



Racial and Ethnic Disparities in Stroke Reperfusion Therapy in the USA

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Abstract

Racial and ethnic inequities in stroke care are ubiquitous. Acute reperfusion therapies, i.e., IV thrombolysis (IVT) and mechanical thrombectomy (MT), are central to acute stroke care and are highly efficacious at preventing death and disability after stroke. Disparities in the use of IVT and MT in the USA are pervasive and contribute to worse outcomes among racial and ethnic minority individuals with ischemic stroke. A meticulous understanding of disparities and underlying root causes is necessary in order to develop targeted mitigation strategies with lasting effects. This review details racial and ethnic disparities in the use of IVT and MT after stroke and highlights inequities in the underlying process measures as well as the contributing root causes. Furthermore, this review spotlights the systemic and structural inequities that contribute to race-based differences in the use of IVT and MT, including geographic and regional differences and differences based on neighborhood, zip code, and hospital type. In addition, recent promising trends suggesting improvements in racial and ethnic IVT and MT disparities and potential approaches for future solutions to achieve equity in stroke care are briefly discussed.

Keywords IV thrombolysis · Endovascular therapy · Mechanical thrombectomy · Stroke disparities · Racial and ethnic disparities

Making the Case for a Focus on Disparities in Stroke Reperfusion Therapy

Racial and ethnic inequities in stroke in the USA are pervasive, including disparities in stroke risk factor prevalence and primary prevention, disparate use of in-hospital acute stroke care procedures and processes, and inequities in post-stroke rehabilitation and recovery as well as secondary prevention [1, 2]. There are several important underlying drivers of healthcare inequities, including differential access to healthcare, differences in quality of care within and between institutions, differences in interfacing with healthcare, and differential delivery of evidence-based care. Care access and quality are estimated to account for ~10–20% of the modifiable contributors to health outcomes [3], while the remaining 80–90% of health outcomes are determined by health behaviors, social and economic factors (e.g., education, income, and community safety), and the physical

environment (housing, air/water quality, etc.). Although care inequities constitute only a relatively small proportion of all modifiable contributors to health outcomes, the focus of this review is on racial and ethnic disparities in acute stroke reperfusion therapy for the following reasons. One, stroke reperfusion therapy and its related care processes readily fall under the purview of physicians and other healthcare providers both individually and collectively, thus allowing for generally unimpeded optimization or modification of care processes. For example, improving door-to-needle times or increasing equity in reperfusion therapy are arguably more readily achievable for healthcare providers than modifying patients' neighborhood, income, or educational attainment. Two, while an opportunity to address ~10–20% of inequities in acute stroke care may appear to be of little significance on first sight, one should consider that ~43% of all stroke deaths in Black people in the USA are preventable and in excess of preventable stroke deaths among White people [4]. Therefore, even a small relative reduction in inequities applicable to a lot of people would have wide implications on a population level with many lives saved or disability prevented. While this thought experiment is based on mortality data, it is likely that the gain to reduce stroke-related disability is similar, with even more consequential societal health

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implications. Three, stroke reperfusion therapies, i.e., the use of IV thrombolysis (IVT) and mechanical thrombectomy (MT), are highly efficacious interventions, i.e., the number needed to treat (NNT) for functional independence after IVT in the 0–3 h window is ~ 10, and the NNT for improvement by at least one point of the modified Rankin Scale after IVT is ~ 3.6 for patients treated within 3 h [5, 6]; the NNT after MT for patients treated within 6 h is ~ 2.6 [7]. These interventions typically set the tone for the course of patients' stroke hospitalizations. In turn, functional status at hospital discharge is strongly correlated with long-term functional status [8, 9]. This suggests that racial and ethnic differences in long-term functional outcomes are largely rooted in differences in functional outcomes at the time of discharge. Disparities in discharge functional status is the consequence of differential use of a number of inpatient acute stroke care processes [10], including reperfusion therapies.

