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Original research article

Pharmacological thrombolysis for acute ischemic stroke treatment: Gender differences in clinical risk factors

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ABSTRACT

Background: In a stroke population, women have a worse outcome than men when untreated. In contrast, there is no significant difference in treated patients. In this study, we determined whether clinical variables represent a promising approach to assist in the evaluation of gender differences in a stroke population.

Methods: We analyzed data from ischemic stroke patients' ≥18 years-old from the stroke registry on rtPA administration and identified gender differences in clinical factors within inclusion and exclusion criteria in a stroke population that received rtPA. Multivariate analysis was used to adjust for patient demographic and clinical variables.

Results: Of the 241 eligible stroke patients' thrombolytic therapy, 49.4% were females and 50.6% were males. Of the 422 patients that did not receive rtPA, more women (235) were excluded from rtPA than men (187) ($P < 0.05$). In the male population, exclusion from rtPA was associated with history of a previous stroke ($P < 0.05$, OR = 2.028), hypertension ($P < 0.05$, OR = 0.519), and NIH stroke score ($P < 0.0001$, OR = 0.893). In female stroke patients, exclusion from rtPA was associated with previous history of stroke ($P < 0.05$, OR = 2.332), diabetes ($P < 0.05$, OR = 1.88) and NIH stroke score ($P < 0.05$, OR = 0.916).

Conclusions: Despite similarities in different areas of stroke care for both men and women, more women with diabetes, previous history of stroke and higher NIH scores are more likely to be excluded from thrombolytic therapy. Men with a previous history of stroke, hypertension and higher NIH scores are more likely to be excluded rtPA even after adjustment for confounding variables.

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1. Introduction

The differences between men and women in incidence and severity of stroke have been investigated by many studies [1–3]. Findings indicate that women have a higher incidence of stroke, and have increased stroke severity, risk of reoccurrence, and poorer clinical outcome. Gender disparity in the response to thrombolytic treatment during acute ischemic stroke has been extensively debated. Many studies [4–6] have attempted to address gender disparity by investigating the relationship between gender and thrombolytic treatment in acute ischemic stroke patients. Since only a small percentage of patients qualify for treatment with rtPA [1], understanding gender differences in the response to thrombolytic treatment with rtPA is important to increase the use of rtPA in an acute ischemic stroke population [1,7,8].

Several studies have demonstrated that in untreated control populations, women have a worse functional outcome than men [1–3]. However, when treated with thrombolytic therapy, no difference in clinical outcome was observed [9]. This study suggests that the use of rtPA in an acute ischemic stroke population may eliminate gender disparity [4,5,10]. In support of this idea, a recent study by Lasek-Bal et al. [4] found that women treated with rtPA following an acute ischemic stroke improved significantly more than men within 24 h. Although the mechanism for the improvement in women is not fully understood, one possibility is that women have a higher percentage of cardioembolic strokes as compared to thromboembolic [11]. This type of thrombus has a greater affinity for rtPA, and responds better to thrombolytic

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treatment [4]. Another possibility is that the observed improvement in functional outcome is due to genetic variability of fibrinolysis inhibitors [5], the neuroprotective effect of exposure to ovarian estrogens [4], and an increased rate of arterial recanalization in women following administration of rtPA [12]. However, studies have also shown that the difference in outcome observed between genders after treatment with rtPA is relatively small [13–16]. The complexity of this issue has also been increased by another study that found that men are three times more likely to have a good functional outcome with rtPA treatment following an acute ischemic stroke [17]. Moreover, the observed gender differences have been attributed to demographic factors such as age [1,2,4,18], comorbidity [2], pre-stroke functional status [2,4], and stroke severity [5,11,18]. Differences in methods and timing of hospital presentation [1,2] and robustness of hospital evaluation [16] may also play a role. Overall, women are less likely than men to receive rtPA treatment [4,18,19].

Therefore it is tempting to speculate that thrombolysis maybe beneficial more to women than to men, as shown by some studies [1,6,7]. One possibility is that the observed difference could be that clinical risk factors associated with thrombolysis efficacy are not present in the same proportions among women presenting with stroke than among men. Our first objective is to identify the different risk factors in rtPA treated population and determine whether these risk factors are different between male and female populations. Since male and female do not present the same exclusion criteria in the general population, our second objective is to determine the effect of gender in the exclusion criteria for rtPA using a prospective registry of data of ischemic stroke patients admitted between 2010 and 2013 to a primary stroke center. We

Table 1
The baseline demographic and clinical characteristics of patients who received rtPA vs. those who did not.

