Migraine-associated stroke: risk factors, diagnosis, and prevention

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INTRODUCTION

Migraine is a common headache disorder characterized by symptoms that typically occur over several hours to a few days. Migraine-associated stroke (also known as migrainous infarction or migraine-induced stroke) is an uncommon complication of migraine identified by ischemic stroke on neuroimaging that corresponds to prolonged aura symptoms in a patient with migraine. This topic will discuss migraine-associated stroke and stroke prevention for patients with migraine.

The general approach to the diagnosis and evaluation of migraine is discussed elsewhere. (See "Pathophysiology, clinical manifestations, and diagnosis of migraine in adults".)

Other risk factors and preventive treatment for ischemic stroke are discussed separately. (See "Overview of secondary prevention of ischemic stroke".)

MIGRAINE-ASSOCIATED ISCHEMIC STROKE

Epidemiology — Migraine and ischemic stroke are both common conditions. The epidemiology of the intersection of migraine and stroke can be examined by the prevalence of migraine in

stroke patients and the prevalence of stroke in patients with migraine. The epidemiology of the risk of stroke due to migraine may be assessed by the incidence of migrainous infarction.

- **Migraine prevalence** — Data on the prevalence of migraine in stroke patients vary in different retrospective studies. A small case-control study of 145 patients in France reported that the relative prevalence of migraine among patients with ischemic stroke was double that of controls (60 versus 30 percent) [1]. In a European World Health Organization (WHO) collaborative study, the prevalence of migraine in patients with all types of stroke compared with controls was 25 versus 13 percent [2]. However, this study has been criticized on several grounds, including the high proportion of migraine with aura patients compared with those without aura and the high incidence of migrainous stroke (between 20 to 40 percent) among the study participants, a finding that does not concur with clinical experience [3].

  Among younger adults with a history of stroke, migraine prevalence rates range between 27 and 34 percent. The Collaborative Group for the Study of Stroke in Young Women found that the prevalence of migraine in females with stroke, other hospitalized patients, and controls was 34, 33, and 24 percent, respectively [4]. In a case-control study of 1668 adults <45 years old with cryptogenic stroke, the prevalence of migraine was 27 percent, compared with 17 percent for matched controls [5]. The applicability of these data to older patients is uncertain. Younger patients have higher baseline prevalence of migraine and lower burden of stroke risks than older patients.

- **Stroke prevalence** – The prevalence of stroke in patients with migraine is low but varies according to cerebrovascular risk factors. In a retrospective cohort of more than 800,000 young adults (age 18 to 44 years) with migraine, the prevalence of ischemic stroke was 1.3 percent [6]. The risk of ischemic stroke was assessed in a population-based cohort study of more than 220,000 patients with migraine from Denmark [7]. The absolute risk of ischemic stroke was modestly higher for both females and males with migraine than matched controls (0.3 and 0.5 percent, respectively). A similar modest increased risk of myocardial infarction was also reported. In a meta-analysis of 11 cohort studies that included more than two million patients with migraine, the pooled risk of ischemic stroke was also found to be higher for patients with migraine than those without (relative risk 1.64, 95% CI 1.2-2.2) [8].

- **Incidence of migrainous infarction** — The reported incidence of stroke due to migraine (migrainous infarction) ranges from 0.8 to 3.4 per 100,000 per year [9,10]. However, the true incidence is unknown due to reporting bias and varied criteria used to identify patients with migraine. In a Taiwanese case-control study involving nearly 240,000

patients, the risk of ischemic stroke over a median of 3.6-year interval was higher for patients with a history of migraine than those without (adjusted hazard ratio [aHR] 1.24, 95% CI, 1.1-1.4) [11]. A meta-analysis of nine observational studies found the pooled relative risk (RR) for ischemic stroke among subjects with any type of migraine was 1.73 (95% CI 1.31-2.29) [12]. The strength of this meta-analysis is limited mainly by the case-control nature of many of the studies, with their inherent susceptibility to recall bias. In addition, the included studies were heterogeneous with regard to subject characteristics and cardiovascular disease definitions.

Case series and stroke registries have reported migrainous infarction accounts for an estimated 0.2 to 0.8 percent of all ischemic strokes [9,13-16]. However, migraine-induced stroke accounted for 13.7 percent of infarcts in young adults in a study that used a strict definition of migrainous infarction [13].

The epidemiology of ischemic stroke and of migraine are reviewed separately. (See "Stroke: Etiology, classification, and epidemiology", section on 'Epidemiology' and "Pathophysiology, clinical manifestations, and diagnosis of migraine in adults", section on 'Epidemiology'.)

Modifiers of risk — Among patients with migraine, the risk of ischemic stroke is elevated in those with specific factors including migraine aura, female sex, smoking, and exposure to hormonal contraception [12]. Similar clinical factors have been reported in other studies [11,17]. In a study of nearly 120,000 patients in Taiwan that compared patients with migraine and a propensity score-matched comparison cohort, migraine was associated with an increased risk of ischemic stroke (aHR 1.2, 95% CI 1.1-1.4) with the highest risk among females aged ≤45 years who had migraine with aura (aHR 4.6, 95% CI 2.5-8.6) [11].

While migraine may confer a risk for stroke, the presence of active migraine headaches may attenuate this risk and indicate a healthy vascular system. In an analysis of patients from the Women's Health Study stratifying patients by present versus past history of migraine, females age ≥45 years old with an elevated risk of future cardiovascular disease were likelier to have a history of migraine than those with a low risk of future cardiovascular disease but less likely to have an active history of migraine (odds ratio [OR] 0.64, 95% CI 0.5-0.8) [18].

Migraine aura — The increased risk of stroke in patients with migraine appears to be driven largely from subjects who have migraine with aura [12,19-21]. In one meta-analysis of 16 cohort studies involving more than 1.1 million patients, migraine was associated with an elevated risk of stroke (aHR 1.4, 95% CI 1.3-1.6) [21]. When stratified by migraine subtype, the risk was elevated for patients with migraine with aura (aHR 1.6, 95% CI 1.3-1.9) but not those with migraine without aura (aHR 1.1, 95% CI 0.9-1.3). In an analysis of more than 27,000 female

health professionals from the Women's Health Study cohort, the adjusted incidence rate of major cardiovascular events was 3.36 per 1000 person-years (95% CI 2.72-3.99) for those with migraine with aura and 2.11 per 1000 person-years (95% CI 1.98-2.24) for those with migraine without aura or no migraine history [22].

In addition, migraine appears to be associated with an elevated perioperative stroke risk, driven largely migraine with aura. In a prospective hospital registry of nearly 125,000 surgical patients, the risk of perioperative ischemic stroke was elevated for patients with and without aura but higher for patients with a history of migraine with aura (adjusted OR [aOR] 2.61, 95% CI 1.6-4.3) than those with migraine without aura (aOR 1.6, 95% CI 1.3-2.1) [23].

Female sex — There is evidence that females with migraine are at an increased risk of ischemic stroke [12,22,24], but the absolute increase in risk of stroke remains low in the absence of other stroke risk factors [19,25,26]. In the Women's Health Study, patients with migraine experienced four additional ischemic stroke events per 10,000 females each year [25]. However, on a population level, the small increase in absolute risk remains important as the prevalence of females with migraine with aura is over 4 percent [27].

- **Impact of age** – The baseline thrombotic stroke incidence appears to be 11 to 21 per 100,000 females age 15 to 49 years old in population-based studies but varies with age, with an estimated incidence of 3 per 100,000 for females 15 to 19 years old up to 64 per 100,000 for females 45 to 49 years old [28,29].

- **Impact of aura** – Meta-analyses have reported the stroke risk to be 2.0 to 2.5 times greater among females with migraine with aura compared with no aura [12,19]. There is some evidence that increased frequency of migraine with aura is related to increased burden of ischemic stroke risk factors [30]. (See 'Migraine aura' above.)

- **Impact of cardiovascular risk factors** – Stroke risk among females is further increased with hypertension, diabetes, and ischemic heart disease [12,29,31,32]. (See 'Modifiers of risk' above.)

Discussions of stroke risk related to estrogen-containing contraception are discussed below. (See 'Estrogen-containing contraception' below.)

Estrogen-containing contraception — The use of estrogen-containing contraception is associated with an increased relative risk of ischemic stroke in patients with migraine [33]. The absolute risk of stroke remains low for most patients who use estrogen-containing contraception, excluding those with migraine with aura.

Studies have estimated a 2- to 16-fold relative risk elevation in this population [33-35]. However, significant limitations of studies of contraception, migraine, and stroke include that they generally combine a wide range of estrogen doses (including doses no longer in typical use), differing progestin components (which may also impact stroke risk), multiple routes of administration (oral pill, vaginal ring, transdermal patch), and different types of migraine (without versus with aura), which other reports have identified as important factors related to stroke risk [36].

