

Cardiac Disease, Depressive Symptoms, and Incident Stroke in an Elderly Population

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Context: Previous research suggests that depression is a risk factor for stroke. However, the reliability of much research is limited by the lack of documentation on the presence of preexistent cardiovascular disease and by the use of limited measures of depression or stroke.

Objectives: To test the hypotheses that (1) clinically relevant depressive symptoms are an independent risk factor of incident stroke in cardiac and noncardiac patients and (2) more chronic and severe depressive symptoms are associated with incident stroke.

Design: A cohort of elderly Dutch people (aged ≥ 55 years) was followed up for 9 years in the Longitudinal Aging Study Amsterdam (baseline measurements were taken in 1992 or 1993, and the study concluded in 2001 or 2002, respectively).

Setting: General community.

Participants: Randomly selected population-based sample (N=2965) without a history of stroke.

Main Outcome Measures: The study end point was a first stroke (nonfatal or fatal). Depression was measured using the National Institute of Mental Health Diagnostic Interview Schedule and the Center for Epide-

miological Studies–Depression Scale. Multivariate Cox proportional hazards regression analyses of stroke incidence were performed. The association of the chronicity and severity of depressive symptoms was studied in extended models with time-dependent variables.

Results: The sample's mean (SD) age was 70.5 (8.7) years, 52.1% were women, and the mean (SD) follow-up was 7.7 (3.1) years. Inclusion of an interaction between cardiac disease and clinically relevant depressive symptoms improved the model for stroke ($P=.03$). In participants with preexistent cardiac disease, but not in participants without cardiac disease, clinically relevant depressive symptoms at baseline (hazard ratio [HR], 2.18; 95% confidence interval [CI], 1.17-4.09) and the severity (range, 0-60; HR, 1.08; 95% CI, 1.02-1.13) and chronicity (HR, 3.51; 95% CI, 1.13-10.93) of symptoms during follow-up were associated with stroke.

Conclusions: Preexistent cardiac disease moderates the association between depressive symptoms and incident stroke. In cardiac patients, baseline depressive symptoms and both the severity and chronicity of symptoms during follow-up are associated with incident stroke.

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DEPRESSION IS HIGHLY prevalent among elderly individuals, with a reported prevalence in the community of 1.8% for major depression, 9.8% for minor depression, and 13.5% for clinically relevant depressive symptoms (CRDSs).¹ Although cross-sectional studies^{2,3} have shown depression to be associated with poor health, functional impairment, decreased quality of life, and greater use of health services, prospective studies⁴ have shown depression and depressive symptoms to be independent determinants of mortality. Recently, myocardial infarction was shown to be a mediator of the higher mortality

of depressed individuals.^{5,6} The biological pathways hypothesized to link depression with cardiovascular disease include sympathetic nervous system activation, dysregulation of the hypothalamic-pituitary-adrenocortical axis, platelet aggregation dysfunction, and inflammation.^{7,8}

Studies investigating whether depression is also a risk factor for the development of cerebrovascular events have yielded mixed results. The recent consensus guideline of the American Heart Association and the American Stroke Association for the prevention of cerebrovascular events does not mention depression as a possible risk factor for stroke.⁹

In a recent meta-analysis,⁵ the pooled relative risk of stroke in those with a depressed mood was 1.4 (range, 1.2-1.8), but this estimated risk was influenced by the methodologic shortcomings and heterogeneity of the studies included. In particular, most of the early studies used limited measures of depression, with only 2 using the *DSM-IV* to diagnose depression. The first of these studies used self-reported data on the occurrence of stroke, and the second used physician-reported *ICD-10*-classified cardiovascular disease.^{10,11} Neither study documented the chronicity and severity of depression. Another source of heterogeneity in studies of the relationship between depressive symptoms and stroke is the possible moderating effect of cardiac disease. Because cardiac disease is an important predictor of stroke, stratifying by cardiac disease divides the population into low- and high-risk populations. If one assumes that the pathophysiologic mechanisms are comparable to those leading to cardiovascular disease in depressed individuals, depression in cardiac patients could aggravate the existing atherosclerotic disease, ultimately leading to stroke. Furthermore, the prevalence and incidence of depression would be expected to be higher in cardiac patients based on the vascular depression hypothesis, which states that subclinical underlying cerebrovascular disease may cause depression.¹²⁻¹⁶ According to this hypothesis, underlying atherosclerotic disease could give rise to both stroke and depression in cardiac patients. Bearing in mind these sources of heterogeneity in earlier studies, we investigated whether the presence, severity, and chronicity of depressive symptoms and major depressive disorder (MDD) are independently associated with incident stroke in elderly patients with or without cardiac disease during a 9-year follow-up.

