Article

Measures Associated With Early, Late, and Persistent Clinically Significant Symptoms of Depression 1 Year After Stroke in the AFFINITY Trial

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ABSTRACT

Objective: To determine the sociodemographic and clinical factors associated with early, late and persistent clinically significant symptoms of depression during the first year after a stroke.

Methods: Cohort study of 1221 men and women recruited within two weeks of stroke onset in Australia, New Zealand and Vietnam. The NIH Stroke Scale (NIHSS) was used to assess the severity of the stroke. Other study measures included age, sex, marital status, living arrangements, function before the stroke, depression before the stroke, modified Rankin Scale (mRS), and treatment with fluoxetine or placebo for 26 weeks. Clinically significant symptoms of depression during the 52 weeks after baseline was the outcome of interest, and its presence was defined by a total PHQ-9 score of 9 or higher at weeks 4, 12, 26 or 52, a clinician diagnosis of depression between assessments, or by pharmacological or psychological treatment of depression during follow up. Participants were classified as not depressed, or as early (initial 12 weeks), late (12 to 52 weeks) or persistent depression (before and after 12 weeks). We used multinomial logistic regression to assess depression risk, with all listed measures entered simultaneously into the model.

Results: The mean age of participants was 63.8 (SD=12.3) years and 775 (63.5%) were male. At baseline, 48 (3.9%) participants had previous treated depression, and 228 (18.7%) had clinically significant symptoms of depression (PHQ-9 $\geq$ 9). 734 (63.3%) participants showed no evidence of depression in the year following the stroke, 208 (17.9%) had early, 86 (7.4%) late, and 131 (11.3%) persistent depression. Increased stroke severity, as measured by doubling of NIHSS scores, was associated with an increased risk of early (Risk Ratio [RR]=2.08, 95%CI=1.65-2.62), late (RR=1.53, 95%CI=1.14-2.06) and persistent clinically significant symptoms of depression (RR=2.50, 95%CI=1.89-3.32). Similar findings were apparent for the mRS, a measure of functional disability. Past depression was associated with increased risk of persistent clinically significant symptoms of depression (RR=6.28, 95%CI=2.88-13.71), as was being married or partnered (RR=3.94, 95%CI=2.42-6.41). The risk of clinically significant symptoms of depression was higher in Australia and New Zealand than in Vietnam.

Conclusion: The severity of neurological and functional deficits increases the risk of post-stroke clinically significant symptoms of depression early and persistently. Depression before stroke, personal relationships and cultural context contribute to mediate depression risk. Interventions that minimise the severity of neurological and functional deficits should decrease the risk of post-stroke clinically significant symptoms of depression.

INTRODUCTION

Clinically significant symptoms of depression affect 1 in every 3 people during the first year after a stroke.[1] Depression is associated with a significant burden[2] and may hinder recovery among stroke survivors. A systematic review of 6 prospective studies involving 3273 stroke survivors found that depression after stroke more than doubled the risk of long-term disability (OR=2.16, 95%CI=1.70-2.77).[3]

A recently updated systematic review of 23 observational studies of factors associated with clinically significant symptoms of depression after stroke reported that only 5 studies had investigated 10 or more factors, and that physical disability was the most consistent risk factor for depression after stroke.[4] Since that review, new prospective studies have confirmed that the risk of post-stroke depression increases with stroke severity.[5,6] However, it remains unclear if stroke severity is a cause, or a consequence of, depression.

The Assessment of Fluoxetine in Stroke Recovery (AFFINITY) trial was designed to determine the effect of fluoxetine treatment on the functional recovery of 1280 stroke survivors.[7] In this secondary, exploratory analysis of the AFFINITY trial cohort, we aimed to determine the prevalence and incidence of depression over 52 weeks, and the sociodemographic and clinical factors associated with depression after stroke. We used the guidelines of the Stroke Recovery and Rehabilitation Roundtable Taskforce to define 12 weeks as the early phase following a stroke,[8] and sought to generate novel and clinically relevant data about the evolution of clinically significant depressive symptoms during different phases of stroke recovery over a 52-week period: early (≤ 12 weeks), late (> 12 weeks) and persistent (both early and late). In line with previous studies,[4] we expected the severity of neurological deficits and functional disability to be the most robust predictors of post-stroke clinically significant symptoms of depression, and anticipated that this association would be particularly robust for those with persistent depressive symptoms.

