Diagnosis, Treatment, and Prevention of Stroke in Transgender Adults

Michael Diaz, MD
Nicole Rosendale, MD

Address
*Department of Neurology, University of California, San Francisco, 1001 Potrero Ave, Bldg 1, Room 101, Box 0870, San Francisco, CA 94110, USA
Email: nicole.rosendale@ucsf.edu

Published online: 11 July 2022
© The Author(s) 2022

This article is part of the Topical collection on Cerebrovascular Disorders

Keywords Transgender health · Stroke · Estrogen · Testosterone · Gender-affirming hormone therapy

Abstract

Purpose of Review To identify the current state of science on stroke in transgender adults and highlight gaps in need of further research. We will review current research on cerebrovascular risk and disease, hormone therapy, and stroke in transgender individuals. Finally, we will provide a framework for healthcare providers to prevent and reduce disparities through inclusive care practices.

Recent Findings Transgender people experience unique stroke risk factors, secondary to both psychosocial stress and health-related behaviors. These include higher rates of HIV, tobacco use, stimulant use, and hepatitis C. The use of gender-affirming hormone therapy may lead to an increased risk for ischemic stroke, but the data are limited and require further research.

Summary Recent research has highlighted the numerous healthcare disparities faced by transgender individuals. Regarding stroke disparities, these are multifactorial and include contributions from health-related behaviors, inadequate access to care, the use of hormonal therapy, and minority stress. Further research is needed to increase access to care and reduce the substantial gap in outcomes for these individuals.
An estimated 1.4 million adults identify as transgender in the USA [1] and this number is expected to grow in the coming years. As terminology continues to evolve (see Table 1), the umbrella term of gender minority has increasingly been used in clinical and research spaces to describe individuals whose gender identity and/or expression does not align with dominant societal expectations based on their assigned sex at birth [2]. This term includes those who identify as transgender, gender fluid, gender expansive, and non-binary, among other identities. Research to date has grouped these identities together despite potential differences in their lived experiences. Given this limitation, we will focus on the transgender population since most literature stems from this group. In 2011, the Institute of Medicine identified transgender adults as an understudied group in need of further health research [3], and in 2016, the National Institutes of Health formally designated sexual and gender minority people (a term inclusive of those who identify as transgender) as a health disparity population for research purposes [4]. Although they represent a large and heterogeneous community, individuals who identify as transgender face common healthcare disparities that translate into poor health outcomes. To date, research has mainly focused on mental health outcomes [5, 6] with relatively little work done to understand physical health disparities in this population [7]. Studies that have evaluated physical health disparities that exist among transgender adults have found increased risk of cardiovascular disease among transgender adults [8, 9]. Most of these studies have focused on HIV [10–12], substance use [13–15], and hormone use [16–19] without significant emphasis on specific vascular disease mechanisms and outcomes. Many of these risk factors may also lead to increased risk for cerebrovascular disease. Stroke, for example, is the fifth leading cause of death in the USA and a leading cause of serious disability [20], but there is a paucity of research on stroke in transgender individuals [21•]. Based on the available literature, this community experiences unique and disproportionate stroke risk factors, which will be further explored in this chapter.

In this chapter, we will provide a framework for caring for transgender patients with stroke. First, we will review issues related to access of care among this population and how this might relate to overall burden of stroke disability. Next, we will explore current research on the unique risk factors for development of cerebrovascular disease among the transgender population, with a particular focus on the role of minority stress. Given the preponderance of literature that focuses on the use of gender-affirming hormone therapy and vascular health, we will critically examine the implications of hormone use with respect to stroke risk and provide a framework for management options in the inpatient setting. While hospitalized, transgender patients might face unique challenges and thus particular attention should be paid to the inpatient management of these individuals. We will then discuss secondary stroke prevention with an emphasis on risk modification strategies. Finally, we will propose future directions for research and areas of crucial importance for clinicians to provide inclusive care for this population.

**An Introduction to Terminology**

To provide inclusive, affirming healthcare, it is critical for clinicians to be comfortable with terminology pertinent to the transgender and gender diverse community (see Table 1). To start, it is important for healthcare providers to appreciate the difference between the terms gender and sex. Sex refers to the chromosomal, genetic, and hormonal biology of an individual and is assigned at birth. Although sex is often discussed in binary terms (male/female), there is a broader diversity that may be recognized at birth or later in life (i.e., during puberty or if an individual experiences infertility).
| **Gender terminology** | **Definition** |
|-----------------------|---------------|
| **Binary** | Refers to the idea that there are only two identities (female/male, woman/man) and often erroneously used to discuss issues of sex and gender in dominant society. |
| **Cisgender** | Describes an individual whose gender identity aligns with their assigned sex at birth. |
| **Cisnormativity** | The concept/assumption that cisgender is the normative gender identity and thus leads to marginalization of those who do not identify as such. |
| **Gender** | A socially created construct referring to the characteristics and qualities associated with a particular gender in a certain culture. |
| **Gender-affirming hormone therapy** | Hormones used to align secondary sex characteristics to one’s gender identity. Also known as cross-sex hormone therapy. |
| **Gender-affirming surgery** | Surgical procedures to align one’s physical body to one’s gender identity. Examples include vaginoplasty, phalloplasty, and metoidioplasty. Outdated terms include “sex change,” “gender reassignment,” and “sex reassignment,” among others. |
| **Gender dysphoria** | Clinically significant discomfort and/or psychological distress pertaining to the incongruence between one’s sex assigned at birth and one’s gender identity due to dominant societal expectations of gender performance. This concept is listed in the DSM-5 but there is considerable controversy as to the appropriateness of this experience as a formal diagnosis. |
| **Gender fluid** | Refers to the concept that someone’s gender identity can change over the course of one’s life; can also be used as a gender identity term by individuals whose gender identity changes or is fluid. |
| **Gender neutral** | The absence of gender, which may be used in contexts like pronouns (they/them), spaces (e.g., bathrooms), or identities. |
| **Gender spectrum** | The idea that gender exists on a continuum rather than a binary, and that individuals may fall somewhere along the continuum and can shift depending on context, stage in life, etc. |
| **Intersex** | An umbrella term used by those with differences of sex development, in which there are variations in reproductive or sex anatomy, which can appear in a person’s chromosomes, genitals, or internal organs. Some intersex traits are identified at birth, while others may not be identified until later. |
| **Non-binary** | An individual who does not identify strictly as man or woman. |
| **Sex** | A term used to describe someone’s biology as male, female, or intersex. This determination is usually based on a combination of physiologic, genetic, anatomic, and hormonal attributes and is typically assigned at birth. |
| **Transgender** | An umbrella term to describe a person whose gender identity differs from assigned sex at birth. Terms within the transgender umbrella include transgender woman or transwoman, transgender man or transman, gender expansive, and genderqueer, among others. |
| **Transsexual** | A term sometimes used in medical literature to describe someone who has undergone medical interventions to align one’s physical appearance more closely with one’s gender identity. Not a synonym for transgender and currently its use should be restricted to those who self-identify as such. |

**Sexual orientation terminology**
Independent from sex assigned at birth is someone’s gender. Gender is a socially created construct referring to the characteristics and qualities that may relate to being masculine or feminine in a certain culture. Gender identity is personal, nuanced, and often dynamic throughout someone’s life.

Sexual orientation refers to someone’s romantic, emotional, or sexual attraction towards other people [22]. This is distinct from gender identity, though both are deeply personal and have the potential to change throughout one’s lifetime.

