Is Sex a Prognostic Factor in Stroke Rehabilitation?  
A Matched Comparison

Stefano Paolucci, MD; Maura Bragoni, MD, PhD; Paola Coiro, MD; Domenico De Angelis, MD; Francesca Romana Fusco, MD; Daniela Morelli, MD; Vincenzo Venturiero, MD; Luca Pratesi, MD

Background and Purpose—We sought to assess the specific influence of sex on rehabilitation results.

Methods.—A case-control study in 440 consecutive patients with sequelae of first ischemic stroke were enrolled in 2 subgroups (males and females) and matched for severity of stroke (evaluated by means of the Canadian Neurological Scale), age (within 1 year), and onset-admission interval (within 3 days). Functional data, evaluated by means of the Barthel Index and the Rivermead Mobility Index, were compared between subgroups. Logistic regressions were used to clarify the role of sex in affecting global autonomy and mobility.

Results.—After rehabilitation treatment, a sex-related difference was observed essentially in the higher levels of response. Indeed, more men than women reached independence in both stair climbing and activities of daily living (ADL), with a higher response and effectiveness on mobility. In multivariate analyses, male patients had a 3 times higher probability than female patients of good autonomy in both stair climbing and ADL (odds ratio [OR]=3.22; 95% CI, 1.67 to 6.18 and OR=2.92; 95% CI, 1.63 to 5.42, respectively). Conversely, female patients had a higher risk of walking with a cane (OR=1.69; 95%, CI 1.04 to 2.76) or of partial autonomy with respect to ADL (OR=1.90; 95% CI, 1.25 to 2.91). No significant difference was found for the other functional parameters.

Conclusions.—Female sex is a mildly unfavorable prognostic factor in rehabilitation results after stroke. (Stroke. 2006;37:000-000.)

Key Words: functional recovery ■ prognostic factors ■ rehabilitation ■ sex ■ stroke

Existing literature on the role of sex in stroke rehabilitation is controversial, as some reports have shown no sex differences in functional outcome,1,2 whereas others have reported a worse functional status in females.3–6 Moreover, in multivariate analyses, other variables such as stroke severity, age, interval before rehabilitation, and cognitive impairment were shown to have a stronger predictive power than sex on functional outcome.7–9 However, in the future, it will be important to recognize whether functional prognosis is similar between sexes in stroke survivors to plan more precise health policies for the senior population. As in most countries, females outnumber men among senior citizens, and such proportions are likely to increase with age. In 2001 in Italy, women were estimated to account for 58.81% of the population aged 65 and older and for 63.64% of the population aged 75 and older.10 In fact, the proportion of females at risk for stroke is most likely estimated to increase, owing to their increasing longevity: a report by the Italian Statistical Institute (ISTAT) in March 2006 calculated an increase in the mean life span of females from 83.3 years in 2005 to 86.6 years in 2030, in comparison with 77.4 years for males in 2005 and 81.0 years by 2030.11

The aim of this study was to evaluate the specific influence of sex on rehabilitation results in ischemic stroke inpatients by using a case-control design. This design allows better characterization of the role of each potential prognostic factor by minimizing the role of other well-recognized risk factors. Our study compared rehabilitation results in 2 subgroups of ischemic patients, men and women, who admitted for rehabilitation of first-stroke sequelae and who were matched for such well-known relevant prognostic factors as severity of stroke (evaluated by means of the Canadian Neurological Scale [CNS], age, and onset-to-admission interval [OAI]).7–8,12–17

Methods

Subject Selection
We evaluated stroke survivors admitted to our rehabilitation unit of the Santa Lucia Foundation (a scientific institute for hospitalization and treatment) for rehabilitation of sequelae of their first ischemic stroke. Exclusion criteria were hemorrhagic lesions and the presence of other chronic disabling pathologies and/or medical conditions that would contraindicate physical therapy. Stroke was defined as a sudden, nonconvulsive, focal neurological deficit persisting for $\geq 24$ hours.18 The diagnosis of stroke was based on history, clinical examination, and neuroradiological findings.
Patients with negative neuroradiological findings were also excluded to avoid enrolling cases with deficits due to uncertain causes. Patients were subjected to clinical, neurological, neuropsychological, neuroradiological, and functional examinations on admission.