METHODS

Study design and participants

AFFINITY was a randomised, parallel group (1:1), double-blind, placebo-controlled trial of fluoxetine 20 mg daily in 1280 adults aged 18 years or older who had a stroke less than 15 days prior to consent. Recruitment took place between 11 January 2013 and 30 June 2019. The primary aim of the study was to investigate the effect of fluoxetine on the functional outcome after 6 months of treatment – the study design the results of the primary analyses have been reported.[7] clinically significant symptoms of depression was a planned secondary outcome[9] and the effect of fluoxetine on depressive symptoms over 6 months has also been reported.[10]

Briefly, we recruited patients admitted to stroke services in Australia, New Zealand and Vietnam. Inclusion required participants to have a post-stroke neurological deficit sufficiently severe to result in a modified Rankin Scale (mRS) score ≥ 1.[11] We excluded adults with history of epilepsy, bipolar disorder, hepatic or renal impairment, hyponatraemia, or exposure to antipsychotic medications or a selective serotonin reuptake inhibitor within the last month. Those who had a life-threatening illness, were pregnant or of childbearing potential and not taking adequate contraception, or who were enrolled in another intervention trial were also excluded. For the present analyses, we also excluded participants with no Patient Health Questionnaire (PHQ-9)[12] assessment at baseline.

Standard protocol

Study protocol and procedures were approved by the Royal Perth Hospital Human Research Ethics Committee – EC2011/131. The Human Research Ethics Boards of all participating sites granted approval for the study. All participants, or their legal surrogates, provided written informed consent. The AFFINITY trial was registered with the Australian and New Zealand Clinical Trials Registry,

ACTRN12611000774921. A detailed description of the study protocol and of all assessments is available online: https://www.affinitytrial.org.

Outcome measures and follow up assessments

Follow-up assessments were undertaken at baseline, and 4, 12, 26 and 52 weeks after randomisation. Data were collected face-to-face, by telephone and through postal questionnaires.[7] Depression was assessed by several measures. The PHQ-9 is a self-administered depression scale that consists of 9 items assessing depressive symptoms that may have occurred during the preceding 2 weeks, with each item being scored on a 4-point scale ranging from 0 (not at all) to 3 (nearly every day).[12] PHQ-9 total scores can range from 0 (no symptoms) to 27 (most symptoms). Scores of 9 or more indicate the potential presence of 'clinically significant symptoms of depression' among stroke survivors.[13] The scale has robust psychometric properties[12] and its scores are sensitive to change over time.[14] As PHQ-9 information is limited to the 2-week period prior to assessment, we also asked participants at the 4 follow up assessments if they had been diagnosed with depression by a clinician after baseline (yes/no), had been prescribed an antidepressant (yes/no), or had received non-pharmacological treatment for depression (yes/no). We considered clinically significant symptoms of depression to be present if the PHQ-9 score was ≥ 9 or if participants endorsed any of the aforementioned questions. We used this information to assign participants to 4 groups: no depression throughout the 52 weeks, clinically significant symptoms of depression during the first 12 weeks only (early depression), clinically significant symptoms of depression after 12 weeks only (late depression), clinically significant symptoms of depression before and after 12 weeks (persistent depression).

Other study measures included age (in years), sex, marital status (married/partnered or not), living arrangements (living alone or with others), presence of disability before the index stroke (none, some but independent, mild need for assistance with some activities, moderate but still able to walk without assistance, moderately severe but able to attend to basic bodily needs, severe dependence in basic

activities of daily living), recruitment country (Vietnam / Australia or New Zealand), the Oxfordshire Community Stroke Project (OCSP) clinical classification of stroke,[15] the National Institute of Health Stroke Scale (NIHSS) to assess the neurological deficits of participants at the time of randomization (scores can range from 0 to 42; higher scores indicate greater severity of deficits),[16] the modified Rankin Scale (mRS) (scores can range from 0 to 6, higher scores indicate greater disability and dependence),[17] depression before stroke that required treatment (yes/no) and random treatment assignment to fluoxetine or placebo for the first 6 months of the study.