Over time, the terminology has become more inclusive to capture the breadth of diverse identities, as seen in the acronym “LGBTQIA+” (lesbian, gay, bisexual, transgender, queer/questioning, intersex, asexual), which has undergone significant changes since its inception in the mid-1980s as “LGB” [23]. There are numerous resources online for the evolving and dynamic glossary of terms [22, 24–26], although for individual clinicians, the most important skill is to be able to ask an individual about their gender and sexuality in an open and non-judgmental manner. We recommend, for example, asking all patients what name and pronoun(s) they use on intake and using

Table 1 (continued)

| Gender terminology          | Definition                                                                                                                                 |
|-----------------------------|--------------------------------------------------------------------------------------------------------------------------------------------|
| Asexual                     | Refers to someone who has little or no interest in sexual contact with another person. Some asexual individuals experience romantic attraction to others while some do not. |
| Bisexual                    | Someone who is attracted to those of the same gender and different gender.                                                                     |
| Gay                         | Someone who is attracted to those of the same gender. Most commonly referring to a man who is attracted to other men.                          |
| Heteronormativity           | The concept that heterosexuality is the normative sexual orientation and thus leads to marginalization of those who do not identify with this orientation. |
| Lesbian                     | Refers to a woman who is attracted to other women. Someone who identifies as lesbian may also identify as gay.                                 |
| LGBTQ                       | An acronym for “lesbian, gay, bisexual, transgender, queer.” The Q can also sometimes refer to “questioning,” that is individuals who may be questioning or exploring their sexuality and/or gender. |
| Pansexual                   | Refers to a person who is attracted to people of all genders and sexes.                                                                      |
| Queer                       | A previously derogatory term used to describe an LGBTQ person which has now been reclaimed by some people within the community. This term may still be seen as derogatory to many in the LGBTQ community and should not be used unless someone self-identifies as queer. |
| Sexual orientation          | A term referring to attraction towards other people (can be emotional, sexual, romantic, etc.).                                                   |
| Sexual and gender minority  | People whose sexual orientation, gender identity or expression, or reproductive development is characterized by non-binary constructs of sexual orientation, gender, and/or sex (as defined by the National Institutes of Health Sexual & Gender Minority Research Office). |
gender-neutral language until this is identified. Failure to do so can lead to reduced patient satisfaction and quality of care [27], which in turn further marginalizes this group by producing unnecessary healthcare-related trauma and potentially leading individuals to avoid healthcare altogether.

Access to Care

A large survey of nearly 20,000 transgender adults showed that nearly one-quarter of the sample avoided healthcare due to anticipated discrimination [28]. This has a major impact on access to care and potential interventions to prevent adverse health events. These concerns are not unfounded, as 19% of respondents to the 2010 National Transgender Discrimination Survey reported that they were refused care due to their gender identity. Further, 28% reported verbal harassment and 2% reported physical assault while trying to seek medical care [29]. An update to these data in 2015 showed that 33% of the respondents who saw a healthcare provider within the past year had at least one negative experience related to being transgender, and 23% of respondents reported that they did not seek healthcare due to fear of being mistreated as a transgender person [30].

In addition to anticipated concerns related to verbal and physical abuse, transgender individuals may also face unique structural and financial barriers preventing access to care [31]. These might include, for example, an electronic health record (EHR) system that does not accurately collect the patient’s gender identity and thus laboratory results may be erroneously flagged as abnormal or appear normal when they are not for that particular individual. The use of the EHR for billing may also lead to denial of necessary services due to gender discordance (for example, denial of a pap smear for a transgender man). Rates of unemployment are also substantially higher among transgender individuals as compared to the general population [32, 33], which may translate to inability to access medical care due to financial concerns. Indeed, the 2015 US Transgender Survey revealed that 33% of respondents did not go to a healthcare provider when needed because they could not afford it [30].

Overall, there are myriad barriers for transgender individuals to seek healthcare and this may explain the downstream effects borne out in the literature regarding disproportionate cardiovascular outcomes (see Fig. 1). For example, an analysis of over 6,000 transgender individuals showed that they were less likely to have health insurance or a primary care physician as compared to cisgender participants [34]. Even those individuals who do have access to care may experience difficulties in insurance coverage, particularly for gender-affirming treatments or surgeries [35]. These disparities in healthcare access can lead to delays in diagnosing important and modifiable stroke risk factors like hypertension and diabetes [36]. Further, transgender individuals might delay their presentation to the hospital for acute emergencies, which is particularly relevant in stroke where “time is brain” [37].
**Individual**
- Knowledge, attitudes, beliefs, and engagement with healthcare
- Internalized transphobia/societal stigma
- Health-related behaviors such as increased risk for substance use

**Interpersonal**
- Estrangement from biological family
- Social networks comprised of other SGM people which can build resiliency
- Clinician-patient relationship may be affected by both conscious and unconscious discrimination/bias

**Institutional**
- Organizational policies regarding workplace discrimination (e.g., access to gender congruent restrooms)
- Policies in healthcare to collect sexual orientation and gender identity, train healthcare professionals to ask for pronoun usage, ensure non-discrimination in access to healthcare

**Community**
- Lack of connectedness and shared spaces such as LGBT Centers in cities to promote wellbeing
- Resources for reducing and/or ending homelessness

**Public Policy**
- Policies that reinforce discrimination and transphobia such as criminalizing gender-affirming care for transgender youth
- Lack of federal policies that protect against discrimination in employment, housing, education, access to healthcare
- Lack of universal healthcare leading to reduced insurance coverage among transgender individuals

**Fig. 1** A conceptual framework for minority stress and its implication in cerebrovascular disease (a social ecological model adapted from McLeroy et al., 1988)
The Minority Stress Model

In 1981, Virginia Brooks developed the theory of minority stress in lesbian women [38]. This was later popularized by Ilan Meyer, who stated that the higher prevalence of mental health disorders among lesbian, gay, and bisexual people was partially explained by stigma, prejudice, and discrimination creating an inherently stressful environment, which in turn translated into mental health issues [39]. This concept was later applied to transgender individuals [40] to understand the unique challenges faced by this population. Over time, this model has been refined to include a variety of stressors, both proximal and distal, and to explain not only mental health disparities but physical as well. Proximal stressors might include anticipation of discrimination and internalized stigma related to one’s sexual orientation and/or gender identity, whereas distal stressors include lived experiences of prejudice or discrimination. Notably in the USA, there are structural issues at play that could negatively impact the health of transgender people, such as legislation passed in many states eliminating discrimination protections for transgender people and restricting access to gender-affirming care [41].

A 2020 systematic review found that minority stress is associated with adverse physical health outcomes, including poorer self-rated physical health, pain, HIV progression, cancer treatment side effects, cardiovascular function, and obesity [42•]. Further research by these authors identified that different subgroups within racial/ethnic and sexual/gender minority identities experienced relationships of differing strength with physical health: for example, among transwomen, victimization experiences had the strongest relationship with physical health whereas among cisgender sexual minority men, prejudice/discrimination experiences had the strongest relationship with physical health [43]. For sexual and gender minority individuals who identified as Hispanic, an accepting environment had the strongest relationship with physical health, whereas for those who identified as White or Asian, a safe current environment was more strongly associated. In contrast, for Black individuals, a safe environment where they were raised was most strongly associated with physical health. This suggests the importance of intersectionality—the complex interactions of social identities such as race, class, gender, and sexual orientation and how they impact lived experiences and social relations—in this relationship [44].