Characteristic	rtPA (N = 241)	No rtPA (N = 422)	p-value
Patient Age in Years:			
Mean ± SD	66.9 ± 14.3	69.6 ± 15.0	0.021*
Range	28, 96	27, 97	
Age Group: No. (%)			
<50 years	31 (12.9)	46 (10.9)	0.087
50–59	41 (17.0)	64 (15.2)	
60–69	61 (25.3)	78 (18.5)	
70–79	55 (22.8)	109 (25.8)	
≥80	53 (22.0)	125 (29.6)	
Gender: No. (%)			
Female	119 (49.4)	235 (55.7)	0.117
Male	122 (50.6)	187 (44.3)	
Race: No. (%)			
Caucasian	199 (82.6)	333 (78.9)	0.495
African-American	39 (16.2)	84 (19.9)	
Other	3 (1.2)	5 (1.2)	
Hispanic Ethnicity: No. (%)	4 (1.7)	6 (1.4)	0.809
Body Mass Index:			
Mean ± SD	28.0 ± 6.6	28.4 ± 7.6	0.547
Range	13, 54	11, 75	
Medical History: No. (%)			
Atrial Fib/Flutter	49 (20.3)	99 (23.5)	0.352
CAD (Coronary Artery Dz)	72 (29.9)	134 (31.8)	0.615
Carotid Stenosis	5 (2.1)	23 (5.5)	0.038*
Diabetes	59 (24.5)	129 (30.6)	0.094
Dyslipidemia	119 (49.4)	208 (49.3)	0.983
CHF	20 (8.7)	62 (14.7)	0.016*
Hypertension	191 (79.3)	326 (77.3)	0.550
Previous Stroke	45 (18.7)	123 (29.1)	0.003*
Previous TIA	28 (11.6)	55 (13.0)	0.596
Peripheral Vascular Dz (PVD)	14 (5.8)	17 (4.0)	0.296
Smoking history	81 (33.6)	100 (23.7)	0.006*
Initial NIH Stroke Scale (Actual):			
Mean ± SD	10.7 ± 6.5	8.1 ± 6.9	<0.001*
Range	0, 25	0, 25	
Initial NIH Stroke Scale Group: No. (%)			
0–9	125 (51.9)	274 (64.9)	0.002*
10–14	51 (21.2)	54 (12.8)	
15–20	37 (15.4)	64 (15.2)	
20–25	28 (11.6)	30 (7.1)	
Risk of Mortality GWTG Ischemic Stroke:			
Mean ± SD	6.47 ± 6.3	5.53 ± 5.6	0.057
Range	0.7, 35.6	0.4, 36.4	

* $P < 0.05$.

analyzed clinical and demographic factors to determine gender disparities in a stroke population in a center with an active patient protocol for rtPA. We demonstrated the use of clinical and demographic variables in the inclusion and exclusion criteria as a promising approach to assist in the evaluation of gender differences in patients with a favorable risk-benefit profile for thrombolytic therapy in a 4.5-h protocol.