- **Estrogen dose** – Increasing estrogen dose appears to increase stroke risk. In a large, population-based cohort study in Denmark, the RR of ischemic stroke increased with increasing doses of ethinyl estradiol (20 mcg dose: adjusted RR 0.88-1.53; 30 to 40 mcg doses: adjusted RR 1.40-2.20) [28]. Compared with those with neither migraine nor combination hormonal contraceptive use, the OR of ischemic stroke was highest among those with migraine with aura using combination hormonal therapy (OR 6.1, 95% CI 3.1-12.1).

- **Aura** – The presence of aura appears to increase the risk of future stroke among patients taking estrogen-containing contraception. In a systematic review of 15 studies, the risk of stroke for individuals using estrogen-containing contraceptives was higher for patients with aura compared with without (with aura: ORs of 6.1, 95% CI 3.1-12.1 versus without aura: OR 1.8, 95% CI 1.1-2.9) [34]. The authors concluded that the review demonstrated "a lack of good quality studies assessing risk of stroke associated with low-dose estrogen use in women with migraine. Further study in this area is needed."

These and other impacts of estrogen-containing contraceptives are discussed in greater detail separately. (See "Combined estrogen-progestin contraception: Side effects and health concerns".)

Other factors

- **Smoking** – Smoking is a risk factor for stroke and also modifies the risk of stroke among patients with migraine. In a meta-analysis of studies assessing the association between migraine and cardiovascular risk factors that evaluated the role of smoking, the risk of ischemic stroke was significantly elevated among patients with migraine who smoke (pooled RR 9, 95% CI 4.2-19.3) [12].

- **Age** – The risk of stroke among patients with migraine appears to be higher for patients age <45 years compared with older patients [12]. This observation may reflect the higher prevalence of migraine among younger patients and/or the increased burden of other vascular risk factors in older patients. (See 'Epidemiology' above.)

Mechanisms — The pathophysiology underlying migraine as a risk factor or cause for stroke is not clear. Prolonged or severe changes in cerebral blood flow have been frequently postulated as the cause of migrainous infarction. However, this assumption has been challenged by the limited supportive data and competing nonvascular causes to migraine that may cause or contribute to the risk of stroke. Multiple cerebral, vascular, hematologic, and cardiac mechanisms have been suggested, including the following:

- **Cerebral and neuronal factors**
  - Prolongation of cortical spreading depression (CSD) and aura [20]
  - Neuronal glutamatergic hyperexcitability resulting in enhanced susceptibility to ischemic depolarizations [37,38]
  - Dysregulated activity of serotonergic raphe cells causing excitotoxicity [39]
- **Vascular factors**
  - Vasospasm and changes in cerebral blood flow [3,40-44]
  - Release of prothrombotic factors or vasoactive peptides [45-50]
  - Endothelial dysfunction [38,51]
- **Prothrombotic factors**
  - Increased platelet aggregability [52-54]
  - Elevated von Willebrand factor [49]
  - Higher prevalence of hypercoagulable states [55]
  - Prothrombotic genetic polymorphisms (eg, the methylenetetrahydrofolate reductase *C677T* variant) [56] (see "Overview of homocysteine", section on 'Disease associations')
- **Cardiac factors**
  - Atrial fibrillation attributed to the autonomic dysfunction associated with migraine [57,58]
  - Myocardial infarction associated with migraine leading to cardioembolism [26,59-62]

None of the postulated mechanisms have been confirmed as a pathophysiological explanation linking stroke and migraine. However, posterior circulation border zone infarcts in migraine have been most frequently attributed to a combination of low flow (hypoperfusion) and local thromboembolism [63,64].

- **Shared risk factors** – In addition, migraine has been associated with other known or putative risk factors for stroke, including:

- Patent foramen ovale (PFO) [65] (see "Pathophysiology, clinical manifestations, and diagnosis of migraine in adults", section on 'Right-to-left cardiac shunt' and "Atrial septal abnormalities (PFO, ASD, and ASA) and risk of cerebral emboli in adults")
- Cervical artery dissection [66] (see "Cerebral and cervical artery dissection: Clinical features and diagnosis", section on 'Associated conditions and risk factors')
- Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) [67] (see "Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)", section on 'Migraine with aura')
- Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like symptoms (MELAS) [68] (see "Mitochondrial myopathies: Clinical features and diagnosis", section on 'MELAS')
- Antiphospholipid antibodies and lupus [69-72] (see "Clinical manifestations of antiphospholipid syndrome", section on 'Neurologic involvement')
- Livedo reticularis and Sneddon syndrome [73-76]
- Sickle cell disease [77] (see "Overview of the clinical manifestations of sickle cell disease", section on 'Neurologic complications')
- Cardiovascular disease including myocardial infarction [26,59-62]

The pathophysiology of migraine is discussed in greater detail separately. (See "Pathophysiology, clinical manifestations, and diagnosis of migraine in adults", section on 'Pathophysiology'.)

Clinical and imaging findings — The clinical features of migraine-associated stroke vary according to the criteria used. Data on clinical features of patients who have had acute migrainous infarction and a complete stroke evaluation are limited. The largest study with modern neuroimaging is a case series of 11 patients with migrainous infarction according to strict criteria who were identified from a stroke database of 8137 patients [78]. All patients reported symptoms at onset similar to previous migraine aura without new or atypical symptoms. However, the previously transient aura symptoms persisted. On diffusion-weighted brain magnetic resonance imaging (MRI) sequences, 4 of the 11 patients had multiple foci of acute infarction, mainly in the posterior circulation, while four had a single area of acute infarction in the posterior circulation territory, and three had isolated infarcts in the middle cerebral artery territory (image 1).

Evaluation and diagnosis of migrainous stroke — It can be difficult to determine migraine as the cause of stroke; there are no diagnostic findings specific to migraine-induced stroke and experts vary in defining migraine-associated stroke [3,40,79-83]. Patients who develop a stroke during a migraine headache should have a comprehensive evaluation to exclude other possible causes.

The diagnosis and evaluation of ischemic stroke are discussed in detail separately. (See "Initial evaluation and management of transient ischemic attack and minor ischemic stroke".)

Diagnostic criteria

- **Migrainous infarction** — The International Classification of Headache Disorders, 3rd edition (ICHD-3) defines migrainous infarction by the following features [83]:
  - (A) A migraine attack fulfilling criteria B and C
  - (B) Occurring in a patient with migraine with aura and typical of previous attacks except that one or more aura symptoms persists for >60 minutes
  - (C) Neuroimaging demonstrates ischemic infarction in a relevant area
  - (D) Not better accounted for by another diagnosis

  Migrainous infarction also may be called migraine-induced stroke [3].

- **Migraine-related stroke** — Some experts have used the term migraine-related stroke for patients whose symptoms do not fulfill all diagnostic criteria for migrainous infarction and also to allow inclusion of patients who have migraine without aura [40]. Since the 1990s, when migraine was thought to have only vascular pathophysiology, several reports have noted the occurrence of migrainous infarction associated with attacks of migraine without aura [79-81]. However, most studies have found no association of migraine without aura and ischemic stroke [83,84]. (See 'Migraine aura' above.)

  Other experts use migraine-related stroke for cases when additional stroke mechanisms coexist with migraine [82].

Differential diagnosis — Both cerebrovascular events and migraine attacks can present as acute transient neurologic events with similar symptoms (table 1). In addition, acute neurologic symptoms that are persistent may also be caused by either migraine or stroke.

Forms of migraine with aura — Migraine with aura occurs in about 15 to 20 percent or more of patients with migraine and may mimic stroke [85]. Neuroimaging may be performed for

patients with atypical migraine features to exclude stroke. (See "Pathophysiology, clinical manifestations, and diagnosis of migraine in adults", section on 'Diagnostic testing'.)

- **Typical aura** – Typical migraine aura symptoms develop gradually over 5 to 20 minutes and last less than one hour per symptom; the most common types involve homonymous visual disturbances. Other common types of migraine aura may manifest as sensory, motor, brainstem, or language disturbances. There is usually little clinical difficulty recognizing these aura symptoms as manifestations of migraine when the auras are brief and precede headaches. In addition, migraine aura is typically characterized by positive symptoms (eg, presence of bright lights or visual aberrations) while stroke symptoms typically involve loss of function or negative symptoms (eg, vision loss). (See "Pathophysiology, clinical manifestations, and diagnosis of migraine in adults", section on 'Migraine aura'.)

