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Sex differences in the impact of acute stroke treatment in a population-based study: a sex-specific propensity score approach

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Abstract

Purpose—We investigated whether sex modifies the association of acute stroke treatment on functional outcome using propensity score (PS) methods to minimize confounding and to explore the differential effects of confounders by sex.

Methods—We included tissue plasminogen activator (tPA) treated ($n = 84$) and nontreated ischemic stroke cases ($n = 143$) from a population-based stroke study (2008–2013). The PS model that estimated the probability of receiving tPA included interactions between sex and treatment predictors. The outcome model included sex, tPA, and their interaction. In addition, sex-specific PS values were included as a continuous covariate and modeled using splines. We compared the results with conventional methods of statistical adjustment.

Results—Conventional methods of adjustment suggested that women receive greater benefit from tPA than men. After taking into consideration that the influence of confounders, specifically age and stroke severity, differed by sex, we found no sex difference in the tPA-functional outcome association ($P = .94$).

Conclusions—Using PS methods that considered confounding of the sex $\times$ treatment interaction, we did not find that the association of tPA with functional outcome differed for women and men. Our findings may have implications for the methodologic approaches used to address confounding in studies that seek to compare stroke treatment effects by sex.

Keywords

Stroke; Sex factors; Therapeutics

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Introduction

Some post hoc analyses of stroke clinical trial data suggest that women may receive greater benefit from acute thrombolysis than men. In a pooled analysis of three major randomized clinical trials of intravenous tissue plasminogen activator (tPA), Kent et al showed that the proportion of men and women who had favorable functional outcomes at 90 days following treatment was similar (38.5% in men vs. 40.5% in women; $P = .50$), whereas among the placebo group, significantly fewer women had favorable outcomes (36.7% in men vs. 30.3% in women; $P = .03$) [1]. Similar results were reported in two subsequent studies, which analyzed data from clinical trials of intra-arterial therapy with prourokinase and uric acid combined with tPA in stroke patients [2–4], but a sex $\times$ treatment interaction was not found in the largest analysis to date from the International Stroke Trial, which considered intravenous tPA administered within 6 hours of symptom onset [5].

Although the hallmark of clinical trials is the control of confounding through randomization, balance in confounding factors within subgroups defined by sex is not guaranteed unless randomization was stratified by sex [6], which was not the case in the aforementioned trials. Within sex groups, if imbalance in confounders (e.g., age and stroke severity) across treatment arms exists, then bias would be introduced in the sex-specific tPA-related outcome results unless these factors were appropriately accounted for in the analysis. Although analyses of the sex $\times$ treatment interactions in clinical trial data have accounted for some confounders in traditional multivariable regression analyses [1,3–5], they have not considered that the associations between confounders and outcome may differ by sex. Further, whether balance in confounders across treatment arms occurred within sex groups is, in part, related to the size of the trials, which varied considerably from 180 subjects to 3,035 subjects. Existing analyses of stroke trial data did not provide information on the distribution of baseline characteristics by treatment arm within sex groups to inform on this balance. Thus, residual confounding could remain.

We sought to investigate whether sex modifies the association of tPA treatment on post-stroke functional outcome using data from an ethnically diverse population-based observational stroke study. We specifically employed a propensity score (PS) modeling approach to reduce the possibility of confounding and to more thoroughly explore the differential role of confounding factors by sex. Like clinical trials, PS methods strive to create groups, in our example tPA-treated versus non-tPA-treated groups, that are equally balanced with respect to factors that influence the outcome of interest, thus minimizing confounding due to treatment selection bias (or confounding by indication). In addition to balancing confounders within treatment groups, we used PS methods to also balance the confounding factors within sex groups.

Methods

Data from ischemic stroke cases identified in the Brain Attack Surveillance in Corpus Christi (BASIC) Project [7,8], a population-based observational cohort stroke surveillance study in south Texas, are used in this analysis. Stroke ascertainment includes active and passive surveillance conducted in seven acute care hospitals. Active surveillance involves

identification of cases through daily screening of hospital admission logs, emergency department records, medical wards, and intensive care units. Passive surveillance involves identifying cases using International Classification of Diseases, Ninth Revision codes for stroke (430–438). All possible strokes undergo validation by a stroke fellowship trained physician blinded to race-ethnicity and age using source documentation.