METHODS

STUDY DESIGN AND POPULATION

This study was conducted within the Longitudinal Aging Study Amsterdam (LASA), which is a prospective cohort study of Dutch people aged 55 to 85 years. The LASA started in 1992, and its methods have been described in detail elsewhere.^{17,18} The general aim of LASA was to study the autonomy and well-being of an aging population. A randomly selected age- and sex-stratified sample (according to expected mortality figures) was drawn from the population registers of 11 municipalities in the Netherlands. The reason for this relative oversampling of older old people (both men and women) and elderly men was to compensate for an anticipated higher unavailability for follow-up among physically frail people. The initial response rate was 62.3%, and nonresponse was associated with age, sex, and urbanicity. The sample first took part in the cross-sectional NESTOR-living arrangements and social networks study¹⁹ and was later interviewed and followed up every 3 years in LASA; 81.7% of the NESTOR-living arrangements and social networks study population participated in LASA, with nonresponse being related to age but not to sex. All interviews were recorded for quality control purposes. All LASA participants without a history of stroke at the baseline measurement were eligible for inclusion (n=3018).

Participants in whom depressive symptoms (51 [1.6%]) or stroke (2 [0.06%]) were not evaluated at baseline were excluded. The remaining 2965 individuals participated in this study

of the association among depressive symptoms, CRDSs, or MDD at baseline and incident stroke in patients with or without cardiac disease at baseline. The mean (SD) follow-up was 7.7 (3.1) years; participants were assessed at baseline and every 3 years. For the extended Cox proportional hazards regression analyses, we required the availability of a baseline and at least 1 follow-up assessment of depression. In total, 412 participants (13.9%) were excluded because they had died or had a stroke before the first follow-up interview, and 328 participants (11.1%) were excluded because they never had a follow-up assessment of depressive symptoms. Unavailability for follow-up of depressive symptoms was associated with an older age, a lower score on the Mini-Mental State Examination (MMSE), more functional limitations, and cardiac disease ($P < .001$ for all). The mean (SD) follow-up for the remaining 2225 participants was 9.1 (1.7) years, with a mean (SD) number of 3.4 (0.8) measurements of depressive symptoms.

MEASUREMENTS

Stroke Morbidity and Mortality

The study end point was the first occurrence of stroke (fatal or nonfatal). Nonfatal strokes were established based on self-report during the 3-yearly interviews and information obtained from general practitioners (GPs) in response to questionnaires sent in 1992-1993, 1995-1996, and 2000-2001. The GPs were asked whether a participant had ever been diagnosed as having a cerebrovascular accident, the year in which it occurred, and whether a specialist had confirmed the diagnosis. Previous research in LASA had shown such self-reported information to be moderately accurate (concordance with GP: $\kappa = 0.56$; 95% confidence interval [CI], 0.48-0.64).²⁰ Therefore, we considered a stroke to have occurred if the self-reported and GP information were consistent or if a cardiac specialist confirmed the GP diagnosis of stroke. Death due to stroke was established based on death certificates registered by the Netherlands Central Bureau of Statistics. Death certificates of deceased participants were 100% complete. Stroke was defined as *ICD-9* codes 431, 433, 434, and 436 and *ICD-10* codes I-61, I-63, and I-64. The event was timed as occurring in the year halfway between the 3-yearly assessments for nonfatal strokes and as the year of death for fatal strokes.

