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Racial and Gender Differences in Stroke Severity, Outcomes and Treatment in Patients with Acute Ischemic Stroke

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Abstract

Background—Previous research has indicated that women and Blacks have worse outcomes following acute ischemic stroke (AIS). Little research has been done to investigate the combined influence of race and gender in the presentation, treatment and outcome of patients with AIS. We sought to determine the association of race and gender on initial stroke severity, thrombolysis and functional outcome after AIS.

Methods—AIS patients who presented to two academic medical centers in the United States (2004–2011) were identified through prospective registries. In-hospital strokes were excluded.

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DISCLOSURES

None

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Stroke severity, measured by admission National Institutes of Health Stroke Scale (NIHSS) scores, treatment with tissue plasminogen activator (tPA), neurologic deterioration (defined by a 2 point increase in NIHSS), and functional outcome at discharge, measured by the modified Rankin Scale (mRS), were investigated. These outcomes were compared across race/gender groups. A sub-analysis was conducted to assess race/gender differences in exclusion criteria for tPA.

Results—Of the 4925 patients included in this study, 2346 (47.6%) were women and 2310 (46.9%) were black. White women had the highest median NIHSS on admission (8) with White men had the lowest median NIHSS on admission (6). There were no differences in outcomes between Black men and White men. A smaller percentage of Black women than White women were treated with tPA (27.6% vs. 36.6%, $p<0.0001$), partially due to a greater proportion of White women presenting within 3 hours (51% vs. 45.5%, $p=0.0005$). Black women had decreased odds of poor functional outcome relative to White women (OR=0.85, 95%CI 0.72-1.00), but after adjustment for baseline differences in age, NIHSS and tPA use this association was no longer significant (OR=1.2, 95%CI 0.92-1.46, $p=0.22$). Black women with a NIHSS on admission of less than 7 were at lower odds of receiving tPA than the other race gender groups, even after adjusting for arriving within 3 hours and admission glucose (OR 0.66, 95%CI 0.44-0.99, $p=0.0433$).

Conclusion—Race and gender were not significantly associated with short-term outcome, although Black women were significantly less likely to be treated with tPA. Black women had more tPA exclusions than any other group. The primary reason for tPA exclusion in this study was not arriving within 3 hours of stroke symptom onset. Given the growth in incident strokes projected in minority groups in the next 4 decades, identifying factors that contribute to Black women not arriving to the ED in time is of great importance.

Keywords

Acute Stroke; Ischemic Stroke; Ethnic Disparities; Treatment Disparities

INTRODUCTION

There are well-documented racial disparities in stroke.(1) The rate of new or incident stroke in Blacks is twice that of their White counterparts.(1) Additionally, stroke mortality is higher in Black Americans.(1) Gender disparities in stroke are becoming increasingly recognized with a disproportionate burden of cerebrovascular disease among women.(2) More strokes occur in women than men, a finding that is only partially explained by their longer lifespan. (3, 4) Studies suggest that women present with more severe neurologic impairments, are less likely to receive acute stroke therapies, and have worse functional outcome at 30 days and 1 year following hospitalization.(5-7) Women also receive lower quality of hospital care compared to men.(8, 9)

To our knowledge there are no studies that investigate the combined effect of race and gender on stroke severity or functional outcomes at discharge. We sought to determine the association of race and gender on initial stroke severity, thrombolysis and functional outcome after acute ischemic stroke (AIS). We hypothesized that race modifies the observed effects of gender.

METHODS

A retrospective cohort study was used to investigate race and gender differences in stroke severity, intravenous tissue plasminogen activator (tPA) use, and functional outcome in patients with AIS. Patients with AIS who presented to two academic stroke centers (Tulane University Medical Center, New Orleans, LA and University of Texas Medical School-Houston, Houston, TX), between 2004 and 2011 were retrospectively identified from prospectively collected stroke registries. In-hospital strokes were excluded. The primary exposures of interest were race, limited to Black or White, and gender. People who identified solely as Hispanic or Asian or other were excluded and people who identified as Hispanic-Whites or Hispanic-Blacks constituted less than 12% of the patient population and were thus included in the race they identified with at admission. Patients were classified into 4 groups: (1) Black men, (2) White men (3) Black Women and (4) White women. Patients who did not self-identify as either White or Black were excluded. Patient demographics, clinical characteristics, admission NIHSS, time from last seen normal to ED arrival, length of stay (LOS), discharge disposition, and discharge modified Rankin Score (mRS) were collected. The outcomes of interest were admission NIHSS, neurologic deterioration (ND, defined as an increase 2 points on the NIHSS score within a 24-hour period during hospitalization),(10) and functional outcome. Functional outcome was defined using discharge mRS score and dichotomized to “good” (discharge mRS 0-2) and “bad” (discharge mRS 3-6). Favorable discharge disposition is defined as being discharged home or to inpatient rehab. A secondary outcome of interest was tPA treatment. Reasons for not treating a patient with tPA were also recorded and compared across groups. The Institutional Review Board at Tulane University and University of Texas Medical School-Houston approved this study.