Acute ischemic stroke cases are invited to participate in an in-person baseline interview and an in-person outcome interview conducted roughly 90 days following stroke. All cases undergo medical record abstraction. Both tPA–treated cases and non-tPA–treated cases arriving within 3 hours of symptom onset (i.e., tPA eligible) identified from November 2008 through September 2013 were eligible for the current analysis. No other exclusion criteria were applied to the non-tPA–treated group apart from onset to arrival time as these data were not collected for the entire time period. If an individual had more than one event, only the first was included.

Prestroke circumstances were ascertained from baseline interviews and medical records. Patients unable to answer a series of orientation questions had a proxy interview. Data collected from the baseline interview included race-ethnicity, marital status, pre-stroke function, and cognitive status. Prestroke function was measured by the modified Rankin scale (mRS) assessed via structured questions in reference to the prestroke period, and was categorized as less than two and greater than equal to two. Pre-stroke cognitive status was measured using the 16-item Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) completed by someone who knew the stroke patient well, which yields a scale ranging from one to five (higher scores represent worse cognitive function) [9].

Data collected from medical records included demographics, tPA, biological and stroke risk factors, and comorbidities. A comorbidity index was created by summing individual risk factors and comorbidities (range: 0–15). The National Institutes of Health Stroke Scale (NIHSS) was ascertained from the medical record or calculated using previously validated methods [10].

Outcomes

Functional outcome was assessed at the in-person 90-day outcome interview using self-reported scales that measure activities of daily living (ADL) and instrumental activities of daily living (IADL) completed by the patient or proxy. The ADL scale measures seven basic functional abilities and the IADL scale includes 15 questions related to daily functioning. Both scales ask the respondent to report the level of difficulty with each task (ranging from one [no difficulty] to four [can only do with help]). The primary outcome was the average of the 22 ADL/IADL items (range one to four with higher scores representing worse functional outcome) [11].

This study was approved by Institutional Review Boards of the University of Michigan and the two local hospital systems. All patients or a proxy signed a written informed consent document.

Statistical analysis

Primary analysis—Previous literature has shown that PS methods to account for confounding are superior to multivariable adjusted models and thus, we chose PS methods for our primary analysis [12]. Typical PS methods strive to create balance between treated and untreated groups with respect to predictors of outcome, thereby obtaining an unbiased estimate of the treatment effect. We modified the typical PS method approach to achieve balance in tPA-treated and tPA-untreated groups within sex groups, thus minimizing the influence of sex-specific confounding factors. With this approach, we strived to create unbiased estimates of the tPA effect within each sex group, and thus an unbiased estimate of the treatment effect difference between the groups. Our sex-specific PS model strategy for adjusting for the non-random assignment to tPA treatment is described in detail in the Supplemental Methods of the Supplemental Material. Briefly, we estimated sex-specific probabilities of being treated with tPA (propensity scores) by fitting a PS model that included tPA status as the outcome and the following variables as predictors: race-ethnicity, age, sex, prestroke mRS, dementia/Alzheimer's disease, atrial fibrillation, log(NIHSS +1), IQCODE. We considered interactions between these covariates and sex, and kept only the interactions between sex and age and between sex and log(NIHSS+) since others were not significant ($P > 0.20$). IQCODE was modeled using splines given its non-linear association with tPA status, with degrees of freedom chosen by generalized cross validation with the GAM package in the R software package. The sex-specific estimates generated by this model are derived from the main effect term for sex and the two sex interactions; the interactions estimate different probabilities for otherwise comparable men and women that are sex-specific beyond what would be predicted by the sex coefficient alone.

We then estimated the effect of tPA on functional outcome by sex by fitting a multivariable linear regression model that included ADL/IADL score as the outcome, sex, tPA treatment status, and their interaction. In addition, we adjusted for the tPA PS in a sex-specific fashion by including sex-specific data-driven, smooth terms of the PS derived from the model described above. Standard errors of estimated coefficients were obtained with 3000 bootstrap iterations. As an alternative to our PS adjustment method, we conducted a sensitivity analysis using inverse probability weighting, also a widely used PS approach. The inverse of the sex-specific PS were used as the weights.

