

# The effect of two easily-implementable modifications in reducing gender disparities in Door-to-Needle time in acute ischemic stroke

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# Abstract

**Introduction:** Door-to-needle (DTN) time is an important factor in managing stroke for which studies have reported delays in women. We aimed to evaluate the effect of some simple modifications on reducing sex disparities, with a focus on DTN.

**Methods:** This longitudinal cohort study was conducted between September 2019, and August 2021, at a comprehensive stroke center. Previously we utilized the conventional “D’s of stroke care” for timely management. Some simple modifications were implemented in September 2020, with a special focus on the time of the neurologist's evaluation (D4-B) and patients' transfer to the stroke unit (D6-B). Patients were analyzed in two groups: group 1, before, and group 2, after employing the modifications. Sex as the main variable of interest along with other selected covariates were regressed towards the DTN, using univariable and multivariable logistic regressions.

**Results:** We enrolled 47 and 56 patients who received intravenous thrombolysis in groups 1 and 2, respectively. Although there was a significant difference in  $DTN \leq 1$  hour between women and men in group 1 (36% vs. 52%,  $p = 0.019$ ), it was not significantly different in group 2 (48% vs. 48.4%,  $p = 0.97$ ). Furthermore, regression analysis showed being female was a significant predictor of  $DTN > 1$  hour in group 1 (aOR= 6.65,  $p = 0.02$ ), while after employing the modifications gender was not a predictor of delayed DTN.

**Conclusion:** Although we have a long way to achieve performance measures in developed countries, we seem to have succeeded in reducing gender disparities in DTN using these simple modifications.

## Introduction

Gender differences in stroke and especially the sex disparities in the treatment of stroke are emerging as an issue of interest in the past decades [1-8]. Stroke, specifically ischemic stroke (IS), is the second leading cause of mortality and disability in the general population and also in women according to the Global Burden of Disease 2019 (GBD) [9, 10]. Among the Iranian population, stroke accounts for 10.46% of total deaths and 12.5% of female deaths [9], with the incidence rates considerably higher than in Western countries [11]. A recent systematic review along with other studies [11, 12] suggested that generally the risk of stroke in Iran is not affected by gender [13].

It is suggested that women have a higher lifetime risk of stroke [1], emphasizing the importance of reducing possible sex disparities in acute stroke settings for providing equal and timely treatment. Previous researches have revealed that even after adjusting for confounders, women have poorer outcomes following a stroke [14]. Older age at the time of stroke, worse pre-stroke functional status, and multiple comorbidities in women are some of the suggested reasons for this issue [14-17]. In the past decade, studies have been conducted on the disparities in the quality of care provided to men and women in the stroke care units [4-6, 18, 19]. Pre-hospital and in-hospital delays in diagnostic and treatment procedures, including delays in door-to-needle time (DTN) - a pivotal factor for patients receiving

recombinant tissue plasminogen activator (r-tPA)- are possible contributors to worse outcomes in women [15, 19-22]. Hence, more attention is drawn to gender disparities in DTN duration recently, albeit the findings are inconsistent [3-5, 18, 19, 23].

The “D’s of stroke care” is a mnemonic device, consisting of 8 substantial steps in acute stroke care, to facilitate the diagnosis and treatment of acute ischemic stroke (AIS) in patients who are eligible for receiving intravenous thrombolysis (IVT) [24, 25]. This study is designed to evaluate the implications of some simple modifications of the conventional algorithm on possible sex disparities, especially focusing on DTN. The modifications of the “modified 8 D’s of stroke care”, discussed in detail in our prior paper [26], were the implementation of (a) the time of neurologist's evaluation (D4-B), as well as (b) the time of patients’ transfer to the stroke unit (D6-B).

## Methods

### Study Setting

This single-center longitudinal cohort study was conducted in two equal periods between September 1, 2019, and August 31, 2021, at a single certified comprehensive stroke center affiliated with Tehran University of Medical Sciences (TUMS), Tehran, Iran. The study was approved and monitored by the ethics committee of the university in conformance with Helsinki Declaration (IR.TUMS.MEDICINE.REC.1399.382) [27]. Our stroke team includes attending neurologists, nurse practitioners, stroke fellows, and neurology residents. Consecutive data of the patients were gathered prospectively and the analyses were conducted retrospectively. Our specialized stroke care team provided the patients with full diagnostic and therapeutic measures.