Depression

Depressive symptoms were measured using the Center for Epidemiological Studies-Depression Scale (CES-D). This is a widely used instrument to measure depressive symptoms in the community.²¹ In LASA, the traditional cutoff of the CES-D of 16 or greater had a sensitivity of 100% and a specificity of 88% for MDD.²² Major depressive disorder was diagnosed using the National Institute of Mental Health Diagnostic Interview Schedule (DIS).²³ Subthreshold depressive disorder (SDD) was diagnosed if a study participant scored 16 or higher on the CES-D but did not meet *DSM-III* diagnostic criteria for MDD on the DIS. The SDD category included 107 respondents with a CES-D score of 16 or higher but no available DIS diagnosis. We use the term CRDSs to refer to the broad category of MDD or SDD, and we use the term *depressive symptoms* to refer to the score on the CES-D (range, 0-60).

The DIS and CES-D were completed every 3 years, which made it possible to estimate the mean severity of depressive symptoms and the chronicity of CRDSs and MDD during the follow-up. The mean severity of depressive symptoms was defined as the mean CES-D score of all observations until the year of the first stroke or censoring divided by the total number of observations in this

Table 1. Baseline Characteristics

Characteristic	Value ^a
Age, mean (SD), y	70.5 (8.7)
MMSE score, mean (SD) ^b	27.0 (2.9)
MDD	58 (2.0)
CRDSs	430 (14.5)
Women	1546 (52.1)
Functional limitations	
≥ 1	1173 (39.6)
Smoking	648 (21.9)
Stage 1 or 2 hypertension	623 (21.0)
Cardiac disease	611 (20.6)
Diabetes mellitus	358 (12.1)
Obesity	457 (15.4)

Abbreviations: CRDSs, clinically relevant depressive symptoms; MDD, major depressive disorder; MMSE, Mini-Mental State Examination.

^aData are presented as number (percentage) of participants (N = 2965) unless otherwise indicated.

^bThe range was from 0 to 30.

interval. The chronicity of MDD was defined as the total number of observations of MDD until the year of the first stroke (or censoring) divided by the total number of observations in this interval. The chronicity of CRDSs was the total number of observations of an MDD or a score on the CES-D of 16 or higher until the year of the first stroke (or censoring) divided by the total number of observations in this interval.

Cardiac Disease

Cardiac disease was defined as myocardial infarction, congestive heart failure, angina pectoris, or cardiac arrhythmia and established at baseline using an algorithm used earlier in LASA.⁶ This algorithm uses 3 sources of information: self-reported, medication, and GP information. We considered only 1 confirmatory source necessary for diagnosis because self-reported cardiac disease is sufficiently accurate in LASA (concordance with GP: $\kappa = 0.69$; 95% CI, 0.65-0.73).²⁰ We used a broad definition of cardiac disease because although it could lead to a type II error (overcorrection), the use of a more restricted definition could lead to a type I error (undercorrection), and we preferred to use the broader category.

Confounders

Sociodemographic variables (sex and age), general health-related variables (functional limitations and cognitive impairments), and important stroke risk factors (diabetes mellitus, smoking, hypertension, and obesity) were included in the analyses as potential confounders. The number of functional limitations was scored with a 3-item questionnaire²⁴ as none, 1, or 2 or more. Cognitive impairments were measured with the MMSE.²⁵ A history of diabetes mellitus was considered present if reported by the respondent, if the person used antidiabetic agents, or if a GP confirmed the diagnosis. The variable smoking included current smoking. Blood pressure was measured every 3 years, preferably from the arm but otherwise from the fingertip. Hypertension was categorized into stage 1 hypertension (a mean systolic blood pressure of 140-159 mm Hg or a mean diastolic blood pressure of 90-99 mm Hg) and stage 2 hypertension (a mean systolic blood pressure of ≥ 160 mm Hg or a mean diastolic blood pressure of ≥ 100 mm Hg).²⁶ Obesity was defined as a body mass index (calculated as weight in kilograms divided by height in meters squared) of 30 or

greater.^{2,27} Antidepressant use was established by asking about the use of medication and by visually checking all of the participants' medications at each 3-yearly assessment.