Statistical Analysis

Baseline differences were first assessed between race and gender separately. Subjects were stratified by race and gender into four groups to assess effect modification by race and gender on outcomes. Student's t-test, Wilcoxon Rank sum, Kruskal Wallis test, ANOVA and Chi-square tests were used to assess differences between groups, as appropriate. Unadjusted logistic regression models were built assessing if the combined race/gender groups were independently associated with the outcomes of interest. Adjusted logistic regression models were used to assess if the combined race/gender groups were independently associated with each outcome. Clinical and baseline variables that were significantly different from Table 1 or Table 2 were incorporated into the adjusted models if univariable statistical significance was < 0.2 .(11) Because of the differences seen in tPA utilization between the stratified groups, a post-hoc analysis comparing tPA exclusions was performed on the stratified groups using Pearson Chi-square tests. We analyzed the exclusion criteria as listed by the FDA. As this was an exploratory analysis, no adjustments were made for multiple comparisons.(12) All tests were performed at the $\alpha=0.05$ level.

RESULTS

Racial and Gender Differences

Gender and Race Baseline and Outcome Characteristics—There were 4925 patients included in this study, of which 2346 (47.6%) were women and 1942 (39.4%) were Black. Demographic variables by race and gender are shown in Table 1. Women have a higher percentage of patients with a poor functional outcome on discharge compared to men (49.6% vs. 43.4%, $p<0.0001$). Men have a higher percentage of favorable discharge disposition compared to women (63.9% vs. 58.2%, $p<0.0001$). A lower percentage of Black patients were treated with tPA compared to Whites (29.9% vs. 34.6%, $p=0.0019$) with a lower percent of Black patients arriving within 3 hours (45.4% vs. 51%, $p=0.0005$) and a higher percentage experiencing neurologic deterioration (17.8% vs. 15.6%, $p=0.0496$). Despite the differences in tPA use and neurologic deterioration, there were no significant differences between Black and White patients with respect to functional outcome at discharge in the crude models. Interactions between race and gender were tested for all of the outcomes of interest, with the only significant interaction being treatment with tPA ($p=0.0019$).

Combined Effects of Race and Gender

Gender and Race Stratified Demographics—Of the women, 989 (42.2%) were Black and of the men 953 (41.3%) were Black. White men were older than Black men (64 vs. 61, $p<0.0001$), and similarly, White women were older than Black women (69 vs. 63, $p<0.0001$). Hypertension was more common in Black men compared to White men (78.9 % vs. 67.2 %, $p<0.0001$) and Black women compared to White women (84.2 % vs. 73.7 %, $p<0.0001$). Atrial fibrillation was more common in White men compared to Black men (15.5 % vs. 9.5%, $p<0.0001$) and White women compared to Black women (23.7 % vs. 10.9%, $p<0.0001$). Demographic variables are fully summarized in Table 2 for the stratified groups.

Differences in Admission NIHSS—Median NIHSS on admission was significantly different across all 4 groups ($p<0.0001$). This was driven by a significant difference in admission NIHSS between Black women and White women (7 vs. 8, $p=0.0144$). The difference in admission NIHSS was not significantly different between Black men and White men (7 vs. 6, $p=0.2748$). After adjusting for age and glucose on admission in the ANOVA model, the difference in admission NIHSS between White women and Black women was no longer significant ($p=0.1673$).

Functional Outcome—Outcome variables are fully summarized in Table 3 for the stratified groups. On hospital discharge, poor functional outcome (mRS 3-6) was greatest among White women (51.5%) and lowest among Black men (43.2%). The 4-group comparison was significant ($p<0.0001$), as was the comparison between Black women and White women ($p=0.0440$). The difference between Black men and White men was not significant.