Secondary analyses—To evaluate the potential impact of not considering differences in confounding by sex, we ran two additional secondary analyses. First, we fitted a conventional multivariable linear regression model regressing functional outcome (ADL/IADL score) on sex, tPA treatment status, the interaction between sex and tPA treatment status, age and NIHSS (Secondary Analysis 1). This model most closely reflects the multivariable approach used to address this research question in the existing observational literature [13]. Second, to evaluate the impact of our PS model approach to control for sex-specific confounding, we compared our results to those obtained from fitting the PS model but without any interactions with sex (only the sex main effect). We then ran the outcome model including sex, tPA treatment status, and their interaction with only a single smooth term for the PS instead of the sex-specific terms (Secondary Analysis 2). This model most closely resembles the multivariable approach used to address this research question in post-

hoc analyses of clinical trial data, where randomization may result in balance in confounders between treatment arms but this balance may not necessarily hold within sex groups [1–5]. To further understand the impact of accounting for sex-specific confounding, we created a scatterplot of the PS values from the PS model that does not include the interactions versus the PS values from the PS model that included the interactions with sex (Primary Analysis), with the dots colored by sex. This plot provides information as to how the sex-specific scores change when we include the interactions.

Results

A total of 384 ischemic stroke cases were eligible for the study (e.g., arrived within three hours of symptom onset and participated in the interview portion of the study). Of these cases, 63 died before the 90-day outcome interview and 59 patients were lost to follow up or refused the interview, resulting in 262 ischemic stroke cases. Among these 262 ischemic stroke cases, 35 patients had at least one missing data point (1 missing education, 20 missing IQCODE, 1 missing IQCODE and smoking, 12 missing outcome, 1 missing outcome and IQCODE). Missing data were not associated with tPA treatment ($P = 0.72$) or with sex ($P = 0.34$).

There were 227 ischemic stroke cases with complete data including 84 tPA-treated cases and 143 non-tPA-treated cases arriving within 3 hours of symptom onset. Table 1 includes descriptive statistics by tPA status for men and women. tPA-treated cases had greater initial stroke severity and more favorable pre-stroke cognitive function scores than non-tPA-treated cases and were less likely to be Mexican American than non-tPA-treated cases ($P < .10$). There were some differences in the associations by sex; age was not associated with tPA in women but in men younger age was significantly associated with tPA use. Greater initial stroke severity was associated with tPA in both men and women although the association was stronger in women compared with men (see sex-specific differences in Table 1). There was a borderline significant association between the comorbidity index and tPA use in men but not in women. There was an association between Alzheimer's disease/dementia and lower use of tPA in men but not women.

The final PS model had good discrimination between tPA-treated and nontreated cases (AUC = 0.82). Mexican Americans, patients with Alzheimer's/dementia, and patients with atrial fibrillation were less likely to receive tPA than non-Hispanic whites or patients without those conditions. Those with better prestroke function were more likely to receive tPA than those with worse prestroke function. The association between prestroke cognitive function was nonlinear (see Supplemental Fig. 1). The association between age and tPA was in the opposite direction in women and men (P for interaction = .14); greater age was associated with a higher odds of tPA in women whereas lower age was associated with greater odds of tPA in men (see Supplemental Fig. 2A). Greater stroke severity was associated with greater odds of tPA; this association was stronger in women compared with men (P for interaction = .18), with the sex difference in the severity-tPA treatment association more pronounced at lower stroke severity (see Supplemental Fig. 2B).

In the full sample, the association of tPA and functional outcome was in the anticipated direction but did not reach significance ($\beta = -0.16$, 95% CI: $-0.48, 0.07$; $P = 0.15$). Table 2 includes results for the primary analysis. In the model including the sex-specific, smoothed PS adjustment and its interaction with sex, there was no evidence of effect modification of the tPA association by sex ($P = .94$); that is functional outcome in those receiving tPA treatment was similar in women ($\beta = -0.15$, 95% confidence interval [CI]: $-0.62, 0.17$) and men ($\beta = -0.26$, 95% CI: $-0.66, 0.20$). In the sensitivity analysis using PS weighting methods instead of adjustment, results were largely similar. Based on the IPW approach, the overall association between tPA and the outcome was -0.20 (95% CI: $-0.55, 0.08$, $P = 0.18$). There was no evidence of effect modification by sex ($\beta = -0.15$, 95% CI: $-0.62, 0.18$ for women and $\beta = -0.16$, 95% CI: $-0.61, 0.17$ for men; P for interaction = 0.78).