The relationship between vascular disease (and specifically stroke) and minority stress remains poorly understood, though two prior studies in HIV-positive men showed changes in cardiovascular gene expression and function after exposure to minority stress [45, 46]. This is an exciting and expanding field of research with the potential to uncover important and possibly addressable upstream causes of poor cardiovascular health in this population. The extent to which this may be applicable to transgender populations remains to be seen, though studies are underway to better understand this relationship [47].
Stroke Risk Factors and Vascular Disease in the Transgender Community

There are currently a paucity of studies examining cerebrovascular health among the transgender community; however, of the information currently available, it seems that this population faces unique and disproportionate stroke risk factors.

A 2017 analysis of over 2,000 transgender survey participants from the 2014–2016 Behavioral Risk Factor Surveillance System showed higher rates of vascular risk factors such as HIV infection, obesity, alcohol use disorder, tobacco use disorder, and sedentary lifestyle as compared to cisgender respondents [48]. Transmen had higher odds of cardiovascular disease compared to ciswomen, and gender-nonconforming individuals had higher odds of cardiovascular disease as compared to both cismen and ciswomen. A subsequent multivariate analysis of these data in 2019 showed that transmen had a substantially increased rate of myocardial infarction compared with cisgender men and women [8], even after adjusting for numerous vascular risk factors including age, diabetes, hypertension, hyperlipidemia, chronic kidney disease, smoking, and exercise. Transwomen had a significantly increased rate of myocardial infarction compared with ciswomen but not cismen. These findings led authors to speculate that increased social stressors, lower socioeconomic status, and higher rates of substance use contribute to these disparities. Due in part to these findings, the American Heart Association published a statement in 2021 highlighting the need to address cardiovascular health in the transgender population [49•].

In terms of risk factors specific to stroke, a case series of eight transwomen admitted for cerebrovascular disease at a single center showed a disproportionate prevalence of stimulant use, tobacco use, hepatitis C, HIV, and prior stroke or transient ischemic attacks in these patients [50]. Although small, this study highlights the need for addressing unique stroke risk factors in this population.

Other stroke risk factors remain incompletely understood in the transgender population. For example, there are inconsistent findings on blood pressure and dyslipidemia in transmen and transwomen, let alone in those who identify outside of the binary [51]. A retrospective study of 247 transgender patients at a gender clinic in Catalonia from 2006 to 2010 showed that transwomen had increases in blood pressure (though within normal range) on follow up but transmen did not [52]. There were no changes in lipid levels in transwomen, but transmen had a general worsening in lipid profiles as evidenced by increased total cholesterol, triglycerides, and low-density lipoprotein (LDL), and decreased high-density lipoprotein (HDL). The Catalonia findings on blood pressure were similar to a previous prospective study from the Netherlands with 37 transgender patients [53], but this showed slightly different results with respect to lipid profiles. In this study, transwomen treated with estrogen had improvement in lipid profile (higher HDL and lower LDL) whereas transmen treated with androgens had similarly worse lipid profiles. In contrast, a Japanese study of 111 transmen showed that those
who used androgens had increased systolic and diastolic blood pressure after
treatment for a mean of 45 months [54].

A retrospective medical chart review of 2517 transwomen and 1358
transmen who visited a gender clinic in the Netherlands from 1972 to 2015
found that those taking hormone therapy had higher incidences of stroke
and venous thromboembolic events as compared to reference cismen and
ciswomen [18]. Both transwomen and transmen taking hormone therapy
were found to have higher risk of myocardial infarction than reference cis-
women. The complex relationship between hormone therapy and stroke will
be reviewed in detail next.

The Role of Hormone Therapy in Stroke

Most of the literature to date regarding transgender individuals and cardio-
vascular outcomes has focused on the use of hormone therapy. For trans-
masculine individuals, this typically refers to the use of testosterone, and for
transfeminine individuals, this usually refers to the use of estrogen. However,
to date, most studies have been small, and therefore, conclusions are some-
what limited.

Mechanistically, there may be multiple factors contributing to the increased
risk of cardiovascular disease among transfeminine people using hormone
therapy. As a result of androgen deprivation, for example, transwomen may
start to experience features of metabolic syndrome, namely increased visceral
fat [55]. The association between estrogen and venous thromboembolism
(VTE) was first identified in cisgender people using oral contraceptives [56],
and it was not until the early 2000s that this was corroborated in postmeno-
pausal cisgender women using estrogen [57]. The pathophysiology remains
somewhat incompletely understood, though it is speculated that decreased
plasma levels of protein S and tissue factor inhibitor are responsible for the
increased activated protein C resistance during hormone use and may explain
the elevated risk of VTE [58]. Overall, the risk of VTE is increased by three
to fivefold in combined oral contraceptive users [59] with typical doses of
estrogen (ethinyl estradiol) in the 20–35 mcg range [60]. The doses used for
postmenopausal cisgender women are typically 17-beta estradiol 1 mg per
day orally or 0.05 mg per day of transdermal estrogen [61, 62]. In contrast,
doses used for transfeminine individuals are typically higher, ranging from 2
to 4 mg daily of oral 17-beta estradiol or 0.025–0.2 mg per day of transdermal
estrogen [63].

A 2014 review paper attempted to understand differences in cardiovascular
pathology between transmen and transwomen [64]. In cisgender popula-
ations, men have higher prevalence of cardiovascular disease than women
and tend to develop disease earlier [65], although women may have higher
mortality and poorer prognoses following an acute cardiovascular event [66].
In contrast, transwomen using estrogen have higher prevalence of cardiovas-
cular events as compared to transmen using testosterone. This finding has
led researchers to posit that the use of estrogen specifically is implicated,
although it should be mentioned that research is primarily retrospective and
thus conclusions regarding causation remain limited. One longitudinal study of mortality of over 1,000 transgender individuals in the Netherlands found that oral ethinyl estradiol was most culpable for increasing the risk of cardiovascular disease [67]. Specifically, use of ethinyl estradiol was associated with a threefold increase in risk of cardiovascular death. For these reasons, this formulation of estrogen is no longer used in gender-affirming care in the USA [68], although patients may still access this outside of the country or off the street if unable to access care. Notably, total mortality was 51% higher in transwomen as compared to the general population in the Dutch study [67]. Prior studies have shown that transdermal estrogen confers a lower risk of VTE as compared to oral estrogen [69, 70] and therefore may be a safer alternative for hormonal therapy.

Hormone Therapy and Ischemic Stroke

Despite the paucity of literature, a 2021 meta-analysis attempted to further uncover the relationship between ischemic stroke and transgender individuals, focusing on the role of hormone therapy [71]. This included a total of 14 studies. One of the studies examined was a large cohort study in the USA that assessed the incidence of VTE, ischemic stroke, and myocardial infarction among nearly 5,000 transgender individuals [17]. This used data from Kaiser Permanente in Georgia and California and followed patients for 4 years with each patient matched to 10 cisgender men and 10 cisgender women. The study found that transwomen had a higher incidence of VTE compared to both cismen and ciswomen (2-year risk differences of 4.1 and 3.4, respectively, and 8-year risk differences of 16.7 and 13.7, respectively). Overall estimates of VTE risk among transfeminine individuals taking estrogen are around 2–6% [67, 69], in contrast to healthy young women taking combined oral contraceptives whose risk is approximately 3–4 per 10,000 person-years [72]. The incidence of MI was higher in transwomen as compared to ciswomen but similar as compared to cismen. Transmen did not have significantly different incidences of cardiovascular events as compared to other groups.