Statistical analyses

We used Stata version 17.0 (StataCorp LLC) to manage and analyse de-identified data. Descriptive statistics summarized the data as counts and proportions (categorical variables) or mean and standard deviation (SD) in the case of numerical continuous measures, such as age. We used a repeated measures logit model to estimate the effect (expressed as odds ratio – OR – and respective 95% confidence interval – 95%CI) of study measures on depression status (yes/no) over 52 weeks (assessments available at baseline 4, 12, 26 and 52 weeks – using all available data), and multinomial logistic regression to investigate the association between baseline measures with early, late and persistent depression (effect expressed as risk ratio – RR and respective 95%CI). As loss to follow up was negligible, imputation was not considered necessary. Spearman rho measured the correlation between NIHSS and mRS scores. We naturally log-transformed NIHSS scores and divided them by the natural log of 2, so that the resulting unit of change represents a doubling of NIHSS scores. We then completed a series of logistic regressions to investigate the association between depression group (early, late or persistent) with mRS and NIHSS scores at baseline (separate analyses for mRS and NIHSS scores because of collinearity between these measures), with estimates adjusted for the effects of age, sex, marital status, living arrangements, baseline disability, country of recruitment, stroke classification, treatment of depression before stroke and trial treatment with fluoxetine or placebo after stroke. We used the resulting coefficient estimates to calculate the adjusted probability of

depression (early, late or persistent) and plotted the fitted probabilities, with the respective 95%CI, according to mRS and NIHSS scores (predict function of Stata). Planned sensitivity analyses followed the same steps described above, but these analyses were limited to people free of clinically significant depressive symptoms at baseline and, subsequently, by using the PHQ-9 only to define early, late and persistent depression. Alpha was set at 5% and all probability estimates were derived from two-tailed tests.

Data availability

The anonymized data that support the findings of this trial are available to other researchers upon request to Prof Graeme Hankey (graeme.hankey@uwa.edu.au) following receipt of a written request and proposal for use of the data, approval by the AFFINITY trial Steering Committee, and establishment of a data sharing agreement.

RESULTS

We excluded 59 of the 1280 participants from these analyses because they had not completed the PHQ-9 at the baseline assessment, resulting is a study sample of 1221 participants (information about volunteers not included in this study have been described elsewhere[18]). Their age ranged from 24 to 92 years (mean=63.8 ± 12.3 years) and 775 (63.5%) of them were men. Partial anterior circulation stroke (PACS) was the most frequent stroke classification (n=532, 43.6%), with 728 (59.6%) participants having a total NIHSS score ≥ 5. NIHSS scores ranged from 0 to 23 (median=6, IQR=3 to 8). A total of 671 (55.0%) participants had mRS scores equal to or greater than 4 at the baseline assessment. At baseline, 48 (3.9%) participants reported past depressive episodes that required treatment, and 228 (18.7%) showed evidence of clinically significant symptoms of depression (PHQ-9 ≥ 9). Table 1 summarises the baseline sociodemographic and clinical characteristics of participants. Adherence to treatment for the 26-week trial was 85.7% for placebo and 86.4% for fluoxetine. The effects of the trial on depressive symptoms have been reported in detail elsewhere.[10]

During the 52 weeks of the study, 450 participants showed evidence of clinically significant symptoms of depression (Table 2). As baseline NIHSS and mRS scores were correlated (Spearman rho = 0.58), we refrained from forcing both at the same time into the models. The odds of clinically significant symptoms of depression decreased with time relative to baseline and were higher among those aged ≥ 70 years and among participants who were married. The odds of clinically significant symptoms of depression increased as mRS scores (disability and dependence) increased and was 3 times higher among participants who had received treatment for depression before their stroke. Sex, living alone, country of residence, pre-stroke disability, stroke classification and treatment with placebo (compared with fluoxetine) did not have a significant effect on the odds of clinically significant symptoms of depression over the 52-week period after the stroke. The doubling of NIHSS scores nearly doubled the odds of clinically significant symptoms of depression during the study (adjusted OR=1.90, 95%CI=1.63-2.22 – after excluding mRS scores from the model because of collinearity with NIHSS).