### Study population

In order to evaluate the possible effect of these modifications on sex disparities in healthcare settings, patients were assessed in two separate groups; group 1 included patients managed with the conventional “D’s of stroke care” between September 1, 2019, and August 31, 2020, and group 2 included patients managed with the “modified 8 D’s of stroke care” between September 1, 2020, and August 31, 2021. Patients’ data were collected from the hospital web-based registry [28]. During the first and second periods, the total number of patients with age  $\geq$  18 who presented to the emergency room with stroke-related symptoms initiated in less than 24 hours were 359 and 412, respectively. Then, of the 217 and 251 patients diagnosed with AIS, 47 and 56 patients were eligible for receiving r-tPA with symptom onset less than 4.5 hours, and were included in this study. Patients who underwent bridging therapy (the combination of r-tPA and mechanical thrombectomy) were excluded. All subjects were provided with written informed consent for treatment, participation, and publication.

### Study measures

The “D’s of stroke care” describes 8 major steps in diagnosis and treatment of stroke to improve obstacles in IVT with r-tPA [24, 25]: detection (D1), dispatch (D2), delivery (D3), door (D4), data (D5), decision (D6), drug (D7), and disposition (D8). Our stroke care team designed two easily-implementable modifications of this algorithm in September 2020, called the “modified 8 D’s of stroke care” with the primary aim of overcoming some of the obstacles in timely treatment in our center [26]. This modified algorithm was developed with a special focus on splitting D4 and D6 steps into the following times: patients’ arrival to the emergency room (D4-A), early assessment by the neurologist (D4-B), neurologist decision on patient’s eligibility to receive r-tPA (D6-A), and patient’s transfer to the stroke care unit (D6-B).

Patients were diagnosed with AIS according to a recent review on the diagnosis and management of AIS and the diagnoses were confirmed by expert neurologists [29]. The patient’s eligibility to receive r-tPA was defined according to the American Heart Association/American Stroke Association (AHA/ASA) guidelines and evaluated by the neurology team [30]. Patients’ stroke severity was assessed using the NIHSS score (National Institute for Health Stroke Scale), and categorized as follow: minor stroke ( $1 \leq \text{NIHSS} \leq 4$ ), moderate stroke ( $5 \leq \text{NIHSS} \leq 15$ ), moderate to severe stroke ( $16 \leq \text{NIHSS} \leq 20$ ), and severe stroke ( $21 \leq \text{NIHSS} \leq 42$ ). Considering the mode of arrival to the hospital, patients were as follow: patients who used the emergency medical services with pre-notification (EMS group), those who were brought to the hospital with personal vehicle (private group), and those who had a stroke during their hospitalization for other reasons (in-hospital group). DTN time was defined as the difference between the door-time and the needle-time and reported by neurology residents. Door-time is defined as the time at which the patient presented at the emergency room (D4 in the conventional algorithm and D4-A in the modified algorithm). For hospitalized patients, the time of examination by the neurologist (D4-B) was considered as the door-time [23]. Needle-time is defined as the time of r-tPA administration (D7). DTN duration was categorized as (a) less than 1 hour and (b) more than 1 hour (delayed DTN) according to recommended DTN by AHA/ASA guidelines [30]. Patients who were admitted to the hospital between 3:00 pm to 7:00 am were defined as out-of-hour admissions (OOHA).

## Statistical Analysis

Continuous variables are presented in mean and standard deviation (SD) or median and interquartile range (IQR) as appropriate. Categorical variables were compared using the chi-squared test. Continuous variables were compared using independent t-test (for normally distributed variables) or Mann-Whitney U test (for non-normally distributed variables). To evaluate the relationship between gender and DTN time > 1 hour (as the primary outcome), univariable and multivariable binary logistic regressions were performed separately for both conventional and modified groups and the results are presented with odds ratio (OR), 95 % confidence interval (CI), and p-value. Covariates included in the multivariable regression were chosen based on the existing literature and our medical knowledge, including age, admission NIHSS, out-of-hour admission, and the mode of arrival [3, 23, 31, 32]. Data were analyzed using SPSS software, version 20. P-values less than 0.05 were considered significant.