The overall initial incidence of stroke was similar across all groups, although subgroup analysis of transwomen who began taking estrogen after enrollment found higher incidences of both VTE and ischemic stroke, though this risk was not evident until 2 years of follow up for VTE and 6 years of follow up for ischemic stroke. Incidence of MI was difficult to ascertain given low sample size. Study authors also performed an analysis of transmen who initiated testosterone therapy, though results were limited given low numbers of events in this group. Although this is an important study in the field of transgender research, important limitations should be highlighted. First, the study subjects were identified through ICD coding rather than self-report, which alters the composition of the sample. Additionally, formulations of estrogen were not divided into categories; therefore, it is unclear how many...
patients experienced cardiovascular events while taking oral versus transdermal estrogen, or older versus newer formulations.

An important disease process to consider in transgender patients taking hormone therapy is migraine with aura given its known association with increased risk for ischemic stroke [73–75]. This risk is particularly high in women taking oral contraceptives who have migraine with aura [76, 77], such that the United States Medical Eligibility Criteria for Contraceptive Use recommends against their use in this population [78]. There are no such guidelines specific to transgender patients; however, studies suggest that hormone therapy does affect migraine in transgender people. For example, one Italian study showed that prevalence of headache increased after use of estrogen in transwomen but decreased after use of testosterone in transmen [79]. In a different study, prevalence of visual aura was higher than expected among transwomen taking estrogen [80]. There is insufficient evidence to recommend complete cessation of hormone therapy in transwomen who experience migraine with aura, but it may be reasonable to switch from oral to transdermal formulations as this is less likely to trigger migraine and has lower risk for thrombosis [81]. Additionally, targeting other modifiable risk factors such as smoking would be valuable to reduce further risk of ischemic stroke in these patients. Overall, an individualized approach with careful discussion of risks and benefits of use of hormone therapy is best for transgender patients with migraine with aura given the lack of evidence on management.

Hormone Therapy and Hemorrhagic Stroke

There are very limited—and often conflicting—data regarding the role of hormone therapy in hemorrhagic stroke, and to date, none has specifically addressed transgender individuals. There are some data to suggest that current oral contraceptive use may increase the risk of subarachnoid hemorrhage (SAH) [82] but not intracerebral hemorrhage (ICH) [83]. A review paper highlighted some of the most salient studies, which have mainly focused on postmenopausal ciswomen taking hormone replacement therapy (HRT) [84]. One of the earliest case–control studies from 1981 assessed 23 women who had died from SAH and did not show a relationship between HRT and SAH [85]. A larger case–control study of 103 women who had suffered from SAH showed that the use of HRT was associated with reduced risk of SAH, but only among postmenopausal women who had a history of smoking [86]. A Swedish cohort study of 23,000 women investigated the relationship between HRT use and both SAH and ICH, and in their analysis, they found that HRT use was associated with a reduced risk of ICH but no association was found between HRT use and SAH [87]. A Danish study of 255 women who experienced non-fatal SAH or ICH did not show an association between current HRT use and SAH or ICH [88]. To date, the largest analysis of nearly 94,000 women in the Women’s Health Initiative assessed the risk of SAH over a 12-year period and found that postmenopausal women on active HRT had a 1.5-fold higher risk of developing SAH even after adjusting for potential
confounders [89]. Given these discrepant findings, it remains unclear how hormone therapy may affect the risk of hemorrhagic stroke, in particular with respect to transgender individuals who may be taking different formulations and dosages of hormone therapy and have different risk factors as compared to postmenopausal ciswomen.

### Hormone Therapy and Cerebral Venous Thrombosis

Although a relatively uncommon cause of stroke, cerebral venous thrombosis (CVT) is an important condition to identify given its diverse clinical presentation and unique management. Representing only 0.5 to 1% of strokes [90], people with CVT are more likely to be assigned female at birth and younger than the average stroke patient [91]. There are certain risk factors that may be relevant to the transgender population, most notably the use of hormone therapy, which will be reviewed further.

The most important risk factor for CVT appears to be a prothrombotic state, either acquired or inherited. There has also been renewed interest in CVT given reports of its association with adenoviral vector vaccines against the coronavirus disease-19 [92–94]. Multiple studies have identified the use of oral contraceptives as a risk factor for development of CVT [91, 95, 96], but data are more limited on hormone replacement therapy in postmenopausal women and even more sparse in the transgender population on estrogen. An Italian retrospective study of 48 patients showed that 25% of postmenopausal women with CVT were on HRT and this was considered an important risk factor [97]. One case report identified a transwoman on 8 mg estradiol daily who suffered from CVT without other known risk factors for hypercoagulability [98]. Another case report highlighted a CVT in a transwoman requiring decompressive surgery for management [99].

Given the potential association between CVT and use of hormone therapy in transfeminine people taking estrogen, there has been some discussion regarding the utility of thrombophilia screening in these individuals. One study of 251 transgender patients found that there was no significant difference in the prevalence of hypercoagulable disorders in these patients as compared to controls and therefore did not recommend routine screening for thrombophilia [100]. Currently, there is a lack of data to support other management decisions for transgender people on hormone therapy, such as withholding vaccines against coronavirus, although it may be reasonable to consider mRNA vaccines instead of adenovirus-based vaccines since these do not appear to carry the same risk for CVT [101]. Other risk factors for development of CVT, such as smoking and obesity, should be addressed and carefully discussed with transgender patients for stroke prevention.

Despite the potential adverse vascular events associated with use of estrogen, it should be emphasized that hormone therapy is medically necessary and is associated with increased quality of life, decreased depression, and decreased anxiety among transgender people [102, 103]. Therefore, healthcare
providers should engage in careful discussions with transgender patients who use hormonal therapy prior to discontinuing such treatments as the benefits may outweigh the risks. Alternatives to abrupt cessation of gender-affirming hormone therapy include lowering the dose to avoid supraphysiologic levels or transitioning from oral to transdermal formulations for estrogens.

Inpatient Hospitalization of Transgender Patients: Room for Improvement

The inpatient setting can be a potentially stressful environment for transgender patients given the prevalence of negative experiences reported in survey data. Examples include violation of patient privacy, improper name and pronoun usage, prohibitions to bathroom use, and inappropriate questions and examinations, among others. The Lambda Legal group, a nonprofit organization working towards improving the civil rights of the LGBT population, created a list of policies for healthcare providers to ensure equal access to quality healthcare for transgender patients [104].

A recent review paper highlighted some of the most important concerns for the acute clinical care of transgender patients [105], including the use of gender-neutral terminology until a patient discloses their pronouns and a thorough surgical history inclusive of an anatomic inventory.

Treatment of Stroke in Transgender Patients

As previously discussed, use of oral estrogen may increase risk of VTE and potentially ischemic stroke in transwomen. Transitioning to transdermal estrogen after a patient suffers from one of these adverse events may be warranted given its lower risk of cardiovascular events. Beyond this, there remain insufficient data to support any other trans-specific treatment protocols for stroke. We recommend following the latest guidelines from the American Heart Association and American Stroke Association for both treatment [106] and prevention [107] of stroke and transient ischemic attacks. In sum, this includes the use of antiplatelet agents or anticoagulation when indicated for ischemic stroke and risk factor modification for prevention of future strokes.