Table 2 also shows results from two secondary analyses that did not consider adjustment for confounding of the sex $\times$ treatment interaction. Compared with our primary analyses, these alternative strategies resulted in stronger treatment effect estimates among women and weaker effect estimates among men. In the conventional linear regression model (Secondary Analysis 1), which included sex, tPA, the interaction between sex and tPA, age and stroke severity, the test of effect modification between sex and tPA suggested a sex by treatment interaction ($P = 0.11$; Table 2), with large differences in the effect estimates compared with the primary analysis. In this model, tPA had a significant protective association in women ($\beta = -0.43$, 95% CI: $-0.76, -0.10$) but no association in men ($\beta = -0.06$, 95% CI: $-0.38, 0.26$) consistent with published literature. In the outcome model, which did not include sex-specific PS terms and was based on fitting the PS model without including any interactions with sex (Secondary Analysis 2), tPA was not significantly associated with functional outcome in women ($\beta = -0.22$, 95% CI: $-0.61, 0.14$) or men ($\beta = -0.16$, 95% CI: $-0.59, 0.24$) and there was no evidence of interaction between sex and tPA treatment (P for interaction = $.80$). This version of the PS model had comparable discrimination with the PS model of the Primary Analysis (AUC=0.81). Although the model from the Secondary Analysis 2 showed no evidence of a sex by tPA treatment interaction, similar to the Primary Analysis, there were large differences in the sex-specific effect estimates from the two analyses and these differences were in the opposite direction by sex. In men, not considering the sex-specific confounding resulted in an effect 38% smaller than the primary analysis. In contrast, in women, not considering the sex-specific confounding resulted in an effect 47% larger than the primary analysis. This finding is visually depicted in Figure 1 which displays the PS values from the PS model that includes the interactions with sex (Primary Analysis) versus the PS model that does not include the interactions (Secondary Analysis 2), with the values colored by sex. At lower predicted probabilities of treatment, the PS values from the model with the interactions with sex resulted in higher probabilities for men and lower for women, with the converse true at higher predicted probabilities of treatment.

Discussion

Previous reports have suggested that the impact of acute stroke thrombolysis on functional outcome is stronger in women than men [1,3,4,13], which if true, would have important clinical implications, as well as impact the design of future stroke treatment trials. However, this investigation, conducted in an observational population-based stroke study using PS

methods to consider the influence of confounding factors by sex, found that the association of tPA with functional outcome was not different for women and men, partly due to sex differences in the confounding roles of age and stroke severity. Specifically, the association between severity and tPA treatment was stronger in women than men, and the association between age and tPA was in opposing directions by sex (e.g., older age was associated with tPA treatment in women in contrast to younger age being associated with tPA in men). That age and stroke severity are associated with tPA treatment and functional outcome is well documented in the literature and also holds in these data [11,13–15]. Therefore, if we do not consider the interactions between severity and age with sex, our estimates of the sex-specific associations between tPA and functional outcome will be biased [16]. Indeed, when we employed alternative strategies that did not consider adjustment for confounding of the sex $\times$ treatment interaction, we observed stronger treatment effect estimates among women and weaker effect estimates among men consistent with the published literature [1–4,13]. Differences were most pronounced in the model which did not employ PS methods, where the estimate for the effect of tPA in women was more than double than our estimate using PS methods which accounted for confounding of the sex $\times$ treatment interaction (i.e., $\beta = -0.15$ for primary analysis compared with $\beta = -0.43$ for model without any PS methods). Therefore, not using the methods that account for sex differences in the role of confounders, such as our PS approach or a multivariable approach with interaction terms, could yield a biased conclusion about the influence of sex on tPA-related outcomes.

Existing secondary analyses of clinical trial data assessing sex differences in tPA treatment are most analogous to our PS strategy where interactions between confounding factors and sex were not included in the estimation of the PSs (Secondary Analysis 2). Like clinical trials, a typical PS strategy, such as that conducted in our secondary analysis, balances treatment groups with respect to predictors of outcome. However, neither of these methods account for covariate imbalance in treatment arms within sex groups. Although results from our secondary analysis also suggested no sex $\times$ treatment interaction, the estimated effects in women and men were considerably different than those in our primary analysis which considered sex-specific confounding. Specifically, excluding the interactions between age and sex and between stroke severity and sex in the PS model and excluding the interaction between sex and the PS resulted in larger effect estimates in women and smaller effect estimates in men. Additional analysis of the clinical trial data using a sex-specific analytic strategy similar to ours could shed light on whether previously published results may have been impacted by inadequate control of confounding factors by sex, particularly age and stroke severity.