Demographic and clinical data included age, race, OAI, years of schooling, side and site of the cerebral lesion, family support, hypertension, diabetes, heart diseases, smoking habit, poststroke seizures, poststroke depression, and the degree of severity of stroke on admission to the rehabilitation unit (evaluated by means of a revised and validated version of the CNS, with a cutoff score of 11.5 for normal patients). As indicated previously, evaluation of mood disorders was obtained by multiple approaches (clinical interview, Hamilton rating scale for depression, observation of patient behavior, and conversation with relatives). Aphasic patients underwent assessment with the Visual Analogue Mood Scale, a nonverbal test validated for aphasic patients. Symptoms of depression were reevaluated after 1 week to rule out cases of sad mood due to the new hospitalization. Symptoms were classified according to Diagnostic and Statistical Manual of Mental Disorders, 4th ed, criteria. Clinically depressed patients were treated with selective serotonin reuptake inhibitors. Clinical syndromes were classified according to the scheme of Bamford as total anterior circulation infarcts (TACIs), partial anterior circulation infarcts (PACIs), posterior circulation infarcts, and lacunar infarcts. Aphasic patients were categorized as Broca’s, Wernicke’s, or global aphasic according to their clinical evaluation and score on a specific test battery, named Esame del Linguaggio II, validated for people who speak Italian.

Unilateral spatial neglect (USN) was diagnosed in patients who scored below the cutoff value in 3 of 4 tests of a specific standardized battery, including the Letter Cancellation Test, the Barrage Test, the Sentence Reading Test, and the Wundt-Jastrow Area Illusion Test.

Each patient (during the acute hospital or rehabilitation stay) underwent at least 1 computerized tomography scan or magnetic resonance imaging brain examination. All computerized tomography scans or magnetic resonance imaging examinations performed in the first 48 hours after the acute event were repeated in the subacute phase.

Functional data included rehabilitation length of stay; number and characteristics of dropouts; activities of daily living (ADL) and mobility status at admission and at discharge (evaluated by means of the Barthel Index [BI] and the Rivermead Mobility Index [RMI], respectively); and gain, effectiveness, and percentage of low and high responders on the rating scales. Effectiveness reflects the proportion of potential improvement.
achieved during rehabilitation, calculated by this formula: (discharge score–initial score)/(maximum score–initial score)×100.\textsuperscript{15} Thus, if a patient achieved the highest score after rehabilitation, the effectiveness was 100%. As previously described, we consider as low or high responders those patients whose treatment effectiveness on ADL and mobility assessments was lower or higher, respectively, than the mean±1SD, because in our final sample, the distribution of effectiveness on both ADL and mobility measures was normal (skewness/SE was −0.435 for effectiveness on the BI and 1.62 for the RMI).

Finally, we evaluated each patient’s autonomy status at admission and at discharge, in terms of both ADL (poor autonomy for a BI score <50; partial autonomy for a BI score from 50 to 90; and full autonomy for a BI score ≥95) and mobility (need for a wheelchair, walking with a cane, walking without cane or other aid, independence in stair climbing). BI and RMI evaluations were performed for all patients by the same 2 physicians (M.B. and L.P), regardless of the patient’s inclusion in the present sample.

Treatment: Physical Rehabilitation

The rehabilitation plan, based essentially on ADL skills, was designed by the same physiatrist (D.M.) for all patients. Individual physiotherapy was started within 24 hours from admission and was performed for 60 minutes twice daily (only once on Saturdays), 6 days per week, throughout the stay. When necessary, patients underwent speech therapy or individual training for USN, swallowing, and bowel and bladder functions. Occupational therapy was administered to all patients with the exception of cases with marked comprehension deficits (21.5% of males and 20% of females). Physiotherapy and language treatment continued throughout the hospital stay, and training for USN lasted for 8 consecutive weeks. Discharge occurred after stabilization of each patient’s clinical status, as evaluated by the same 2 physiatrists (M.B. and L.P), regardless of the patient’s inclusion in the present sample.