- **Other forms of migraine** – Some forms of migraine present with motor or brainstem symptoms that may mimic transient ischemic attack (TIA) or acute stroke. These include:

  - Sporadic and familial hemiplegic migraine (see "Hemiplegic migraine")
  - Migraine with brainstem aura (see "Migraine with brainstem aura")
  - Retinal or ocular migraine (see "Pathophysiology, clinical manifestations, and diagnosis of migraine in adults", section on 'Retinal migraine')

  Hemiplegic and brainstem auras may also be prolonged, requiring neuroimaging evaluation to distinguish from acute stroke.

- **Migraine aura without headache** – Migraine aura that occurs without headache may be difficult to distinguish from stroke symptoms. This form of migraine was previously known as acephalgic migraine and migraine with acute-onset aura. These symptoms are more common in patients over age 50 years and may also be called late-life migraine accompaniments [86]. Imaging may be required to exclude stroke as cause to these symptoms.

- **Persistent aura without infarction** – Prolonged symptoms may last for the entire headache, for several days or weeks, or in some cases leave a permanent neurologic deficit. Many such patients have neuroimaging evidence of acute stroke, indicating migrainous infarction. However, some patients have persistent aura without infarction if the aura lasts one week or longer with no evidence of infarction. (See "Pathophysiology,

clinical manifestations, and diagnosis of migraine in adults", section on 'Complications of migraine'.)

The general approach to the differential diagnosis of migraine is reviewed separately. (See "Pathophysiology, clinical manifestations, and diagnosis of migraine in adults", section on 'Differential diagnosis'.)

Other causes of stroke presenting with headache — Some patients with ischemic or hemorrhagic cerebrovascular conditions may present neurologic symptoms and headache or with isolated headache without associated focal neurologic impairment, such as weakness, numbness, aphasia, or visual dysfunction [3]. Specific stroke symptoms vary according to the brain regions impacted and some small cerebrovascular lesions may not produce neurologic deficits. Headache may occur due to activation of nociceptors in vascular walls from acute thrombosis or those in dural membranes from local mass effect of bleeding or edema. Cerebrovascular conditions that may commonly present with isolated headache include:

- **Intracranial hemorrhage**
  - **Subarachnoid hemorrhage** – Aneurysmal subarachnoid hemorrhage (SAH) frequently presents with acute onset (thunderclap) severe headache [87]. Other patients may present with a prodrome or less severe headaches, frequently called "sentinel headaches" up to several days prior to overt SAH [88]. (See "Aneurysmal subarachnoid hemorrhage: Clinical manifestations and diagnosis", section on 'Clinical presentation'.)
  - **Subdural and epidural hematomas** – Acute intracranial bleeding in the potential spaces adjacent to the nociceptor-containing dural membranes can present with acute or chronic headaches. Epidural hematomas may present with headache due to bleeding between the dura and inner table of the skull, but additional neurologic deficits from mass effect on the underlying brain tissue are common, such as hemiparesis or impaired consciousness. Similarly, subdural hematomas (SDH), due to bleeding between the dura and arachnoid membranes, can present with headache with or without other neurologic deficits. Patients with chronic SDH are likelier to present with nonfocal symptoms such as isolated headache, but symptoms may be progressive if the bleeding expands. (See "Intracranial epidural hematoma in adults" and "Subdural hematoma in adults: Etiology, clinical features, and diagnosis".)
  - **Intracerebral hemorrhage** – For patients with intracerebral hemorrhage (ICH), headache may occur acutely at stroke onset or may occur within hours of onset as the hematoma gradually expands and begins to compress pain sensitive intracranial structures such as larger arteries and the meninges. Large volume intracerebral

hemorrhages may present with headache that is typically associated with nausea and/or vomiting and a decreased level of consciousness due to mass effect of the bleeding and brain compression. (See "Spontaneous intracerebral hemorrhage: Pathogenesis, clinical features, and diagnosis", section on 'Clinical presentation'.)

- **Ischemic stroke** – Headache can occasionally occur with TIA or ischemic stroke due to acute arterial thromboembolism. For patients with ischemic stroke of large vessel origin, headache may occur prior to, during, or after stroke onset [89]. In one prospective study of 284 patients with acute ischemic stroke, concomitant headache during the early phase of stroke was reported by 38 percent [90]. Although the cause is often unclear, several plausible mechanisms have been postulated, including vascular dilation as a homeostatic response to ischemia and direct arterial irritation by thrombus, embolism, or dissection [91]. (See "Clinical diagnosis of stroke subtypes", section on 'Associated symptoms'.)

  Headache may be common with specific ischemic stroke presentations and causes, including the following:

  - **Cervical internal carotid artery dissection** – Cervical internal carotid artery dissection may occasionally present with isolated headache or as a migraine mimic with visual scintillating scotomata [92,93]. One study of 161 patients found that nearly 70 percent of cervical carotid and vertebral dissections were associated with headache, and headache was the initial symptom in 33 to 47 percent [94]. Another study found that 19 of 21 patients with angiographically documented carotid dissection had ipsilateral head pain in one or more regions such as the orbit, frontal region, and side of the head [95]. The head pain was typically acute and severe, and neck pain occurred as well in 12 patients. Approximately three quarters of the 21 patients had ischemic events related to the dissection, with the headache preceding the ischemic symptoms in about half.

    The relationship of dissection with headache is further complicated because approximately half of patients with cervical artery dissection also have a prior history of migraine. (See 'Mechanisms' above.)

  - **Insular cortex infarction** – Ischemic stroke involving the insula may present with headache [96]. One study using MRI lesion mapping found that infarctions in the insular cortex were significantly associated with headache, perhaps related to the role of this region in pain processing [97]. Headache is uncommon in subcortical small vessel stroke syndromes. (See "Clinical diagnosis of stroke subtypes" and "Overview of the evaluation of stroke".)

- **Posterior circulation infarction** – Multiple observational studies have reported an association between headache and acute ischemic stroke involving the posterior arterial circulation [96,98-100]. A meta-analysis of observational studies of adults with ischemic stroke found that the prevalence of headache in patients with posterior circulation stroke was nearly twice that of patients with anterior circulation stroke (OR 1.9, 95% CI 1.4-2.6) [101].

  Migraine has also been associated with the presence of asymptomatic stroke-like lesions in the posterior circulation on brain MRI in patients without a clinical history of stroke. (See 'Subclinical brain lesions' below.)

- **Malignant hemispheric infarction** – Headache due to cerebral edema may develop in patients with large ischemic strokes but is typically associated with additional neurologic deficits. (See "Malignant cerebral hemispheric infarction with swelling and risk of herniation".)

- **Cerebral venous thrombosis** – Headache is the most common clinical feature of cerebral venous thrombosis (CVT) being present in nearly 90 percent of patients [102]. Headache characteristics in CVT may be focal or diffuse and can mimic migraine but are frequently gradually progressive. (See "Cerebral venous thrombosis: Etiology, clinical features, and diagnosis", section on 'Headache'.)

- **Reversible cerebral vasoconstriction syndromes** – Reversible cerebral vasoconstriction syndrome (RCVS) is a group of conditions characterized by reversible narrowing of the cerebral arteries. The clinical presentation of RCVS is usually dramatic with sudden, severe "thunderclap" headaches that simulate aneurysmal SAH; however, in patients with RCVS, thunderclap headaches often recur over a span of one to four weeks. The etiology of RCVS is unknown, though the reversible nature of the vasoconstriction suggests an abnormality in the control of cerebrovascular tone.

  Recurrence of an episode of RCVS is rare, but some patients develop chronic headaches after RCVS, which are usually migrainous in nature.

  RCVS is discussed in greater detail separately. (See "Reversible cerebral vasoconstriction syndrome".)

- **Others** – Headache may also be a presenting feature of other cerebrovascular conditions. These conditions share a common pathophysiology involving failure of cerebral blood flow autoregulation or endothelial dysfunction [103].

- Reversible posterior leukoencephalopathy syndrome [104] (see "Reversible posterior leukoencephalopathy syndrome")
- Hypertensive encephalopathy [103,105] (see "Moderate to severe hypertensive retinopathy and hypertensive encephalopathy in adults")
- Cerebral hyperperfusion syndrome [106] (see "Complications of carotid endarterectomy", section on 'Hyperperfusion syndrome')
- Stroke-like migraine attacks after radiation therapy (SMART) [107] (see "Delayed complications of cranial irradiation", section on 'Migraine-like headache (SMART) syndrome')
- Cerebral arteriovenous malformation (AVM) [108,109] (see "Brain arteriovenous malformations", section on 'Clinical presentation')
- Moyamoya disease and syndrome [110] (see "Moyamoya disease and moyamoya syndrome: Etiology, clinical features, and diagnosis", section on 'Other manifestations')
- Vasculitis involving the central nervous system (both primary and systemic) [111-114] (see "Primary angiitis of the central nervous system in adults" and "Overview of and approach to the vasculitides in adults")
- CADASIL [115,116] (see "Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)", section on 'Migraine with aura')

Some of these conditions may present with headaches that have migrainous features. Patients with cerebral AVMs may present with migraine-like attacks that lateralize to the same cerebral hemisphere [108,109,117]. Migraine-like headaches are a frequent and early manifestation of both SMART syndrome and CADASIL and may be the sole symptom in some patients.

