Sex Differences in Quality of Life in Stroke Survivors
Data From the Tinzaparin in Acute Ischaemic Stroke Trial (TAIST)

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Background and Purpose—Female sex is predictive of poor functional outcome in stroke, even after correction for prognostic factors. Poor quality of life (QoL) is observed in stroke survivors with lower scores seen in the most disabled patients. We used data from the Tinzaparin in Acute Ischaemic Stroke Trial (TAIST) to assess the relationship between sex and QoL after ischemic stroke.

Methods—TAIST was a randomized, controlled trial assessing the safety and efficacy of tinzaparin versus aspirin in 1484 patients with acute ischemic stroke. QoL was measured at 180 days postrandomization using the Short Form-36 health survey, which assesses QoL across 8 domains. The relationship between sex and each domain was assessed using ordinal regression, both unadjusted and adjusted for key prognostic factors.

Results—Of the 1484 patients randomized into TAIST, 216 had died at 180 days postrandomization. A total of 1268 survivors were included in this analysis, 694 males (55%) and 574 females (45%). Females tended to score lower than males across all QoL domains (apart from general health); statistically significant lower scores were seen for physical functioning (OR: 0.58, 95% CI: 0.47 to 0.72), vitality (OR: 0.79, 95% CI: 0.64 to 0.98), and mental health (OR: 0.75, 95% CI: 0.61 to 0.93). The results for physical functioning and mental health remained significant after adjustment for prognostic variables (OR: 0.73, 95% CI: 0.58 to 0.92; OR: 0.76, 95% CI: 0.60 to 0.95, respectively).

Conclusions—QoL, in particular physical function and mental health domains, is lower in female patients after stroke. This difference persists even after correction for known prognostic factors such as age and stroke severity. (Stroke. 2007;38;2960-2964.)

Key Words: acute stroke ■ functional outcome ■ ischemic stroke ■ quality of life ■ sex

Q

uality of life (QoL) is widely recognized to be impaired after stroke1,2 and is related to poststroke disability and handicap.3 It is clear that both motor and nonmotor symptoms play an important role in recovery after stroke.4 As such, there is an increasing call for trials to monitor QoL in addition to other measures such as modified Rankin scale and Barthel Index to give a broader assessment of outcome after stroke.5

Outcome in female patients with stroke has been reported to be worse than in males with an increased risk of dependency and institutionalization.5–7 However, female patients with stroke tend to be older and more frail, which accounts for some of the worse prognosis. The relationship between QoL and sex is unclear; whereas some studies have observed lower QoL scores in females,8–11 others have detected no sex difference.7,12–14 We sought to further assess the relationship between sex and QoL using data from the Tinzaparin in Acute Ischemic Stroke Trial (TAIST).15

Methods

Subjects
TAIST compared the safety and efficacy of tinzaparin (low-molecular-weight heparin) given at high dose (175 IU/kg anti-Xa per day), tinzaparin at medium dose (100 IU/kg anti-Xa per day), and aspirin (300 mg once daily) in patients with acute ischemic stroke.15 Subjects were included within 48 hours of stroke onset. All data were collected prospectively as part of the trial protocol.15

Quality of Life
QoL was measured at 180 days after randomization by a face-to-face interview15 using the Short Form-36 health survey,16 which assesses QoL across 8 domains: physical functioning, physical role, bodily pain, general health, vitality, social functioning, emotional role, and mental...
heath.16 We used the transposed versions for each domain, so each are scored from zero to 100 with zero relating to the worst state of QoL and 100 relating to the best state.16 Summary scores were also calculated for the 4 physical and 4 mental domains.17 All patients completed the assessment themselves and proxies were not used.

### Outcome

Outcome was measured using the modified Rankin Scale and Barthel Index at 180 days postrandomization.15

### Statistical Methods

Prognostic baseline factors were compared by sex using Fisher’s exact test for categorical data and the Wilcoxon test for ordinal or continuous data. The relationships among sex, QoL domains, functional outcome, and discharge disposition were assessed using ordinal regression or logistic regression, both unadjusted and adjusted for 8 key prognostic factors: age, baseline systolic blood pressure, severity (Scandinavian Stroke Scale), premorbid modified Rankin Scale, premorbid residency, history of myocardial infarction, stroke type (cardioembolic, large artery), and treatment group. To compensate for the imbalance in age between the sexes, 2 matched analyses were also performed: (1) individual males and females were paired for age (within 3 years) and severity (within 3 points); and (2) on age and severity (like in [1]), previous myocardial infarction, and type of stroke (cardioembolic, large artery). All analyses were performed using SAS (SAS Institute). When missing data occurred, patients were excluded. Significance was considered at $P<0.05$ and 95% CIs are given.