## Results

Baseline characteristics of female and male patients in both conventional (group 1) and modified algorithm (group 2) groups are shown in table 1. The mean age of females was 73.5 in group 1 and 75.64 in group 2. Female patients were significantly older at the time of stroke than men in group 1 (p-value: 0.004). However, no significant difference was observed in this regard in group 2. Stroke severity based on categorized NIHSS was significantly different between men and women in group 2, with a higher proportion of females presented with moderate and moderate-to-severe stroke than men (100% of females versus 74% of males presented with at least moderate severity, p-value= 0.019). During the whole study period, more than 80% of both genders were transferred to the hospital with pre-notification by emergency medical services (EMS). Considering cardiovascular risk factors, apart from smoking status, no significant differences were observed between men and women in either of the groups. Additionally, in-hospital mortality was not significantly different between men and women during the whole study period (table 1).

After employing the modifications, in women, median DTN was decreased from 75 to 65 minutes and the 75<sup>th</sup> percentile from 90 to 74 minutes which is clinically considerable, however, the difference was not statistically significant (p-value for medians: 0.11 and for means: 0.36). Furthermore, in the conventional group, women significantly less often had DTN ≤ 1 hour compared to men (36% versus 52%, p-value=0.019), while after employing the modifications, DNT time was not significantly different between them anymore (48% of females versus 48.4 % of males, p-value = 0.97) (table 1).

Binary logistic regression findings in the conventional and modified algorithm groups are shown in table 2. Variables such as age, mode of arrival, NIHSS at admission, and out-of-hour admissions, were not significantly related to DTN > 1 hour, in both groups, neither in univariable nor multivariable analyses. Univariable regression showed a significant relationship between gender and having DTN > 1 hour in the conventional group: females' odds for having DTN > 1 hour was 3.72 times that of males (p-value= 0.03). After adjusting for possible confounders, being female was still a significant predictor for having DTN > 1 hour in the conventional group, with the odds ratio increasing to 6.65 (p-value= 0.02). Interestingly, after employing the modified algorithm, female gender was not a significant predictor of having DTN > 1 hour, even after adjusting for other covariates (p-value in univariable model= 0.98, p-value in multivariable model= 0.77) (table 2). Notably, the presence of the COVID-19 pandemic during the second period of this study might have affected the outcomes, which is considered a limitation. Nevertheless, we have attempted to consider every possible confounder in the analyses.

## Discussion

We found that although DTN was previously affected by gender in our center, using the conventional algorithm, after employing the modifications, being female was no longer associated with delayed DTN, even after adjusting for important covariates (in the conventional group, females had almost 4 times odds for delayed DTN as males, which increased almost to 6.5 times, as evinced by the results of the multivariable regression). This finding implies that using these two easily-implementable modifications (combining the cardinal eight steps of the conventional "D's of stroke care" with two sub-steps, including

the time of neurologist's evaluation (D4-B) and patients' transfer to the stroke unit (D6-B)) are plausible to alleviate sex disparities in DTN time, thereby improving females' stroke outcomes. This result is consistent with findings from GWTG-Stroke (Get with The Guidelines-Stroke) study that showed adhering to a stroke performance program could narrow the gap in performance measures between men and women [4].

Regarding the other sex disparity parameters between men and women, we found that female patients were significantly older at the time of stroke than men in the first period, although this was not the case with the second group. The age difference in the first period was consistent with previous findings that reported women were significantly older at the time of stroke [7, 33-36]. While no significant difference was observed in the severity of stroke between men and women during the first period, the pattern of presentation has changed in the second group, with a higher proportion of women presenting with moderate and moderate-to-severe stroke compared to men. This finding aligns with previous claims that women had a higher stroke severity at admission [4, 7, 36]. There were no sex differences considering the mode of arrival and in-hospital mortality between men and women during the whole study period.