Transgender patients may benefit from individualized approaches with respect to risk factor modification, as previous research shows that this population shares unique stroke risk factors as compared to cisgender stroke survivors. For example, tobacco use may be more prevalent among transgender adults [108] and can increase the risk of thrombosis for patients taking estrogen [109, 110]; thus, concerted efforts at smoking cessation in this population are warranted.
Neurorehabilitation and Transgender Considerations

In the aftermath of a stroke, many patients will require some form of rehabilitation to improve their functional status. It has been estimated that the age-adjusted stroke death rate declined by 13.6% in the USA between 2007 and 2017 [111], suggesting a growing population of stroke survivors and increased need for comprehensive post-stroke care.

Long-term studies on stroke recovery highlight the ubiquity of deficits after stroke, with one Israeli study showing that more than 30% of stroke survivors have persistent deficits in a variety of settings [112]. In the USA, there have been recent studies describing racial and gender healthcare disparities in terms of stroke survival and recovery, though there are no studies describing disparities in terms of these outcomes with respect to transgender individuals. A systematic review in 2017 addressed the need for increased awareness of neurodisability among this population [113]. Authors found 3 prior studies of stroke recovery in the sexual minority population but none for transgender patients. They uncovered the importance of strong social support as a key factor in building resilience among transgender patients through an Australian survey of 169 transgender individuals [114], which may be useful for improving outcomes in neurorehabilitation.

There are several potential interventions to improve the care of transgender patients in rehabilitation centers after neurologic injury. This starts with capturing inclusive demographic information on admission to better understand their presence in such facilities as well as needs. Policies that explicitly include statements on gender diversity and non-discriminatory practices are also essential to minimizing concerns from patients. If able, we would recommend the use of single stall restrooms with gender-neutral signs to minimize discomfort for gender diverse patients. If single stall restrooms are not available, individuals should be empowered to use the restroom that most closely aligns with their gender identity. Finally, educating healthcare providers and other staff who work at rehabilitation centers in using inclusive language might make patients feel less stigmatized and more able to participate in therapy to maximize their recovery.

Conclusion and Future Directions

The transgender population faces numerous systemic and structural barriers that translate into overall worse health outcomes. Decreased access to healthcare and higher rates of discrimination, for example, interplay with health-related behaviors such as increased rates of substance use to further drive healthcare disparities with respect to vascular disease and stroke. These behaviors can be explained through the framework of the minority stress model, which posits that high rates of stigma and traumatic experiences lead to coping strategies such as substance use that further perpetuate disparities [13, 115]. From limited data, it appears that transgender patients have unique
stroke risk factors, some of which may be modifiable and future research should focus on these to reduce gaps in care. More research is needed to better understand the role of hormone therapy in stroke, but there is currently insufficient evidence to support abruptly discontinuing gender-affirming treatments in the aftermath of a vascular event.

On a policy and institutional level, several changes should be made to improve healthcare for transgender individuals. Increasing access to healthcare through enhanced coverage of both routine and gender-affirming medical care is one avenue for improvement. Accurate collection of demographic information in the medical record pertaining to sexual and gender orientation would enable further studies to capture the heterogeneity of this population and address other potentially unidentified disparities. Additionally, requiring education in training programs as well as continuing medical education for healthcare providers to address overrepresented stroke risk factors among transgender patients could reduce the likelihood of developing cerebrovascular disease. A 2019 survey of American Academy of Neurology member neurologists revealed that while the majority were aware of local and national barriers that inhibit sexual and gender minority people from using healthcare services, a third would not tailor neurologic care based on a patient’s identity, and 43% believed that sexual and gender minority identity had no bearing on the management of neurologic illness [116].

Future research should follow transgender patients longitudinally to better understand both risk factors and outcomes for stroke. Research may also benefit from adopting a more nuanced approach to better compare groups of transgender people, as there is ongoing controversy regarding the comparison of transwomen to cismen and transmen to ciswomen in medical literature with changing levels of hormones and body composition [117]. Rather than retrospective studies correlating the use of gender-affirming hormone therapy with vascular disease and stroke, longitudinal or even randomized studies would offer more definitive causality and enable clinicians to make evidence-based decisions. The Population Research in Identities and Disparities for Equality (PRIDE) Study is a large, national, longitudinal cohort study currently underway to investigate health patterns in sexual and gender minority people and we look forward to these results [7]. Focusing on stroke risk and outcomes will be important given the rapidly aging population of the USA and the expectation that gaps will remain in addressing unique needs of the transgender population.

Declarations

Conflict of Interest
Michael Diaz does not have existing conflicts of interest. Nicole Rosendale does not have existing conflicts of interest.