Our study findings also differ from an observational study conducted by Canadian Stroke Network investigators who sought to test whether an interaction between sex and tPA treatment was present in their large population-based registry of stroke patients. Similar to the clinical trial analyses, they found that women who were not treated with tPA fared worse than untreated men but women achieved similar outcomes to men when treated [13]. However, while the Canadian study adjusted for prognostic factors in their multivariable model (e.g., factors associated with outcome), they did not consider whether the nature of confounding by these factors differed by sex as we did in our analysis, which may account for our disparate findings.

There is a growing literature on the selection of interactions geared toward subgroup analyses in clinical trials, but less research is available on the approaches to examining confounding of interactions for observational data as we have here [17–20]. Our approach to utilizing PS methods to understand sex differences in the effect of stroke treatment is based on the idea of first obtaining an unbiased treatment effect in each sex group, and then comparing the effects between sex groups. This approach could be extended to other studies which seek to evaluate subgroup differences in stroke treatment effects in observational studies. We were limited by sample size constraints and thus fitted a single PS model including a small number of interaction terms between sex and some predictors of treatment. Data permitting, fully sex-stratified PS models would likely yield better control for confounding. Conducting studies which evaluate different approaches to variable selection for propensity models, when the focus is modification of exposure effects, is a needed next step to fully understand the best PS approaches for this setting.

Our study has some limitations. As noted above, the number of variables that we were able to consider in our PS model was limited by sample size. Therefore, there may be other factors that we did not include that serve as confounders of the tPA and functional outcome association, and the confounding effects of these factors may differ by sex. It is also possible that we over-fit our PS model given the limited number of individuals receiving tPA treatment; however, we were conservative in our inclusion of factors in the PS model. Further, we did not have data on all tPA contraindications for the full study time period beyond onset to arrival time; however, our PS model did consider variables previously shown to be associated with tPA use. In our PS model-building approach, we considered interactions between sex and variables that were found to be associated with tPA treatment. It is possible that this approach missed some interactions, although by using a less strict cut-point (P for interaction less than .20), we aimed to be more liberal in including potential interactions. We were also limited in our power to detect a tPA $\times$ sex interaction in the outcome models; however, the estimated magnitude of the sex difference in outcome was not clinically meaningful (0.11 difference in ADL/IADL scale ranging from 1 to 4). Our primary analysis was focused on complete cases without missing data and therefore, bias may have been introduced if the data were not missing at random. However, missing data was not common and was unrelated to sex and to tPA treatment. Thus, the results are likely not impacted by the complete case analysis. Our study is limited to one community and therefore results may not be generalizable.

Conclusions

Age and stroke severity may serve as confounders of the previously observed sex $\times$ stroke treatment interaction on functional outcome. Using PS-based strategies that considered the sex differences in the influence of these confounders, we found smaller stroke treatment effect sizes in women and larger treatment effect sizes in men compared with statistical approaches that did not consider how age and stroke severity interact with sex. Our findings may have implications for the methodologic approaches used to address confounding in future studies that seek to compare stroke treatment effects by sex.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