STATISTICAL ANALYSES

All primary variables and covariates were checked for normality, colinearity, and proportionality of hazards. Missing data for covariates were restored by imputation of the most reported value, and the results for analyses with or without imputed data were checked for differences.²⁸ Baseline characteristics for participants with or without depressive symptoms were compared using χ^2 and *t* tests. Univariate Cox proportional hazards analyses of first strokes were conducted for primary and secondary variables. Models of stroke incidence, which included interaction terms of depression variables (depressive symptoms, CRDSs, and MDD) by cardiac disease status, were tested by multivariate Cox proportional hazard regression analyses. Subsequently, the sample was stratified for cardiac disease, and the relationship between depression variables and incident stroke was examined by multivariate Cox proportional hazard regression analysis. We used extended Cox proportional hazard models to examine the association between the severity of depressive symptoms or the chronicity of CRDSs or MDD and incident stroke, with these depression variables and possible confounders as time-dependent variables.²⁹

RESULTS

BASELINE CHARACTERISTICS

The mean (SD) age of the 2965 elderly study participants (52.1% female) was 70.5 (8.7) years, and 39.6% had 1 or more functional limitations (**Table 1**). At baseline, 58 (2.0%) had MDD and 372 (12.5%) had SDD. Myocardial infarction was reported in 285 (9.6%), congestive heart failure in 256 (8.7%), angina pectoris in 283 (9.5%), and cardiac arrhythmia in 132 (4.4%). The CRDSs at baseline were associated with older age ($P < .001$), female sex ($P < .001$), more functional limitations ($P < .001$), poorer performance on the MMSE ($P < .001$), smoking ($P = .04$), diabetes mellitus ($P = .03$), and cardiac disease ($P < .001$).

The overall rate of stroke was 7.7 per 1000 person-years: the rate of first nonfatal stroke was 2.8 per 1000 person-years, and the rate of fatal stroke was 4.9 per 1000 person-years. The rate of incident stroke was higher, but not significantly so, among participants with CRDSs at baseline ($P = .10$), as shown in **Table 2**. On univariate analysis, cardiac disease at baseline ($P < .001$), older age ($P < .001$), poorer MMSE performance ($P < .01$), more functional limitations ($P < .01$), diabetes mellitus ($P < .001$), and hypertension ($P < .001$) were associated with a higher incidence of stroke. The use of antidepressants (49 participants [1.7%]) was not associated with incident stroke (hazard ratio [HR], 0.35; 95% CI, 0.05-2.52; $P = .30$).

INTERACTION BETWEEN CARDIAC DISEASE AND DEPRESSIVE SYMPTOMS

Fully corrected survival functions for incident stroke, stratified for cardiac disease status and the presence of CRDSs, are presented in the **Figure**. The hazard for in-

Table 2. Stroke Rates and Univariate Cox Regression on Incident Stroke

Variable	No. of Strokes per 1000 Person-years	Wald Statistic	HR (95% CI)	P Value
CRDSs				
No	7.4	2.64	1.39 (0.94-2.10)	.10
Yes	10.11			
Cardiac disease				
No	6.7	11.91	1.78 (1.28-2.47)	< .001
Yes	11.9			

Abbreviations: CI, confidence interval; CRDSs, clinically relevant depressive symptoms; HR, hazard ratio.

incident stroke was higher in those with cardiac disease and CRDSs compared with those with cardiac disease but without CRDSs. Multivariate Cox proportional hazards regression demonstrated that inclusion of the interaction term CRDS \times cardiac disease (HR, 2.46; 95% CI, 1.09-5.56; $P = .03$) significantly improved the model for incident stroke ($\chi^2 = 4.7$, $P = .03$), as did inclusion of the interaction term depressive symptoms \times cardiac disease (HR, 1.06; 95% CI, 1.01-1.11; $P = .01$). Other potentially relevant interaction terms, such as depressive symptoms \times diabetes mellitus ($P = .65$), depressive symptoms \times stage 1 hypertension ($P = .69$), depressive symptoms \times stage 2 hypertension ($P = .93$), and depressive symptoms \times smoking ($P = .85$), were not significantly related to incident stroke.

