Explanatory factors for the increased mortality of stroke patients with depression

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ABSTRACT

Objective: To identify explanatory factors for the association between depression and increased mortality up to 5 years after stroke.

Methods: In this cohort study, data from the South London Stroke Register (1998–2013) were used. Patients (n = 3,722) were assessed at stroke onset. Baseline data included sociodemographics and stroke severity. Follow-up at 3 months included assessment for depression with the Hospital Anxiety and Depression Scale (scores ≥7 = depression). Associations between depression at 3 months and mortality within 5 years of stroke were estimated with Cox regression models adjusted for age, sex, ethnicity, and stroke severity, and subsequently adjusted for possible explanatory factors for the association. These factors, introduced into the model individually, included comorbidities at baseline, smoking and alcohol use, compliance with medication, treatment with selective serotonin reuptake inhibitors (SSRIs), social support, and activities of daily living at 3 months.

Results: A total of 1,354 survivors were assessed at 3 months: 435 (32.1%) had depression and 331 (24.4%) died within 5 years. Survivors with depression had a greater risk of mortality (hazard ratio [HR] 1.41 [95% confidence interval (CI) 1.13–1.77]; $p = 0.002$). The association between depression and mortality was strongest in patients younger than 65 years. Adjustment for comorbidities, smoking and alcohol use, SSRI use, social support, and compliance with medication did not change these associations. SSRIs started after stroke were associated with higher mortality, independently of depression at 3 months (HR 1.72 [95% CI 1.34–2.20]; $p < 0.001$).

Conclusion: Depression after stroke is associated with higher mortality, particularly among younger patients. Stroke survivors taking SSRIs have an increased mortality. The association between depression and mortality is not explained by other individual medical factors. *Neurology*® 2014;83:2007–2012

GLOSSARY

CI = confidence interval; **GCS** = Glasgow Coma Scale score; **HADS** = Hospital Anxiety and Depression Scale; **HR** = hazard ratio; **SLSR** = South London Stroke Register; **SSRI** = selective serotonin reuptake inhibitor.

Depression has a prevalence of around 30% in the long term after stroke, with most patients developing their first symptoms shortly after the acute event.[1,2] Depression after stroke is more prevalent among those with severe strokes, disability, and cognitive impairment, and has been found to be independently associated with higher mortality.[3,4] A number of medical and social factors have been proposed to underlie the relationship between depression and mortality. They include younger age, lifestyle factors such as smoking and heavy alcohol use, lack of compliance with medication, comorbidities such as diabetes and heart failure, use of antidepressants, and social isolation.[5–12] These explanatory factors have been reported in studies not specifically investigating stroke survivors[5,6,8–11] or presented in the discussion of systematic reviews of depression and risk of mortality after stroke.[7,12]

Since depression is independently associated with higher mortality, we could also hypothesize that antidepressants may have a positive effect on the long-term prognosis of stroke patients.

However, it has been reported that antidepressants are associated with adverse outcomes, including higher risk of stroke and mortality.[7,13]

A better understanding of the association between depression and mortality would strengthen the evidence for causality, improve the therapeutic approach to stroke survivors with mood disorders, and provide important prognostic information on survival.

This study investigates the association between depression 3 months after stroke and all-cause mortality up to 5 years, and examines the role of potential explanatory factors in this association. The effect of selective serotonin reuptake inhibitors (SSRIs) on mortality, and on the association between depression and mortality, is specifically investigated.

METHODS The study conformed to Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) study design recommendations.[14]

Patients with first-ever strokes were recruited from the South London Stroke Register (SLSR), a prospective population-based cohort study.[15] Data from patients registered in the SLSR between 1998 and 2012 and followed up until June 30, 2013, were used. The definition of stroke proposed by the WHO was used.[16] To increase completeness of notification, 16 overlapping referral sources were used.[15] SLSR fieldworkers registered patients during the acute phase of stroke. Data on age, sex, and ethnicity (white, black, and other ethnicity) were collected.[15] Stroke severity measures were also recorded, including Glasgow Coma Scale score (GCS), categorized as severe (3–8), moderate (9–12), or mild (13–15); levels of impairment; urinary incontinence; and paresis.[15] Other data collected at baseline included regular medication taken before stroke, medical history of diabetes, hypertension, congestive heart failure, ischemic heart disease, and atrial fibrillation.

