbins L, Friedman H. MRI in migraineurs. Headache. 1992;32:507–8.
75. Roberto G, Raschi E, Piccinni C, Conti V, Vignatelli L, D'Alessandro R, De Ponti F, Poluzzi E. Adverse cardiovascular events associated with triptans and ergotamines for treatment of migraine: systematic review of observational studies. Cephalalgia. 2015;35:118–31.
76. Rodríguez-Osorio X, Sobrino T, Brea D, Martínez F, Castillo J, Leira R. Endothelial progenitor cells: a new key for endothelial dysfunction in migraine. Neurology. 2012;79:474–9.

77. Rovaris M, Bozzali M, Rocca MA, Colombo B, Filippi M. An MR study of tissue damage in the cervical cord of patients with migraine. J Neurol Sci. 2001;183:43–6.
78. Sacco S, Olivieri L, Bastianello S, Carolei A. Comorbid neuropathologies in migraine. J Headache Pain. 2006;7:222–30.
79. Sacco S, Cerone D, Carolei A. Comorbid neuropathologies in migraine: an update on cerebrovascular and cardiovascular aspects. J Headache Pain. 2008;9:237–48.
80. Sacco S, Degan D, Carolei A. Diagnostic criteria for CADASIL in the International Classification of Headache Disorders (ICHD-II): are they appropriate? J Headache Pain. 2010;11:181–6.
81. Sacco S, Ripa P, Carolei A. Migraine attributed to genetic disorder: proposal of a new category. Cephalalgia. 2011;31:760–2.
82. Sacco S, Carolei A. Is migraine a modifiable risk factor for ischemic stroke? Potentially not. Am J Med. 2011;124:e9.
83. Sacco S, Ricci S, Carolei A. Migraine and vascular diseases: potential implications for management. Cephalalgia. 2012;32:785–95.
84. Sacco S, Ornello R, Ripa P, Pistoia F, Carolei A. Migraine and hemorrhagic stroke: a meta-analysis. Stroke. 2013;44:3032–8.
85. Sacco S, Ripa P, Grassi D, Pistoia F, Ornello R, Carolei A, Kurth T. Peripheral vascular dysfunction in migraine: a review. J Headache Pain. 2013;14:80.
86. Sacco S, Kurth T. Migraine and the risk for stroke and cardiovascular disease. Curr Cardiol Rep. 2014;16:524.
87. Sacco S, Ornello R, Ripa P, Tiseo C, Degan D, Pistoia F, Carolei A. Migraine and risk of ischaemic heart disease: a systematic review and meta-analysis of observational studies. Eur J Neurol. 2015;22:1001–11.
88. Sacco S, Pistoia F, Degan D, Carolei A. Conventional vascular risk factors: their role in the association between migraine and cardiovascular diseases. Cephalalgia. 2015;35:146–64.
89. Scher AI, Gudmundsson LS, Sigurdsson S, Ghambaryan A, Aspelund T, Eiriksdottir G, van Buchem MA, Gudnason V, Launer LJ. Migraine headache in middle age and late-life brain infarct. JAMA. 2009;301:2563–70.
90. Schwaag S, Nabavi DG, Frese A, Husstedt IW, Evers S. The association between migraine and juvenile stroke: a case–control study. Headache. 2003;43:90–5.
91. Schürks M, Rist PM, Bigal ME, Buring JE, Lipton RB, Kurth T. Migraine and cardiovascular disease: systematic review and meta-analysis. BMJ. 2009;339:b3914.
92. Schürks M, Rist PM, Shapiro RE, Kurth T. Migraine and mortality: a systematic review and meta-analysis. Cephalalgia. 2011;31:1301–14.
93. Schwartz SM, Petitti DB, Siscovick DS, Longstreth Jr WT, Sidney S, Raghunathan TE, Quesenberry Jr CP, Kelaghan J. Stroke and use of low-dose oral contraceptives in young women: a pooled analysis of two US studies. Stroke. 1998;29:2277–84.
94. 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.
95. Sproule DM, Kaufmann P. Mitochondrial encephalopathy, lactic acidosis, and strokelike episodes: basic concepts, clinical phenotype, and therapeutic management of MELAS syndrome. Ann N Y Acad Sci. 2008;1142:133–58.
96. Stam AH, Weller CM, Janssens AC, Aulchenko YS, Oostra BA, Frants RR, van den Maagdenberg AM, Ferrari MD, van Duijn CM, Terwindt GM. Migraine is not associated with enhanced atherosclerosis. Cephalalgia. 2013;33:228–35.
97. Stang PE, Carson AP, Rose KM, Mo J, Ephross SA, Shahar E, Szklo M. Headache, cerebrovascular symptoms, and stroke: the Atherosclerosis Risk in Communities Study. Neurology. 2005;64:1573–7.
98. Sternfeld B, Stang P, Sidney S. Relationship of migraine headaches to experience of chest pain and subsequent risk for myocardial infarction. Neurology. 1995;45:2135–42.
99. Swartz RH, Kern RZ. Migraine is associated with magnetic resonance imaging white matter abnormalities: a meta-analysis. Arch Neurol. 2004;61:1366–8.
100. Tietjen GE, Sacco S. Migraine makes the stroke grow faster? Neurology. 2015;85:1920–1.

101. Tzourio C, Tehindrazanarivelo A, Iglésias S, Alpérovitch A, Chedru F, d'Anglejan-Chatillon J, Bousser MG. Case–control study of migraine and risk of ischaemic stroke in young women. BMJ. 1995;310:830–3.
102. Tzourio C, Iglesias S, Hubert JB, Visy JM, Alpérovitch A, Tehindrazanarivelo A, Biousse V, Woimant F, Bousser MG. Migraine and risk of ischaemic stroke: a case–control study. BMJ. 1993;307:289–92.
103. Vahedi K, Chabriat H, Levy C, Joutel A, Tournier-Lasserve E, Bousser MG. Migraine with aura and brain magnetic resonance imaging abnormalities in patients with CADASIL. Arch Neurol. 2004;61:1237–40.
104. Velentgas P, Cole JA, Mo J, Sikes CR, Walker AM. Severe vascular events in migraine patients. Headache. 2004;44:642–51.
105. Wabnitz A, Bushnell C. Migraine, cardiovascular disease, and stroke during pregnancy: systematic review of the literature. Cephalalgia. 2015;35:132–9.
106. Wammes-van der Heijden EA, Rahimtoola H, Leufkens HG, Tijssen CC, Egberts AC. Risk of ischemic complications related to the intensity of triptan and ergotamine use. Neurology. 2006;67:1128–34.
107. Wang YC, Lin CW, Ho YT, Huang YP, Pan SL. Increased risk of ischemic heart disease in young patients with migraine: a population-based, propensity score-matched, longitudinal follow-up study. Int J Cardiol. 2014;172:213–6.
108. Wessman M, Terwindt GM, Kaunisto MA, Palotie A, Ophoff RA. Migraine: a complex genetic disorder. Lancet Neurol. 2007;6:521–32.
109. Ziegler DK, Batnitzky S, Barter R, McMillan JH. Magnetic resonance image abnormality in migraine with aura. Cephalalgia. 1991;11:147–50.