2. Materials and methods

2.1. Research design

This study consisted of retrospective data collected from Greenville Memorial Hospital (GMH) ischemic stroke population as approved by the Greenville Hospital System Ethics Committee. Greenville Memorial Hospital is a primary stroke center serving patients from an 8-county region located in upper South Carolina. All patients were treated between January 2010 and December 2013 in the Stroke Unit of the Greenville Memorial Hospital. A total of 2138 ischemic stroke patients were admitted to GMH. Of those, 62 patients were excluded who received rtPA at an outside facility, and 663 were eligible for receipt of rtPA at GMH. Of the 663 eligible patients, 241 patients were treated with rtPA within 4.5 h of the onset of stroke symptoms according to the National Institute of Neurological Disorders and Stroke criteria [20]. The remaining 422 patients were excluded from thrombolytic therapy because they did not meet the inclusion criteria according to the NINNDS Stroke Initiative [20]. Data were first divided into groups receiving rtPA and those that did not. The following factors were subject to analysis using the National Institutes of Health Stroke Scale (NIHSS): the age at which stroke occurred, the presence of stroke risk factors such as Atrial Fibrillation/Flutter, CAD (Coronary Artery Disease), Carotid Stenosis, Diabetes, Dyslipidemia, CHF, Hypertension, Previous Stroke, Previous TIA, Peripheral Vascular Disease (PVD), history of smoking, and neurological status during the first day of stroke. The presence of risk factors for stroke was determined by analyzing the patient history using medical documentation obtained upon admission to the Stroke Unit. We determined the rate of rtPA use according to the eligibility criteria and calculated the rate of receipt of rtPA among patients arriving within 4.5 h of stroke symptom onset. Patients that received rtPA and those that did not, were divided into subgroups based on gender. This approach allowed us to evaluate gender differences by considering both the inclusion and exclusion criteria in the efficacy and safety outcomes of intravenous rtPA treatment using a clinical registry and systematic analysis. Procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional or regional) or with the Declaration of Helsinki 1975, Hong Kong 1989 revision.

2.2. Data analysis

We compared the characteristics of patients receiving rtPA with the characteristics of patients not receiving rtPA. Specifically, we examined demographic characteristics and stroke severity as measured by the retrospective NIH Stroke Scale (NIHSS). The main

Table 2
Characteristics of Stroke Patients excluded and included for rtPA by Gender [N = 663 patients eligible forrtPA].

Characteristic	rtPA			No rtPA		
	Male	Female	p-value	Male	Female	p-value
No. of Patients	122	119		187	235	--
Age Group: No. (%)						
<50 years	16 (13.1)	15 (12.6)	0.002*	20 (10.7)	26 (11.1)	<0.001*
50–59	28 (23.0)	13 (10.9)		38 (20.3)	26 (11.1)	
60–69	36 (29.5)	25 (21.0)		50 (26.4)	28 (11.9)	
70–79	27 (22.1)	28 (23.5)		44 (23.5)	65 (27.7)	
≥80	15 (12.3)	38 (31.9)		35 (18.7)	90 (38.3)	
Race: No. (%)						
Caucasian	101 (82.8)	98 (82.4)	0.832	146 (78.1)	187 (79.6)	0.449
African-American	20 (16.4)	19 (16.0)		40 (21.4)	44 (18.7)	
Other	1 (0.8)	2 (1.7)		1 (0.5)	4 (1.7)	
Medical History: No. (%)						
Hypertension	95 (77.9)	96 (80.7)	0.592	136 (72.7)	190 (80.9)	0.048*
Diabetes	34 (27.9)	25 (21.0)	0.216	53 (28.3)	76 (32.3)	0.376
Coronary Artery Disease	45 (36.9)	27 (22.7)	0.016*	67 (35.8)	67 (28.5)	0.109
Atrial Fib/Flutter	17 (13.9)	32 (26.9)	0.013*	35 (18.7)	64 (27.2)	0.040*
Previous Stroke	23 (18.9)	22 (18.5)	0.942	47 (25.1)	76 (32.3)	0.106
Previous TIA	14 (11.8)	14 (11.5)	0.944	24 (12.8)	31 (13.2)	0.914
Congestive Heart Failure	5 (4.1)	15 (12.6)	0.017*	18 (9.6)	44 (18.7)	0.009*
Carotid Artery Stenosis	5 (4.1)	0 (0)	0.026*	14 (7.5)	9 (3.8)	0.100
Peripheral Vascular Disease	9 (7.4)	5 (4.2)	0.292	7 (3.7)	10 (4.3)	0.791
History of Smoking	51 (41.8)	30 (25.2)	0.006*	63 (33.7)	37 (15.7)	<0.001*
Initial NIH Stroke Scale Group: No. (%)						
0–9	65 (53.3)	60 (50.4)	0.248	134 (71.6)	140 (59.6)	0.063
10–14	23 (18.9)	28 (23.5)		21 (11.2)	33 (14.0)	
15–20	23 (18.9)	14 (11.8)		23 (12.3)	41 (17.5)	
20–25	11 (9.0)	17 (14.3)		9 (4.8)	21 (8.9)	
Risk of Mortality GWTG Ischemic Stroke:						
Mean ± SD	6.38 ± 5.7	6.57 ± 6.9	0.818	4.92 ± 5.5	5.97 ± 5.7	0.072