Sixty-two (5.1%) participants were lost during follow up, of whom 41 died. 1159 participants contributed valid data for the longitudinal study (98.2% of those alive). We limited the analyses to these participants because of uncertainty regarding the depression grouping of those who were not available for assessment. Of 425 participants with clinically significant symptoms of depression, 208 showed evidence of early clinically significant symptoms of depression, 86 showed evidence of late clinically significant symptoms of depression, and 131 of persistent clinically significant symptoms of depression (early and late in the trial). Table 3 summarises the association between baseline sociodemographic and clinical measures with early, late and persistent depression. Treatment for depression before the index stroke was associated with increased risk of persistent depression, as was living in Australia or New Zealand compared to Vietnam, and being married. Total Anterior Circulation Stroke (TACS) was associated with increased risk of late clinically significant symptoms

of depression, as was being married. eFigure 1 show the distribution of participants with no depression and with early, late and persistent clinically significant symptoms of depression according to their mRS scores at baseline and 52 weeks. Figure 1 shows that the probabilities of early, late and persistent clinically significant symptoms of depression increased with increasing baseline mRS and NIHSS scores. The association between the probability of depression and mRS and NIHSS scores was similar for early and persistent clinically significant symptoms of depression (nearly linear), but for late depression the association was only robust for participants with high (i.e., worse) mRS and NIHSS scores.

The doubling of baseline NIHSS scores was associated with an increase in the risk of early (RR=2.08, 95%CI=1.65-2.62), late (RR=1.53, 95%CI=1.14-2.06) and persistent clinically significant symptoms of depression (RR=2.50, 95%CI=1.89-3.32). These results were adjusted for the effects of age, sex, marital status, living arrangements, country of recruitment, function before the stroke, classification of stroke, treatment for depression before stroke and treatment with trial fluoxetine after stroke.

We completed a sensitivity analysis that excluded 228 prevalent cases of depression (PHQ-9 $\geq$ 9) at baseline. The results are summarised in eTable 1. The association between clinically significant symptoms of depression groups and mRS scores weakened for mRS values < 5, but the association with country of recruitment and treatment for depression before stroke persisted. The direction of all other associations remained unchanged, but were no longer statistically significant for marital status. Additional analyses showed that the adjusted effect of the associations between doubling of NIHSS scores and post-stroke depression groups (prevalent cases excluded) remained statistically significant (RR=1.71, 95%CI=1.18-2.48 for early depression; RR=1.46, 95%CI=1.09-1.97 for late depression; RR=1.52, 95%CI=1.09-2.14 for persistent depression). This association between doubling of NIHSS scores and depression groups were similarly robust when participants who had shown evidence of clinically significant symptoms of depression at baseline (i.e., PHQ-9 $\geq$ 9) were retained in the