### Results

#### Subjects

Of the 1484 patients randomized into TAIST, 216 had died at 180 days postrandomization: 113 males (14%) and 103 females (15%). Hence, 1268 survivors were included in this analysis: 694 males (55%) and 574 females (45%). The baseline characteristics of included patients by sex are shown in Table 1. Many prognostic factors were similar by sex, although females were older, more likely to have atrial fibrillation, a stroke of cardioembolic types, have lower premorbid functional status (modified Rankin Scale [mRS]), more likely to be in a nursing home, and were less likely to have sustained a previous myocardial infarction or had a stroke of the large artery type.

#### Quality of Life

Females had lower QoL scores than men, in particular relating to physical functioning, vitality, and mental health (Table 2). When adjusted for key prognostic factors (age, baseline systolic blood pressure, Scandinavian Stroke Scale, history of myocardial infarction, stroke type, premorbid mRS, residency, and treatment group), the differences in physical functioning and mental health remained statistically significant with females reporting scores that were approximately 25% lower than males (Table 2). Physical and mental summary QoL scores did not differ by sex after adjustment.

#### Outcome

The mRS differed significantly by sex with females having a worse functional outcome at 6 months (unadjusted $P=0.001$; adjusted $P=0.26$; Table 2, Figure 1). Similarly, Barthel Index scores were lower in females (unadjusted $P<0.0001$, adjusted $P=0.13$; Table 2). A poor functional outcome (mRS) was associated with lower physical ($r=-6.3$, $P<0.0001$) and mental ($r=-0.2$, $P<0.0001$) QoL domains. Mortality was similar between males and females (Table 2). At 6 months

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**Table 1. Baseline Characteristics by Sex**

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Males</th>
<th>Females</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects, %</td>
<td>1268</td>
<td>694</td>
<td>574</td>
<td>...</td>
</tr>
<tr>
<td>Age, years</td>
<td>70.7 (11.1)</td>
<td>68.4 (10.8)</td>
<td>73.4 (10.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Premorbid mRS</td>
<td>0 [1]</td>
<td>0 [0]</td>
<td>0 [1]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Premorbid living at home</td>
<td>1212 (95.6)</td>
<td>674 (97.1)</td>
<td>538 (93.7)</td>
<td>0.004</td>
</tr>
<tr>
<td>Premorbid nursing home</td>
<td>5 (0.4)</td>
<td>0 (0)</td>
<td>5 (0.9)</td>
<td>0.02</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>156 (22)</td>
<td>156 (22)</td>
<td>157 (23)</td>
<td>0.50</td>
</tr>
<tr>
<td>Previous stroke, %</td>
<td>148 (11.8)</td>
<td>81 (11.8)</td>
<td>67 (11.9)</td>
<td>0.99</td>
</tr>
<tr>
<td>Previous transient ischemic attack, %</td>
<td>213 (17.4)</td>
<td>120 (17.9)</td>
<td>93 (16.8)</td>
<td>0.64</td>
</tr>
<tr>
<td>Atrial fibrillation, %</td>
<td>126 (18.2)</td>
<td>57 (15.4)</td>
<td>69 (21.3)</td>
<td>0.05</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>200 (15.9)</td>
<td>117 (17.1)</td>
<td>83 (14.5)</td>
<td>0.25</td>
</tr>
<tr>
<td>Previous myocardial infarction, %</td>
<td>159 (15.2)</td>
<td>120 (17.6)</td>
<td>69 (12.2)</td>
<td>0.01</td>
</tr>
<tr>
<td>TOAST classification</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardioembolic</td>
<td>276 (21.9)</td>
<td>132 (19.1)</td>
<td>144 (25.3)</td>
<td>0.01</td>
</tr>
<tr>
<td>Large artery</td>
<td>412 (32.8)</td>
<td>263 (38.2)</td>
<td>149 (26.2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Lacunar</td>
<td>502 (39.8)</td>
<td>268 (38.8)</td>
<td>234 (41.0)</td>
<td>0.45</td>
</tr>
<tr>
<td>Treatment assignment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin, %</td>
<td>418 (33.0)</td>
<td>223 (32.1)</td>
<td>195 (34.0)</td>
<td>0.51</td>
</tr>
<tr>
<td>Medium-dose tinzaparin, %</td>
<td>435 (34.3)</td>
<td>246 (35.4)</td>
<td>189 (32.9)</td>
<td>0.37</td>
</tr>
<tr>
<td>High-dose tinzaparin, %</td>
<td>415 (32.7)</td>
<td>225 (32.4)</td>
<td>190 (33.1)</td>
<td>0.81</td>
</tr>
</tbody>
</table>