Data Analysis and Statistics

We first compared baseline and discharge data of the 2 subgroups and discharge values for each subgroup with their admission values by both parametric and nonparametric analyses. To identify the role of each potential risk factor, we performed several logistic regressions (forward stepwise, Wald) using, as dependent variables, the low and high response to treatment on BI and RMI, and the degree of autonomy at discharge, in terms of both ADL (full, partial, or poor autonomy) and mobility (need for a wheelchair, walking with a cane, walking without cane or other aid, independence in stair climbing). Independent variables (coded; when not different were assigned a value of 0 = when absent and 1 = when present) were as follows: male (or female) sex, severity of stroke (coded as 1 for a CNS score <6 and 0 for a CNS score ≥6), age <50 years, age 50 to 64 years, age 65 to 84 years, age ≥85 years, higher schooling (coded as 0 for ≤8 years and 1 for >8 years, according to Italian education laws), right hemiparesis/plegia, TACI, PACI, lacunar infarcts, posterior circulation infarcts, presence of depression, smoking habit, arterial hypertension, heart disease, diabetes, and USN; and Broca’s, Wernicke’s, or global aphasia. Data analyses were performed with the SPSS 11.5 statistical package.

Results

Two hundred twenty male patients were successfully matched with 220 female patients with respect to CNS, age, and OAI. Mean age of the entire sample was 67.64 ± 11.87 years (range, 20 to 88 years). Clinical characteristics of the subgroups are shown in Table 1.

As shown in the table, the 2 subgroups had analogous demographic, neurological, and neuropsychological data. However, some differences were observed between sexes.
Indeed, arterial hypertension and years of schooling (without a difference in the percentage of patients with high schooling) were more common in men, whereas depression and a lower basal RMI score were more common in women (although of a similar percentage to no walking cases at admission).

As shown in Table 2 and the Figure, although men and women had a similar neurological recovery, as shown by the similar discharge CNS values, functional recovery was better in men, essentially in the higher levels of response and without more powerful prognostic factors. In other words, when 2 patients had the same basal neurological severity at the beginning of rehabilitation, were of the same age, and had the same OAI, male patients had a higher probability to be independent in both ADL and stair climbing. No difference was found in the lower levels of response (low independence at discharge, need for a wheelchair at discharge).

Even though previous reports showed no sex differences in functional outcome,1,2 our data about the poorer functional prognosis in women are consistent with more recent reports, wherein a greater disability in women was observed in both the acute and subacute phases after stroke.3–6 Moreover, the probability for women to obtain full autonomy was nearly equal in our case histories to that reported by Lai and coworkers28 (odds ratio = 0.41; 95% CI, 0.24 to 0.73 versus odds ratio = 0.51; 95% CI, 0.32 to 0.79). Finally, the discrepancy between our data and those

Comparison of mobility status at admission and discharge (adm indicates admission and disch, discharge). Men had a significantly higher percentage of patients who were independent in stair climbing ("P<0.001) and a significantly lower percentage who were walking with cane ("P<0.05).

### Discussion

The question whether male or female patients experience the same functional prognosis is currently inconclusive and merits further studies. Our data show that functional recovery was better in men, essentially in the higher levels of response and without more powerful prognostic factors. In other words, when 2 patients had the same basal neurological severity at the beginning of rehabilitation, were of the same age, and had the same OAI, male patients had a higher probability to be independent in both ADL and stair climbing. No difference was found in the lower levels of response (low independence at discharge, need for a wheelchair at discharge).

