Mortality at 12 and 24 Months After Stroke May Be Associated With Depressive Symptoms at 1 Month

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Background and Purpose—Previous studies have reported mood symptoms after stroke to be a risk factor for later mortality. The purpose of the study was to examine whether mood symptoms at 1 month after stroke may be a risk factor for mortality at 12 and 24 months.

Methods—As a cohort within a randomized controlled trial, 448 hospital patients were seen at 1 month after stroke and were randomized into a trial of psychological therapy. Follow-up was at 12 and 24 months. Mood symptoms were assessed by the Present State Examination and the General Health Questionnaire (GHQ)-28. Measures of disability before and after stroke and of cognitive impairment after stroke were also taken at 1 month. Mortality was determined at 12 and 24 months after stroke.

Results—In logistic regression analyses, mortality at 12 months was associated unifactorially with scoring on the GHQ-D subscale (odds ratio [OR] 2.4, 95% CI 1.3 to 4.5) and scoring in the highest quartile of the GHQ (OR 3.1, 95% CI 1.1 to 8.8). In multiple logistic regression analyses, only GHQ-D remained a significant predictor after controlling for other known predictors. At 24 months, scoring on GHQ-D (OR 2.4, 95% CI 1.4 to 4.1) and in the highest GHQ quartile (OR 2.2, 95% CI 1.0 to 4.8) was significantly associated with mortality in unifactorial analyses. Scoring on the GHQ-D remained a predictor of mortality after controlling for other variables. Psychiatric disorder, such as major depression (according to International Classification of Diseases, 10th Revision), was not statistically significantly associated with increased mortality at 12 or 24 months.

Conclusions—Mood symptoms on a self-reported rating scale were associated with 12- and 24-month mortality after stroke, after adjustment for factors associated with stroke severity. The result is in keeping with other evidence that depressive symptoms are a risk factor for death from vascular disease. (Stroke. 2001;32:696-701.)

Key Words: affect ■ cohort studies ■ depression ■ mortality

Research in heart disease and stroke suggests that depression may be an independent risk factor for vascular disease. For example, 3 recent studies have reported that men with depression are more likely to develop ischemic heart disease.1-3 In established coronary artery disease, major depression is associated with an increased risk of myocardial infarction4 and with increased rates of angina after myocardial infarction.5 Major depression may also be associated with increased mortality after myocardial infarction, even after adjustment for cardiac risk factors.6 Another study from the same group suggests that the risk resides in general psychological distress (eg, as measured by questionnaire) rather than a diagnosable psychiatric syndrome such as major depression.7

There have been fewer studies examining depression as a risk in stroke. A recently published cohort study from the United States found an increased mortality from stroke in people who had self-reported depressive symptoms at recruitment 29 years previously; this association remained significant after adjusting for known clinical and behavioral risk factors.8 Two small studies have reported that patients who were depressed in the early weeks after stroke had higher mortality at 15 months and at 10 years.9,10

If a causal link between depression and stroke mortality can be established, then it has clinical and theoretical implications; therefore, well-designed replications are needed. In the present study, we report a cohort enrolled within a randomized controlled trial, in which we examined the effect of depression identified 1 month after stroke on mortality at 12 and 24 months after stroke. Because of the findings of Lesperance et al,7 suggesting a role for depression symptoms below diagnostic criteria, we defined depression both by standardized clinical interview and the application of research diagnostic criteria and by scores on a self-reported questionnaire.

Subjects and Methods
The present study was undertaken in the context of a randomized controlled trial of psychological treatment after stroke. In the trial,
Patients who had been admitted to the hospital in Leeds and Bradford were randomized to receive treatment as usual, volunteer visits, or problem-solving therapy delivered by a psychiatric nurse. The primary aim of the trial was to evaluate the effect of problem-solving therapy on depression at 6 and 12 months after stroke; we have described the study therapy elsewhere. Because all the subjects were assessed for depression at recruitment and followed up at 12 and 24 months, we were able to analyze the cohort to examine the effect of depression as an independent risk factor for mortality.

Patients were assessed at 1 month after stroke and recruited if they met the following criteria: definite clinical diagnosis of stroke (not subarachnoid hemorrhage), sufficient speech and use of English for interview (as judged by interviewer), sufficient cognitive abilities to benefit from therapy (we defined this as Mini-Mental State Examination [MMSE] score of ≥20 rather than the usually quoted threshold because we were interested in the ability to participate in a simple psychological therapy rather than in the presence of diagnosable but mild cognitive impairment), local residence and living independently before stroke, no concurrent illness likely to dominate the pattern of care (approximately equivalent to Rankin handicap scores of 4 or 5), and written consent. We did not recruit patients with subarachnoid hemorrhage, because the trial was an evaluation of psychological intervention in patients admitted to general medical and neurology wards rather than those admitted under the care of neurosurgeons.