1. Kent DM, Price LL, Ringleb P, Hill MD, Selker HP. Sex-based differences in response to recombinant tissue plasminogen activator in acute ischemic stroke: a pooled analysis of randomized clinical trials. *Stroke*. 2005; 36(1):62–5. [PubMed: 15569865]
2. Chamorro A, Amaro S, Castellanos M, Segura T, Arenillas J, Marti-Fabregas J, et al. Safety and efficacy of uric acid in patients with acute stroke (URICO-ICTUS): a randomised, double-blind phase 2b/3 trial. *Lancet Neurol*. 2014; 13(5):453–60. [PubMed: 24703208]
3. Hill MD, Kent DM, Hinchey J, Rowley H, Buchan AM, Wechsler LR, et al. Sex-based differences in the effect of intra-arterial treatment of stroke: analysis of the PROACT-2 study. *Stroke*. 2006; 37(9):2322–5. [PubMed: 16888269]
4. Llull L, Laredo C, Renu A, Perez B, Vila E, Obach V, et al. Uric acid therapy improves clinical outcome in women with acute ischemic stroke. *Stroke*. 2015; 46(8):2162–7. [PubMed: 26159792]
5. IST Collaborative Group. Sandercock P, Wardlaw JM, Lindley RI, Dennis M, Cohen G, Murray G, et al. The benefits and harms of intravenous thrombolysis with recombinant tissue plasminogen activator within 6 h of acute ischaemic stroke (the Third International Stroke Trial [IST-3]): a randomised controlled trial. *Lancet*. 2012; 379(9834):2352–63. [PubMed: 22632908]
6. Cui L, Hung HM, Wang SJ, Tsong Y. Issues related to subgroup analysis in clinical trials. *J Biopharm Stat*. 2002; 12(3):347–58. [PubMed: 12448576]
7. Smith MA, Risser JM, Moye LA, Garcia N, Akiwumi O, Uchino K, et al. Designing multi-ethnic stroke studies: the Brain Attack Surveillance in Corpus Christi (BASIC) project. *Ethn Dis*. 2004; 14(4):520–6. [PubMed: 15724771]
8. Piriyaawat P, Smajsova M, Smith MA, Pallegar S, Al-Wabil A, Garcia NM, et al. Comparison of active and passive surveillance for cerebrovascular disease: The Brain Attack Surveillance in Corpus Christi (BASIC) Project. *Am J Epidemiol*. 2002; 156(11):1062–9. [PubMed: 12446264]
9. Jorm AF. A short form of the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE): development and cross-validation. *Psychol Med*. 1994; 24(1):145–53. [PubMed: 8208879]
10. Williams LS, Yilmaz EY, Lopez-Yunez AM. Retrospective assessment of initial stroke severity with the NIH Stroke Scale. *Stroke*. 2000; 31(4):858–62. [PubMed: 10753988]
11. Lisabeth LD, Sanchez BN, Baek J, Skolarus LE, Smith MA, Garcia N, et al. Neurological, functional, and cognitive stroke outcomes in Mexican Americans. *Stroke*. 2014; 45(4):1096–101. [PubMed: 24627112]
12. Cepeda MS, Boston R, Farrar JT, Strom BL. Comparison of logistic regression versus propensity score when the number of events is low and there are multiple confounders. *American journal of epidemiology*. 2003; 158(3):280–7. [PubMed: 12882951]
13. Shobha N, Sylaja PN, Kapral MK, Fang J, Hill MD, Investigators of the Registry of the Canadian Stroke N. Differences in stroke outcome based on sex. *Neurology*. 2010; 74(9):767–71. [PubMed: 20194917]
14. Adams HP Jr, Davis PH, Leira EC, Chang KC, Bendixen BH, Clarke WR, et al. Baseline NIH Stroke Scale score strongly predicts outcome after stroke: A report of the Trial of Org 10172 in Acute Stroke Treatment (TOAST). *Neurology*. 1999; 53(1):126–31. [PubMed: 10408548]

15. Reed SD, Cramer SC, Blough DK, Meyer K, Jarvik JG. Treatment with tissue plasminogen activator and inpatient mortality rates for patients with ischemic stroke treated in community hospitals. *Stroke*. 2001; 32(8):1832–40. [PubMed: 11486113]
16. Liu, A. Is the impact of smoking on lung cancer risk different between men and women?. Montreal, Quebec, Canada: McGill University; 2011.
17. Yuan M, Joseph VR, Zou H. Variable selection and estimation. *Ann Appl Stat*. 2009; 3:1738–57.
18. Choi NH, Li W, Zhu J. Variable selection with the strong hereditary constraint and its oracle property. *J Am Stat Assoc*. 2010; 105:354–64.
19. Bien J, Taylor J, Tibshirani R. A lasso for hierarchical interactions. *Ann Stat*. 2013; 41(3):1111–41. [PubMed: 26257447]
20. Burke JF, Sussman JB, Kent DM, Hayward RA. Three simple rules to ensure reasonably credible subgroup analyses. *BMJ*. 2015; 351:h5651. [PubMed: 26537915]

Fig. 1.

Scatter plot of the propensity score (PS) values from the PS model that included interactions with sex (Primary Analysis) versus the PS model that did not include the interactions with sex (Secondary Analysis 2), with the values colored by sex.

Table 1

Baseline characteristics by tissue plasminogen activator (tPA) use and sex ($n = 227$). Brain Attack Surveillance in Corpus Christi Project, Nueces County, TX (2009–2013).