DEPRESSIVE SYMPTOMS AND INCIDENT STROKE IN PATIENTS WITH AND WITHOUT CARDIAC DISEASE

Stratification of the sample into those with or without cardiac disease at baseline showed that in patients with cardiac disease the presence of CRDSs at baseline was associated with a higher incidence of stroke even after correction for possible confounders (HR, 2.18; 95% CI, 1.17-4.09; $P = .02$) (**Table 3**).

The extended multivariate Cox proportional hazards regression model for first stroke included time-dependent depression variables (the mean severity of depressive symptoms, the chronicity of CRDSs, and the chronicity of MDD), possible confounders measured at baseline, and changes in hypertension or functional limitations during the follow-up period. The chronicity of CRDSs during follow-up was an independent predictor of incident stroke (HR, 3.51; 95% CI, 1.13-10.93; $P = .03$). The chronicity of MDD was not significantly associated with incident stroke (HR, 5.59; 95% CI, 0.77-40.56; $P = .09$). In addition, the mean severity of depressive symptoms during follow-up was significantly associated with an incident stroke (HR, 1.08; 95% CI, 1.02-1.13; $P = .005$). Results were similar for men and women, and correction for cardiac medication did not significantly influence the associations found.

The CRDSs at baseline were not significantly associated with incident stroke in patients without cardiac disease at baseline (Table 3) and neither were the chronicity of CRDSs nor the mean severity of symptoms during follow-up.

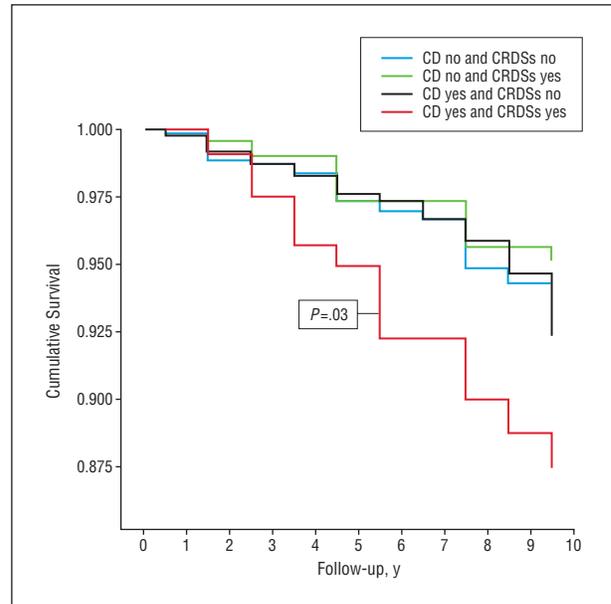


Figure. Survival function (Cox regression) for incident stroke at means of covariates. CD indicates cardiac disease; CRDSs, clinically relevant depressive symptoms.

COMMENT

This study shows that cardiac disease moderates the association between CRDSs and incident stroke. In cardiac patients, there seemed to be a dose-response effect in that both the severity and the chronicity of depressive symptoms during follow-up were predictors of incident stroke. This relationship was not observed in patients without cardiac disease at baseline.

Our findings are in line with previous research of the relationship between depressive symptoms and the incidence of stroke in populations with a high cardiovascular risk, such as patients with hypertension or diabetes mellitus,³⁰⁻³² and offer an explanation for negative results. They are also consistent with previous studies^{12,33,34} reporting a poorer cardiac prognosis and an increased mortality among cardiac patients with depression. Our study shows that the cerebrovascular prognosis of cardiac patients with depressive symptoms is worse, as is the cardiac prognosis, and this may be a factor underlying the higher mortality seen in depressed cardiac patients.