From an original stroke population of 1387 consecutive admissions, we excluded those with severe cognitive impairment (n=210) or language disorder (n=179) and those who were too ill to participate in the psychological therapy (n=369). Other exclusions were based on place of residence and involvement in other trials (n=187), and there were 92 refusals of consent to participate in the trial. There were 2 protocol violations leading to exclusion; therefore, the sample was composed of 448 hospitalized stroke patients who had been recruited to the trial.

Measures

Initial assessments were undertaken by a trained research interviewer, who collected basic biographical data, including age and whether the patient lived alone and could name a career. History of previous stroke was obtained from the patient and the medical record.

Physical functional status was assessed by using the Barthel Index, a measure of activities of daily living, which is scored 0 to 20, with higher scores indicating greater independence. An assessment was made of the patient’s poststroke and prestroke abilities. The Barthel Index may be recoded to form categories: a score of 20 indicates no disability, and scores of ≥12 are generally taken to indicate an ability to live independently in the community. The Frenchay Activities Index measures social function and is scored 0 to 45, with higher scores indicating greater social activity. Patients were asked to rate their prestroke activity. There are no published threshold scores, so we used the median score to categorize patients.

The MMSE is a measure of cognitive ability, designed originally to screen for dementia in the elderly. The measure is scored 0 to 30, with a lower score indicating greater cognitive impairment. A threshold score of <24 may be used to categorize patients as cognitively impaired.

The General Health Questionnaire (GHQ)-28 is a measure of general psychological distress and is scored 0 to 28, with higher scores indicating greater distress. In neurological inpatients, scores of ≥12 are taken to indicate the probable presence of psychiatric disorder. Because this threshold masks much variation, we also analyzed the GHQ-28 by quartiles (scores 0 to 1, 2 to 5, 6 to 9, and 10 to 28). The GHQ-28 also has 4 subscales: somatic (A), anxiety and insomnia (B), social dysfunction (C) and severe depression (D). There are no “caseness” thresholds for the subscales, so we categorized patients by the median score on each.

The short-form Present State Examination is a standardized semistructured psychiatric interview, which allows the reliable identification of psychiatric symptoms when it is administered by a trained interviewer, as in the present study. With minor additions to the interview, International Classification of Diseases, 10th Revision (ICD-10) psychiatric diagnoses can be derived from Present State Examination ratings; we used the ICD-10 research diagnostic criteria.

Patient survival at 12 and 24 months was determined through general practitioners and checked, for untraceable patients, through the Office for National Statistics, which also provided certified causes of death. Data were analyzed by using SPSS 9.0.

Results

The sample had a median age of 72 years, with slightly more men (54%) than women. Almost 40% of the patients lived alone before the stroke, although only 10% were unable to name a career. Most patients were functionally independent before the index stroke, although 21% had suffered a previous stroke (see Table 1).

Similar rates of depression were obtained by using the different criteria used in the present study: 100 (22.3%) patients met ICD-10 research criteria for major depression; 85 (19.1%) patients scored above the probable “caseness” cutoff of ≥12 on the GHQ-28. Depression at 1 month after stroke was significantly associated, at the 95% level, with lower prestroke and 1-month poststroke Barthel scores (see Table 1). Depression was also associated with being female, with lower MMSE scores, and with being incontinent at 1

| TABLE 1. Characteristics of the Sample at Initial Interview 1 Month After Stroke |
|--------------------------------------------|-------------------|-------------------|-------------------|-------------------|-------------------|
| All Patients (N=448)                       | Patients With Major Depression (N=100) | Patients Without Major Depression (N=348) | Difference |
| Age, y                                      | 70.7±11.6         | 70.1±11.9         | 70.9±11.5         | T=0.65, P=0.51   |
| Female, n (%)                               | 207 (46.2)        | 53 (63.0)         | 154 (44.2)        | $\chi^2=2.39, P=0.12$ |
| Previous stroke, n (%)                      | 94 (21.0)         | 24 (24.0)         | 70 (20.1)         | $\chi^2=0.71, P=0.40$ |
| Prestroke Barthel ≤20, n (%)                | 132 (29.5)        | 41 (41.0)         | 91 (26.1)         | $\chi^2=8.24, P=0.004$ |
| Poststroke Barthel ≤20, n (%)               | 245 (54.7)        | 49 (49.0)         | 154 (44.2)        | $\chi^2=0.71, P=0.40$ |
| Poststroke Barthel ≤12, n (%)               | 155 (34.6)        | 40 (40.0)         | 115 (33.0)        | $\chi^2=1.66, P=0.20$ |
| MMSE ≤24, n (%)                             | 367 (71.9)        | 92 (92.0)         | 275 (79.0)        | $\chi^2=8.83, P=0.005$ |
| Urinary incontinence, n (%)                 | 124 (27.7)        | 35 (35.0)         | 89 (25.6)         | $\chi^2=3.45, P=0.06$ |

Values are mean ±SD or as indicated.
month after stroke, but these associations did not reach statistical significance.