* $P < 0.05$.

outcome measure was the identification of exclusive and inclusive criteria for rtPA treated patients after implementing the less restrictive criteria of 4.5 h prior to onset of stroke. Bivariate group comparisons between patients with rtPA group and the no rtPA group were determined using χ^2 analysis for categorical data and the Student *t*-test for continuous data. The population was then subdivided into males and females and a multivariable binary logistic regression was performed to examine clinical factors that influenced exclusion from the rtPA group. We analyzed gender differences in patients excluded and included in rtPA treatments using a logistic regression model adjusted for known to be related demographic factors (race, age) and pre-specified confounding factors (age, hypertension, blood glucose, atrial fibrillation, baseline and post treatment NIHSS). Data were analyzed using SAS software version 9.1 (SAS Institute, Cary, NC).

3. Results

Between January 2010 and December 2013, a total of 2138 acute ischemic stroke patients were admitted at the Stroke Unit of Greenville Memorial Hospital (GMH). Of the 2138 patients, 633 were eligible to receive rtPA with 62 being excluded who received rtPA at an outside facility. Less than half of the eligible patients received rtPA (n = 241), while 422 were not eligible to receive rtPA. The baseline demographic characteristics are summarized in Table 1. Of the 241 eligible patients, 49.4% of females and 50.6% of males received rtPA. Of the 422 excluded patients, 55.7% were females and 44.3% were males.

Table 2 presents gender differences in variables of comparison for the non-rtPA and the rtPA groups. There was a significant difference by gender ($P < 0.0001$) in the age group category for both the rtPA group and the non-rtPA group. For the non-rtPA group, there was a gender difference ($P = 0.048$) as more women with hypertension were excluded from receiving rtPA when compared with men, whereas in the rtPA group there was no gender difference ($P > 0.05$). A gender difference ($P = 0.016$) was observed in the percentage of patients with carotid artery disease that received rtPA as more men with carotid artery disease were given rtPA. However, there was no gender difference ($P > 0.05$) in the percentage of excluded patients with carotid artery disease. With regard to stroke patients with atrial fibrillation/flutter, there was a gender difference ($P < 0.05$) in both the rtPA and the non-rtPA groups as more women were included and excluded respectively. A similar pattern of gender difference ($P < 0.05$) in which more women were excluded and included in both the rtPA and non-rtPA groups was observed for acute ischemic stroke patients with congestive heart failure, suggesting parallel differences between women and men with atrial fibrillation/flutter and CHF as etiology and risk factors. A gender difference ($P = 0.026$) was observed in patients with carotid artery stenosis, where more men were observed in the rtPA group, and no woman was included. However, there was no gender difference ($P > 0.05$) in the non-rtPA group. Among patients with a history of smoking, more men were observed in the rtPA group and the non-rtPA group ($P < 0.05$), indicating a gender difference in the inclusion and exclusion of men and women stroke patients with a history of smoking in the treatment with rtPA. There was no significant gender difference in either the rtPA or non-rtPA groups for diabetes, previous stroke, previous TIA, and PVD ($P > 0.05$).

Overall, there was no gender difference in exclusion and inclusion criteria for stroke patients with diabetes and within the age group category ($P > 0.05$; Table 2). However, we observed a gender difference in the inclusion criteria for patients with carotid artery disease, atrial fibrillation/flutter, congestive heart failure, carotid artery stenosis, and smoking ($P < 0.05$; Table 2). Similarly, a gender difference was observed in the exclusion of patients with a history of hypertension, atrial fibrillation/flutter, congestive heart failure, and smoking ($P < 0.05$; Table 2).