*Frequency (%), mean (standard deviation), or median (interquartile range); comparison by Fisher’s exact test, $\chi^2$ test, or Mann Whitney $U$ test.
postrandomization, more males than females were residing in their own home; conversely, more females than males were residing in a nursing home (Table 2; Figure 2).

Matching of Data by Sex

Repeating the analysis on matched subsets of the TAIST data gave comparable results to the unmatched analysis (Figure 3). The age- and severity-matched data and the age, severity, myocardial infarction, and stroke type-matched data both showed that females had consistently worse QoL than males for all domains with statistically significant differences for physical functioning and mental health in both data sets and additionally vitality and social functioning in the age- and severity-matched data.

Discussion

The main finding in this study of patients with acute ischemic stroke is that female patients have lower QoL scores at 6 months than males, especially in the domains of physical function and mental health and possibly vitality. Similar findings have been seen in earlier studies of QoL post-stroke8–11 as well as female patients with ischemic heart disease.18 Earlier studies in stroke limited statistical adjustment to age,11 whereas we were able to correct for additional prognostic factors, including severity and comorbidity. Furthermore, previous studies have assigned a score of zero to patients who have died,1 which may exaggerate lower scores in females because they have a trend to increased mortality (as seen here). However, our findings were not confounded in

Table 2. Quality of Life Domains and Summary Scores, Functional Outcome, and Discharge Disposition by Sex*

<table>
<thead>
<tr>
<th></th>
<th>Male (n=694)</th>
<th>Female (n=574)</th>
<th>Unadjusted†</th>
<th>Adjusted‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. (%)</td>
<td>694 (55)</td>
<td>574 (45)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical functioning</td>
<td>50 [20–80]</td>
<td>35 [10–60]</td>
<td>0.58 (0.47–0.72)</td>
<td>0.73 (0.58–0.92)</td>
</tr>
<tr>
<td>Role–physical</td>
<td>25 [0–75]</td>
<td>0 [0–75]</td>
<td>0.90 (0.72–1.13)</td>
<td>0.92 (0.72–1.17)</td>
</tr>
<tr>
<td>Bodily pain</td>
<td>72 [51–100]</td>
<td>72 [51–100]</td>
<td>0.93 (0.75–1.15)</td>
<td>0.92 (0.73–1.16)</td>
</tr>
<tr>
<td>General health</td>
<td>62 [42–77]</td>
<td>60 [45–77]</td>
<td>1.25 (0.68–2.29)</td>
<td>1.32 (0.70–2.51)</td>
</tr>
<tr>
<td>Vitality</td>
<td>50 [35–70]</td>
<td>50 [35–65]</td>
<td>0.79 (0.64–0.98)</td>
<td>0.86 (0.69–1.08)</td>
</tr>
<tr>
<td>Social functioning</td>
<td>75 [50–100]</td>
<td>62.5 [37.5–100]</td>
<td>0.83 (0.67–1.03)</td>
<td>0.87 (0.69–1.10)</td>
</tr>
<tr>
<td>Role–emotional</td>
<td>66.7 [0–100]</td>
<td>66.7 [0–100]</td>
<td>0.94 (0.75–1.18)</td>
<td>0.93 (0.73–1.19)</td>
</tr>
<tr>
<td>Mental health</td>
<td>72 [56–88]</td>
<td>68 [52–84]</td>
<td>0.75 (0.61–0.93)</td>
<td>0.76 (0.60–0.95)</td>
</tr>
<tr>
<td>Physical summary</td>
<td>37.2 [30.0–45.9]</td>
<td>35.5 [28.6–43.8]</td>
<td>0.78 (0.62–0.97)</td>
<td>0.88 (0.70–1.10)</td>
</tr>
<tr>
<td>Mental summary</td>
<td>49.1 [38.7–57.7]</td>
<td>48.1 [38.1–58.3]</td>
<td>0.91 (0.73–1.13)</td>
<td>0.87 (0.69–1.10)</td>
</tr>
<tr>
<td>mRS</td>
<td>2 [1–3]</td>
<td>3 [1–4]</td>
<td>1.41 (1.15–1.72)</td>
<td>1.13 (0.91–1.41)</td>
</tr>
<tr>
<td>Barthel Index</td>
<td>95 [75–100]</td>
<td>90 [65–100]</td>
<td>0.66 (0.54–0.81)</td>
<td>0.84 (0.67–1.05)</td>
</tr>
<tr>
<td>Living at home (%)</td>
<td>545 (82)</td>
<td>369 (67)</td>
<td>0.45 (0.34–0.58)</td>
<td>0.56 (0.41–0.77)</td>
</tr>
<tr>
<td>Nursing home (%)</td>
<td>68 (10)</td>
<td>102 (18)</td>
<td>1.99 (1.43–2.77)</td>
<td>1.36 (0.93–1.99)</td>
</tr>
</tbody>
</table>