Follow-up 3 months after stroke was by postal questionnaire or interview. At follow-up, patients were screened for depression using the Hospital Anxiety and Depression Scale (HADS).[17] HADS has been validated in stroke patients, showing good performance both when it is used by an interviewer and when it is self-administered[18] (optimum performance when scores above 7 in the HADS depression subscale are used to identify depression: sensitivity 0.82, specificity 0.76).[17] No information could be recorded from patients with impaired communication that the SLSR fieldworker judged would give invalid data. Disability was also assessed 3 months after stroke using the Barthel Index[19]: scores of 0–14 were categorized as severe disability, 15–19 moderate disability, and 20 independent. Other data collected at 3 months included smoking habit (smoker or nonsmoker), weekly alcohol consumption (less than 1 unit, less than 14 units, 14–21 units, more than 21 units), and social support: Do you see as much of your relatives or friends as you would like? (Yes/No). Medication taken regularly was recorded as well at 3 months, including SSRIs (never, started before stroke, or started after stroke), antihypertensive medication, and diabetes medication. Mortality within 5 years of stroke was recorded by the SLSR fieldworkers and verified by the Office for National Statistics.[20]

Statistical methods. Cox regression was used to analyze the association between depression at 3 months and all-cause mortality within 5 years of stroke. All models were adjusted for age, sex, ethnicity, and stroke severity measures (GCS, incontinence, and hemiparesis). Different models were constructed with further adjustment for potential explanatory factors for the association. The first model was adjusted for comorbidities at baseline (diabetes, hypertension, congestive heart failure, ischemic heart disease, and atrial fibrillation). All other models were adjusted for potential explanatory factors collected at 3 months. The second model was adjusted for smoking and alcohol consumption, adjustment for treatment of hypertension and diabetes was conducted in the third model, adjustment for social support in the fourth, disability in the fifth, and use of SSRIs at 3 months in the sixth model.

Most explanatory variables, including depression, had some missing data. A separate category was assigned, e.g.: Paresis 0 (No), 1 (Yes), and 2 (Missing). Sensitivity analysis was conducted to compare estimates obtained when the category for missing data was included and when it was not included. Most estimates were consistent with those based on complete data so the results obtained using missing data categories were reported. Any differences observed between estimates obtained with and without the missing data category were presented. Further testing of the robustness of the results was conducted using mortality at 3 years as the outcome. Any differences between the associations with mortality at 3 and 5 years were reported.

Interactions between age and depression, and between age and antidepressants, were tested. Where a significant interaction was observed, the models' results for the main effects and for the interactions were reported separately.

Standard protocol approvals, registrations, and patient consents. Patients or their relatives gave written informed consent to the SLSR fieldworkers at the moment of registration. The ethics committees of Guy's and St. Thomas' Hospital National Health Service Foundation Trust, King's College Hospital Foundation, National Hospital for Nervous Diseases, Queen's Square Hospital, St. George's Hospital, and Westminster Hospital approved the study.

RESULTS Of the 3,722 patients recruited by the SLSR between 1998 and 2012, 1,068 (28.7%) died before the 3-month assessment and 956 (25.7%) were lost to follow-up at 3 months. Among the 1,698 (45.6%) patients who were followed up, 1,354 (79.7%) were able to complete the HADS, 435 (32.1%) of them were categorized as depressed, and 331 (24.4%) had died within 5 years. A total of 25 (5.7%) of the patients with depression were taking SSRIs at the time of stroke, 67 (15.4%) started taking them after stroke, and 132 (30.3%) died within 5 years of stroke. The prevalence of depression was not significantly different by age (<65/≥65) or sex categories. The baseline and follow-up characteristics of these patients are presented in tables 1 and 2.

Subjects with depression showed higher mortality within 5 years (hazard ratio [HR] 1.41 [95% confidence interval (CI) 1.13–1.77]; $p = 0.002$). A significant interaction between age and depression was observed, and consequently the results were stratified by age. In patients under 65 years of age, the association between depression and mortality was stronger

Table 1	Baseline characteristics of patients assessed for depression at 3 months	
Baseline variables	No. (%)	
Age >64 y	847 (62.6)	
Female sex	623 (46.0)	
Ethnicity		
White	902 (66.6)	
Black	354 (26.1)	
Other	82 (6.1)	
Unknown	16 (1.2)	
Glasgow Coma Scale score		
3-8	33 (3.4)	
9-12	103 (7.6)	
13-15	1,174 (86.7)	
Unknown	44 (3.2)	
Paresis		
No	240 (17.7)	
Yes	657 (48.5)	
Unknown	457 (33.7)	
Incontinence		
No	991 (73.2)	
Yes	313 (23.1)	
Unknown	50 (3.7)	
SSRI use		
No	1,082 (79.9)	
Yes	55 (5.1)	
Unknown	217 (16.0)	
History of diabetes		
No	1,032 (76.2)	
Yes	276 (20.4)	
Unknown	46 (3.4)	
History of congestive heart failure		
No	1,088 (80.3)	
Yes	54 (4.0)	
Unknown	212 (15.7)	
History of hypertension		
No	449 (33.2)	
Yes	856 (63.2)	
Unknown	49 (3.6)	
History of ischemic heart disease		
No	713 (52.7)	
Yes	154 (11.4)	
Unknown	487 (36.0)	
History of atrial fibrillation		
No	1,136 (83.9)	
Yes	160 (11.8)	
Unknown	58 (4.3)	

Abbreviation: SSRI = selective serotonin reuptake inhibitor.