Even though previous reports showed no sex differences in functional outcome,1,2 our data about the poorer functional prognosis in women are consistent with more recent reports, wherein a greater disability in women was observed in both the acute and subacute phases after stroke.3–6 Moreover, the probability for women to obtain full autonomy was nearly equal in our case histories to that reported by Lai and coworkers28 (odds ratio = 0.41; 95% CI, 0.24 to 0.73 versus odds ratio = 0.51; 95% CI, 0.32 to 0.79). Finally, the discrepancy between our data and those

<table>
<thead>
<tr>
<th>TABLE 3. Results of Logistic Regression Analyses With Autonomy in Both ADL and Mobility as Dependent Variables</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Independent Variables</strong></td>
</tr>
<tr>
<td>---------------------------</td>
</tr>
<tr>
<td>Male sex</td>
</tr>
<tr>
<td>Female sex</td>
</tr>
<tr>
<td>CNS score ≥ 6</td>
</tr>
<tr>
<td>Age &lt;50 years</td>
</tr>
<tr>
<td>Age 50–64 years</td>
</tr>
<tr>
<td>Age 75–84 years</td>
</tr>
<tr>
<td>Age ≥85 years</td>
</tr>
<tr>
<td>TACI</td>
</tr>
<tr>
<td>USN</td>
</tr>
<tr>
<td>PACI</td>
</tr>
<tr>
<td>Global aphasia</td>
</tr>
</tbody>
</table>

**Only models with a significant role for sex and only variables that significantly entered the equations are shown.**

For stair climbing, prediction accuracy was 85.5%; model significance χ²=99.49, df 3, P<0.001.

For walking with a cane, prediction accuracy was 76.0%; model significance χ²=31.78, df 4, P<0.001.

For high responders in mobility, prediction accuracy was 78.3%; model significance χ²=54.99, df 4, P<0.001.

For autonomy in ADL, prediction accuracy was 79.8%; model significance χ²=86.16, df 4, P<0.001.

For partial autonomy in ADL, prediction accuracy was 63.6%; model significance χ²=38.95, df 3, P<0.001.
in previous reports regarding the prevalence of institutionalization (higher in women in the reports of Kapral et al and Glader et al29) may be due both to the age difference of the sample and different social factors between Italy and other countries. However, as previously noted, the aforementioned studies did not closely investigate the rehabilitation period. Moreover, the greatest differences were found to be related to mobility, which is an aspect seldom evaluated in previous studies.

Because the study design ruled out the influence of other well-known prognostic factors such as stroke severity, age, and OAI,27,28,30,31 we can conclude that the better functional prognosis in men is mainly due to a sex difference. The only other basal variable that was significantly different between the sexes and is potentially relevant to functional outcome was the prevalence of depression, which we and others have found is higher in women.22,33 However, in our sample, depression did not enter any multivariate models, and therefore, its role in affecting functional and mobility status was of minor importance, at least partly because of the antidepressant treatment received.

The reason for such sex-related difference is unclear and difficult to explain. A major reason might be the interaction between sex-related differences in muscular strength, greater in men at all ages,34 and age. This difference between sexes may increase in the elderly, because the observed decline in muscle strength with aging is also related to a reduction in physical activity,34 normally different between sexes. In a recent Italian report, it has been observed that in people ≥65 years old, only 30.6% of women versus 47.85% of men performed some physical activity.35 Moreover, in elderly women, a negative correlation between the level of physical activity and body mass index has been observed.34 The difference in functional outcome between the sexes might also be due to the different approaches to their disabilities, with women showing greater insecurity36 and being more open in requesting help from others, and men often being more confident and likely to disguise their need for help.

Care must be taken in generalizing our results. In particular, this was not a population-based study, and therefore, not all stroke survivors were included. In addition, it was performed in a population admitted to a rehabilitation hospital, who were therefore selected on the basis of the need for physical rehabilitation. Furthermore, because these patients were selected to be matched, the study sample represents only a fraction of all stroke patients admitted to the study facility during the study period. Despite these limitations, our study provides further evidence of a better functional prognosis in male patients.

Acknowledgment
The authors thank Gertrude H. Lynch for style editing.

Disclosures
None.

References
Is Sex a Prognostic Factor in Stroke Rehabilitation?: A Matched Comparison
Stefano Paolucci, Maura Bragoni, Paola Coiro, Domenico De Angelis, Francesca Romana Fusco, Daniela Morelli, Vincenzo Venturiero and Luca Pratesi

Stroke. published online November 2, 2006;
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2006 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/early/2006/11/02/01.STR.0000248456.41647.3d.citation

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/