Methodological challenges when studying disparities can arise from a trade-off between low patient numbers and high degree of statistical uncertainty when attempting granular reporting on each racial/ethnic group and the loss of information when lumping together various racial and ethnic minority groups in order to obtain meaningful statistical estimates. While combining different racial and ethnic minority groups may at times be methodologically sound and necessary, in particular when there is little heterogeneity in the observed effect among the different individual race/ethnicity groups, it is highly encouraged to report estimates for each race and ethnicity groups separately [11]. The lumping together of several or all racial/ethnic minority groups can mask the magnitude in treatment inequities in the most disenfranchised group(s) because the relatively better faring other groups are attenuating the overall effect for the entire "racial minority" group; this is particularly the case when the most disenfranchised also have low numerical representation in the data. In stroke disparities, a common theme across various stroke-related procedures and process measures is that Black patients consistently fare worse than their other racial minority counterparts. As such, it is highly discouraged to combine Black patients with other racial/ethnic minority groups so as to avoid underestimating the disparity magnitude in Black individuals and to allow for a nuanced understanding of differences by various racial and ethnic groups [12]. Whenever possible, reporting of estimates for each individual racial and ethnic minority groups should occur [11].

This narrative review summarizes and contextualizes the available evidence on racial and ethnic disparities in acute reperfusion therapies. Specifically, this review discusses the current knowledge on racial and ethnic disparities in IVT and MT. The underlying individual and systemic causes are discussed, and an outlook to potential solution is provided. While disparities in stroke care are a global issue, this

review focuses on race disparities in the USA. Differences in language proficiency and socioeconomic status, although tied to disparities based on race and ethnicity, are beyond the scope of this review and are not specifically discussed.

Thrombolysis

IVT has been the cornerstone of acute ischemic stroke therapy since the mid-to-late 1990s and is associated with improved long-term outcomes [13, 14]. The benefit of IVT is time-dependent, and fast administration of IVT, e.g., via a short door-to-needle (DTN) time, is associated with better short-term and long-term outcomes in clinical practice [15, 16]. DTN time is an important quality metric in stroke care with a target of < 60 min in the majority of patients [17]. Due to efficient building of systems of care and increasing stroke awareness in the population, rates of IVT use in the USA have significantly increased in all-comers in recent years, now exceeding 10% of all ischemic stroke patients [18].

Racial and Ethnic Disparities in Stroke Thrombolysis

In the USA, racial and ethnic disparities in the use of IVT after stroke have been demonstrated in various settings. Lower use of IVT in Black patients has been consistently demonstrated across various data sources, including the National Inpatient Sample (NIS), Get-With-The-Guidelines (GWTG), and other datasets [19–31], and this association is independent of the severity of the neurological deficit as assessed by the NIH Stroke Scale [20, 22]. Black patients have ~ 10–20% lower odds of receiving IVT than White patients, and their IVT rates are ~ 1–2 percentage points lower than their White counterparts, translating to ~ 1500 Black stroke patients annually who do not undergo IVT but would have received IVT if rates for White and Black patients were equal [18]. Similarly, although studies specific to Asian American/Pacific Islander (AA/PI) patients are sparse, data from GWTG and the NIS suggest that IVT use is lower in AA/PI patients compared to their White counterparts [22, 30, 32]. The data in Hispanic patients have been less consistent, with some studies suggesting a disparity [19, 26, 29, 33], while others found no significant differences in IVT use in Hispanic compared to White patients [22, 25, 31, 33, 34]. Reasons for this may include the heterogeneity of Hispanic patient populations [33] and the studied time period, i.e., disparities in Hispanics may have been particularly dynamic over time. This is evidenced by data from the NIS suggesting that a gradual relative increase in IVT in Hispanic patients in recent years has led to the closing of the disparity gap in IVT use among Hispanic patients,

while IVT disparities in Black and AA/PI populations have persisted [18, 30]. Only a few studies report specifically on the use of IVT in Native American patients, in part due to relatively low patient numbers in various datasets; however, data from the NIS suggest that IVT is underutilized in Native Americans at a magnitude comparable to Black patients [22, 26].

