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Cerebrovascular Disorders (D Jamieson, Section Editor)

Diagnosis, Treatment, and Prevention of Stroke in Transgender Adults

Michael Diaz, MD[1]
Nicole Rosendale, MD[1,*]

Address
[*,1]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

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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.

Introduction

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).

Table 1 A glossary of terminology

Gender terminology	
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 metoidoplasty. 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	

Table 1 (continued)

Gender terminology	
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).

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

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].

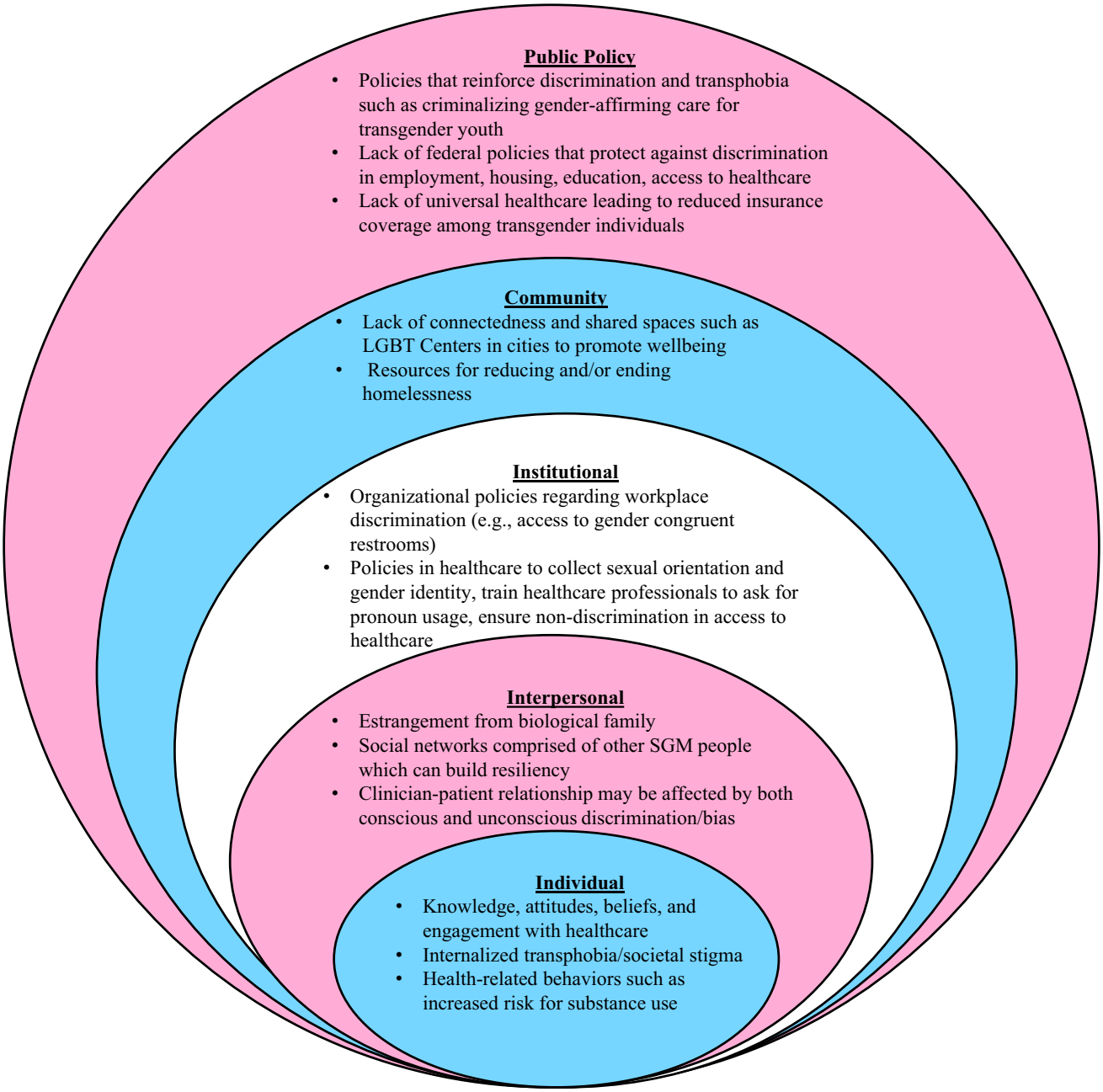

Fig. 1 A conceptual framework for minority stress and its implication in cerebrovascular disease (a social ecological model adapted from McLeroy et al., 1988)

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 ciswomen. 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 cardiovascular outcomes has focused on the use of hormone therapy. For transmasculine 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 somewhat 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 postmenopausal 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 populations, 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 cardiovascular 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.

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