Univariate analysis revealed gender differences associated with age, carotid artery stenosis, atrial fibrillation, congestive heart failure, coronary artery disease, and history of smoking for the inclusion criteria. For the exclusion criteria, age, hypertension, atrial fibrillation, congestive heart failure and smoking history were associated with gender differences. In order to adjust for confounding effects of these variables, a multivariate binary logistic regression was performed to determine factors associated with rtPA exclusion. Table 3 identify five factors that are positively associated with rtPA exclusion; carotid artery stenosis (OR = 3.244, $P = 0.026$), history of a previous stroke (OR = 2.092, $P < 0.001$), increasing age (OR = 1.017, $P = 0.033$), hypertension (OR = 0.585, $P = 0.019$), previous stroke (OR = 2.092, $P = 0.001$), and calculated NIH stroke scale during admission (OR = 0.908, $P < 0.001$). Following multivariate analysis, after adjusting for confounding variables the effect of gender on the exclusion criteria disappeared.

Table 3
Factors Associated with rtPA Exclusion in the Total Population.

	P Value	Odds Ratio	95% C.I. for OR	
			Lower	Upper
Increasing Age	0.033	1.017	1.001	1.033
BMI	0.578	1.006	0.984	1.030
NIH Stroke Scale	<0.001*	0.908	0.868	0.949
Risk of Mortality GWTG	0.187	1.037	0.982	1.095
Female Gender	0.347	1.187	0.831	1.695
Hispanic Ethnicity	0.683	0.725	0.155	3.392
Caucasian	0.926	0.919	0.155	5.443
African American	0.740	1.362	0.219	8.486
Atrial Fibrillation	0.753	1.079	0.673	1.728
Coronary Artery Disease	0.661	0.914	0.613	1.365
Carotid Artery Stenosis	0.026*	3.244	1.148	9.162
Diabetes	0.137	1.361	0.907	2.042
Dyslipidemia	0.241	0.802	0.555	1.159
Congestive Heart Failure	0.127	1.591	0.877	2.885
Hypertension	0.019*	0.585	0.374	0.915
Previous Stroke	0.001*	2.092	1.366	3.205
Previous TIA	0.775	0.926	0.549	1.563
Peripheral Vascular Disease	0.116	0.526	0.237	1.171
Smoking	0.238	0.773	0.504	1.186

* $P < 0.05$.

Table 4
Factors Associated with rtPA Exclusion in the Male Population.

	P Value	Odds Ratio	95% C.I. for EXP(B)	
			Lower	Upper
Increasing Age	0.134	1.019	0.994	1.043
BMI	0.483	1.014	0.975	1.055
NIH Stroke Scale	0.001*	0.893	0.836	0.954
Risk of Mortality GWTG	0.386	1.036	0.956	1.123
Hispanic Ethnicity	0.902	0.875	0.105	7.319
Caucasian	0.513	0.352	0.016	7.997
African American	0.705	0.543	0.023	12.934
Atrial Fibrillation	0.401	1.383	0.649	2.949
Coronary Artery Disease	0.534	0.834	0.471	1.478
Carotid Artery Stenosis	0.174	2.223	0.703	7.035
Diabetes	0.865	0.95	0.527	1.713
Dyslipidemia	0.148	0.668	0.387	1.154
Congestive Heart Failure	0.23	1.976	0.649	6.015
Hypertension	0.041*	0.519	0.277	0.974
Previous Stroke	0.034*	2.028	1.055	3.897
Previous TIA	0.969	0.985	0.457	2.125
Peripheral Vascular Disease	0.222	0.495	0.16	1.531
Smoking	0.828	0.937	0.519	1.692

* $P < 0.05$.

Table 5
Factors Associated with rtPA Exclusion in the Female Population.

	P Value	Odds Ratio	95% C.I. for EXP(B)	
			Lower	Upper
Increasing Age	0.212	1.014	0.992	1.035
BMI	0.904	1.002	0.973	1.032
NIH Stroke Scale	0.007*	0.916	0.86	0.977
Risk of Mortality GWTG	0.366	1.036	0.96	1.117
Hispanic Ethnicity	0.561	0.501	0.049	5.167
Caucasian	0.894	1.166	0.123	11.083
African American	0.684	1.626	0.157	16.824
Atrial Fibrillation	0.876	0.952	0.515	1.761
Coronary Artery Disease	0.87	1.051	0.579	1.908
Carotid Artery Stenosis	0.999	1.08	0	0
Diabetes	0.035*	1.88	1.046	3.377
Dyslipidemia	0.653	0.888	0.529	1.49
Congestive Heart Failure	0.438	1.337	0.642	2.783
Hypertension	0.338	0.723	0.372	1.404
Previous Stroke	0.005*	2.332	1.298	4.192
Previous TIA	0.715	0.872	0.418	1.818
Peripheral Vascular Disease	0.337	0.551	0.163	1.861
Smoking	0.103	0.584	0.305	1.116

* $P < 0.05$.