Causes and Mechanisms of Disparities in Stroke Thrombolysis

While the lower use of IVT in racial minorities is well described, the underlying mechanisms are not fully understood. The underlying causes for racial disparities in IVT use are complex and multifactorial since IVT use is the end result of a cascade of events, including pre- and in-hospital processes. Delay in presentation is one common reason for differential use of IVT by race. Indeed, racial and ethnic minority patients have greater delay in arrival to the ED compared to their White counterparts [21, 24, 35–37]. Similarly, racial and ethnic minorities are less likely to arrive by ambulance and more likely to arrive by car or other means [31, 33–35, 37–40]. Lower use of ambulances among racial and ethnic minorities may not simply be a matter of preference or lack of knowledge or health literacy. Many patients are aware of surprise ambulance bills, i.e., bills to the patient for an emergent ambulance ride to the hospital which are not covered by insurance and commonly are upwards of \$1000 per ground ambulance ride. The fear of additional costs for an ambulance ride may dissuade some patients and families, particularly those who are economically vulnerable, from calling an ambulance at the time of a stroke, thus resulting in delayed presentation [41, 42]. Geographical variations of ambulance costs, i.e., higher price tags in areas characterized by a higher proportion of people below the poverty line and with low education attainment, highlight the complex intertwining of race, income, education, and location of residence as determinants of inequities [41]. Once in the ED, DTN times are longer among Black but not Asian patients compared to their White counterparts [32, 43, 44]. Longer DTN times may partly be due to the generally longer ED wait times among Black stroke patients, including those who are eligible for IVT [39], and higher likelihood of Black patients presenting to hospitals without formalized stroke care pathways [45, 46]. It is conceivable that the compounding of the aforementioned delays leads to IVT ineligibility among some racial/ethnic minority patients because they cannot be treated with IVT within the traditional window of <4.5 h from last know well; however, delay in presentation alone does not sufficiently explain the observed racial/ethnic differences in IVT, as evidenced by several studies

that have shown that IVT rates are lower in Black patients even among those patients who are presenting within the appropriate IVT time window [21, 24, 25, 28, 31].

Reports that racial and ethnic minority patients are more likely to refuse thrombolytic therapy have to be viewed in context and are unlikely reflective of racial differences in personal risk-benefit analysis or preferences [27, 47]. Refusal of any offered therapy in the healthcare setting occurs in the context of prior experiences in the healthcare system, individual patient-provider rapport, and counseling and information-giving by the provider(s) offering the therapy. Prior experiences of discrimination and racism, distrust in the healthcare system, and unconscious bias affecting communication behavior and counseling by providers may contribute to differential acceptance of proposed therapies. Therefore, it is important to examine the underlying potentially modifiable root causes of “refusal”. Without accounting for the context, the use of the term “refusal” should be discouraged since it carries negative connotations in that it directs blame towards the patient.

Mechanical Thrombectomy

Endovascular therapy has been a treatment option for ischemic stroke caused by large vessel occlusions (LVOs) for over 20 years [48], but it was not until the publication of several seminal clinical trials in 2015 that MT became the standard of care for patients presenting with LVOs in the anterior circulation within 6 h of onset [7, 49–54]. Subsequently, MT was shown to also be highly efficacious in anterior circulation LVOs in the extended time window up to 24 h after last known well and in basilar artery occlusion [55–58]. Disparities in utilization of MT are particularly impactful on a population level considering the relatively high likelihood of poor outcome after LVO strokes in absence of MT and the large effect size of the benefit of MT (NNT ~2.6 to reduce disability in patients who are treated within 6 h [7] and NNT ~3.2 for functional independence in patients treated up to 24 h) [59]. In other words, treatment disparities in a highly efficacious procedure for a condition that carries high likelihood of disability or death in a relatively common disease can have tremendous impact on health outcomes on a population level.