There is a discrepancy between study findings on gender disparities in DTN duration. The FL-PR CReSD Study (Florida-Puerto Rico Collaboration to Reduce Stroke Disparities) suggested after adjusting for multiple covariates, including the ones that we accounted for, being female is an independent predictor for having  $DTN \leq 1$  hour (OR: 0.81, CI: 0.72-0.92) [3]. Similarly, large registry-based longitudinal studies from GWTG-Stroke also found that women had significantly less odds for having DTN within 1 hour (OR:0.83) [4]. A study among Dutch patients also revealed a significant relationship between female gender and having severely extended DTN (OR 1.17, 95% CI 1.05–1.31) [23]. In contrast, according to the European studies, the average DTN for men and women were almost identical or differ only for a few minutes (2013; DTN in women: 67 [48-92] versus 66 [47-90] in men (P-value: 0.002), 2014; DTN: 49 [34-70] in women versus 48 [35-68] in men) [5, 18].

Generally, delayed diagnosis and the inability to determine eligibility are some of the most important reasons for DTN delay [19]. Various reasons are suggested for longer DTN in women, although these reasons are not clear yet [20]. Some of these factors are related to the physicians' decisions on patients' eligibility, while some others are patient-related factors. Regarding the former factors, studies suggested that physicians may be more reluctant to use r-tPA in women because they tend to be older or present with more severe stroke than men [35-37]. Additionally, several studies have revealed an increased prevalence in stroke mimics as well as non-traditional stroke manifestations in women which could affect physicians' decisions considering the patients' eligibility for receiving r-tPA [7, 38-40]. Moreover, previous studies suggested women are less likely to receive timely neuroimaging which could lead to longer DTN [37, 41], although some other studies found no disparity in this regard [34]. Considering the patient-related factors, some researches showed that women are less likely to consent to thrombolysis [4, 42]. Another possible rationale is that women are more likely to be widowed or living alone, resulting in delayed symptoms recognition, later hospital arrival, difficulty in obtaining the time of symptom onset

from a family member, and ultimately eventuating in difficulty with physicians' decision on the patient's eligibility to receive r-tPA [17, 35].

## **Limitations and Strengths**

This study was conducted at a single certified comprehensive stroke center, where various local factors might be different from hospitals in other countries, limiting its generalizability. However, our results were in line with some of the large multicenter studies. We attempted to consider every possible factor that could affect the association between gender and DTN, though there might be some residual undetected confounding factors. We will gather more data in the following years and make every effort to treat both men and women as fast as possible.

## **Conclusion**

After the implementation of two sub-steps to the conventional "D's of stroke care" during the critical moments after occurring ischemic stroke, the disparity in the DTN between men and women reduced, and being female was not a significant predictor of delayed DTN anymore. It can thus be suggested that the implementation of these simple modifications, in which more emphasis is placed on the timing of visit by a neurologist (D4-B), as well as the time of patient's transfer to the stroke care unit (D6-B), could help reduce DTN difference between men and women. However, the reasons for sex disparities in stroke care are numerous, necessitating further development of quality improvement programs with a special focus on interventions to reduce such disparities.

## **Declarations**

### **Acknowledgment**

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### **Statement of Ethics**

Study approval statement: Research Ethics Committees of School of Medicine-Tehran University of Medical Sciences approved and monitored the algorithm in conformance with the Helsinki Declaration (identification code: IR.TUMS.MEDICINE.REC.1399.382).

Consent to participate statement: Written informed consent was obtained from individuals for treatment, participation, and publication.

### **Conflict of Interest Statement**

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## Author Contributions

B.P, S.H, M.K, and F.A had substantial contributions to the conception of the study. M.G, G.F, P.B, Me. J designed the study. S.H, M.S, M.K, R.A, F.A, M.A, M.V, and B.P were involved in the conduction of the study and data collecting. Ma. J, S.I, and P.B analyzed the data. Z.R, G.F, R.A, H.M, and M.S were involved in the interpretation of data. Me. J, Ma. J, and S.I drafted the first manuscript. M.G, H.M, Z.R, M.A, and M.V critically revised the manuscript. All authors have approved the final manuscript, and they take responsibility for the work and are fully confident in the accuracy and integrity of the work of other group authors.

## Data Availability Statement

Research data are not publicly available due to legal grounds, however, it is accessible on demand.

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## Tables

Tables 1-2 are in the supplementary files section.

## Supplementary Files

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