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

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

1. Herman JL, Flores AR, Brown TNT, Wilson BDM, Conron KJ. Age of individuals who identify as transgender in the United States. 2017 [cited 2022 Apr 11]. Available from: https://escholarship.org/uc/item/45f0k759
2. Klein DA, Paradise SL, Goodwin ET. Caring for transgender and gender-diverse persons: what clinicians should know. Am Fam Physician. 2018;98(11):645–53.
3. Institute of Medicine (US) Committee on Lesbian, Gay, Bisexual, and Transgender Health Issues and Research Gaps and Opportunities. The health of lesbian, gay, bisexual, and transgender people: building a foundation for better understanding [Internet]. Washington (DC): National Academies Press (US); 2011 [cited 2022 Apr 11]. (The National Academies Collection: Reports funded by National Institutes of Health). Available from: http://www.ncbi.nlm.nih.gov/books/NBK64806/
4. Director's Message for October 6, 2016 [Internet]. NIMHD. [cited 2022 Mar 8]. Available from: https://www.nimhd.nih.gov/about/directors-corner/messages/message_10-06-16.html
5. Carmel TC, Erickson-Schroth Laura. Mental health and the transgender population. J Psychosoc Nurs Ment Health Serv. 2016 Dec 1;54(12):44–8.
6. Bockting WO, Miner MH, Swinburne Romine RE, Hamilton A, Coleman E. Stigma, mental health, and resilience in an online sample of the US transgender population. J Psychosoc Nurs Ment Health Serv. 2016 Dec 1;54(12):44–8.
7. Rocking WO, Minin MH, Swinburne Romine RE, Hamilton A, Coleman E. Stigma, mental health, and resilience in an online sample of the US transgender population. J Psychosoc Nurs Ment Health Serv. 2016 Dec 1;54(12):44–8.
8. Alzahrani T, Nguyen T, Ryan A, Dwairy A, McCaffrey J, Yunus R, et al. Cardiovascular disease risk factors and myocardial infarction in the transgender population. Circ Cardiovasc Qual Outcomes. 2019;12(4):e005597.
9. Howerton I, Harris JK. Transgender identity and cardiovascular disease. Transgender Health [Internet]. 2021 Aug 19 [cited 2022 Apr 11]. Available from: https://www.liebertpub.com/doi/abs/10.1089/trgh.2020.0188
10. Wansom T, Guadamuz TE, Vasas S. Transgender populations and HIV: unique risks, challenges and opportunities. J Virus Erad. 2016;2(2):87–93.
11. Lake JE, Clark JL. Optimizing HIV prevention and care for transgender adults. AIDS Lond Engl. 2019;33(3):363–75.
12. Gosiker BJ, Lesko CR, Rich AJ, Crane HM, Kitahata MM, Reisner SL, et al. Cardiovascular disease risk among transgender women living with HIV in the United States. PLoS ONE. 2020;15(7):e0236177.
13. Connolly D, Gilchrist G. Prevalence and correlates of substance use among transgender adults: a systematic review. Addict Behav. 2020;111:106544.
14. Delahanty J, Ganz O, Hoffman L, Guillery J, Crankshaw E, Farrell M. Tobacco use among lesbian, gay, bisexual and transgender young adults varies by sexual and gender identity. Drug Alcohol Depend. 2019;191(1):161–70.
15. Wheldon CW, Wiseman RP. Tobacco use among transgender and gender non-conforming adults in the United States. Tob Use Insights. 2019 Jan 1;12:1179173X19849419.
16. Fabris B, Bernardi S, Trombetta C. Cross-sex hormone therapy for gender dysphoria. J Endocrinol Invest. 2015;38(3):269–82.
17. Getahun D, Nash R, Flanders WD, Baird TC, Becerra-Culqui TA, Cromwell L, et al. Cross-sex hormones and acute cardiovascular events in transgender persons. Ann Intern Med. 2018;169(4):205–13.
18. Nota NM, Wiepjes CM, de Blok CJM, Gooren L, Kreukels BPC, den Heijer M. Occurrence of acute cardiovascular events in transgender individuals receiving hormone therapy. Circulation. 2019;139(11):1461–2.
19. Wierckx K, Elaut E, Declercq E, Heylen G, Cuypere GD, Taes Y, et al. Prevalence of cardiovascular disease and cancer during cross-sex hormone therapy in a large cohort of trans persons: a case–control study. Eur J Endocrinol. 2013;169(4):471–8.
20. Tsao CW, Aday AW, Almarzooq ZI, Alonso A, Beaton AZ, Bittencourt MS, et al. Heart disease and stroke statistics—2022 update: a report from the American Heart Association. Circulation. 2022;145(8):e153-639.
21. Rosendale N, Wong JO, Flatt JD, Whitaker E. Sexual and gender minority health in neurology: a scoping review. JAMA Neurol. 2021 Jun 1;78(6):747–54.
Review paper highlighting literature to date regarding neurologic healthcare disparities among sexual and gender minority patients.
22. Glossary of Terms [Internet]. Human rights campaign. [cited 2022 Mar 8]. Available from: https://www.hrc.org/resources/glossary-of-terms
23. Haymer M, Buckler-Amabilis S, Lawrence K, Tye M. Language and history of the LGBTQ community. In: Lehman JR, Diaz K, Ng H, Petty EM, Thakuntha M, Eckstrand K, editors. The equal curriculum: the student and educator guide to LGBTQ health [Internet]. Cham: Springer International Publishing; 2020 [cited 2022 Jan 10]. p. 1–12. Available from: https://doi.org/10.1007/978-3-030-24025-7_1
24. PFLAG National Glossary of Terms [Internet], PFLAG. 2016 [cited 2022 Jan 10]. Available from: https://pflag.org/glossary
25. GLAAD Media Reference Guide-Transgender Terms [Internet]. GLAAD. 2022 [cited 2022 Apr 8]. Available from: https://www.glaad.org/reference/trans-terms
26. Terminology and definitions | gender affirming healthcare for the transgender population. Clin Biochem. 2014;47(10):983–7.
27. Mizock L, Lewis TK. Trauma in transgender populations: risk, resilience, and clinical care. J Emot Abuse. 2008;8(3):335–54.
28. Komot L, Corey KM, Barrett BJ, McCabe SE. Healthcare avoidance due to anticipated discrimination among transgender people: a call to create trans-affirmative environments. SSM - Popul Health. 2020;1(11):100608.
29. Grant J, Mottet L, Tanis J, Herman JL, Harrison J, Keisling M. National transgender discrimination survey report on health and health care. 2010.
30. James S, Herman J, Rankin S, Keisling M, Mottet L, Anafi M. The report of the 2015 U.S. transgender survey. 2016 [cited 2022 Mar 24]; Available from: https://nccvir.dspacedirect.org/handle/20.500.11990/1299
31. Roberts TK, Fantz CR. Barriers to quality health care for the transgender population. Clin Biochem. 2014;47(10):983–7.
32. Leppel K. Labor force status of transgender individuals. In: Zimmermann KE, editor. Handbook of labor, human resources and population economics [Internet]. Cham: Springer International Publishing; 2020 [cited 2022 Jan 3]. p. 1–16. Available from: http://link.springer.com/10.1007/978-3-319-57365-6_83-2
33. Drydakis N. The economics of being LGBT. A review: 2015–2020 [Internet]. GLO Discussion Paper; 2021 [cited 2022 Mar 10]. Report No.: 980. Available from: https://www.econstor.eu/handle/10419/246076
34. dickey lore m., Budge SL, Katz-Wise SL, Garza MV. Health disparities in the transgender community: exploring differences in insurance coverage. Psychol Sex Orientat Gend Divers. 2016;3(3):275–82.
35. Learmonth C, Vilia R, Lambert C, Goldhammer H, Keuroghlian AS. Barriers to insurance coverage for transgender patients. Am J Obstet Gynecol. 2018;219(3):272.e1-272.e4.
36. O’Donnell MJ, Xavier D, Liu L, Zhang H, Chin SL, Rao-Melacini P, et al. Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study. The Lancet. 2010;376(9735):112–23.
37. Time is brain—quantified | stroke [Internet]. [cited 2022 Mar 24]. Available from: https://www.ahajournals.org/doi/full/10.1161/01.STR.0000196957.55928.9b
38. Brooks VR. Minority stress and lesbian women. Lexington Books; 1981. 246 p.
39. Meyer IH. Prejudice, social stress, and mental health in lesbian, gay, and bisexual populations: conceptual issues and research evidence. Psychol Bull. 2003;129(5):674–97.