**Mortality at 12 Months**

At 12 months, we were unable to establish the status of 2 patients who had moved abroad, leaving no contact details. Of the 446 traceable patients, 45 (10.1%) had died. Causes of death were as follows: recurrent stroke in 17 (37.8%), cardiovascular disease in 10 (22.2%), and other causes in 18 (40.0%). No patient died as a result of suicide, and there was no statistically significant difference between depressed and nondepressed patients in the cause of death.

The relationship between independent variables assessed at 1 month and mortality at 12 months was examined by logistic regression. Independent variables were categorized (see Subjects and Methods) and were assessed individually. All the mood measures showed a trend for higher scores to be associated with increased mortality, but only 2 measures (GHQ-D “severe depression” and GHQ quartiles) were statistically significant. The odds ratio for mortality was 3.1 between the lowest and highest scoring quartiles (see Table 2), with the rate of mortality 5% in the lowest quartile and 14% in the highest (see Figure 1). Those scoring $10$ on the GHQ-D severe depression subscale had an odds ratio for mortality of 2.4 compared with those scoring 0.

We conducted multiple logistic regression analyses to assess whether impaired mood was associated with increased mortality after controlling for the effects of recognized physical predictors (older age, lower MMSE scores, lower poststroke Barthel score, having suffered a previous stroke, and urinary incontinence). We did this separately for the GHQ quartiles and the GHQ-D subscale.

Multiple logistic regression showed that higher GHQ-D score, greater age, lower MMSE scores, and lower poststroke Barthel scores were all associated with an increased risk of dying within 12 months of stroke (see Table 3). Other variables, including treatment condition in the trial, were not significantly associated with mortality. In a separate regression analysis, the statistically significant effects of GHQ quartiles were lost after controlling for other predictors (see Table 4).

**Mortality at 24 Months**

A further 20 patients had died between 12 and 24 months after stroke, giving a total of 65 (14.6%) deaths for 446 patients in 24 months. As at 12 months, no patient had died as a result of suicide.

As at 12 months, the relationship between independent variables assessed at 1 month and mortality at 24 months was examined by logistic regression. The GHQ quartiles and subscale GHQ-D were statistically significantly associated with mortality; major depression at 1 month was associated with mortality, but the result was not statistically significant (see Table 2). Mortality among those in the lowest GHQ quartile was 11% compared with a mortality of 23% among those in the highest quartile (see Figure 2).

A multiple regression analysis assessed whether impaired mood was an independent predictor of increased mortality...
after controlling for the effects of recognized physical predictors, as at 12 months. This showed that the effects of scoring $\geq 1$ on the GHQ-D subscale remained statistically significant, even after controlling for the effects of age, cognitive status, and known physical predictors (see Table 3). The effects of the GHQ quartiles did not remain statistically significant after controlling for other predictors (see Table 4).

**Discussion**

We have found that mood symptoms, as measured by the GHQ, reported within 1 month of stroke, were associated with 12- and 24-month mortality after adjustment for other risk factors identified in the present study: age, cognitive impairment, urinary incontinence, and level of physical disability after stroke. Major depression diagnosis and mortality were not associated statistically, although the data showed a trend in that direction. One possible explanation for the absence of a statistical relationship is a lack of statistical power associated with binary variables, such as major depression.

The strength of association between mood and mortality is considerably lower than that reported by Morris and colleagues.\(^5,10\) Does this result represent a true association, or could it be due to chance, bias, or confounding? We used several measures of mood in the analyses, raising the possibility of a false-positive result from multiple testing. The use of $>1$ mood measure was unavoidable if we were to test alternative hypotheses on the nature of depression, which predicts mortality, because previous research has suggested that either major depression or general psychological distress may be important. However, we cannot entirely exclude multiple testing as an explanation for our finding.