Racial and Ethnic Disparities in Mechanical Thrombectomy

Despite an overall increase in the use of MT in recent years across all racial and ethnic groups, underutilization of MT has been consistently reported for Black stroke patients with LVO in administrative as well as clinical registry data in

various time periods [22, 30, 60–65]; however, it is noteworthy that the magnitude of the disparity has been decreasing since 2015, possibly in part due to the increasing organization of stroke care and the resulting implementation of stroke pathways for LVO treatment [64]. Similarly, MT is underutilized in Native Americans at a magnitude comparable to Black patients [22, 62], mirroring observations of underutilization of IVT among Native Americans. In contrast, studies using data from the NIS, state administrative data, and GWTG found no difference in MT utilization in Hispanic compared to White patients [22, 30, 60–62, 64]. Similarly, analyses of NIS and GWTG data suggests that there are no disparities in MT use among AA/PI individuals [22, 30, 62, 64]. These observations highlight two important points common to disparities in medicine. One, there can be, and often is, substantial heterogeneity of disparities between various race and ethnicity groups. Two, Black people commonly fare worse than their other non-White racial/ethnic minority counterparts. Therefore, particular emphasis should be placed on addressing disparities among Black individuals; doing so would not only address disparities among the most disenfranchised but also effectively impact health on a population level.

Causes and Mechanisms of Disparities in Mechanical Thrombectomy

Some process measures described for IVT are equally applicable to MT, including delay in presentation, since they depend on symptom recognition and pre-hospital factors common to both IVT and MT. Process measures unique to stroke patients with LVOs eligible for MT include rate of transfer to a thrombectomy center and door-to-groin puncture times. Similar to racial and ethnic disparities in IVT use, Black patients with LVO who are transferred to a thrombectomy-capable or comprehensive stroke center (CSC) or who present directly to a CSC have longer arrival times than comparable White patients [65, 66]. Black and Hispanic LVO patients are more likely to present as “walk-ins,” e.g., via private vehicle, as opposed to via emergency medical services (EMS) or transfer, and have significantly longer door-to-groin puncture times compared to their White counterparts [66]. The fear of ambulance costs may dissuade some patients and families to activate EMS, and this may contribute to lower use of ambulances in racial and ethnic minorities [41, 42]. Data on disparities in MT use among patients presenting “early,” i.e., sufficiently early to undergo MT within 6 h of last known well, are sparse and inconsistent, with some studies suggesting lower proportion of MT in Black LVO patients while others found no association [61, 65]. Although further data are needed to clarify the extent to which lower rates of MT among otherwise eligible LVO

patients contribute to the overall observed disparity, this may suggest that factors impeding timely arrival at a MT center, e.g., delay in symptom recognition, mode of arrival, and rate of transfer to a MT center, may be a more impactful driver of the overall disparity than factors that are in play after arrival at the MT performing hospital. This is supported by findings from a single-center study suggesting that Black LVO patients had significantly longer delay in presentation, while there were no differences in door-to-groin puncture time, procedure times, or recanalization rates [67]. In this study, Black LVO patients had significantly higher odds of mortality compared to their White counterparts, but the association between race and mortality was substantially attenuated and lost statistical significance after accounting for time from stroke onset to presentation [67]. Of note, when discussing “delay in presentation” for LVO patients undergoing MT, it is important to recognize that this commonly refers to the presentation to an MT-capable hospital. In patients who are transferred to an MT-capable hospital, this includes not only pre-hospital time but also the time at the first hospital referring the patient to the MT-capable hospitals. Longer wait times, delay in symptom recognition and imaging, as well as delay in transport may all result in delay in presentation to the MT-capable hospital and may result in some patients being ineligible by the time they arrive. While studies examining racial and ethnic inequities in interhospital transfers are sparse and methodologically challenging, analysis of data from the Center for Medicare & Medicaid Services suggest that Black stroke patients have lower adjusted odds of interhospital transfer [68]. Delays in interhospital transfer as a contributor to racial and ethnic disparities for stroke patients undergoing MT are further supported by a 2018 study which found that Hispanic patients with LVO were less likely to be transported to an MT-capable facility via helicopter than their White counterparts even when controlling for distance to a MT-capable hospital, particularly in the southern region of the USA [69].