Table 4 identifies three factors that are associated with rtPA exclusion in the male stroke patient population, history of a previous stroke (OR = 2.028, P = 0.034), hypertension (OR = 0.519, P = 0.041), and calculated NIH stroke scale during admission (OR = 0.893, $P < 0.001$). Similar analysis for factors that were associated with rtPA exclusion in the female stroke patient population (Table 5) revealed three factors that were associated with rtPA exclusion; diabetes mellitus (OR = 1.88, P = 0.35), history of previous stroke (OR = 2.332, P = 0.005), and calculated NIH stroke scale during admission (OR = 0.916, P = 0.007).

4. Discussion

In general, whether there are gender differences in the treatment with rtPA is yet to be fully determined, as some studies suggest that women have better clinical outcomes than men following intravenous thrombolysis [1,4], while some suggest no gender difference [9]. Moreover, it is not clear whether there are gender differences in timing of presentation with acute ischemic stroke to the hospital, decision-making for treatment, and treatment with rtPA [1]. While women are known to have a poorer clinical outcome following the occurrence of stroke [1], studies suggest that women are less likely to receive rtPA compared with men [14,15,21,22]. For instance, in a meta-analysis of a hospital-based study, women were 22% less likely to receive IV rtPA [14], and the observed differences decreased when only the patients eligible for rtPA were considered [14]. Previous investigations of rtPA and gender differences have not led to a clear understanding of the problem or to feasible strategies to eliminate the disparity. In this study, first we used univariate analysis to identify the different risk factors in acute ischemic stroke population treated with rtPA, and determined whether these risk factors are different between male and female populations. Next, following the identification of gender differences with different demographic and clinical variables, we then adjusted for a number of variables using multivariate analysis, and the observed gender difference in the univariate analysis disappeared. We did further adjustments for the stroke population, female and male and population to identity factors associated with exclusion of either male or female from rtPA.

Univariate analysis showed gender differences were associated with age, past medical history including congestive heart failure, coronary artery disease, carotid artery stenosis, and history of smoking. Most of the observed differences in the medical history and demographic factors have been reported in other studies [8,23–27]. In our study, women were more likely to be excluded due to hypertension, atrial fibrillation, and congestive heart failure, age and this corroborate with other studies [25,28–31]. Similar to the female result, we observed that more men were likely to be excluded because of their age, and history of heart disease. Men were more likely to be excluded because of history of smoking, coronary artery disorder and carotid artery stenosis. Although previous studies reported that men were more likely to have prior stroke [29,30] and diabetes [30,32], we did not observe and significant difference in race, diabetes mellitus, previous stroke, and peripheral vascular disease. We found that women are more likely to be excluded due to atrial fibrillation, and this corroborated with other studies [29,33].

Atrial fibrillation is a direct risk factor for ischemic stroke [34,35], and the risk of stroke is known to double in men, but increases more than 4-fold in women in patients that have coronary artery disease and atrial fibrillation. Women with atrial fibrillation are known to have greater thromboembolic risk when not on anticoagulants[36]. Our finding that more women with atrial fibrillation and congestive heart failure were excluded from rtPA suggest that though women suffer from worse effects of atrial fibrillation and congestive heart failure than men, the administration of both IV and intra-arterial rtPA has an greater beneficial effect in women. Increased clinician awareness of the fact that more women with atrial fibrillation, congestive heart failure during acute ischemic stroke are excluded in rtPA treatment may help to improve the management of patients with atrial fibrillation during acute ischemic stroke events.