analyses (eTable 2). We repeated the analyses after restricting the diagnosis of clinically significant symptoms of depression to participants who had a recorded PHQ-9 ≥ 9 (we used a similar approach to define early, late and persistent depression). Again, the doubling of NIHSS scores were associated with early (RR=2.05, 95%CI=1.65-2.54), late (RR=1.52, 95%CI=1.03-2.24) and persistent depression (RR=2.82, 95%CI=1.95-4.09) (adjusted for all other measures – eTable 3). Other statistically significant associations arising from the latter model that indicated an increase in risk for early depression were mild to moderate disability before the index stroke, recruited from Australia or New Zealand compared with Vietnam, Lacunar Stroke (LACS) classification and treatment for depression before stroke. In addition to doubling of NIHSS scores, country of randomisation (Australia or New Zealand vs Vietnam) was the only measure associated with increased risk of late clinically significant symptoms of depression. These analyses also showed that the adjusted risk of persistent clinically significant symptoms of depression was higher for participants aged ≥ 70 years and for those who had received treatment for depression before stroke, while not being married/partnered was associated with lower risk. Finally, we examined the association between depression group and the context of the assessment. Of the 208 participants with early depression, 100 (48.1%) completed a face-to-face assessment, 104 (50.0%) were assessed via the telephone or skype, 1 (0.5%) was assessed via postal questionnaire or email, and for 3 participants (1.5%) the context of the assessment was not recorded. For the 86 participants with late depression, the respective numbers were 17 (19.8%), 69 (80.2%), 0 and 0, whereas for the 131 with persistent depression they were 48 (36.6%), 82 (62.6%) 0 and 1 (0.8%). Multinomial logistic regression showed that the risk of early and persistent depression was lower among participants assessed by phone or skype than among those assessed face-to-face (RR=0.35, 95%CI=0.24-0.50 and RR=0.39, 95%CI=0.25-0.62, respectively), but not for late depression (RR=1.10, 95%CI=0.60-2.02).

DISCUSSION

The one-year follow up of AFFINITY trial participants confirmed that the risk of clinically significant symptoms of depression increases with the severity of stroke (NIHSS) and degree of disability and dependence (mRS). The association between stroke severity and clinically significant symptoms of depression was particularly strong for participants who experienced the emergence of depressive symptoms during the first 3 months after stroke and those who were depressed early and continued to be depressed 6 or 12 months later (persistent clinically significant symptoms of depression). We also found that the risk of clinically significant symptoms of depression was highest amongst those aged 70 years or over, who were married or had received treatment for depression before their stroke. The association with marital status and depression before stroke was particularly noticeable for participants with persistent depression. Lacunar strokes (LACS) were associated with increased risk of early depression, whereas TACS increased the risk of late clinically significant symptoms of depression.

We recruited a large sample of participants within two weeks of their stroke. However, only a small proportion of those recruited had severe strokes and none had no symptoms (silent stroke). This limited our ability to examine the association between clinically significant symptoms of depression and the entire range of stroke severity, which seems to be a common difficulty of longitudinal studies designed to investigate depression after stroke.[4] Moreover, the reliance of the assessment of depressive symptoms on the person's ability to communicate verbally resulted in the exclusion of participants with marked aphasia. In contrast, the recruitment of a cohort with mild to moderately disability associated with strokes minimised the number of participants lost during follow up and reduced the effects of survivorship bias.

Our study sample was recruited from multiple stroke services in Australia, New Zealand and Vietnam. The diagnosis of clinically significant symptoms of depression was more frequent in Australia and New Zealand than in Vietnam, which may represent an expression of cultural

differences or differing access to the relevant mental health services. Evidence from other studies suggest that cultural factors are important in the way emotional distress is expressed by Vietnamese people living in Australia (more frequently) and Vietnam (less frequently),[19] and this may explain our findings at least in part. Hence, caution is required when attempting to generalise these results to other cultural contexts.

The assessment of stroke followed standard clinical guidelines,[7] while the assessment of depression relied on the serial use of the PHQ-9 and participants' self-reported clinician diagnosis of depression or depression treatment. A meta-analysis of PHQ-9 validation studies showed that cut-points between 8 and 11 yield acceptable sensitivity and specificity for the diagnosis of major depression in various clinical settings,[20] including stroke services.[13] However, as the PHQ-9 limits its assessment to the preceding 2-weeks, clinically relevant symptoms arising and resolving between assessments may be missed. Hence, we also asked participants at each assessment whether they had been told by a healthcare professional they had depression or whether antidepressant treatment or talking therapy had been offered. This increased the proportion of people identified as depressed from 31.5% with the PHQ-9 only to 36.9%, a figure that is consistent with that reported by other studies using different approaches to establish the presence of depression.[1] The validity of this approach is uncertain compared with structured clinical interviews designed to ascertain the presence of current and past depressive episodes. If bias was introduced, it was most likely toward the null hypothesis by decreasing sensitivity in identifying cases of depression.