Geographic and Hospital Contributions to Racial and Ethnic Disparities in Stroke Reperfusion Therapies

Systemic contributions to racial and ethnic inequities in care quality and outcomes have been increasingly recognized in recent years, including the recognition of structural racism as a major driver of cardiovascular and stroke outcomes [70, 71]. Structural differences adversely affecting equity in care and outcomes may be related to hospital and geographic characteristics, e.g., US region, rural vs. urban location, neighborhood proximity, stroke center designation, and for-profit status. Geographic and regional characteristics impacting stroke care include differences

in population density, racial and age composition of the population, local practice patterns, and legislative frameworks. Specifically, clustering of patients in neighborhoods with longer wait times for ambulance arrival, longer emergency department (ED) wait times, and a higher density of safety net hospitals providing low-quality care in areas with a high proportion of racial/ethnic minoritized groups may be the direct result of structural racism, social segregation, and neighborhood redlining [70, 72, 73]. Racial and ethnic differences in IVT use in the USA vary by geographic region. Lower use of IVT in racial and ethnic minority patients in the USA overall is driven by vast disparities in a few geographic regions, most prominently the South Atlantic region, while there are no significant IVT disparities in some other US regions [74]. The impact of geographic and regional differences on disparities in IVT is further highlighted by the differences in IVT rates and stroke metrics among different subpopulations of Hispanic people. In the Florida-Puerto Rico Collaboration to Reduce Stroke Disparities (FL-PR CRESD) study, Hispanic stroke patients in Puerto Rico had lower IVT rates and longer DTN times than Hispanic individuals living in Florida [33, 44].

Aside from geographic region, rural and non-metropolitan hospitals have lower IVT and MT rates compared to urban and metropolitan hospitals. Black patients receiving care at rural hospitals have the lowest rates of IVT and MT among all combinations of race and rural categories [75, 76]. The intersection between rural and racial disparities is further highlighted by studies suggesting that racial minorities with stroke are less likely to undergo interhospital transfer [68], and MT-eligible Hispanic stroke patients with LVO who are awaiting transfer to a MT-capable center are less likely to be transferred via helicopter [69].

Place of residence, zip code, and neighborhood have a profound impact on health outcomes, life expectancy, and quality of care [77–81]. As a result of housing discrimination, residential segregation, and racialized economic segregation, racial and ethnic minorities commonly cluster in a relatively small number of low-income neighborhoods and zip codes [72]. Stroke incidence is higher among people living in low income neighborhoods and zip codes [82]. Since the patient racial composition of a given hospital reflects the racial composition of the community it serves, a majority of racial minority patients receive care at just a few hospitals, sometimes referred to as minority serving hospitals [83]. Racial differences in the use of IVT are particularly pronounced at minority-serving hospitals where minority men and women are least likely to receive IVT [23]. This magnifies the overall health impact of the underlying inequity on a population level since the inequity is largest in hospitals where minority stroke patients are most likely to receive care. Root causes for hospital-level inequities may include

limited resources resulting in lower or delayed availability of technological advances or stroke specialists and a lack of organized stroke care [84].

The formalization of organized stroke care in certified stroke centers provides the protocols and infrastructure for expedited evaluation and treatment of patients with suspected stroke. Care at certified stroke centers has numerous benefits and is associated with higher quality of care, including higher use of IVT and better functional outcomes [85–89]. The overall number of certified stroke centers has steadily increased in the USA in recent years [90]; however, this increase has disproportionately favored new certifications in high-income and predominantly White neighborhoods, while hospitals operating in communities with a high proportion of racial and ethnic minority patients largely lack certified stroke centers [45, 46]. Stroke center designation partially mitigates racial disparities in stroke care, including disparities in IVT use [35], but does not abolish stroke care inequities [19, 61]. Regardless, due to the geographically uneven distribution, the higher rates of IVT in stroke centers compared to hospitals without stroke center certification primarily benefit the people who receive care there, i.e., people from high-income and predominantly White neighborhoods. Similarly, lower rates of IVT and MT in American Indian individuals may partially be explained by a lack of certified stroke centers in proximity of reservations or other areas of residence with a high proportion of American Indian individuals [91].