Other conditions in the differential diagnosis of stroke are reviewed elsewhere. (See "Differential diagnosis of transient ischemic attack and acute stroke".)

Migraine coincidental with stroke — Migraine or other headache may occur coincidentally with stroke since both are common conditions. With advancing age, the prevalence of migraine decreases, while that of stroke increases. In addition, stroke risk factors such as hypertension, diabetes, and heart disease are more common in older age groups.

Migraine and stroke may occur together as presenting features of or covariables for other conditions such as antiphospholipid antibody syndrome and CADASIL. (See 'Mechanisms' above.)

Management — The general approach to the acute stroke treatment of patients with migraine is similar to other patients without migraine. Acute stroke management is discussed in detail separately. (See "Initial assessment and management of acute stroke", section on 'Ischemic stroke management'.)

Treatment aimed at primary or secondary stroke prevention in patients with migraine or nonspecific headache is not well studied, but an approach combining stroke risk factor control with migraine prophylaxis seems most reasonable. Patients with additional stroke risk factors such as hypertension, tobacco use, or high-estrogen-containing oral contraception should be informed about the increased stroke risk, and efforts should be taken to minimize risks.

- **Education** – Patients with migraine should be taught to recognize the early warning signs of stroke to prevent confusion between migraine aura and TIA (table 1) and to seek appropriate intervention. Similarly, clinicians should be aware of the potentially increased risk of stroke in the migraine population and should not dismiss focal symptoms in their evaluation of these patients. (See "Differential diagnosis of transient ischemic attack and acute stroke", section on 'Distinguishing transient attacks'.)

- **Managing medications** – Specific medication management strategies for patients with stroke and migraine are discussed below. (See 'Managing medications that impact stroke risk' below.)

General preventive therapy for stroke and treatment of migraine are discussed in greater detail separately.

- (See "Overview of primary prevention of cardiovascular disease".)
- (See "Overview of secondary prevention of ischemic stroke".)
- (See "Acute treatment of migraine in adults".)
- (See "Preventive treatment of episodic migraine in adults".)

OTHER MIGRAINE-ASSOCIATED CEREBROVASCULAR MANIFESTATIONS

Intracerebral hemorrhage — Most studies have reported on the association between migraine and ischemic stroke. However, migraine has been identified as a possible risk factor for other cerebrovascular conditions, including intracerebral hemorrhage [26]. The relationship

of migraine with intracerebral hemorrhage is supported by a meta-analysis of eight studies (four case-control and four cohort), which found that the overall pooled effect estimate of hemorrhagic stroke was 1.48 (95% CI 1.16-1.88) for subjects with any migraine [118].

Subclinical brain lesions — Several prospective population-based studies have found an association between migraine with aura and silent infarct-like lesions on brain MRI [14,63,119-121]. However, the etiology, nature, and clinical significance of the MRI lesions reported in these studies remains unclear [121,122].

Two patterns of brain lesions have been associated with migraine with aura:

- **Infarct-like lesions in the posterior circulation territory** – In a population-based study of 4689 subjects from Iceland, subjects were evaluated at a mean age of 51 years and then reevaluated at a mean age of 76 years by interview and brain MRI. Those subjects who reported migraine with aura at the initial evaluation had an increased risk of infarct-like lesions 25 years later (adjusted odds ratio [aOR] 1.4, 95% CI 1.1-1.8) [120]. This result was driven mainly by an increased risk of cerebellar infarct-like lesions in the subgroup of females who had migraine with aura (odds ratio [OR] 1.9, 95% CI 1.4-2.6). Migraine with (but not without) aura was also associated with an increased risk for subclinical posterior circulation territory infarct-like lesions in a cross-sectional study of Dutch adults aged 30 to 60 years [119]. Most lesions were in the cerebellum. In another study report, patients with migraine had a significantly increased prevalence of small infratentorial hyperintense lesions, most located in the mid-pons [123].

- **White matter lesions** - A 2013 systematic review and meta-analysis of four clinic-based case-control studies found that white matter lesions were more common in subjects with migraine compared with controls [121]. The association was significant for migraine with aura (OR 1.68, 95% CI 1.07-2.65) but not for migraine without aura (OR 1.34, 95% CI 0.96-1.87). By contrast, a subsequent population-based study found that severe white matter disease was associated with migraine without aura (OR 1.87, 95% CI 1.04-3.37) but not with migraine with aura (OR 0.55, 95% CI 0.17-1.83) [124]. In this study, a history of migraine was not associated with white matter lesion progression over time [124].

MANAGING MEDICATIONS THAT IMPACT STROKE RISK

Indications for antithrombotic therapy — The indications for antithrombotic therapy are not impacted by migraine, either with or without aura.

- **Primary prevention** – Primary prevention of stroke with aspirin or other antiplatelet therapy is **not** warranted for patients with migraine with or without aura in the absence of cardiovascular risk factors. (See "Aspirin in the primary prevention of cardiovascular disease and cancer", section on 'Assessing benefits and risks'.)

- **Secondary prevention** – Secondary stroke prevention with antiplatelet or anticoagulant medications is warranted for patients with and without migraine who have a history of transient ischemic attack (TIA) or stroke. (See "Overview of secondary prevention of ischemic stroke", section on 'Antithrombotic therapy'.)

Use of estrogen-containing therapies — While estrogen-containing therapies are associated with an increased risk of venous thromboembolism and ischemic stroke, these medications can be used safely in many patients with migraine depending on the migraine characteristics (no aura), estrogen indication (contraception or therapy for menopause symptoms), dose, delivery (oral, transdermal), and relative benefits compared with risks. However, estrogen-containing medications are typically avoided in patients with migraine with aura who have a history of stroke or are at elevated risk for cardiovascular disease, including stroke. The cardiovascular impact of estrogen-containing contraceptives is reviewed separately. (See "Combined estrogen-progestin contraception: Side effects and health concerns", section on 'Cardiovascular effects'.)

Hormonal contraception — The decision to start or continue estrogen-containing contraceptive therapy in patients with migraine involves shared decision making after discussing individual risks and benefits of therapy and alternative options. Estrogen-containing contraceptives include oral pills, transdermal patches, and vaginal rings (figure 1). (See "Contraception: Counseling and selection".)

- **Without aura** – Patients experiencing migraine without aura who are otherwise candidates for estrogen-containing contraception can safely use estrogen-containing contraceptives, including oral pills, transdermal patches, and vaginal rings [125-127]. If contraceptive pills are selected, formulations containing ≤35 mcg of ethinyl estradiol, or the equivalent, are preferred (table 2). Patients who elect estrogen-containing contraceptives should be younger than 35 years if they are smokers and do not have other cardiovascular, thromboembolism, or stroke risk factors [125-127].

  Detailed discussions, including supporting data, on candidates and risks related to estrogen-containing contraception are presented separately.

  - (See "Combined estrogen-progestin oral contraceptives: Patient selection, counseling, and use", section on 'Candidates'.)

- (See "Combined estrogen-progestin contraception: Side effects and health concerns".)

- **With aura** – Individuals with aura are generally not candidates for estrogen-containing contraceptives [31,125-128]. However, high-quality studies specific to low-dose estrogen products are lacking [34]. Therefore, the use of estrogen-containing contraception in patients with aura should be individualized. For those with a clear indication for estrogen-containing contraceptives, such as endometriosis or those who desire this method after a clear discussion of the risks, their use may be reasonable.

  Presentation of the data regarding candidates for estrogen-containing contraception, contraindications, and risks associated with use are discussed separately.

  - (See "Combined estrogen-progestin oral contraceptives: Patient selection, counseling, and use".)

  - (See "Combined estrogen-progestin contraception: Side effects and health concerns".)

- **Consideration of other medical conditions** – We and other experts use comprehensive tables of medical conditions and personal characteristics from the World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC) to counsel patients regarding safe use of the various hormonal methods of contraception [125,126]. (See "Combined estrogen-progestin oral contraceptives: Patient selection, counseling, and use", section on 'Candidates'.)