Although our cohort was derived from a randomised placebo-controlled trial of fluoxetine, the intervention had no significant effect on pre-defined depression outcomes.[10] Residual confounding and confounding by unmeasured factors, such as severity of neurological deficits during follow up or apathy, could mediate some of the association between mRS and NIHSS scores at baseline and depression over 1 year, but discrepancy between baseline and follow up deficits would have to be

large to negate our findings. The close correlation between our measures of mRS and NIHSS scores and the complete follow up mRS assessments for all participants supports the validity of our findings that early severity and disability associated with stroke are associated with an increased risk of depression.

Our results are consistent with those of previous systematic reviews[4,21] and extend their findings by considering the concurrent effects of relevant sociodemographic and clinical measures and by showing that adults with depression before stroke are particularly vulnerable to persistent depressive symptoms after stroke. Unexpectedly, participants who were not married or partnered had lower risk of persistent depressive symptoms than married participants.[4,22] This could be due to selection bias (e.g. unmarried depressed stroke survivors being less willing or able to consent to participate in the study), attrition bias (higher mortality among those who were not married, precluding the opportunity to become depressed), ascertainment bias (i.e., spouses alert to the presence of depressive symptoms) or to the subjective perceived burden of care on the spouse associated with post-stroke neurological disabilities..[23] Further research is needed to explore the external validity of this finding. We also found that early clinically significant symptoms of depression were associated with LACS, whereas late clinically significant symptoms of depression were associated with TACS. Other studies have found evidence of greater psychological distress among TACS stroke survivors,[24,25] although previous attempts to link lesion location with the development of post-stroke depression have all but dismissed any association.[26]

Daily treatment with 20 mg of fluoxetine was not associated with decreased risk of clinically significant symptoms of depression during follow up, which raises questions about the efficacy of fluoxetine for the treatment and prevention of depression after stroke[10] or, alternatively, about the validity of the diagnosis of depression in this population. Apathy, for example, is frequent among stroke survivors and its clinical presentation can overlap with that of depression.[27] It is possible that

some of our participants with depression, particularly those with persistent symptoms, may have been apathetic as a consequence of their stroke, which would explain their poor response to antidepressant treatment. A more detailed assessment of apathy would have been required to address this issue.

In conclusion, our results confirmed that the severity of neurological and functional deficits increase the risk of post-stroke clinically significant symptoms of depression early and persistently. We also found that adults with past history of depression are more likely to experience persistent symptoms of depression during the year following the stroke, with personal relationships and cultural context also contributing to modulate risk. The prevention of post-stroke depression requires the use of strategies capable of minimising the severity of neurological and functional deficits,[28,29] as well as the introduction of appropriate measures to support high risk individuals.

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Table 1. Sociodemographic and clinical characteristics of participants at the baseline assessment[†]

		Total number of participants = 1221 n (%)
Age in years	< 60 60-69 ≥ 70	447 (36.6) 372 (30.5) 402 (32.9)
Female sex		446 (36.5)
Marital status not married or partnered		285 (23.3)
Living alone		141 (11.5)
Country	Vietnam Australia New Zealand	691 (56.6) 492 (40.3) 38 (3.1)
Function before stroke	No difficulties Difficulties not disabling Mild disability Moderate disability Mod/Severe disability	1099 (90.0) 83 (6.8) 24 (2.0) 13 (1.1) 2 (0.2)
Stroke classification	POCS Haemorrhagic LACS PACS TACS Uncertain*	216 (17.7) 174 (14.2) 217 (17.8) 532 (43.6) 75 (6.1) 7 (0.6)
NIHSS group	Mild Moderate Moderately severe to severe	493 (40.4) 699 (57.2) 29 (2.4)
Modified Rankin Score (mRS)	1 2 3 4 5	140 (11.5) 149 (12.2) 261 (21.4) 578 (47.3) 93 (7.6)
Depression before stroke requiring treatment		48 (3.9)
PHQ-9 ≥ 9 (depressed)		228 (18.7)
Assigned treatment with placebo[#]		607 (49.7)