Recent Progress and the Path Forward

Disparities in care and care processes, unlike laws of biology and physics, are dynamic and subject to change, i.e., the disparity gap for care processes may narrow or widen over time. Although interventions to mitigate disparities must target causes of inequities on all levels [92], many of which occur before the occurrence of the stroke (e.g., inequities in socioeconomic opportunities, obesity and diabetes prevention, access to healthy food, preventative care, and hypertension treatment), disparities in acute stroke care processes are in the realm of physicians with expertise in stroke care. Interventions targeting stroke reperfusion therapies have high return-on-investment because IVT and MT are common and highly efficacious therapies and because the systems of care infrastructure required for equitable delivery of reperfusion therapy is evidence-based and endorsed by professional societies [17]. While it is the goal of disparity interventions to eliminate care inequities on the base of race and ethnicity altogether, lasting successes in interventions mitigating disparities in stroke care have been sparse. This is in part due to the complexity and interconnection of social determinants, which also result in challenges in assessing the

effectiveness of disparities interventions in the real world. Factors influencing the presence and magnitude of disparities not only include interventions specifically developed to address disparities, but also include general practice and policy changes and the implementation of new care protocol and processes, for example, the increasing organization of stroke care, i.e., the establishment of certified stroke centers and implementation of systems facilitating high-quality stroke care aids in mitigating disparities, probably in part by reducing the amount of individualized decision-making by providers that may be susceptible to bias. Regardless of the underlying reasons, recent evidence suggests that there has indeed been progress in mitigating racial and ethnic disparities in stroke reperfusion therapy. Specifically, the use of IVT in racial and ethnic minority groups has been increasing in recent years at higher rates than among White patients [18]. As a result, the IVT disparity gap has recently been narrowing significantly for Black people and has disappeared altogether for Hispanic people [18]. Similarly, racial disparities in MT use have narrowed significantly since the widespread and routine use of MT for LVOs in the anterior circulation stroke in 2015 [64].

Despite this recent progress, disparities in IVT and MT use have persisted in particular for Black individuals. In addition, the road to progress is not a one-way street, and it cannot be assumed that recent trends indicating improvement in disparities in reperfusion therapy will simply continue on auto pilot. Thus, further efforts are needed to preserve, and build upon, recent progress to eliminate disparities in the use of reperfusion therapy and other stroke procedures. In parallel with the development and implementation of interventions to address disparities, ongoing meticulous documentation of their extent and context is needed. Due to the fluidity of disparities, the implementation of mitigation strategies must be informed by, and adapt to, up-to-date data on the status quo. In keeping with the underlying mechanisms, future efforts must take a multipronged approach and focus on both individual and system-level factors and drivers. While details on the specifics of stroke interventions are beyond the scope of this review, strategies must include community engagement such as stroke education on symptom recognition via community-based interventions, the efficacy of which has been shown anecdotally [93–95]. Strategies will also include provider-centric interventions, including implicit bias training and interventions to ensure culturally sensitive patient-provider communication behavior [96]. Strategies targeting implicit bias and communication behavior will likely require a systematic approach to universally implement effective interventions on an ongoing basis since the effects of anti-bias training often fade over time [97]. Any serious implementation of strategies that call for additional professional development training for providers to combat bias and improve patient-provider

communication behavior will also require the dedication of additional resources to compensate already overstretched providers for their commitment.

System-level interventions should address the relative paucity of certified stroke centers in low-income and predominantly minority neighborhoods, which appears to be driven largely by economic considerations [45]. Although care providers are in a position to mitigate disparities, policymakers and regulatory agencies are arguably best positioned to implement lasting systemic changes to mitigate disparities on any level in society, including in healthcare. Ongoing advocacy by physicians, healthcare providers, and groups representing patient interests is needed to intersect with policymakers and articulate patients' needs to them. In the context of stroke care, policymakers and regulatory agencies should create conditions to ensure that hospitals in low-income neighborhood have resources comparable to those in high-income neighborhoods, including timely access to stroke specialists, advanced imaging, and resources to address language barriers. Policymakers and regulatory agencies must also work towards protecting patients from surprise ambulance bills to facilitate equity in pre-hospital care. It will take a combination of approaches addressing each of these underlying factors in order to achieve sustainable equity in stroke care regardless of patient race/ethnicity and place of living, but recent improvements in disparities in stroke reperfusion therapy suggest that we are on the right path forward.

Declarations

Conflict of Interest None.

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