*Median (interquartile range); comparison by ordinal regression or logistic regression, unadjusted and adjusted.
†OR (95% CIs).
‡Adjustment for age, baseline systolic blood pressure, baseline severity, premorbid mRS, premorbid residency, history of myocardial infarction, stroke type (cardioembolic, large artery), and treatment group.

Figure 1. Functional outcome (mRS) at 180 days by sex. Death was excluded as for analysis of QoL.
this manner because patients who had died were excluded from this analysis.

Despite demonstrating a relationship between sex and individual domain scores, we did not show any major relationship between summary scores and sex when adjusting for other prognostic factors. This is in keeping with previous work\textsuperscript{19,20} and is not surprising because the summation of domains can lead to the loss of data. At present, there is little evidence to support the use of such summary scores.\textsuperscript{20}

Females also had a worse functional outcome, whether judged using the mRS or Barthel Index. These scales largely measure physical disability and dependency so it is unsurprising that the functional and physical QoL domains are interrelated and differ similarly by sex.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure2}
\caption{Discharge disposition (residency) at 180 days by sex. Death was excluded as for analysis of QoL.}
\end{figure}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure3}
\caption{Comparison of QoL by sex: unmatched and matched analyses. Plot shows OR and 95\% CIs from ordinal regression analysis. All models adjusted for age, baseline systolic blood pressure, baseline severity, premorbid mRS, premorbid residency, history of myocardial infarction, stroke type (cardioembolic, large artery), and treatment group. PF indicates physical functioning; RP, role physical; BP, bodily pain; GH, general health; V, vitality; SF, social functioning; RE, role emotional; MH, mental health.}
\end{figure}
One possible explanation for the sex difference may arise from a difference in coping and adaptation patterns. In other illnesses, marked sex differences can be discerned, and the role of coping and adaptive strategies in stroke is a newly developed field of interest. Females have also been shown to report lower QoL in a general population. Another explanation for this difference may be the place of residence 6 months poststroke with many more females residing in a nursing home than males. QoL is likely to be well rated in an institution than at home.

This study has several limitations. First, the data come from a randomized, controlled trial, which excluded both very mild and very severe strokes. Excluding mild strokes will tend to cause a floor effect in QoL domains, well recognized when using the Short Form-36. (Excluding patients with very severe strokes is less of a problem because many die and therefore would not contribute QoL data.) Second, QoL was assessed at only one time point (6 months poststroke) despite temporal trends being recognized in both physical and mental domains of QoL. Third, depression and QoL are associated with each other with patients with depression having a lower QoL. Although female patients with stroke have an increased prevalence of poststroke depression, we could not take account of this because TAIST did not collect the relevant information. Finally, although the Short Form-36 is one of the most widely used measures of QoL, it may not meet the specific demands of measuring QoL after stroke as well as other measures and may not accord sufficient priority to the subjective priorities of patients with stroke in what is important in their QoL. Despite these limitations, these data come from a large high-fidelity trial and exhibit external validity.

In summary, female patients with stroke have a lower QoL, especially in the domains of physical and mental health, which is independent of age, stroke severity, and etiological type and other comorbid factors. Females also have a worse functional outcome. Because medicinal interventions such as aspirin and alteplase administration improve functional outcome, it will be important to determine whether QoL can also be modified therapeutically poststroke. Acknowledgments

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Disclosures

P.M.W.B. is Stroke Association Professor of Stroke Medicine. P.M.W.B. was the Principal Investigator for the TAIST Trial. G.B., P.P.D.D., D.L., D.O., and E.B.R. were members of the TAIST Advisory Committee. P.M.W.B. received honoraria from Leo Pharma A/S.

References

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