[†]59 participants who did not complete the PHQ-9 at randomisation were excluded from all analyses.
NIHSS: National Institute of Health Stroke Scale.
LACS: Lacunar stroke; PACS: Partial Anterior Circulation stroke; POCS: Posterior Circulation stroke; TACS: Total Anterior Circulation stroke
*Uncertain includes 3 cases with unrecorded classification and 4 whose diagnosis of stroke was questionable.
[#]Participants were randomly assigned treatment with fluoxetine or placebo for 26 weeks (6 months).

Table 2. Odds of stroke participants showing evidence of clinically significant symptoms of depression[‡] over a period of 52 weeks according to their baseline characteristics (n=1221).

		Odds Ratio (OR)[†]	95%CI OR
Weeks in the study	Baseline	1	Reference
	4	**0.79**	**0.66-0.95**
	12	**0.69**	**0.57-0.83**
	26	**0.64**	**0.53-0.77**
	52	**0.83**	**0.69-0.99**
Age in years	< 60	1	Reference
	60-69	1.15	0.87-1.53
	≥ 70	**1.49**	**1.13-1.98**
Female sex		1.09	0.86-1.38
Marital status not married or partnered		**0.49**	**0.33-0.71**
Living alone		1.42	0.90-2.23
Country	Vietnam	1	Reference
	Australia / New Zealand	1.13	0.87-1.47
Mild to moderately severe disability before stroke		1.41	0.82-2.42
Stroke classification	POCS	1	Reference
	Haemorrhagic	0.90	0.61-1.34
	LACS	1.02	0.70-1.47
	PACS	0.97	0.71-1.33
	TACS	1.53	0.97-2.42
	Uncertain*	1.62	0.46-5.71
mRS score	1	1	Reference
	2	2.26	1.25-4.09
	3	**3.04**	**1.78-5.22**
	4	**3.09**	**1.85-5.16**
	5	**5.98**	**3.31-10.80**
Depression before stroke requiring treatment		**3.08**	**1.95-4.86**
Assigned treatment with placebo[#]		1.06	0.85-1.32

[‡]Clinically significant symptoms of depression defined by a total PHQ-9 score ≥ 9 or participant reported clinician diagnosis of depression or introduction of an antidepressant during the study or referral for non-pharmacological treatment of depression. Depression affected 450 (36.9%) participants over 52 weeks. The total number of participants was 1221 and the number of valid observations collected over time 5907.

[†]Odds ratio derived from multivariate logistic regression of panel data. All listed measures were entered simultaneously in the model and the reported risk ratios indicate the main effect of the exposures. Bold print used to highlight statistically significant associations relative to the reference group.

95%CI: 95% confidence interval.

NIHSS: National Institute of Health Stroke Scale.

mRS: Modified Rankin Scale.

LACS: Lacunar stroke; PACS: Partial Anterior Circulation stroke; POCS: Posterior Circulation stroke; TACS: Total Anterior Circulation stroke

*Uncertain includes 3 cases with unrecorded classification and 4 whose diagnosis of stroke was questionable.

[#]Participants were randomly assigned treatment with fluoxetine or placebo for 26 weeks (6 months).

The interaction between sex and marital status on depression status was not significant: p=0.492)

Table 3. Risk ratio of stroke participants showing evidence of early, late and persistent clinically significant symptoms of depression[‡] over a period of 52 weeks according to their baseline characteristics (no depression used as reference).