40. Hendricks ML, Testa RJ. A conceptual framework for clinical work with transgender and gender nonconforming clients: an adaptation of the minority stress model. Prof Psychol Res Pract. 2012;43(5):460–7.
41. Walch A, Davidge-Pitts C, Safer JD, Lopez X, Tangpricha V, Iwamoto SJ. Proper care of transgender and gender diverse persons in the setting of proposed discrimination: a policy perspective. J Clin Endocrinol Metab. 2021;106(2):305–8.
42. Flentje A, Heck NC, Brennan JM, Meyer IH. The relationship between minority stress and biological outcomes: a systematic review. J Behav Med. 2020 Oct;43(5):673–94. Comprehensive review article displaying the complex relationship between minority stress and physical healthcare disparities among transgender patients.
43. Flentje A, Clark KD, Cicero E, Capriotti MR, Lubensky ME, Sauceda J, et al. Minority stress, structural stigma, and physical health among sexual and gender minority individuals: examining the relative strength of the relationships. Ann Behav Med Publ Soc Behav Med. 2021 Jun 22;kaab051.
44. Harris A, Bartlow S. Intersectionality: race, gender, sexuality, and class. In: DeLamater J, Plante RF, editors. Handbook of the sociology of sexualities [Internet]. Cham: Springer International Publishing; 2015 [cited 2022 Jan 7]. p. 261–71. (Handbooks of Sociology and Social Research). Available from: https://doi.org/10.1007/978-3-319-17341-2_15
45. Flentje A, Kober KM, Carrico AW, Neilands TB, Flowers E, Heck NC, et al. Minority stress and leukocyte gene expression in sexual minority men living with treated HIV infection. Brain Behav Immun. 2018;70:335–45.
46. Henge UR, Reimann G, Schäfer A, Goos M. HIV-positive men differ in immunologic but not catecholamine response to an acute psychological stressor. Psychoneuroendocrinology. 2003;28(5):643–56.
47. Rich AJ, Williams I, Mallik M, Wirtz A, Reisner S, DuBois LJ, et al. Biopsychosocial mechanisms linking gender minority stress to HIV comorbidities among black and Latina transgender women (LITE Plus): protocol for a
mixed methods longitudinal study. JMIR Res Protoc. 2020;9(4):e17076.
48. Downing JM, Przedworski JM. Health of transgender adults in the U.S., 2014–2016. Am J Prev Med. 2018 Sep;55(3):336–44.
49. Streed CG, Beach LB, Caceres BA, Dowshen NL, Moreau KL, Mukherjee M, et al. Assessing and addressing cardiovascular health in people who are transgender and gender diverse: a scientific statement from the American Heart Association. Circulation. 2021 Aug 10;144(6):e136–48.
50. LaHue SC, Torres D, Rosendale N, Singh V. Stroke characteristics, risk factors, and outcomes in transgender adults: a case series. Neurologist. 2019;24(2):66–70.
51. Irwig MS. Cardiovascular health in transgender people. Rev Endocr Metab Disord. 2018;19(3):243–51.
52. Quirós C, Patrasciou I, Mora M, Aranda GB, Hanzu FA, Gómez-Gil E, et al. Effect of cross-sex hormone treatment on cardiovascular risk factors in transsexual individuals. Experience in a specialized unit in Catalonia. Endocrinol Nutr. 2015 May 1;62(5):210–6.
53. Elbers JMH, Giltay EJ, Teerlink T, Scheffer PG, Asscheman H, Seidell JC, et al. Effects of sex steroids on components of the insulin resistance syndrome in transsexual subjects. Clin Endocrinol (Oxf). 2003;58(5):562–71.
54. Emi Y, Adachi M, Sasaki A, Nakamura Y, Nakatsuka M. Increased arterial stiffness in female-to-male transsexuals treated with androgen. J Obstet Gynaecol Res. 2008;34(5):890–7.
55. Gooren LJ, Giltay Ej, Bunck MC. Long-term treatment of transsexuals with cross-sex hormones: extensive personal experience. J Clin Endocrinol Metab. 2008;93(1):19–25.
56. Vessey M, Mant D, Smith A, Yeates D. Oral contraceptives and venous thromboembolism: findings in a large prospective study. Br Med J Clin Res Ed. 1986;292(6519):526.
57. Miller J, Chan BKS, Nelson HD. Postmenopausal estrogen replacement and risk for venous thromboembolism. Ann Intern Med. 2002;136(9):680–90.
58. Tchaikovski SN, Rosing J. Mechanisms of estrogen-induced venous thromboembolism. Thromb Res. 2010;126(1):5–11.
59. van Vlijmen EFW, Veeger NJGM, Middeldorp S, Hamulyák K, Prins MH, Büller HR, et al. Thrombotic risk during oral contraceptive use and pregnancy in women with factor V Leiden or prothrombin mutation: a rational approach to contraception. Blood. 2011 Aug 25;118(8):2055–61; quiz 2375.
60. Sech LA, Mishell DR. Oral steroid contraception. Womens Health Lond Engl. 2015;11(6):743–8.
61. Maclennan AH, Broadbent JL, Lester S, Moore V. Oral oestrogen and combined oestrogen/progestogen therapy versus placebo for hot flushes. Cochrane Database Syst Rev. 2004 Oct 18;(4):CD002978.
62. Steingold KA, Laufer L, Chetkowski RJ, DeFazio JD, Matt DW, Meldrum DR, et al. Treatment of hot flushes with transdermal estradiol administration. J Clin Endocrinol Metab. 1985;61(4):627–32.
63. Hembree WC, Cohen-Kettenis PT, Gooren L, Hannema SE, Meyer WJ, Murad MH, et al. Endocrine treatment of gender-dysphoric/gender-incongruent persons: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2017;102(11):3869–903.
64. Gooren LJ, Wierckx K, Giltay EJ. Cardiovascular disease in transsexual persons treated with cross-sex hormones: reversal of the traditional sex difference in cardiovascular disease pattern. Eur J Endocrinol. 2011 Apr 1;164(4):635–42.
65. Rossouw JE. Hormones, genetic factors, and gender differences in cardiovascular disease. Cardiovasc Res. 2002;53(3):550–7.
66. Gao Z, Chen Z, Sun A, Deng X. Gender differences in cardiovascular disease. Med Nov Technol Devices. 2019;1(4):100025.
67. Asscheman H, Giltay EJ, Megens JA, Ronde W (Pim) de, Trotsenburg MAA van, Gooren LJG. A long-term follow-up study of mortality in transsexuals receiving treatment with cross-sex hormones. Eur J Endocrinol. 2011 Apr 1;164(4):635–42.
68. Guidelines for the primary and gender-affirming care of transgender and gender nonbinary people | gender affirming health program [Internet]. [cited 2022 Mar 8]. Available from: https://transcare.ucsf.edu/guidelines
69. Van Kesteren PJM, Asscheman H, Megens JA, Gooren LJG. Mortality and morbidity in transsexual subjects treated with cross-sex hormones. Clin Endocrinol (Oxf). 1997;47(3):337–43.
70. Downing JM, Przedworski JM. Health of transgender adults receiving hormone therapy. Ann Intern Med. 2017;167(4):256–67.
71. Ignacio KHD, Diestro JDB, Espritui AL, Pineda-Franks MC. Stroke in male-to-female transgenders: a systematic review and meta-analysis. Can J Neurol Sci. 2022;49(1):76–83.
72. Vandenbroucke JP, Rosing J, Bloemenkamp KWM, Middeldorp S, Helmerhorst FM, Bouma BN, et al. Oral contraceptives and the risk of venous thrombosis. N Engl J Med. 2001;344(20):1527–35.
73. Spector JT, Kahn SR, Jones MR, Jayakumar M, Dalal D, Nazarian S. Migraine headache and ischemic stroke: an updated meta-analysis. Ann Intern Med. 2010;123(7):612–24.
74. Hu X, Zhou Y, Zhao H, Peng C. Migraine and the risk of stroke: an updated meta-analysis of prospective cohort studies. Neurol Sci Off J Ital Neurol Soc Ital Soc Clin Neurophysiol. 2017;38(1):33–40.
75. Schürks M, Rist PM, Bigal ME, Buring JE, Lipton RB, Kurth T. Migraine and cardiovascular disease: systematic review and meta-analysis. BMJ. 2009;27(339):b3914.
76. Tepper NK, Whitman MK, Zapata LB, Marchbanks PA, Curtis KM. Safety of hormonal contraceptives among women with migraine: a systematic review. Contraception. 2016;94(6):630–40.
77. Champaloux SW, Tepper NK, Monsour M, Curtis KM, Whiteman MK, Marchbanks PA, et al. Use of combined hormonal contraceptives among women with migraines and risk of ischemic stroke. Am J Obstet Gynecol. 2017;216(5):489.e1-489.e7.