Menopausal hormone therapy — Concerns have been raised that estrogen-containing hormone therapy for symptoms of menopause may increase stroke risk. However, available data conflict, in part because of variables such as patient age and medical comorbidities as well as estrogen dose and route of administration. These issues are reviewed in detail in related content. (See "Menopausal hormone therapy and cardiovascular risk".)

The safety of menopausal hormone therapy, either estrogen alone or estrogen plus progestin, in patients with migraine varies by migraine type and the patient's thromboembolic risk.

- **Patients who should avoid estrogen** – We **avoid** estrogen-containing menopausal hormone therapy for patients with migraine with aura and a history of stroke or those who are otherwise at high risk (eg, >10 percent 10-year risk) for cardiovascular disease including stroke (calculator 1). For these patients, we use nonhormonal options that are not associated with an elevated risk of thromboembolic complications. (See "Menopausal hot flashes", section on 'Nonhormonal pharmacotherapy'.)

- **Estrogen use acceptable** – Menopausal estrogen therapy is acceptable for patients with migraine with or without aura and otherwise at low risk of cardiovascular disease (ie, ≤10 percent 10-year risk). The rationale is that the estrogen therapy for menopausal symptoms is not a supraphysiologic dose (as it is with estrogen-containing contraceptives).

  - (See "Menopausal hormone therapy: Benefits and risks".)

  - (See "Treatment of menopausal symptoms with hormone therapy".)

  Additional discussion on use of estrogen therapy in peri- and postmenopausal patients with migraine is discussed separately. (See "Estrogen-associated migraine headache, including menstrual migraine", section on 'Peri- and postmenopause'.)

Medications to avoid — Some medications are **avoided** in those who have migraine with aura and a history of stroke, TIA, or cardiovascular disease due the risk of cerebral ischemia. These include vasoconstrictive medications:

- Triptans
- Ergotamine derivatives
- Serotonin antagonists (eg, pizotifen and methysergide)

In a case-control study of patients prescribed ergotamine or triptans, 188 patients hospitalized with ischemic events were age and sex-matched with 689 controls. Ergotamine overuse was a risk factor for ischemic complications (odds ratio [OR] 2.55, 95% CI 1.22-5.36); but triptan overuse was not [129]. However, cases of cardiac arrest, cerebral infarcts, and spinal cord infarcts have been reported in the setting of triptan use [130-134].

We also **avoid** long-term use of nonsteroidal antiinflammatory drugs (NSAIDs) in older patients and in patients with other uncontrolled risk factors for stroke due to the elevated risk of thrombotic cardiovascular events [135]. (See "NSAIDs: Adverse cardiovascular effects", section on 'NSAIDs and cardiovascular events'.)

We suggest that beta blockers should **not** be used as initial therapy for migraine prophylaxis in patients over age 60 years and in patients who smoke. Compared with other antihypertensive drugs in the primary treatment of hypertension, beta blockers may be associated with a higher rate of stroke and other cardiovascular events. (See "Choice of drug therapy in primary (essential) hypertension".)

The safety of calcitonin gene-related peptide antagonists has not been established for patients with a migraine with aura and a history of or uncontrolled risk factors for stroke [136,137].

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Stroke in adults".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Stroke (The Basics)" and "Patient education: Medicines after an ischemic stroke (The Basics)" and "Patient education: Migraines in adults (The Basics)")

- Beyond the Basics topics (see "Patient education: Migraines in adults (Beyond the Basics)" and "Patient education: Stroke symptoms and diagnosis (Beyond the Basics)" and "Patient education: Ischemic stroke treatment (Beyond the Basics)").

SUMMARY AND RECOMMENDATIONS

- **Migraine-associated ischemic stroke**

  - **Epidemiology** – The reported incidence of stroke due to migraine (migrainous stroke) ranges from 0.8 to 3.4 per 100,000 per year.

    Clinical factors associated with an elevated risk of stroke in patients with migraine include (see 'Modifiers of risk' above):

- Patients with migraine with aura
- Female patients
- Patients who smoke
- Patients who take estrogen-containing contraception
- Patients age <45 years

- **Clinical and imaging findings** – Clinical symptoms of migraine-associated stroke are typically similar to previous migraine aura without new or atypical symptoms. However, the previously transient aura symptoms persist for longer duration. Infarction is frequently located in the posterior circulation and may be multifocal. (See 'Clinical and imaging findings' above.)

- **Diagnosis** – Migrainous infarction occurs in a patient with migraine with aura that is typical of previous attacks except that one or more aura symptoms persists for >60 minutes. Neuroimaging demonstrates ischemic infarction in a relevant area. (See 'Diagnostic criteria' above.)

- **Differential diagnosis** – Both cerebrovascular events and migraine attacks can present as acute transient neurologic events with similar symptoms (table 1). In addition, acute neurologic symptoms that are persistent may also be caused by either migraine or stroke.

- **Management** – The general approach to the acute stroke treatment of patients with migraine is similar to other patients without migraine. Treatment aimed at primary or secondary stroke prevention in patients with migraine involves combining stroke risk factor control with migraine prophylaxis. Patients should be taught to recognize the early warning signs of stroke to prevent confusion between migraine aura and transient ischemic attack (TIA) (table 1) and to seek appropriate intervention. (See 'Management' above.)

- **Migraine and other stroke subtypes** – Migraine has been identified as a possible risk factor for other cerebrovascular conditions, including intracerebral hemorrhage and silent infarct-like lesions on brain MRI. (See 'Other migraine-associated cerebrovascular manifestations' above.)

- **Managing medications that impact stroke risk**

  - **Antithrombotic therapy** – Primary prevention of stroke with aspirin is **not** warranted for patients with migraine with or without aura in the absence of cardiovascular risk factors. Secondary stroke prevention with antiplatelet or anticoagulant medications is

warranted for patients with and without migraine who have a history of TIA or stroke. (See 'Indications for antithrombotic therapy' above.)

- **Estrogen-containing therapies** – While estrogen-containing therapies are associated with an increased risk of thromboembolism, these medications can be used safely in select patients with migraine depending on the migraine characteristics (no aura), estrogen dose, and relative benefits compared with risks. (See 'Use of estrogen-containing therapies' above.)

  - **Hormonal contraception** – We suggest that patients with migraine with aura **avoid** estrogen-containing contraceptives (**Grade 2C**). We give similar guidance to patients with other forms of migraine and an additional risk factor for stroke.

    Patients who are nonsmokers <35 years, without aura, and have no additional thromboembolic risk factors may consider estrogen-containing contraceptives. If oral contraceptives are selected, we prefer formulations containing 35 mcg or less of estrogen. (See 'Hormonal contraception' above.)

  - **Menopausal hormone therapy** – We suggest that patients with migraine with aura and a history of stroke or at high risk for future cardiovascular disease (calculator 1) **avoid** estrogen-containing menopausal hormone therapy (**Grade 2C**). Menopausal estrogen therapy is acceptable for patients with migraine with or without aura who are at low risk of cardiovascular disease, including stroke (ie, ≤10 percent 10-year risk). (See 'Menopausal hormone therapy' above.)

- **Migraine medications to avoid** – We **avoid** triptans, ergotamine derivatives, serotonin antagonists, and long-term use of nonsteroidal antiinflammatory drugs (NSAIDs) for patients with migraine with aura and a history of stroke or cardiovascular disease. We do not use beta blockers for patients over age 60 years and those who smoke. (See 'Medications to avoid' above.)