A second possibility is that bias may have affected the results. Observer bias is unlikely, because the significant mood measure was self-rated. Bias may result from studying hospital samples, when a spurious association can be found between variables that are both independently associated with risk of hospitalization (Berkson's bias)\(^23\); this is unlikely, since multiple regression showed that the GHQ-D score was a predictor of mortality independent of measures of stroke severity. Mortality data were obtained for all but 2 patients, thus excluding bias from incomplete follow-up.

The third possibility is that there was residual confounding, particularly arising from an association between severity of physical illness and depressive symptoms, which was not detected through the available measures. Against this interpretation is our finding that the one significant GHQ subscale measured depressive thinking, whereas confounding of phys-

<table>
<thead>
<tr>
<th>GHQ-D subscale $\geq 1$</th>
<th>12 Months</th>
<th>24 Months</th>
</tr>
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<tbody>
<tr>
<td>OR</td>
<td>95% CI</td>
<td>P</td>
</tr>
<tr>
<td>GHQ-D subscale $\geq 1$</td>
<td>2.0</td>
<td>1.0–4.1</td>
</tr>
<tr>
<td>Age (compared with &lt;60-y group)</td>
<td></td>
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<tr>
<td>60–69 y</td>
<td>3.3</td>
<td>0.36–30</td>
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<tr>
<td>70–79 y</td>
<td>9.8</td>
<td>1.2–77</td>
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<tr>
<td>80+ y</td>
<td>12</td>
<td>1.4–96</td>
</tr>
<tr>
<td>Urinary incontinence</td>
<td>4.0</td>
<td>1.5–11</td>
</tr>
<tr>
<td>MMSE $&lt;24$</td>
<td>2.5</td>
<td>1.2–5.0</td>
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<tr>
<td>Poststroke Barthel (compared with patients scoring 20)</td>
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<tr>
<td>12–19</td>
<td>0.90</td>
<td>0.42–1.9</td>
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<tr>
<td>&lt;12</td>
<td>1.4</td>
<td>0.48–5.0</td>
</tr>
<tr>
<td>Prestroke Frenchay $&lt;27$</td>
<td>1.2</td>
<td>0.58–2.4</td>
</tr>
<tr>
<td>Sex (female)</td>
<td>1.1</td>
<td>0.54–2.2</td>
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<tr>
<td>Previous stroke</td>
<td>0.80</td>
<td>0.33–1.9</td>
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<td>Random group allocation (compared with treatment as usual)</td>
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<tr>
<td>Problem-solving therapy</td>
<td>1.1</td>
<td>0.49–2.6</td>
</tr>
<tr>
<td>Volunteer visits</td>
<td>1.1</td>
<td>0.50–2.6</td>
</tr>
</tbody>
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Figure 2. Mortality (%) at 24 months after stroke, by GHQ-28 score at 1 month.
ical illness and somatic mood symptoms would be more likely in subscales A and C (somatic and social dysfunction items). Because of the nature of the study design, we were not able to assess all the stroke-related variables (eg, not every patient had a brain scan).

One possibility that we have not been able to explore is the confounding arising from a link between depressive symptoms after stroke and prior life events. It is possible that stressful life events might be a risk both for depression and for recurrent stroke or myocardial infarction.24 The mechanisms by which mood symptoms may be associated with increased mortality are behavioral or physiological. Suggested physiological explanations include alterations in autonomic control of cardiac rhythm (eg, those manifested by reduced heart rate variability)25 and increased platelet reactivity26 in depressed patients. Some support for this idea is provided by a meta-analysis of psychological treatments after myocardial infarction,27 which found that treatment not only reduced distress but also apparently led to lower blood pressure, heart rate, and cholesterol levels. Possible behavioral explanations include continued higher levels of smoking and alcohol consumption among depressed patients and lesser adherence to medical treatment.28 We were not able to measure all these factors (because of funding restrictions and problems of rater burden in a psychological treatment trial); therefore, the present study offers no evidence about the nature of any link that does exist.

One interesting implication of our results is that the psychological factor most strongly associated with mortality after stroke may not be depressed mood, per se, but general psychological distress or negative thoughts, such as feeling that life is not worth living or a feeling of personal worthlessness (items on the GHQ-D subscale). This finding is broadly in keeping with recent work into psychological predictors of mortality after myocardial infarction.6 This is the largest cohort study of mortality and depression after stroke. Its findings are ambiguous and therefore need replication, with further attempts to identify and adjust for confounders and more detailed characterization of psychological variables that might act as risk factors. At the same time, a descriptive study of the frequency of possible mediating variables (physiological and behavioral) in depressed and nondepressed stroke patients would help to clarify their possible involvement in any process whereby depressive symptoms have an impact on mortality after stroke.

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