In an unadjusted logistic regression model with White men as the reference group, poor functional outcome was not significantly different for Black women vs. White men

(OR=1.14, 95%CI 0.97-1.34 $p=0.1018$) or Black men vs. White men (OR= 0.97, 95%CI 0.82-1.14, $p=0.7018$). There was also no difference between Black women and Black men (OR=1.18, 95%CI 0.99-1.41, $p=0.0729$). White women were at greater odds of having poor functional outcome compared to White men (OR=1.35, 95%CI 1.17-1.56, $p<0.0001$) in the unadjusted model. This association was no longer significant after adjusting for age, NIHSS at baseline and tPA use (OR=0.99, 95%CI 0.82-1.19, $p=0.9128$).

The unadjusted logistic regression model for Black women compared to only White women shows that Black women were at decreased odds of poor functional outcome (OR=0.85, 95%CI 0.72-0.99, $p=0.0442$). Once age, tPA use and admission NIHSS were adjusted for in the model, this association no longer remained (OR=1.2, 95%CI 0.92-1.46, $p=0.2172$).

Differences in tPA Utilization—The 4-group comparison shows a significant difference between the groups for tPA treatment ($p<0.0001$). Fewer Black women were treated with tPA than White women (27.6% vs. 36.6%, $p<0.0001$), while there was no difference in tPA treatment rates between Black men and White men (29.1% vs. 32.3%, $p=0.0900$). Black women had more overall contraindications to tPA compared to White women (73.5% vs. 62.7%, $p<0.0001$). Among those with documented tPA exclusion, we assessed for differences by race and gender (Table 4). Black women arrived outside of the 3-hour time window more often than White women, White men, and Black men.

Among patients who presented with baseline NIHSS >14 ($n=1160$), a significantly smaller proportion of Black women arrived at the hospital within the 3-hour window compared to all other patients, but this difference was not large (48.5% vs. 51.5%, $p=0.0230$). Among patients who presented with baseline NIHSS from 7-14 ($n=787$) there was no statistically significant difference in 3-hour time window arrival between Black women and all other patients (44.6% vs. 55.4%, $p=0.8952$). The largest difference was noted for the patients with baseline NIHSS of <7 ($n=2084$) with higher percentages of Black women presenting outside the 3-hour time window than all other patients (64.6% vs. 35.4%, $p=0.0098$). Black women with a NIHSS on admission of less than 7 were at lower odds of receiving tPA than the other race gender groups, even after adjusting for arriving within 3 hours and admission glucose (OR 0.66, 95%CI 0.44-0.99, $p=0.0433$).

DISCUSSION

In the four group stratified analysis, despite what we hypothesized, White women had more severe baseline strokes compared to all other groups, particularly compared to Black women. Further investigation into this association showed that the relationship was explained by differences in age and baseline glucose (as shown in the adjusted models)—both of which are well-described predictors of poor outcome after stroke.(13, 14)

White women were at higher odds of poor functional outcome when compared to both White men and Black women in the unadjusted models, which is consistent with previous studies illustrating women are at increased odds of poor functional outcome, however, where our study begins to differ from previous research is after adjustment for age, admission NIHSS, and tPA use this difference was no longer significant.(5, 6, 15) Prior

studies did not adjust for these variables, and may not have had the data available to adjust for these variables. Our study is unique in that the two centers have a higher than average treatment rate with tPA, which could account for why previous studies have shown a difference in functional outcome whereas after adjustment our study did not. After adjustment for differences between groups we observed no overt differences in outcome solely based on gender or race. These findings are encouraging given previous reports that women and blacks experience worse outcome following stroke.(16-18)

Regardless of the non-statistically significant associations shown between gender/race groups and outcome there is still the concern that Black women were less likely to be treated with tPA. In our sample, there was no difference in tPA treatment rates between women and men. This is in contrast to prior reports showing that women had an approximately 30% lower likelihood of receiving tPA compared to men.(19) In our study White women had the highest tPA utilization of the stratified groups. Furthermore, our data shows that there were no differences between tPA utilization between Black men and White men, and no difference between White men and White women. Our data suggest that the tPA treatment discrepancy develops in Black women, largely due to delayed presentation, particularly in those with admission NIHSS <7 (about half of the sample). There were no differences between race and gender with regard to tPA treatment utilization after adjusting for time from last seen normal, which is unique considering previous findings have shown racial differences exist even after controlling for time from last seen normal.(20) It may be that in areas with a high proportion of Blacks and in centers with high tPA utilization, the phenomenon of tPA disparity is abolished among races.(20, 21)