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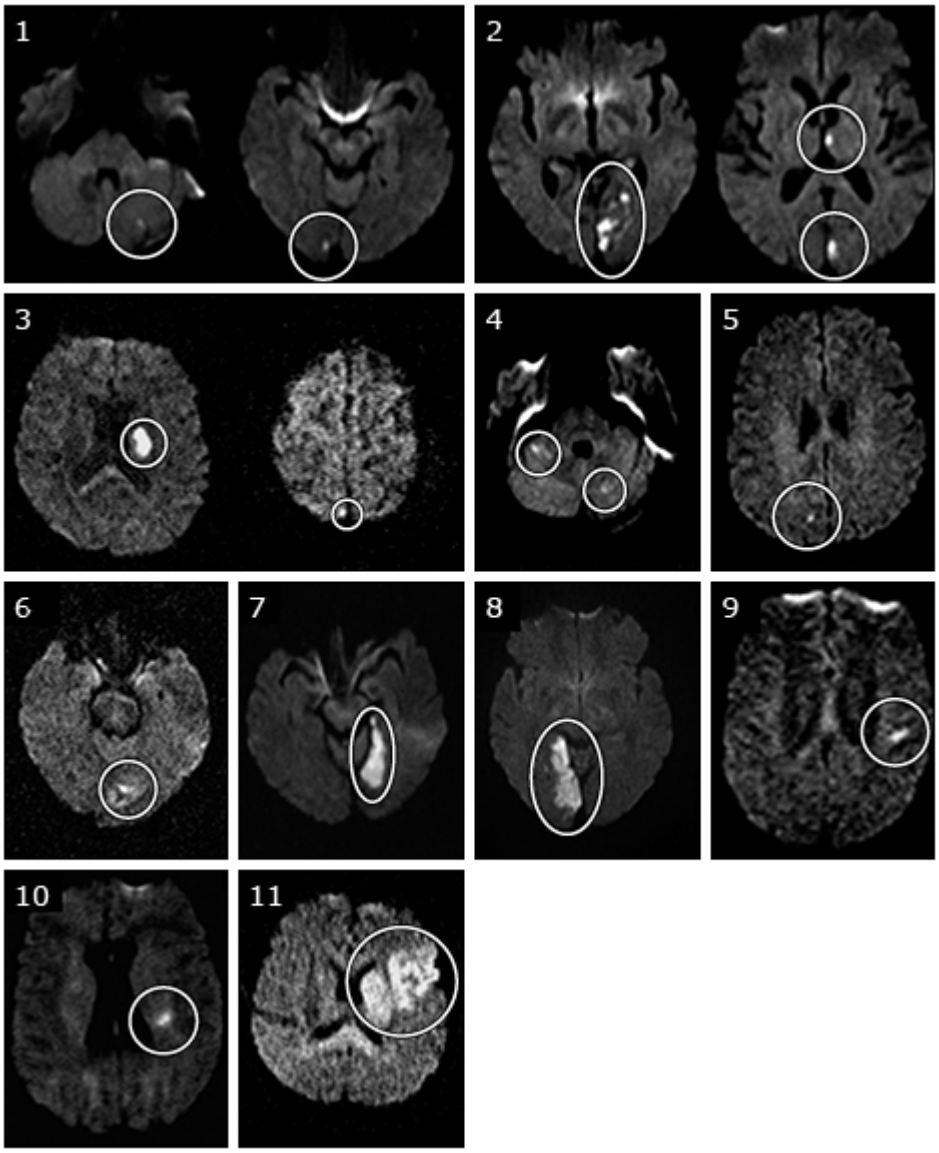
Topic 3344 Version 45.0

GRAPHICS

Brain MRI migrainous infarction



Diffusion-weighted imaging lesion patterns of 11 patients with migrainous infarction. Patients 1 through 4 have multiple small lesions, patients 5 through 8 have isolated lesions in the posterior circulation territory, and patients 9 through 11 have isolated lesions in the middle cerebral artery territory.

MRI: magnetic resonance imaging.

Graphic 57203 Version 9.0

Clinical features of seizures, syncope, and other paroxysmal neurologic events in adults

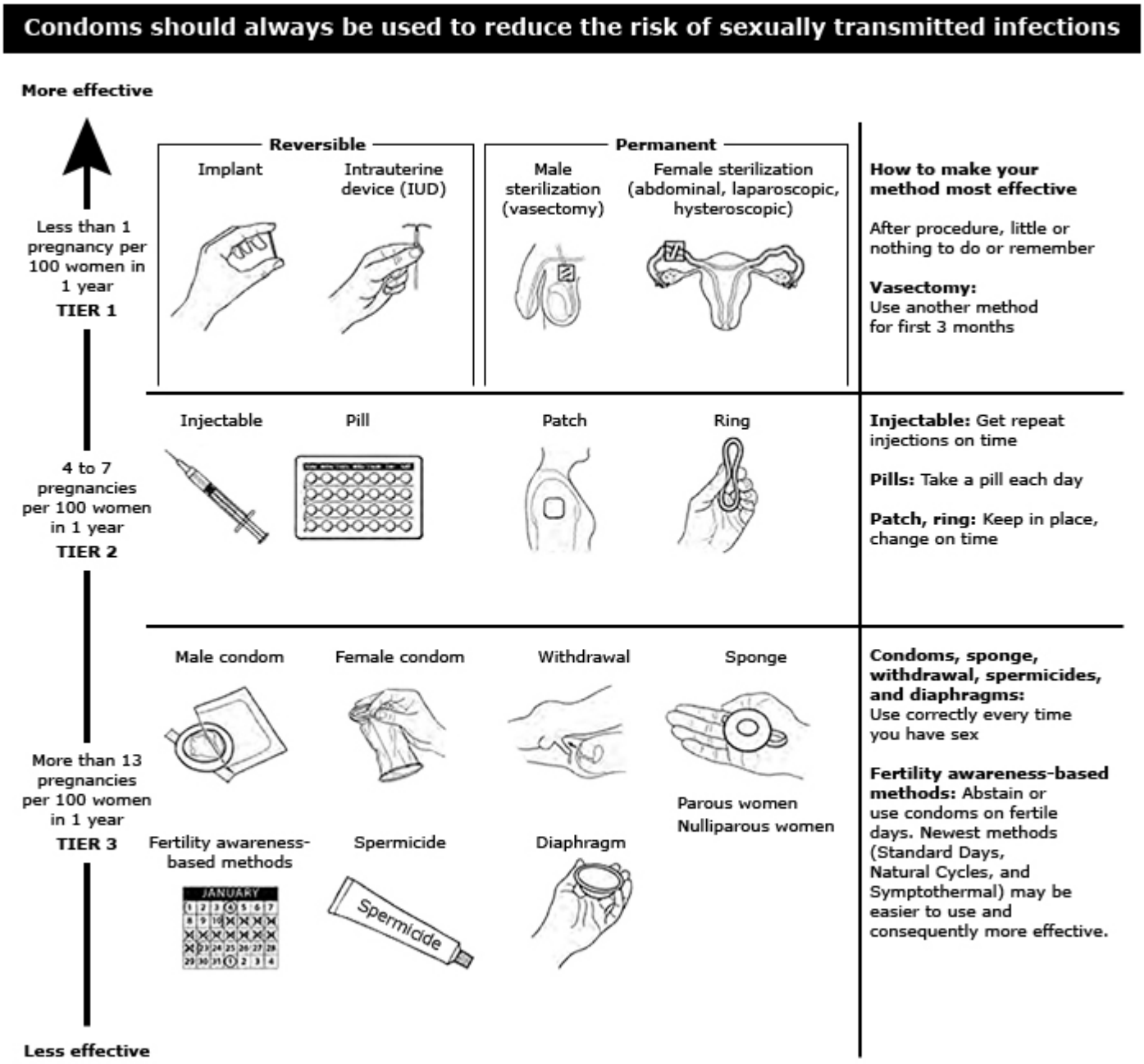
	Clinical features	Duration	Recall of the event	Diagnostic tools
Focal seizure	Initial symptoms depend on location in brain; motor and visual symptoms usually "positive" (eg, shaking, jerking, flashing lights, or visual distortion); may have anatomic "march" over seconds; some progress rapidly to GTC	Usually <2 minutes; can be difficult to distinguish ictal from postictal phase	Variable depending on whether consciousness is impaired	EEG may show interictal spikes (poor sensitivity); ambulatory EEG if episodes are frequent enough; MRI may show structural lesion
Generalized seizure	Sudden alteration or loss of consciousness without warning; some have myoclonic jerks or staring; tongue-biting and urinary incontinence may occur (for GTC)	<5 minutes (for GTC); <1 minute for absence	Complete amnesia; patient may recall initial focal symptoms	EEG may show generalized spike-and-wave characteristic of specific syndrome MRI usually normal for generalized epilepsy syndromes, may show structural lesion if focal onset
Psychogenic nonepileptic seizure	Fluctuating, asynchronous motor activity, often with eye closure, side-to-side head or body movements, pelvic thrusting; most occur in front of a witness; fully or partially alert	Rarely <1 minute; often prolonged (>30 minutes)	Variable	Video-EEG monitoring

	despite bilateral motor activity; tongue-biting is rare			
Syncope	Transient loss of consciousness resulting in loss of postural tone; prodrome of lightheadedness, warm or cold feeing, sweating, palpitations, pallor; myoclonic jerks or tonic posturing may occur, especially if patient is kept upright; no or minimal post-event confusion	1 to 2 minutes	Patient can recall prodromal symptoms, if present; lack of warning may suggest cardiac source	ECG; echocardiography if structural cardia disease is suspected; ambulatory ECG monitoring if arrhythmia is suspected; orthostatic blood pressure measurements
Transient ischemic attack (TIA)	Rapid loss of neurologic function due to interrupted blood flow; symptoms depend on vascular territory but are typically "negative" (eg, weakness, numbness, aphasia, visual loss); intensity is usually maximal at onset; consciousness usually preserved	Several minutes to a few hours	Usually complete unless language areas involved	MRI/MRA, CTA, vascular risk factors
Migraine aura	Positive and/or negative neurologic symptoms, most often visual and sensory, evolving gradually over ≥5	Up to 1 hour	Complete	Personal or family history of migrain

	minutes (slower onset than TIA or focal seizure); slow spread of positive followed by negative symptoms, if present, is very characteristic; usually followed by headache			
Panic attack	Palpitations, dyspnea, chest pain, lightheadedness, sense of impending doom; associated hyperventilation may result in perioral and distal limb paresthesias	Minutes to hours	Complete	History of anxiety or depressive symptoms, triggering events or stressors
Transient global amnesia	Prominent anterograde amnesia (inability to form new memories) and variable retrograde amnesia; patient is disoriented in time, asking repetitive questions; other cognitive and motor functions spared; rare in adults younger than 50 years	1 to 10 hours (mean 6 hours)	Complete amnesia for the main episode; retrograde amnesia resolves within 24 hours	Clinical diagnosis; negative MRI and toxicology screens

GTC: generalized tonic-clonic; EEG: electroencephalography; MRI: magnetic resonance imaging; ECG: electrocardiogram; MRA: magnetic resonance angiography; CTA: computed tomography angiography.