78. Curtis KM, Tepper NK, Jatlaoui TC, Berry-Bibee E, Horton LG, Zapata LB, et al. U.S. medical eligibility criteria for contraceptive use, 2016. MMWR Recomm Rep Morb Mortal Wkly Rep Recomm Rep. 2016 Jul 29;65(3):1–103.

79. Aloisi AM, Bachiocco V, Costantino A, Stefani R, Cecarelli I, Bertaccini A, et al. Cross-sex hormone administration changes pain in transsexual women and men. Pain. 2007;132(Suppl 1):S60–7.

80. Pringsheim T, Gooren L. Migraine prevalence in male to female transsexuals on hormone therapy. Neurology. 2004;63(3):593–4.

81. MacGregor EA, van den Brink AM. Transgender and migraine. In: Maassen van den Brink A, MacGregor EA, editors. Gender and migraine [Internet]. Cham: Springer International Publishing; 2019 [cited 2022 Jun 10]. p. 113–27. (Headache). Available from: https://doi.org/10.1007/978-3-030-02988-3_9

82. Algra AM, Klijn CJM, Helmerhorst FM, Algra A, Rinkel GJE. Female risk factors for subarachnoid hemorrhage: a systematic review. Neurology. 2012;79(12):1230–6.

83. Plu-Bureau G, Hugon-Rodin J, Maitrot-Mantelet L, Canonico M. Hormonal contraceptives and arterial disease: an epidemiological update. Best Pract Res Clin Endocrinol Metab. 2013;27(1):35–45.

84. Paganini-Hill A. Hormone replacement therapy and stroke: risk, protection or no effect? Maturitas. 2001;38(3):243–61.

85. Adam S, Williams V, Vessey MP. Cardiovascular disease and hormone replacement treatment: a pilot case-control study. Br Med J Clin Res Ed. 1981;282(6272):1277–8.

86. Longstreth WT, Nelson LM, Koepsell TD, van Belle G. Subarachnoid hemorrhage and hormonal factors in women: a population-based case-control study. Ann Intern Med. 1994;121(3):168–73.

87. Falkeborn M, Persson I, Terënt A, Adami HO, Lithell H, Bergström R. Hormone replacement therapy and the risk of stroke: follow-up of a population-based cohort in Sweden. Arch Intern Med. 1993;153(10):1201–9.

88. Pedersen AF, Lidegaard Ø, Kreiner S, Ottensen B. Hormone replacement therapy and risk of non-fatal stroke. The Lancet. 1997;350(9087):1277–83.

89. Qureshi AI, Malik AA, Saeed O, Defilippo A, Suri CLM. High risk of cerebral-vein thrombosis in carriers of a prothrombin-gene mutation and in users of oral contraceptives. N Engl J Med. 1998;338(25):1793–7.

90. Opaskar A, Scharf EL, Chilungu MJ, Kelly AG. Transgender venous thrombosis. Neurrol Clin Pract. 2017;7(6):331–3.

91. Lopes CCB, da Silva VTF, Lucio JEDC, Yamashita RHG, Comerlatti LR, Luanto LT, et al. Malignant cerebral venous thrombosis in a transgender patient: intraoperative aspect of vein of Trolard thrombosis. Arq Neuropsiquiatr. 2021;79(79):938–9.

92. Ropper AH, Klein JP. Cerebral venous thrombosis. N Engl J Med. 2005;352(17):1791–8.

93. Pottégård A, Lund LC, Karlstad Ø, Dahl J, Andersen M, Hallsjö J, et al. Arterial events, venous thromboembolism, thrombocytopenia, and bleeding after vaccination with Oxford-AstraZeneca ChAdOx1-S in Denmark and Norway: population based cohort study. BMJ. 2021;5(373):n1114.

94. Tu TM, Yi SJ, Koh JS, Saffari SE, Hoe RHM, Chen GJ, et al. Incidence of cerebral venous thrombosis following SARS-CoV-2 infection vs mRNA SARS-CoV-2 vaccination in Singapore. JAMA Netw Open. 2022;5(3):e222940.

95. Bortolotti M, Tavassoli A, Sirimanne S, Zhang PQ, Rota LU, et al. High rate of cerebral-vein thrombosis in carriers of a prothrombotic condition. The Cerebral Venous Sinus Thrombosis Study Group. BMJ. 1998 Feb 21;316(7131):589–92.

96. Martinelli I, Sacchi E, Landi G, Taillori E, Duca F, Mannucci PM. High risk of cerebral-vene thrombosis in carriers of a prothrombin-gene mutation and in users of oral contraceptives. N Engl J Med. 1998;338(25):1793–7.

97. Terazzi E, Mittino D, Ruda R, Cerrato P, Monaco F, Sciolla R, et al. Cerebral venous thrombosis: a retrospective multicentre study of 48 patients. Neur. Sci. 2005;25(6):311–5.

98. Ropper AH, Klein JP. Cerebral venous thrombosis. N Engl J Med. 2005;352(17):1791–8.
for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2019;50(12):e344-418.

107. Kleindorfer DO, Towfighi A, Chaturvedi S, Cockroft KM, Gutierrez J, Lombardi-Hill D, et al. 2021 Guideline for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline from the American Heart Association/American Stroke Association. Stroke. 2021;52(7):e364-467.

108. Buchting FO, Emory KT, Scout, Kim Y, Fagan P, Vera LE, et al. Transgender use of cigarettes, cigars, and e-cigarettes in a national study. Am J Prev Med. 2017 Jul 1;53(1):e1–7.

109. Lidegaard Ø. Smoking and use of oral contraceptives: impact on thrombotic diseases. Am J Obstet Gynecol. 1999 Jun 1;180(6, Supplement):S357–63.

110. Wessler S. Estrogen-associated thromboembolism. Ann Epidemiol. 1992;2(4):439–43.

111. Virani SS, Alonso A, Benjamin EJ, Bittencourt MS, Callaway CW, Carson AP, et al. Heart disease and stroke statistics—2020 update: a report from the American Heart Association. Circulation. 2020;141(9):e139-596.

112. Gadidi V, Katz-Leurer M, Carmeli E, Bornstein NM. Long-term outcome poststroke: predictors of activity limitation and participation restriction. Arch Phys Med Rehabil. 2011;92(11):1802–8.

113. Moreno A, Laoch A, Zasler ND. Changing the culture of neurodisability through language and sensitivity of providers: creating a safe place for LGBTQIA+ people. NeuroRehabilitation. 2017;41(2):375–93.

114. Bariola E, Lyons A, Leonard W, Pitts M, Badcock P, Couch M. Demographic and psychosocial factors associated with psychological distress and resilience among transgender individuals. Am J Public Health. 2015;105(10):2108–16.

115. Kidd SA, Veltman A, Gately C, Chan KJ, Cohen JN. Lesbian, gay, and transgender persons with severe mental illness: negotiating wellness in the context of multiple sources of stigma. Am J Psychiatr Rehabil. 2011;14(1):13–39.

116. Rosendale N, Ostendorf T, Evans DA, Weathers A, Sico JJ, Randall J, et al. American Academy of Neurology members’ preparedness to treat sexual and gender minorities. Neurology. 2019;93(4):159–66.

117. Harper J, O’Donnell E, Khorashad BS, McDermott H, Witcomb GL. How does hormone transition in transgender women change body composition, muscle strength and haemoglobin? Systematic review with a focus on the implications for sport participation. Br J Sports Med. 2021;55(15):865–72.

Publisher’s Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.