The Effect of Age and Sex on Clinical Outcome after Intravenous Recombinant Tissue Plasminogen Activator Treatment in Patients with Acute Ischemic Stroke

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Background: There are conflicting results regarding the effect of intravenous (IV) recombinant tissue plasminogen activator (rtPA) stroke treatment between men and women. Studies evaluating the impact of sex differences on functional outcome in relation to different age groups are nonexistent. *Aim:* The objective of the study is to examine the influence of sex differences in relation to age on the prognosis after IV rtPA treatment in acute stroke patients. *Methods:* In this cohort study, 887 patients with acute ischemic stroke were treated with rtPA. Functional outcome after 3 months was determined with the modified Rankin Scale (mRS). Good outcome was defined as an mRS score of 2 or lower. Age was stratified in decades (41-50, 51-60, 61-70, 71-80, and >80 years). Multivariable analyses were performed with adjustment for age, sex, stroke severity (National Institutes of Health Stroke Scale [NIHSS]), and stroke subtype (Trial of Org 10172 in Acute Stroke Treatment). *Results:* Fifty-five percent of the patients were men. The mean age was 67.4 (men) and 72.0 (women) years. Fifty-six percent of the men and 45% of the women had a favorable outcome ($P = .001$). After adjustment for NIHSS score and stroke subtype, the women had a better outcome in the age group 51-60 years compared with men (odds ratio [OR] .38, 95% confidence interval [CI] .15-.96). In the age group >80 years, men had a better outcome than women (OR 2.69, 95% CI 1.21-5.96). There were no significant differences in the other age groups. *Conclusion:* Men and women have different prognoses after IV rtPA treatment for acute ischemic stroke, which also depends on age. Women in middle age appear to have a better outcome than men, whereas at a more advanced age men appear to have a better outcome than women. **Key Words:** Acute stroke—stroke outcome—rtPA treatment—age difference—sex difference.

Introduction

Sex differences in etiology and prognosis after ischemic stroke have gained increasing attention over the recent years. Ischemic stroke is one of the leading causes of death in women.[1] Women are much more at risk of stroke than men because of their longer life expectancy and older age at stroke onset.[2] The stroke subtype also differs between men and women. For instance, women have more often cardioembolic strokes due to higher prevalence of atrial fibrillation.[3] Whether there is a different effect of intravenous (IV) recombinant tissue plasminogen activator (rtPA) treatment in men and women is a matter of debate, and several studies reveal conflicting results on this topic. Some authors reported that men have a better functional outcome after IV rtPA treatment than women,[4] while others found superior[5] or comparable outcome in women.[6,7] The influence of both age and sex on the response to IV rtPA treatment is unclear and may be one of the reasons for the ambiguity of the literature on this topic.

The aim of the present study is to compare the functional outcome after IV rtPA treatment for ischemic stroke between both sexes in relation to age.

Methods

Patients

All consecutive patients with acute ischemic stroke and treated with IV rtPA at the University Medical Center Groningen, The Netherlands, were included in a prospective registry from April 2002 until January 2014. The patients were treated within 4.5 hours with IV rtPA .9 mg/kg to a maximum of 90 mg. Ten percent of the total dose was given as a bolus and the remaining 90% in the next hour according to the protocol that has been described earlier.[8] Stroke subtypes were determined according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification. This classification comprises the following categories: large-artery atherosclerosis (embolus/thrombosis), cardioembolism (atrial fibrillation), small-vessel occlusion (lacune), stroke of other determined etiology, and stroke of undetermined etiology.[9] Demographic and clinical information was recorded, including sex, age, and vascular risk factors. Hypertension was defined as a self-reported history of hypertension or use of antihypertensive medications, or a blood pressure consistently measured above 140/90 mm Hg. Diabetes was defined as a self-reported history of diabetes, or use of medications for diabetes, or an elevated fasting blood glucose level higher than 7.1 mmol/L. Hyperlipidemia was defined as a self-reported history of hyperlipidemia or use of medications against hyperlipidemia, or a serum cholesterol level higher than 6.5 mmol/L or a serum low-density lipoprotein level higher than 3.5 mmol/L. Atrial fibrillation was defined as a history of atrial fibrillation recorded on electrocardiogram or detected on electrocar-diogram during the hospitalization. Myocardial infarction was defined as a self-reported history of myocardial infarction. Smoking was defined as a current smoker.[8] Stroke severity before treatment was assessed according to the National Institutes of Health Stroke Scale (NIHSS), an ordinal scale with scores ranging from 0 to 42, wherein a higher score reflects a more severe stroke. The onset to treatment time was registered.

Outcome

Functional outcome after 3 months was evaluated using the modified Rankin scale (mRS).[10] The mRS is an ordinal scale with 7 grades (0-6). A favorable outcome was defined as an mRS score of 0-2, which is equivalent to independency for daily activities. An unfavorable outcome was defined as an mRS score of 3-6, reflecting death or dependency.

Statistics

Differences in baseline characteristics between both sexes were analyzed with χ^2-test and the Mann–Whitney U test. Variables that differed significantly with a *P* value less than .10 between both sexes were selected as covariates for multivariable logistic regression analysis. In the multivariable analysis, the dependent variable was a favorable outcome (mRS score of 0-2). Age, sex, onset to treatment time, NIHSS score, and TOAST classification were also included because these are well-known prognostic factors in acute ischemic stroke. A backward selection approach was used to eliminate insignificant variables from the regression model. Finally, we stratified the outcome in subgroups based on sex and age. Age was stratified in the following groups: 41-50, 51-60, 61-70, 71-80, and older than 80 years.

All statistical analyses were performed using SPSS version 20.0 (SPSS Inc., Chicago, IL).

Results

Patient Population

Nine hundred nineteen patients with ischemic stroke were treated with IV rtPA, of which 32 patients were excluded from analysis because of lack of follow-up at 3 months. Of the remaining 887 patients, 490 (55%) were men. The mean onset to treatment time is 153 minutes in women and 150 minutes in men. There were 8 protocol violations in which the 4.5-hour time window was exceeded (range from 272 to 529 minutes). These were patients with a wake-up stroke (n = 3) with no early ischemic changes or less than one third of the affected arterial territory on initial brain computerized tomography scan and patients (n = 5) with a stuttering course or with a basilar artery thrombosis. Baseline characteristics are presented in Table 1. Women were significantly older with a mean age at onset of 72 years versus 67.4 years in men