Table 2	Characteristics at 3 months of patients assessed for depression	
Follow-up variable	No. (%)	
Smoker		
No	999 (73.9)	
Yes	343 (25.4)	
Unknown	10 (0.7)	
Alcohol consumption (units per week)		
<1	765 (56.5)	
<1-14	372 (27.5)	
14-21	52 (3.8)	
>21	78 (5.8)	
Unknown	87 (6.4)	
Antihypertensives		
Hypertension on medication	597 (44.9)	
Hypertension not on medication	242 (17.9)	
No hypertension	498 (36.8)	
Hypertension treatment unknown	17 (1.3)	
Diabetes medication		
Diabetes on medication	204 (15.1)	
Diabetes not on medication	72 (5.3)	
No diabetes	1,078 (79.6)	
Unknown	0	
Treatment with SSRIs		
No	1,196 (88.3)	
Yes, started before stroke	5 (4.1)	
Yes, started after stroke	96 (7.1)	
Unknown	7 (0.5)	
Social support		
Yes	920 (67.9)	
No	210 (15.5)	
Unknown	224 (16.5)	

Abbreviation: SSRI = selective serotonin reuptake inhibitor.

than in those 65 years or over (HR 3.29 [95% CI 1.75–6.19]; $p < 0.001$). Among patients 65 or over, mortality was still increased, but the difference between those with and without depression was not statistically significant (HR 1.24 [95% CI 0.98–1.59]; $p = 0.074$) (table 3). Adjustment for comorbidities, smoking and alcohol use, management of hypertension and diabetes, social support, and use of SSRIs did not change the associations between depression and mortality (table 3).

Twenty-one (38.2%) of those on SSRIs at baseline and 36 (37.5%) on SSRIs at 3 months died within 5 years. There was a not significant increase of mortality among those who were on SSRIs before stroke (HR 1.25 [95% CI 0.85–1.83]; $p = 0.250$). However, SSRIs started after stroke

Table 3 Association between depression 3 months after stroke and mortality at 5 years

	Mortality, all ages			Mortality, patients under 65 y			Mortality, patients 65 y or over		
	HR	95% CI	p Value	HR	95% CI	p Value	HR	95% CI	p Value
Basic model[a]	1.41	1.13-1.77	0.002	3.29	1.75-6.19	<0.001	1.24	0.98-1.59	0.074
Basic model[a] further adjusted for hypertension, diabetes, ischemic heart disease, heart failure, and atrial fibrillation	1.55	1.24-1.93	<0.001	3.42	1.82-6.43	<0.001	1.37	1.07-1.75	0.011
Basic model[a] further adjusted for smoking and alcohol consumption	1.35	1.07-1.69	0.010	3.06	1.63-5.77	0.001	1.18	0.92-1.51	0.183
Basic model[a] further adjusted for treatment with hypertension and diabetes medication	1.38	1.11-1.73	0.004	3.34	1.78-6.29	<0.001	1.21	0.95-1.54	0.123
Basic model[a] further adjusted for social support	1.34	1.07-1.68	0.011	3.14	1.67-5.90	<0.001	1.21	0.95-1.55	0.117
Basic model[a] further adjusted for disability	1.07	0.85-1.35	0.548	2.44	1.29-4.62	0.006[b]	0.94	0.74-1.21	0.660
Basic model[a] further adjusted for treatment with SSRIs	1.38	1.100-1.72	0.005	3.04	1.61-5.73	0.001[b]	1.22	0.96-1.56	0.107

Abbreviations: CI = confidence interval; HR = hazard ratio; SSRI = selective serotonin reuptake inhibitor.
[a] Basic model: adjusted for age, sex, ethnicity, and stroke severity.
[b] This result could not be confirmed in the analysis without missing data categories.

were independently associated with a significant increase in mortality within 5 years of stroke (HR 1.72 [95% CI 1.34–2.20]; $p < 0.001$). No significant interaction between age and antidepressants was identified.

The analysis without missing data gave estimates that were consistent with the ones obtained with missing data categories. There were 2 exceptions: in patients under 65, the association between depression and mortality when adjusting for disability, and when adjusting for SSRI use at 3 months, became not significant in the analysis without missing data. The analysis with mortality at 3 years as an outcome gave results that were consistent with the ones obtained when mortality at 5 years was used.

