

# Lacunar Infarcts, Depression, and Anxiety Symptoms One Year after Stroke

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*Background:* Mood disorders are frequent after stroke and are associated with poorer quality of life. Previous studies have reported conflicting results as to stroke subtype in the incidence of poststroke mood disorders. We explored the relationship between subcortical ischemic stroke subtype (lacunar) and presence of such symptoms at 1 year after stroke. *Methods:* Anonymized data were accessed from the Virtual International Stroke Trials Archive. Stroke subtypes were classified according to the Trial of Org 10172 in Acute Stroke Treatment classification. Depression and anxiety symptoms were assessed using Hospital Anxiety and Depression Scale. We investigated independent predictors of depression and anxiety symptoms using a logistic regression model. *Results:* Data were available for 2160 patients. Almost one fifth of the patients developed both anxiety and depression at 1-year follow-up. After adjusting for confounders, the lacunar subtype was least associated with both anxiety (odds ratio [OR] = .61; 95% confidence interval [CI] = .46-.80) and depression symptoms (OR = .71; CI = .55-.93) versus other stroke subtypes. *Conclusions:* Lacunar strokes have a weaker association with presence of anxiety and depression symptoms compared with other subtypes. **Key Words:** Stroke—lacunar infarcts—mood disorders—anxiety—depression—HADS.

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Additional information may be found in the online version of this article.

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## Introduction

Mood disorders are common post stroke. Depression affects around one third of patients at 1 month after stroke.<sup>1</sup> Anxiety occurs even more frequently than depression, affecting up to 40% of stroke survivors.<sup>2</sup> Different stroke pathological subtypes may be associated with differing psychological sequelae, and it has been suggested that small stroke lesions located in the subcortical white matter (i.e., lacunar strokes) have a reduced risk of developing mood disturbances after stroke.<sup>3</sup> Nonetheless, the relationship between lacunar strokes and mood is not completely understood, and data are conflicting. A recent meta-analysis suggested that the risk of developing depression was unaffected by the underlying stroke subtype.<sup>4</sup> However, Appelros and Viitanen<sup>5</sup> reported lower rates of depression symptoms in patients with lacunar strokes after 1 year of follow-up, whereas results from the Secondary Manifestations of Arterial Disease Magnetic Resonance study showed that subcortical infarcts faced

a higher risk of depressive symptoms.<sup>6</sup> Furthermore, cerebral small-vessel disease, of which lacunar strokes are 1 manifestation, is classically associated with depression.

We aimed to explore the relationship between subcortical stroke etiological subtype (i.e., lacunar subtype) and presence of depression and anxiety symptoms at 1 year after ischemic stroke by analyzing data from the Virtual International Stroke Trial Archive (VISTA).

## Methods

We accessed patient level data from the VISTA prevention resource and conducted a retrospective analysis. VISTA is an academic collaboration with the aim of providing access to patient trial data to perform exploratory analyses to help plan and design future clinical trials.<sup>7</sup> Ethical approval was not required because data were anonymized.

We included patients with ischemic stroke and available data to assess stroke subtype. All included patients underwent extensive investigation to determine the stroke subtype, including radiological exams (computed tomography or magnetic resonance imaging), blood tests, thoracic and neck vessel imaging, and cardiac assessment, where appropriate. The qualifying ischemic stroke was classed by original trial investigators according to the method described in the Trial of Org 10172 in Acute Stroke Treatment (TOAST).<sup>8</sup> According to TOAST, small-artery cerebral (lacunar) infarction was diagnosed when the following were present: (1) retained consciousness and higher cerebral function, (2) normal computed tomography or magnetic resonance scan or presence of subcortical or brainstem small infarct; either (3) a classical lacunar syndrome or a nonclassical lacunar syndrome; and (4) no evidence of both cardioembolism and ipsilateral large-vessel stenosis (>50%). We extracted baseline variables including demographic data (age and sex), clinical symptoms (aphasia, neglect, and arm and leg paralysis), and past medical history (history of hypertension, diabetes, atrial fibrillation, ischemic heart disease, peripheral artery disease, depression, or cigarette smoke exposure). Stroke severity was quantified using Oxford Handicap Scale at the time of the enrollment in the source study. Our primary outcomes of interest included depression and anxiety symptoms 1 year after the index stroke as measured using the Hospital Anxiety and Depression Scale (HADS) on a voluntary basis by study investigators. From the pooled available data, we extracted patients in which HADS was measured directly by study investigators at 1-year follow-up. Outcome data were dichotomized 1-year HADS-A and HADS-D using a score of 8 or higher as our "screen positive" cutoff.<sup>9</sup>

### Statistical Analyses

We described the general characteristics of the study population using basic descriptive statistics. We dichotomized

stroke subtype into small-artery occlusion (lacunar) versus other stroke subtypes. We developed a multivariate logistic regression model for both depression and anxiety symptoms adjusting for confounders identified as statistically significant factors ( $P < .10$ ) retained from univariate analysis. Variables with  $P$  values less than .05 were considered independently associated with outcomes. Statistical analysis was carried out by using SPSS for Windows (version 22.0; IBM Corp., Armonk, NY).

## Results

We identified 5721 patients with diagnosis of ischemic stroke at baseline and available TOAST classification. A total of 63 (1%) of patients were lost at follow-up, whereas 170 (3%) patients died within 1 year. Of 4910 patients remaining, follow-up data describing HADS score were available for 2160 (44%) patients (Supplementary Fig. S1). Patients where no HADS data were available were younger and had higher baseline neurological impairment. More small-artery occlusive events had HADS data than other stroke types (52% versus 48%,  $P < .001$ ) (Supplementary Table S1).

Comparisons of available baseline patient characteristics between lacunar and other stroke subtypes are shown in Table 1. Functional independence, history of depression, and impaired cognitive function showed no differences across the 2 groups. At baseline, motor impairment (both arm and leg), aphasia, and neglect were more frequent among nonlacunar stroke subtypes ( $P < .001$ ).

At 1 year post stroke, anxiety symptoms were present in 421 (19.5%) patients and depression symptoms in 416 (19.3%) patients. Anxiety and depression were strongly correlated ( $\rho = .71$ ,  $P < .001$ ).

Unadjusted analysis suggested that lacunar stroke subtype had a weaker association with both anxiety (16.9% versus 22.3%, odds ratio [OR] = .71, 95% confidence interval [CI] = .58-.88) and depression (17.6% versus 21.1%, OR = .80, 95% CI = .64-.99) symptoms than other stroke types.

In the multivariable models adjusting for age, sex, disability at baseline, diabetes, history of depression, initial stroke severity, arm paralysis, leg paralysis, aphasia, and neglect, our analyses suggested that lacunar stroke subtype was independently associated with reduced risk of both 1-year anxiety (OR = .65, 95% CI = .51-.85) and depression (OR = .71, 95% CI = .55-.93) compared to other stroke types (Table 2). There was a gender effect because male sex was less likely associated with both anxiety (OR = .45; 95% CI = .35-.58) and depression symptoms (OR = .68; 95% CI = .53-.88). History of depression was the factor most strongly associated with anxiety and depression, whereas the worst functional status was associated only with depression but not with anxiety at 1-year follow-up. Among stroke symptoms, arm paralysis and neglect were consistently associated with both depression and anxiety

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