		Early depression N=208 RR (95%CI)[†]	Late depression N=86 RR (95%CI)	Persistent depression N=131 RR (95%CI)
Age in years	< 60	1 (Reference)	1 (Reference)	1 (Reference)
	60-69	1.08 (0.73-1.58)	0.82 (0.45-1.51)	0.95 (0.57-1.59)
	≥ 70	1.01 (0.67-1.54)	1.07 (0.60-1.89)	1.27 (0.77-2.10)
Female sex		1.26 (0.90-1.77)	1.52 (0.94-2.46)	1.35 (0.89-2.06)
Marital status not married or partnered		0.71 (0.43-1.17)	0.57 (0.27-1.19)	**0.31 (0.15-0.63)**
Living alone		1.41 (0.75-2.66)	0.86 (0.34-2.17)	1.46 (0.64-3.35)
Country	Vietnam	1 (Reference)	1 (Reference)	1 (Reference)
	Australia / New Zealand	1.04 (0.70-1.53)	**3.20 (1.86-5.51)**	**2.18 (1.36-3.49)**
Mild to moderate disability before stroke		1.61 (0.64-4.00)	2.13 (0.71-6.40)	1.09(0.34-3.52)
Stroke classification	POCS	1 (Reference)	1 (Reference)	1 (Reference)
	Haemorrhagic	1.41 (0.81-2.48)	1.78 (0.75-4.19)	0.70 (0.33-1.46)
	LACS	**1.80 (1.06-3.03)**	1.43 (0.60-3.37)	0.92 (0.46-1.82)
	PACS	0.95 (0.59-1.53)	1.77 (0.87-3.61)	1.16 (0.68-1.99)
	TACS	1.77 (0.85-3.73)	**3.78 (1.46-9.76)**	1.79 (0.78-4.09)
	Uncertain*	—	4.19 (0.38-49.67)	1.70 (0.16-17.83)
mRS at baseline	1	1 (Reference)	1 (Reference)	1 (Reference)
	2	**3.43 (1.53-7.71)**	1.57 (0.57-4.31)	1.57 (0.52-4.73)
	3	**4.50 (2.12-9.54)**	1.31 (0.50-3.43)	**3.09 (1.19-8.02)**
	4	**3.42 (1.65-7.10)**	1.88 (0.80-4.44)	**4.30 (1.76-10.51)**
	5	**8.59 (3.49-21.16)**	**3.61 (1.23-10.58)**	**11.12 (3.92-31.56)**
Depression before stroke requiring treatment		1.33 (0.50-3.59)	1.80 (0.61-5.27)	**5.96 (2.74-12.96)**
Assigned treatment with placebo[#]		1.07 (0.78-1.47)	0.91 (0.58-1.45)	1.15 (0.78-1.71)

[‡]Clinically significant symptoms of depression defined by a total PHQ-9 score ≥ 9 or participant reported clinician diagnosis of depression or introduction of an antidepressant during the study or referral for non-pharmacological treatment of depression. A total of 734 (63.3%) participants showed no evidence of depression over 52 weeks. The analyses were limited to the 1159 participants who were alive and had not been lost by week 52.

[†]Risk ratio (RR) derived multinominal logistic regression. All listed measures were entered simultaneously in the model and the reported risk ratios indicate the main effect of the exposures. Bold print used to highlight statistically significant associations.

95%CI: 95% confidence interval.

mRS: Modified Rankin Scale.

LACS: Lacunar stroke; PACS: Partial Anterior Circulation stroke; POCS: Posterior Circulation stroke; TACS: Total Anterior Circulation stroke

*Uncertain includes 3 cases with unrecorded classification and 4 whose diagnosis of stroke was questionable.

[#]Participants were randomly assigned treatment with fluoxetine or placebo for 26 weeks (6 months).

FIGURE LEGEND

Figure 1. The figures depict the fitted adjusted probability of depression (navy blue line) according to the baseline modified Rankin Scale (mRS, top row) and the baseline National Institute of Health Stroke Scale (bottom row). The grey lines show the 95% confidence limits of the fitted probability. The panels show the probability of early depression (left panels – within first 12 weeks post-stroke), late depression (mid panels – depression onset between 12 and 52 weeks), and persistent depression (right panels – depression both early and late in the study).