DISCUSSION Depression is associated with an increased mortality in the long term after stroke and this association is stronger among younger stroke survivors. Comorbidities, smoking and alcohol intake, management of hypertension and diabetes, disability, social support, and treatment with SSRIs do not affect the association between depression and mortality. SSRIs started after stroke were independently associated with higher mortality up to 5 years after the acute event.

This study has strengths and limitations. One limitation is the loss to follow-up, associated with stroke cohort studies of elderly survivors. Part of the missing data were due to the inability of some patients with cognitive or communication impairment to respond to the follow-up questionnaires. The regression analysis with

and without categories for missing data suggests that while some sociodemographic groups are more likely to be missing than others, this had little impact when analyzing the association between depression and mortality. The SLSR is a large population-based cohort of stroke patients with long-term follow-up. It provides the least biased sampling frame, and good statistical power, allowing for an in-depth investigation of the nature of the association between depression and mortality in the long term after stroke. The assessment of depression with a screening scale instead of a diagnostic tool may represent a limitation. A recent review suggested that another depression scale could be more accurate than HADS. However, the authors of this review also reported that further research is needed to confirm the optimal tool for identifying depression after a stroke since a limited number of heterogeneous studies are available.[17] This study did not take prestroke depression into account, which can increase subsequent stroke mortality.[7] Nonetheless, prestroke depression also predicts depression after stroke,[21] which may be what leads to higher mortality in the long term after stroke. Some studies have investigated the association between depression and mortality in patients with other conditions,[5,6,8–11] and another one focused on depression-executive-dysfunction syndrome to explain the association between depression and mortality after stroke.[22] One strength of this study, adding to the evidence presented by previous literature, is the observation of a range of clinical and social explanatory factors for the association between depression and long-term

mortality after stroke. Social support was measured with a single not validated question. Even though this question has been used before, giving plausible results,[23,24] it would have been better to have a validated and more accurate measure for social support.

The onset of depression at an older age may be associated with a lower rate of relapse and better response to treatment and this may explain the different association between depression and mortality in each age category.[8]

The association between depression and higher mortality is independent of the medical factors analyzed in this article. Other factors, including the neurologic, sociologic, psychological, endocrine, immunologic, and inflammatory disorders observed in depressed patients,[6,7] may be more explanatory of the association between depression and mortality after stroke. Unmeasured case mix variables could also be affecting part of these findings. It may also be that the association between depression and mortality is multifactorial and no individual factor can explain it completely.

The association between SSRIs and increased mortality may be explained because patients who take SSRIs have more severe depression.[7,10] An alternative explanation could be that the use of SSRIs at 3 months is associated with depression shortly after stroke, which is strongly associated with recurrent episodes of depression that may increase mortality in the long term.[4,24] Another possibility is that SSRIs have side effects that increase mortality in the long term. Antidepressants have been shown to improve mood in patients with physical diseases and specifically in stroke patients.[25,26] However, previous studies on the nonpsychological effects of antidepressants report contradictory results. There are 2 systematic reviews reporting an association between SSRIs and a reduced mortality of patients with acute cardiovascular events,[27] and a limited but significant improvement in dependence, disability, and neurologic impairment in the first few years after stroke.[28] Most studies included in these reviews had short follow-up; therefore, the long-term negative effects of SSRIs may not have been observed. A large cohort study observing more than 60,000 primary care patients in the United Kingdom reported that SSRIs were associated with increased risk of falls, strokes, ischemic heart disease, self-harm, fractures, and all-cause mortality.[13] The association between SSRIs and mortality may also be affected by the time in which the medication is taken. While our results show that SSRI use after stroke is associated with mortality in the long term, another study found an association between prestroke SSRI use and increased mortality within a year of the acute event.[29] While SSRIs may be a useful tool in the management of stroke, their safety in the long term needs further research.

Clinicians should consider the poorer prognosis of stroke survivors with depression, particularly if they are young, acknowledging that no individual medical factor can explain this association. Further studies could address the association between depression and specific causes of death such as cardiovascular disease. The significantly increased mortality among those who take SSRIs should also be considered when managing depression in stroke survivors. Depression and its associated outcomes require periodic clinical assessment as well as effective and safe interventions in the long term after stroke.

AUTHOR CONTRIBUTIONS

C.D.A.W. and A.G.R. secured the funding. L.A., S.A., S.L.C., C.D.A.W., and A.G.R. designed the study. L.A. collected part of the data. L.A., S.A., and S.L.C. conducted the analysis. L.A., S.A., S.C., C.D.A.W., and A.G.R. cowrote the paper.

STUDY FUNDING

DISCLOSURE

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