The primary reason for tPA exclusion in this study was not arriving within 3 hours of stroke symptom onset. This finding has been reported previously; although, there are discrepancies in the literature.(20, 22) Explanations for the difference in ED arrival between racial and gender groups are likely multi-factorial, and may include differences in underlying knowledge of stroke signs and symptoms as well as social factors, geographic factors, economic factors, etc.(23) Knowledge of stroke symptoms among the general population is poor, with 30-60% of people not knowing any stroke signs,(24) with Blacks being among the patients with the poorest understanding of stroke signs compared to other racial groups.(25) Our findings show that Black women with less severe strokes are less likely to present within 3 hours of symptom onset. In order to reduce these delays in hospital presentation, particularly in patients with less severe strokes, patient education is necessary to increase awareness of the signs and symptoms of a stroke. As discussed by previous researchers, a better understanding of how social factors, such as insurance, provider mistrust etc., attribute to stroke awareness.(1) It is important for stroke centers to identify which symptoms of stroke are not as widely understood and address these symptoms while providing stroke education.

Our study is not without limitations. This is a retrospective review where data collection occurs as part of each site's prospective stroke registry. Both centers are academic medical centers that treat a high proportion of Blacks. Both centers also administer tPA to a much higher percentage of AIS patients than the national average (30% compared to ~4%). Interestingly, both centers experience a higher than average number of patients who present

within the treatment time window (41% compared to ~25%).(26) Additionally, both centers have treated patients off label with tPA. The analysis of reasons for tPA exclusion only assess patients who were not treated with tPA. Although these factors make it possible to perform a stratified analysis, they may also reduce the generalizability of our findings. Furthermore, a large proportion of patients who did not receive tPA lacked clear documentation as to why they were ineligible for treatment or why treatment was not provided. We may have been unable to detect differences in race gender groups with regard to tPA exclusion criteria given that every possible exclusion is not systematically collected on every patient that was not treated furthermore patients may have been treated although they had exclusions to tPA treatment. This study includes only short-term outcomes, as we were not able to follow patients after discharge. Although long-term functional outcome cannot be evaluated directly, disability status at discharge has been shown to be a significant predictor of functional outcome at 90 days.(27) Additionally, Hispanic Whites were included in the White category as we did not have complete information on ethnicity for all participants. This may have biased our estimates.

This unique study investigating the stratification of combined race and gender elucidates some of the findings from previous studies investigating gender and race alone. Our study was able to associate the low tPA treatment rates previously reported in women to Black women. In a similar manner, we found that White women were driving the poor functional outcome previously reported in women. In addition, our study identified Black women with less severe strokes as the group not presenting to the hospital within the treatment window. Given the growth in incident strokes projected in minority groups in the next 4 decades, identifying factors that contribute to Black women not arriving to the ED in time is of great importance.(28) The possibility of targeted interventions in the future should be aimed at this high-risk group. It is critical for stroke centers to identify their individualized barriers to treatment and assess where weaknesses in stroke education exist so that further morbidity and mortality can be prevented.

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Table 1**Baseline and Outcome Differences Between Gender and Race**