Smoking is directly associated with recanalization and reperfusion, and smokers have a better response to tissue rtPA for the treatment of stroke than nonsmokers [37,38]. In general, rtPA acts more specifically in smokers, thereby counterbalancing the adverse pathophysiological effect of smoking, and the mechanism underlying the smoking-thrombolysis paradox is not fully understood. Our data suggest that although men smokers suffer from worse effect and exclusion, more men have a better chance of recovery if rtPA is given in time, indicating that the administration of rtPA has a greater beneficial effect in men. More women than men with hypertension were excluded from rtPA, while the inclusion criteria revealed equal percentages of men and women with hypertension receiving rtPA. Our finding is consistent with previous studies [33,39] indicating that women presenting with acute stroke and are hypertensive may be at higher risk for being excluded from rtPA due to severely elevated BP. Although high blood pressure may lead to poor health outcomes if left unmanaged [40], both women and men with controlled hypertension have shown to have positive outcomes following treatment with rtPA [41].

In unadjusted results, analysis showed gender differences were associated with age, past medical history including congestive heart failure, coronary artery disease, carotid artery stenosis, and history of smoking. After adjusting for gender, age, race, past and comorbidities, the effect of gender disappeared. In the adjusted model, increasing age was associated with the exclusion from rtPA in the total stroke population. The unadjusted gender differences in our stroke population could have been confounded by increasing age, indicating that gender differences may reflect age-related differences in decision making about administration of rtPA. Moreover, patients with increasing age especially > 80, combines a range of comorbidities including carotid artery stenosis, hypertension and previous stroke conditions. Further adjustment to analyze factors associated with the exclusion in the female acute ischemic stroke population revealed that women are more likely to be

excluded based on initial NIH scale scoring, diabetes, and previous stroke. Similar adjustment for the male stroke population indicated that men are more likely to be excluded based on hypertension, previous stroke and initial NIH scale scoring.

Eligibility alone is not a major contributor to gender differences in intravenous rtPA [14,15,22]. Our current study indicates that the exclusion criterion is equally meaningful. Gender differences in stroke symptoms have important implications for several reasons. For example, symptom presentation plays an important role in determining rtPA treatment regimens and in understanding any gender differences in treatment response. When the exclusion criteria is also considered in the determination of gender differences, a number of clinical and demographic factors may account for any observed difference. This may include stroke symptom etiology, and age. Moreover, diagnostic stringency, or use of stricter criteria for contraindications in the exclusion criteria of the methodological and clinical variables, could influence gender differences in the observed results. It is possible that the stricter the diagnostic criteria for stroke, the greater the exclusion and gender differences in treatment response. In this context, the old NINNDS guideline [42] which, has stricter criteria for exclusion may have contributed to the observed gender differences seen in our results. It is also possible that there are different patterns in how stroke symptoms develop in men and women, with exponential and differential effects that could account for gender differences. Because women have more incidence of stroke and are less likely to recover, the effect of stroke is thought to be greater in women than in men [43]. Although the incidence of stroke in terms of age-specific are higher in men when compared with women, however, due to women's increased longevity, higher incidence of stroke are recorded at older age for women than men[8]. In addition, functional outcomes in stroke-related disability and quality of life are poorer in women than in men[44]. In general, when compared with men, women are reported to be older, have more contraindications, more likely to be widow and less likely to receive social support [44,45]. Since an adjustment for confounding variables did not account for a gender difference in treatment outcomes [28,46], the severity of stroke has also been proposed to account for a gender difference in treatment outcomes [43,47]. However, existing data on stroke severity did not reveal a gender difference[47], indicating that more studies are needed to investigate the biological and clinical factors associated with stroke in both men and women treated with rtPA. The main limitation of this study is the use of data from the old NINNDS guideline. Gender issues need to be explored using the new AHA guidelines [48,49], as well as large clinical databases such as the Third IST (IST-3). In addition, inclusion of gender differences as part of the pre and post rtPA treatment outcomes would add value to future studies.

5. Conclusion

A major finding of this study is that women are most likely to be excluded from rtPA if they are diabetic, have a history of previous with higher NIH scores during treatment with rtPA, while men with a previous history of stroke, hypertension and higher NIH scores are more likely to be excluded from thrombolytic therapy.

Disclosure of potential conflicts of interest

Authors report no conflicts of interest.

Research involving human participants and/or animals

This study is a retrospective data analysis.

Informed consent

All authors contributed to this manuscript and support the submission.

Conflict of interest

All authors disclose that there is no any actual or potential conflict of interest including any financial, personal or other relationships with other people or organizations within three years of beginning the submitted work that could inappropriately influence, or be perceived to influence, our work.

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