Variable	Female ($n = 123$)				Male ($n = 104$)			
	Non-tPA ($n = 74$)		tPA ($n = 49$)		Non-tPA ($n = 69$)		tPA ($n = 35$)	
	% or Median	N or (Q1, Q3)	% or Median	N or (Q1, Q3)	% or Median	N or (Q1, Q3)	% or Median	N or (Q1, Q3)
Sociodemographics								
Age	76.5	62, 82	78.0	66, 83	72.0	63, 80	67.0	57, 75
Mexican American	66.2	49	57.1	28	68.1	47	54.3	19
High school education	31.1	23	34.7	17	42.0	29	25.7	9
Married	39.2	29	38.8	19	72.5	50	71.4	25
Insurance (yes vs. no)	79.7	59	75.5	37	55.1	38	51.4	18
Pre-stroke factors								
Modified Rankin scale < 2	33.8	25	42.9	21	53.6	37	65.7	23
IQCODE	3.2	3.0, 3.5	3.2	3.0, 3.4	3.1	3.0, 3.4	3.0	3.0, 3.3
Nursing home residence	9.5	7	8.2	4	4.3	3	0.0	0
Initial stroke severity (NIHSS)	4.0	2.0, 9.0	12.0	7.0, 16.0	3.0	2.0, 7.0	10.0	5.0, 16.0
Risk factors and comorbidities								
Hypertension	82.4	61	87.8	43	85.5	59	85.7	30
Diabetes	41.9	31	40.8	20	39.1	27	37.1	13
High cholesterol	55.4	41	53.1	26	59.4	41	40.0	14
Coronary artery disease/myocardial infarction	31.1	23	32.7	16	50.7	35	45.7	16
Atrial fibrillation	24.3	18	20.4	10	24.6	17	11.4	4
History of stroke/TIA	35.1	26	34.7	17	33.3	23	25.7	9
Body mass index	28.2	23.2, 35.1	27.4	24.9, 31.5	27.2	25.0, 31.8	28.2	25.1, 33.1
Current/former smoker	21.6	16	24.5	12	50.7	35	48.6	17
Excessive alcohol intake	5.4	4	4.1	2	14.5	10	11.4	4
Alzheimer/dementia	17.6	13	14.3	7	13.0	9	0.0	0
Cancer	8.1	6	16.3	8	13.0	9	8.6	3
Chronic obstructive pulmonary disease	10.8	8	8.2	4	10.1	7	8.6	3

Variable	Female (n = 123)						Male (n = 104)					
	Non-tPA (n = 74)			tPA (n = 49)			Non-tPA (n = 69)			tPA (n = 35)		
	P		N or (Q1, Q3)	P		N or (Q1, Q3)	P		N or (Q1, Q3)	P		N or (Q1, Q3)
	% or Median	% or Median		% or Median	% or Median		% or Median	% or Median				
Heart failure	12.2	9	12.2	6	1.00	4.3	3	8.6	3		.40	
End-stage renal disease	5.4	4	10.2	5	.48	5.8	4	0.0	0		.30	
Epilepsy	2.7	2	2.0	1	1.00	4.3	3	11.4	4		.22	
Parkinson	0.0	0	4.1	2	.16	1.4	1	0.0	0		1.00	
Comorbidity index (Range: 0–15)	3.0	2.0, 4.0	3.0	2.0, 5.0	.96	4.0	3.0, 5.0	3.0	2.0, 4.0		.06	

Q1 = 25th percentile; Q3 = 75th percentile; TIA = transient ischemic attack.

Table 2

Sex-specific associations between treatment with tissue plasminogen activator (tPA) and functional outcome (total ADL/IADL score; range 1–4, higher scores worse function; $n = 227$). Brain Attack Surveillance in Corpus Christi Project, Nueces County, TX (2009–2013)

Model	Female		Male		<i>P</i> for test of interaction between sex and tPA
	Estimate for tPA	95% CI*	Estimate for tPA	95% CI*	
Primary analysis					
PS analysis with sex interactions in PSM, and between PS and sex in outcome model	−0.15	−0.62 to 0.17	−0.26	−0.66 to 0.20	.94
Secondary analyses					
Conventional regression analysis regressing functional outcome on sex, tPA, sex × tPA, age, NIHSS	−0.43	−0.76 to 0.10	−0.06	−0.38 to 0.26	.11
PS analysis without sex interactions in PS, nor between PS and sex in outcome model	−0.22	−0.61 to 0.14	−0.16	−0.59 to 0.24	.80

* 95% CI and *P*-value were calculated based on t-distribution of 3000 bootstrap estimates for primary and secondary analyses and 95% CI and *P*-value were calculated based on a robust standard error for conventional regression analysis.