	Women (N=2372)	Men (N=2605)	p-value	Black (N=1942)	White (N=2983)	p-value
Age, median (range)	68 (15-100)	63 (26-100)	<0.0001	62 (25-100)	67 (13-100)	<0.0001
Past Medical History, %						
Atrial Fibrillation	430 (18.2%)	345 (13.3%)	<0.0001	197 (10.2%)	573 (19.2%)	<0.0001
Diabetes	802 (33.9%)	788 (30.3%)	0.0059	686 (35.5%)	888 (29.8%)	<0.0001
Hypertension	1847 (78.1%)	1863 (71.6%)	<0.0001	1579 (81.6%)	2089 (70.2%)	<0.0001
Hyperlipidemia	604 (29.5%)	674 (31.3%)	0.2688	398 (27.4%)	873 (31.8%)	0.0030
Congestive Heart Failure	248 (11.7%)	218 (9.6%)	0.0256	195 (12.5%)	268 (9.6%)	0.0027
NIHSS at admission, median (range)	8 (0-40)	6 (0-40)	<0.0001	7 (0-40)	7 (0-40)	0.4270
Stroke Etiology, %			0.0001			<0.0001
Cardioembolic	783 (33.4%)	795 (30.9%)		547 (28.6%)	1018 (34.6%)	
Large Vessel	477 (20.3%)	669 (26.0%)		436 (22.8%)	697 (23.7%)	
Small Vessel	364 (15.5%)	412 (16%)		378 (19.7%)	387 (13.1%)	
Cryptogenic	82 (3.5%)	82 (3.1%)		89 (4.5%)	69 (2.3%)	
Other	638 (27.2%)	612 (23.8%)		466 (24.3%)	775 (26.3%)	
tPA use, %	679 (33.2%)	706 (32.5%)	0.6745	434 (29.9%)	949 (34.6%)	0.0019
Arrived with 3 hrs, %	1000 (48.9%)	1062 (49%)	0.9441	659 (45.4%)	1399 (51%)	0.0005

NIHSS denotes National Institutes of Health Stroke Scale score, tPA tissue plasminogen activator, LOS length of stay, mRS modified Rankin Scale score.

Table 2

Baseline Demographic Information for the Stratified groups

	Black Men (N=953)	White Men (N=1626)	p-value	Black Women (N=989)	White Women (N=1357)	p-value	4 group comparison p-value
Age, median (range)	61 (13.8)	64 (13.9)	<0.0001	63 (15.8)	69 (15.8)	<0.0001	<0.0001
Past Medical History, %							
Atrial Fibrillation	90 (9.5%)	252 (15.5%)	<0.0001	107 (10.9%)	321 (23.7%)	<0.0001	<0.0001
Diabetes	296 (31.1%)	480 (29.5%)	0.4066	390 (39.7%)	408 (30.1%)	<0.0001	<0.0001
Hypertension	750 (78.9%)	1092 (67.2%)	<0.0001	829 (84.2%)	997 (73.7%)	<0.0001	<0.0001
Hyperlipidemia	307 (32.3%)	549 (33.8%)	0.4345	307 (31.2%)	419 (30.9%)	0.9052	0.3527
Congestive Heart Failure	98 (13.3%)	118 (7.8%)	<0.0001	97 (11.8%)	150 (11.7%)	0.9474	0.0001
NIHSS at admission, median (range)	7 (0-40)	6 (0-40)	0.2748	7 (0-40)	8 (0-40)	0.0144	<0.0001
Stroke Etiology, %			<0.0001			<0.0001	<0.0001
Cardioembolic	281 (29.8%)	507 (31.6%)		266 (27.3%)	511 (38%)		
Large Vessel	233 (24.7%)	428 (26.7%)		203 (20.8%)	269 (20%)		
Small Vessel	177 (18.8%)	230 (14.4%)		201 (20.6%)	157 (11.7%)		
Cryptogenic	50 (5.2%)	30 (1.8%)		39 (4%)	39 (2.9%)		
Other	265 (27.2%)	407 (25.4%)		265 (27.2%)	328 (27.4%)		
tPA use, %	273 (29.1%)	522 (32.3%)	0.0938	269 (27.6%)	492 (36.6%)	<0.0001	<0.0001