Comparison of effectiveness of contraceptive methods



Other methods of contraception:

- Lactational amenorrhea method – LAM is a highly effective, **temporary** method of contraception
- Emergency contraception – Emergency contraceptive pills or an IUD (copper or LNG) after unprotected intercourse substantially reduces risk of pregnancy

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LNG: levonorgestrel.

Adapted from: U.S. Selected Practice Recommendations for Contraceptive Use, 2013: Adapted from the World Health Organization Selected Practice Recommendations for Contraceptive Use, 2nd Edition. MMWR Morb Mortal Wkly Rep 2013; 62:1.

Additional information from:

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Graphic 57795 Version 10.0

Selected hormonal contraceptives: Oral contraceptives (birth control pills) and other delivery methods

Progestin (mg)*	Estrogen (micrograms)	United States brand name	Notes
Monophasic combinations			
Drospirenone (3)	Ethinyl estradiol (20)	▪ Beyaz ▪ Jasmiel ▪ Lo-Zumandimine ▪ Loryna ▪ Nikki ▪ Vestura ▪ Yaz	Also approved for acne and premenstrual dysphoric disorder. In patients with conditions requiring chronic therapy with medications that may increase potassium, monitor serum potassium during the first treatment cycle and periodically thereafter if patient begins medication or develops a condition that increases risk for hyperkalemia. Packaged as active tablets for 24 days and placebo for 4 days; except Beyaz, which contains 451 mcg of levomefolate per tablet (24 active tablets and 4 levomefolate tablets).
Levonorgestrel (0.09)	Ethinyl estradiol (20)	▪ Amethyst ▪ Dolishale	
Levonorgestrel (0.1)	Ethinyl estradiol (20)	▪ Afirmelle ▪ Aubra EQ ▪ Aviane ▪ Balcoltra ▪ Delyla ▪ Falmina ▪ Joyeaux ▪ Lessina ▪ Lutera ▪ Sronyx ▪ Tyblume ▪ Vienva	Packaged as active tablets for 21 days and placebo for 7 days.
Norethindrone acetate (1)	Ethinyl estradiol (20)	▪ Aurovela 24 FE ▪ Blisovi 24 Fe ▪ Charlotte 24 Fe chewable	Packaged as active pills for 24 days and ferrous fumarate for 4 days.

		tablets ▪ Finzala chewable tablets ▪ Gemmily capsules ▪ Hailey 24 Fe ▪ Junel Fe 24 ▪ Larin 24 Fe ▪ Merzee capsules ▪ Mibelas 24 Fe chewable tablets ▪ Microgestin 24 Fe ▪ Minastrin 24 Fe chewable tablets ▪ Tarina 24 Fe ▪ Taysofy capsules ▪ Taytulla capsules	
		▪ Aurovela FE 1/20 ▪ Blisovi FE 1/20 ▪ Hailey FE 1/20 ▪ Junel FE 1/20 ▪ Larin Fe 1/20 ▪ Loestrin Fe 1/20 ▪ Microgestin FE 1/20 ▪ Tarina FE 1/20 EQ	Packaged as active tablets for 21 days and ferrous fumarate for 7 days.
		▪ Aurovela 1/20 ▪ Junel 1/20 ▪ Larin 1/20 ▪ Loestrin 1/20	Packaged as active tablets for 21 days (does not contain iron).

		▪ Microgestin 1/20	
Norethindrone (0.8)	Ethinyl estradiol (25)	▪ Kaitlib Fe chewable tablets ▪ Layolis FE chewable tablets	Packaged as active tablets for 24 days and ferrous fumarate for 4 days.
Desogestrel (0.15)	Ethinyl estradiol (30)	▪ Apri ▪ Cyred ▪ Cyred EQ ▪ Enskyce ▪ Isibloom ▪ Juleber ▪ Kalliga ▪ Reclipsen	Packaged as active tablets for 21 days and placebo for 7 days.
Drospirenone (3)	Ethinyl estradiol (30)	▪ Ocella ▪ Safyral ▪ Syeda ▪ Tydemy ▪ Yasmin ▪ Zumandimine	In patients with conditions requiring chronic therapy with medications that may increase potassium, monitor serum potassium during the first treatment cycle and periodically thereafter if patient begins medication or develops a condition that increases risk for hyperkalemia. Packaged as active tablets for 21 days and placebo for 7 days; except Safyral and Tydemy, which contain 451 mcg of levomefolate per tablet (21 active tablets and 7 levomefolate tablets).
Levonorgestrel (0.15)	Ethinyl estradiol (30)	▪ Altavera ▪ Ayuna ▪ Chateal EQ ▪ Kurvelo ▪ Levora 0.15/30 ▪ Marlissa ▪ Portia-28	Packaged as active tablets for 21 days and placebo for 7 days.
Norethindrone acetate (1.5)	Ethinyl estradiol (30)	▪ Aurovela Fe 1.5/30 ▪ Blisovi Fe 1.5/30	Packaged as active tablets for 21 days and ferrous fumarate for 7 days.

		▪ Junel FE 1.5/30 ▪ Hailey FE 1.5/30 ▪ Larin Fe 1.5/30 ▪ Loestrin Fe 1.5/30 ▪ Microgestin FE 1.5/30	
		▪ Aurovela 1.5/30 ▪ Junel 1.5/30 ▪ Hailey 1.5/30 ▪ Larin 1.5/30 ▪ Loestrin 1.5/30 ▪ Microgestin 1.5/30	Packaged as active tablets for 21 days (does not contain iron).
Norgestrel (0.3)¶	Ethinyl estradiol (30)	▪ Cryselle-28 ▪ Elinest ▪ Low-Ogestrel ▪ Turqoz	Packaged as active tablets for 21 days and placebo for 7 days.
Ethynodiol diacetate (1)	Ethinyl estradiol (35)	▪ Kelnor 1/35 ▪ Zovia 1/35	Packaged as active tablets for 21 days and placebo for 7 days.
Norethindrone (0.4)	Ethinyl estradiol (35)	▪ Balziva ▪ Briellyn ▪ Philith ▪ Vyfemla	Packaged as active tablets for 21 days and placebo for 7 days.
		▪ Wymzya Fe chewable tablets	Packaged as active tablets for 21 days and ferrous fumarate for 7 days.
Norethindrone (0.5)	Ethinyl estradiol (35)	▪ Necon 0.5/35 (28) ▪ Nortrel 0.5/35 (28) ▪ Wera	Packaged as active tablets for 21 days and placebo for 7 days.
Norethindrone (1)	Ethinyl estradiol (35)	▪ Alyacen 1/35 ▪ Dasetta 1/35 ▪ Nortrel 1/35 (28) ▪ Nylia 1/35 ▪ Pirmella 1/35	Packaged as active tablets for 21 days and placebo for 7 days. Nortrel 1/35 is also available as a 21-da regimen (packaged without placebo).

