Depression and the Risk of Stroke in Women
An Identification and Treatment Paradox
Cheryl Bushnell, MD, MHS

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Major depressive disorder is defined in the DSM-IV-TR as depressed mood or loss of interest or pleasure in usual activities, along with a constellation of other depressive symptoms that persist for >2 weeks, are atypical for usual behavior, cause significant distress or impairment, and are not attributable to bereavement or a medical condition.1 The lifetime prevalence of depression is ~13% to 16% and is 5% to 7% in 1 year, more commonly affecting women than men.1 The presence of depressive symptoms has been established as an important outcome after stroke.2 The Northern Manhattan Study reported that early depressive symptoms are a risk for future disability.3 Multiple studies, though not all,4 now contribute to the evidence that depression is also a risk factor for first-ever stroke.5,6

Adding to these studies and published in this issue of Stroke, Pan et al7 have analyzed >80 000 women in the Nurses’ Health Study cohort who were stroke-free at the time of the initial screen for depressive symptoms. Using the Mental Health Index (MHI-5) scores, a subscale of the Short-Form 36 Health Status Survey, collected in 1992, 1996, and 2000, the investigators assessed the relationship between clinically significant depressive symptoms (MHI-5 score ≤52) and incident stroke from 2000 to 2006. For the purposes of analyzing depression, this was defined as an MHI-5 score ≤52, physician-diagnosed depression, or antidepressant medication use. For the 1033 incident strokes documented in the follow-up period, depression was associated with an ~30% increased risk of total stroke (hazard ratio [HR] = 1.29; 95% CI, 1.13–1.48).7 A past history of depression alone (without antidepressant medication use) was not associated with risk of stroke, but women who used antidepressant medications were at an increased risk, whether they had a clinically significant MHI-5 score or diagnosed depression (HR = 1.39; 95% CI, 1.15–1.69) or not (HR = 1.31; 95% CI, 1.03–1.67). However, when analyzed by stroke type, only ischemic stroke in the setting of an MHI-5 score <52 or diagnosed depression with medication use was independently associated with risk, although the association was attenuated, once vascular risk factor status was added to the model. The small number of hemorrhagic stroke cases precluded adequate power for this analysis.7 Therefore, this study adds to the growing literature that is now showing an association between depressive symptoms and incident stroke, although the effect is modest. Other studies have shown a similar magnitude of the association, such as the INTERSTROKE study (odds ratio = 1.35; 95% CI, 1.10–1.66),8 the Health and Retirement Study (HR = 1.25; 95% CI, 1.12–1.39),9 and the Baltimore Epidemiological Catchment Area Study (odds ratio = 3.08; 95% CI, 1.26–7.52) cohorts.8 In addition, the INTERSTROKE study calculated the population-attributable risk for each risk factor in their case-control analysis, and the population-attributable risk for depression was 5.2%.

There are several limitations of this study. The depression assessment was done for the 1992, 1996, and 2000 study interviews; therefore, the change in depression immediately before the index stroke was not known. Other mood disorders, such as bipolar disorder, were not measured. This particular type of mood disorder is an important risk for vascular disease and risk factors in women.9 In addition, power was limited when the data were separated by stroke type, particularly ischemic stroke versus hemorrhagic stroke. Also, there were a large number of strokes of unknown type, which is unusual for such a large cohort of women with otherwise well-characterized events. One wonders that within the unknown stroke types whether conversion disorders or stroke mimics might have been included, thereby biasing the results toward an association with depression. Another weakness is the lack of diversity in the population, as strokes are more prevalent in black women, although depression is less common than in whites.10

This article highlights an important paradox: Depression appears to be a risk factor for stroke, but so is the use of antidepressant medications used to treat depression. The complexities of depression and its various types and severity, the associations between depression and risk factors, and the compliance with treatment for vascular risk factors, as well as depression treatment, make studies such as this difficult to interpret. Other confounders include the prescription of antidepressant medications for conditions other than depression, such as headaches, syncope, or menopausal symptoms. It is also unclear whether these medications are prescribed for depressive symptoms versus major depressive disorder that meets the DSM-IV-TR criteria.1

As discussed by Pan et al,7 there are multiple mechanisms for depression as a potential risk factor. One important
mechanism is neuroendocrine effects, that is, imbalances in the hypothalamic-pituitary axis. Another obvious mechanism may be related to the depressed patients’ lack of motivation for leading a healthy lifestyle. This could be manifested by eating a poor diet, getting poor sleep, and importantly, being physically inactive. In addition, depression may be occurring as a result of having vascular risk factors. For example, medications for hypertension, diabetes, and hypercholesterolemia may cause side effects that may trigger depression in patients who know they must take such medications indefinitely to treat these chronic conditions. In addition, the fear of having a stroke may exacerbate underlying depression and anxiety.

The association between antidepressant medications and stroke reported by Pan et al.\textsuperscript{11} is consistent with a recent study from Taiwan.\textsuperscript{11} Using a case-crossover design to study exposure to antidepressants in the 7- to 14-day window before stroke hospitalization, the investigators showed that in >24,000 patients, exposure during this window was associated with an \(\approx 50\%\) increase in risk of stroke after adjustment for risk factors (odds ratio = 1.48; 95\% CI, 1.37–1.59). Of those with at least 1 antidepressant prescription in the year before hospitalization for stroke, only 36\% had a diagnosis of a mood disorder.\textsuperscript{11} All types of antidepressants were associated with a similar magnitude of risk, although for ischemic strokes, selective serotonin reuptake inhibitors had the strongest association (odds ratio = 4.11; 95\% CI, 2.93–5.76).\textsuperscript{11} One important question that has yet to be answered is whether the use of these medications is a surrogate for the severity of disease. In addition, cause and effect cannot be established because it may be impossible to separate the severity of the disease from the use of medication. Only carefully designed prospective studies would be able to answer this specific question.

What is known is that the treatment of poststroke depression improves outcomes. Williams et al.\textsuperscript{12} showed in a randomized, controlled trial that addressing poststroke depression with the Activate-Initiate-Monitor case management approach, in addition to selective serotonin receptor inhibitor therapy, led to a significant response in depression and increased likelihood of remission compared with usual care.

What should be the primary prevention approach be, based on these results? First, screen for depression with validated scales, and use guides to determine the risk.\textsuperscript{13} In addition, the guidelines for cardiovascular disease prevention in women clearly state that patients with established cardiovascular disease should be screened for depression and treated accordingly because of the risk of poor outcomes.\textsuperscript{14} The data are also clear that depression increases poststroke disability and mortality and can lead to physical decline in patients with stroke.\textsuperscript{15} As for the methods of treatment, moderate to severe depression should be treated according to current guidelines,\textsuperscript{1} but it is just as important that women be screened and treated for their vascular risk factors.

Is the difference between the risk of incident versus recurrent stroke with depression and/or antidepressant medications due to the improvement in stroke risk management after the first stroke and perhaps better adherence to the regimen? Clearly more studies are needed to sort through the absolute risk of stroke in depressed patients and to separate the risk from the disease and the use of antidepressants. Untreated poststroke depression has negative consequences on outcomes, but whether this is true in primary prevention is not known. The focus should be on identification of depression, along with identification of other stroke risk factors, holistic approaches to both, and an emphasis on a healthy lifestyle, regardless of the presence of depressive symptoms.

**Disclosures**

None.

**References**


**Key Words:** stroke care ■ epidemiology ■ women ■ minorities
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