Table 3

Outcome Information for the Stratified Groups

	Percent or Median (range)	Crude OR (95%CI) or Beta (SE)	p-value	Adjusted OR (95%CI) or Beta (SE)	p-value
Neurologic Deterioration					
Women	390 (16.6%)	1.02 (0.88-1.19)	0.7423	1.05 (0.87-1.26)	0.5833
Men	419 (16.3%)	Ref	Ref	Ref	Ref
Blacks	339 (17.8%)	1.16 (1.00-1.36)	0.0498	0.94 (0.78-1.14)	0.5429
Whites	462 (15.6%)	Ref	Ref	Ref	Ref
Black Women	181 (18.6%)	1.21 (0.98-1.49)	0.0770	1.06 (0.82-1.36)	0.6748
Black Men	158 (16.9%)	1.08 (0.87-1.34)	0.4992	0.74 (0.55-0.99)	0.0412
White Women	206 (15.3%)	0.96 (0.78-1.17)	0.6683	0.92 (0.73-1.14)	0.4367
White Men	256 (15.9%)	Ref	Ref	Ref	Ref
LOS					
Women	5 (1-44)	-0.367 (0.16)	0.0214	-0.180 (0.15)	0.2171
Men	5 (1-79)	Ref	Ref	Ref	Ref
Blacks	5 (1-56)	0.537 (0.16)	0.0010	-0.108 (0.15)	0.4825
Whites	5 (1-79)	Ref	Ref	Ref	Ref
Black Women	5 (1-39)	0.069 (0.14)	0.7573	-0.303 (0.21)	0.1472
Black Men	5 (1-95)	0.920 (0.23)	<0.0001	0.025 (0.22)	0.9082
White Women	5 (1-44)	-0.109 (0.21)	0.5977	-0.097 (0.18)	0.5921
White Men	5 (1-79)	Ref	Ref	Ref	Ref
mRS at Discharge					
Women	3 (0-6)	0.224 (0.05)	<0.0001	0.007 (0.09)	0.8516
Men	3 (0-6)	Ref	Ref	Ref	Ref
Blacks	3 (0-6)	-0.074 (0.05)	0.1402	0.089 (0.04)	0.0397
Whites	3 (0-6)	Ref	Ref	Ref	Ref
Black Women	3 (0-6)	0.131 (0.07)	0.0582	0.094 (0.06)	0.1114
Black Men	3 (0-6)	-0.040 (0.07)	0.5672	0.075 (0.06)	0.2311
White Women	4 (0-6)	0.267 (0.06)	<0.0001	-0.011 (0.05)	0.8354

	Percent or Median (range)	Crude OR (95%CI) or Beta (SE)	p-value	Adjusted OR (95%CI) or Beta (SE)	p-value
White Men	3 (0-6)	Ref	Ref	Ref	Ref
Poor Functional Outcome					
Women	49.6%	1.27 (1.14-1.43)	<0.0001	0.99 (0.86-1.16)	0.9642
Men	43.4%	Ref	Ref	Ref	Ref
Blacks	45.3%	0.92 (0.82-1.03)	0.1477	1.10 (0.94-1.29)	0.2428
Whites	47.4%	Ref	Ref	Ref	Ref
Black Women	47.3%	1.14 (0.97-1.34)	0.1018	1.09 (0.88-1.35)	0.4465
Black Men	43.2%	0.97 (0.82-1.14)	0.7018	1.10 (0.88-1.38)	0.3922
White Women	51.5%	1.35 (1.17-1.56)	<0.0001	0.99 (0.82-1.19)	0.9128
White Men	43.9%	Ref	Ref	Ref	Ref

* adjusting for age, NIHSS on admission and tPA use

Table 4

Differences in Race and Gender with Exclusion Criteria for tPA for Patients who Have information on Exclusion Criteria

	Black Men (N=953)	White Men (N=1626)	P-value	Black Women (N=989)	White Women (N=1357)	p-value
Blood Glucose too High/Low	1 (0.15%)	3 (0.2%)	0.7867	3 (0.39%)	0	0.0549
Did not present within 3 hours	349 (52.4%)	735 (50.2%)	0.3470	437 (57%)	591 (47.4%)	<0.0001
Elevated BP	7 (1.1%)	4 (0.27%)	0.0429	7 (0.91%)	10 (0.80%)	0.7897
Hypodensity on CT	48 (7.2%)	70 (4.8%)	0.0233	45 (5.9%)	68 (5.5%)	0.6868
PLT Count < 100,000	3 (0.45%)	4 (0.27%)	0.6846	4(0.52%)	0	0.0208
Elevated INR >1.7	6 (0.9%)	28 (1.9%)	0.0842	9 (1.2%)	23 (1.8%)	0.2445
Other Contraindications	105 (15.8%)	246 (16.8%)	0.0030	126 (16.5%)	191 (15.3%)	0.3500
No Documented contra-indication	211 (31.7%)	483 (32.9%)	0.5966	202 (26.4%)	465 (37.3%)	<0.0001

BP denotes blood pressure, CT computed tomography of the head, PLT platelet, INR international normalized ratio.