Norgestimate (0.25)	Ethinyl estradiol (35)	▪ Estarylla ▪ Femynor ▪ Mili ▪ Mono-Linyah ▪ Nymyo ▪ Sprintec 28 ▪ VyLibra	Packaged as active tablets for 21 days and placebo for 7 days.
Cyproterone (2)	Ethinyl estradiol (35)	▪ Cleo-35 ▪ Cyestra-35 ▪ Diane-35	Labeled approval in Canada is for treatment of acne; provides reliable contraception if taken as recommende for treatment of acne. Packaged as active tablets for 21 days. Not available in the United States; Canadian product shown.
Ethynodiol diacetate (1)	Ethinyl estradiol (50)	▪ Kelnor 1/50	Packaged as active tablets for 21 days and placebo for 7 days. **NOTE: Pills containing 50 mcg of ethinyl estradiol are not indicated fo routine contraceptive use because of increased risk of cardiovascular events compared with lower-dose oral contraceptive pills.**
Drospirenone (3)	Estetrol (14.2) NOTE: Estetrol strength listed in **milligrams (mg)**	▪ Nextstellis	Packaged as active tablets for 24 days and placebo for 4 days. In patients with conditions requiring chronic therapy with medications that may increase potassium, monitor serum potassium during the first treatment cycle and periodically thereafter if patient begins medication or develops a condition that increases risk for hyperkalemia.
Nomegestrol acetate (2.5)	Estradiol (as hemihydrate) (1.5) NOTE: Estradiol strength listed in **milligrams (mg)**	▪ Zoely	Packaged as active tablets for 24 days and placebo for 4 days. Not available in the United States; United Kingdom and European Union product shown.
Multiphasic combinations			

Dienogest (0,2,3,0)	Estradiol valerate (3,2,2,1) NOTE: Estradiol strength listed in **milligrams (mg)**	▪ Natazia	Packaged as active tablets for 26 days and placebo for 2 days.
Norethindrone acetate (1,0)	Ethinyl estradiol (10,10)	▪ Lo Loestrin Fe	Packaged as active tablets for 26 days and ferrous fumarate for 2 days.
Desogestrel (0.15,0,0)	Ethinyl estradiol (20,0,10)	▪ Azurette ▪ Kariva ▪ Mircette ▪ Pimtrea ▪ Simliya ▪ Viorele ▪ Volnea	Packaged as active tablets for 26 days and placebo for 2 days.
Norethindrone acetate (1,1,1)	Ethinyl estradiol (20,30,35)	▪ Tilia Fe ▪ Tri-Legest Fe	Also approved for acne. Packaged as active tablets for 21 days and ferrous fumarate for 7 days.
Norgestimate (0.18,0.215,0.25)	Ethinyl estradiol (25,25,25)	▪ Tri-Lo-Estarylla ▪ Tri-Lo-Marzia ▪ Tri-Lo-Mili ▪ Tri-Lo-Sprintec ▪ Tri-Vylibra Lo	Packaged as active tablets for 21 days and placebo for 7 days.
Desogestrel (0.1,0.125,0.15)	Ethinyl estradiol (25,25,25)	▪ Velivet	Packaged as active tablets for 21 days and placebo for 7 days.
Levonorgestrel (0.05,0.075,0.125)	Ethinyl estradiol (30,40,30)	▪ Enpresse-28 ▪ Levonest ▪ Trivora (28)	Packaged as active tablets for 21 days and placebo for 7 days.
Norgestimate (0.18,0.215,0.25)	Ethinyl estradiol (35,35,35)	▪ Tri-Estarylla ▪ Tri-Linyah ▪ Tri-Mili ▪ Tri-Nymyo ▪ Tri-Sprintec ▪ Tri-VyLibra	Also approved for acne. Packaged as active tablets for 21 days and placebo for 7 days.
Norethindrone (0.5,0.75,1)	Ethinyl estradiol (35,35,35)	▪ Alyacen 7/7/7 ▪ Dasetta 7/7/7 ▪ Nortrel 7/7/7 ▪ Nylia 7/7/7	Packaged as active tablets for 21 days and placebo for 7 days.

		▪ Pirmella 7/7/7	
Norethindrone (0.5,1,0.5)	Ethinyl estradiol (35,35,35)	▪ Aranelle ▪ Leena	Packaged as active tablets for 21 days and placebo for 7 days.
Extended combinations (91-day regimens)			
Levonorgestrel (0.1,0)	Ethinyl estradiol (20,10)	▪ Camrese Lo ▪ LoJaimiess ▪ LoSeasonique	Packaged as a 91-day regimen: 84 days of the combination and 7 days of 10 mcg ethinyl estradiol only.
Levonorgestrel (0.15,0.15,0.15,0)	Ethinyl estradiol (20,25,30,10)	▪ Fayosim ▪ Quartette ▪ Rivelsa	Packaged as a 91-day regimen: 84 days of the combination and 7 days of 10 mcg ethinyl estradiol only.
Levonorgestrel (0.15,0)	Ethinyl estradiol (30,10)	▪ Amethia ▪ Ashlyna ▪ Camrese ▪ Daysee ▪ Jaimiess ▪ Seasonique ▪ Simpesse	Packaged as a 91-day regimen: 84 days of the combination and 7 days of 10 mcg ethinyl estradiol only.
Levonorgestrel (0.15)	Ethinyl estradiol (30)	▪ Introvale ▪ Iclevia ▪ Jolessa ▪ Setlakin	Packaged as a 91-day regimen: active tablets for 84 days and placebo for 7 days.
Continuous combinations			
May use any monophasic 21/7 combination (eg, Amethyst [levonorgestrel 0.09 mcg-ethinyl estradiol 20 mcg]) by taking active hormone pills for 28 or more days continuously. Any progestin may be used, and higher doses of ethinyl estradiol may be used in some women. Refer to UpToDate topic.			
Progestin-only			
Norethindrone (0.35)	None	▪ Camila ▪ Deblitane ▪ Errin ▪ Heather ▪ Incassia ▪ Jencycla ▪ Lyleq ▪ Lyza ▪ Nora-BE ▪ Norlyroc	Packaged as active tablets for 28 days.

		▪ Sharobel	
Drospirenone (4)	None	▪ Slynd	Packaged as active tablets for 24 days and placebo for 4 days. In patients with conditions requiring chronic therapy with medications that may increase potassium, monitor serum potassium during the first treatment cycle and periodically thereafter if patient begins medication or develops a condition that increases risk for hyperkalemia.
Norgestrel (0.075)	None	▪ Opill	Packaged as active tablets for 28 days. Approved for over-the-counter use in the United States.
Desogestrel (0.075)	None	▪ Cerazette ▪ Cerelle ▪ Hana ▪ Lovima ▪ Zelleta	Packaged as active tablets for 28 days. Not available in the United States or Canada; United Kingdom product shown.
Transdermal patch, weekly			
Norelgestromin (releases 0.15 mg/day)	Ethinyl estradiol (releases 35 mcg/day)	▪ Xulane ▪ Zafemy	May have diminished efficacy in women ≥90 kg. A new patch is applied every 7 days for 3 weeks followed by a patch-free week. These products are therapeutically equivalent to Ortho Evra patch, which is no longer available in the United States
Levonorgestrel (releases 0.12 mg/day)	Ethinyl estradiol (releases 30 mcg/day)	▪ Twirla	Contraindicated in women with BMI ≥30 kg/m^2 due to decreased efficacy and increased risk of VTE. Diminished efficacy was observed in women with BMI ≥25 kg/m^2. A new patch is applied every 7 days for 3 weeks followed by a patch-free week.
Vaginal ring, monthly			
Etonogestrel (releases 0.12 mg/day)	Ethinyl estradiol (releases 15 mcg/day)	▪ NuvaRing ▪ EluRyng ▪ EnilloRing	Ring is inserted for 3 weeks followed by 1 week without ring in place. A new ring is inserted 7 days after the last was removed.

		▪ Haloette	
Segesterone (releases 0.15 mg/day)	Ethinyl estradiol (releases 13 mcg/day)	▪ Annovera	Ring is inserted for 3 weeks followed by 1 week without ring in place. The ring is then reinserted for the first 21 days of subsequent 28-day cycles. One system provides contraception for 13 28-day cycles (1 year). Not yet adequately evaluated in women with BMI >29 kg/m^2.

- Oral and IUD emergency contraceptive options are listed in a table that is available separately in UpToDate.
- Generic (non-branded) products are also available for most combination oral contraceptives in the United States.
- Descriptions are for US-available products unless noted otherwise. Consult local product information before use.

BMI: body mass index; Fe: contains iron; IUD: intrauterine device; VTE: venous thromboembolism.

* Different progestins are not equivalent on a milligram basis. Refer to the UpToDate overview of combined hormonal contraceptives for guidance on selection.

¶ The progestin norgestrel contains two isomers; only levonorgestrel is bioactive. The amount of norgestrel in each tablet is twice the amount of levonorgestrel.

Adapted from:

1. The Medical Letter on Drugs and Therapeutics, October 8, 2018; Vol. 60 (1557): 161-168.

2. The Medical Letter on Drugs and Therapeutics, May 15, 2023; Vol. 65 (1676): 73-82.

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Graphic 69223 Version 56.0