Table 3. Multivariate Cox Regression on Incident Stroke After Stratification for Cardiac Disease

Variable	No Cardiac Disease			Cardiac Disease		
	Wald Statistic	HR (95% CI)	P Value	Wald Statistic	HR (95% CI)	P Value
Baseline variables ^a						
MDD	0.64	0.44 (0.06-3.22)	.42	1.70	2.66 (0.61-11.56)	.19
CRDSs	1.15	0.73 (0.41-1.30)	.28	5.95	2.18 (1.17-4.09)	.02
Depressive symptoms (continuous)	0.90	0.99 (0.96-1.01)	.34	8.98	1.05 (1.02-1.08)	.003
Time-dependent variables ^b						
Chronicity of MDD	0.42	0.39 (0.02-6.86)	.52	2.90	5.59 (0.77-40.56)	.09
Chronicity of CRDSs	0.02	0.94 (0.38-2.31)	.90	4.69	3.51 (1.13-10.93)	.03
Mean symptom severity (range, 0-60)	0.64	0.98 (0.94-1.03)	.42	7.75	1.08 (1.02-1.13)	.005

Abbreviations: CI, confidence interval; CRDSs, clinically relevant depressive symptoms; HR, hazard ratio; MDD, major depressive disorder.

^aCorrected for age, sex, Mini-Mental State Examination score, smoking, functional limitations, hypertension, diabetes mellitus, and obesity.

^bCorrected for age, sex, Mini-Mental State Examination score, smoking, diabetes mellitus, obesity, functional limitations, and hypertension (baseline) and for a change in functional limitations or hypertension during follow-up (time dependent).

Nevertheless, these findings have some limitations. First, stroke was not confirmed by neuroimaging and, thus, no distinction was made between ischemic and hemorrhagic stroke. Pathophysiologically, depression would be expected to be primarily associated with ischemic stroke. Misclassification due to overreporting of stroke is probably not a major issue because self-reported stroke had to be confirmed by a GP or a specialist. Although there was selective dropout, with the more frail individuals being more likely to have missing data on depression during follow-up, this would tend to lead to a conservative estimate of the relationship between depressive symptoms and incident stroke. The relatively few participants with an MDD at baseline ($n=58$) limited the power to find associations between MDD and stroke. However, the use of a broader category of CRDSs, which included MDD and SDD, is in line with research showing that subsyndromal depressive states form a continuum with major depression in elderly populations.³⁵⁻³⁷ Furthermore, the strongest results were found when depressive symptoms were used as a continuous measure (based on the CES-D), and the results for time-dependent analysis of an association between MDD and stroke in cardiac patients pointed in the same direction. Last, we did not fully control for the severity of cardiac disease because of the lack of electrocardiographic or ultrasonographic information.¹²

As strong points, we used a clinical diagnosis of depression in combination with a valid measurement of depressive symptoms and required confirmation of self-reported stroke by the patients' GPs, a method that has been validated in LASA,²⁰ or by information obtained from the death certificate. We also assessed depressive disorders and symptoms, functional limitations, and blood pressure during follow-up, which enabled us to use adjusted extended Cox proportional hazards models with time-dependent variables. These extended models are probably more realistic because depression has a fluctuating course, and these models incorporate all available information about depression and depressive symptoms. We also distinguished between participants with and without cardiac disease at baseline, which enabled us to establish that cardiac disease mod-

erates the relationship between stroke and depressive symptoms.

To understand how cardiac disease moderates the association between depression and stroke morbidity and mortality, we initially have to consider why depression is associated with incident stroke in cardiac patients. Depression could aggravate atherosclerosis and in this way worsen the prognosis of cardiac patients, which could explain the dose-response effect that we found. Suggested pathways by which depression could specifically affect the vascular system of cardiac patients are a diminished heart rate variability, altered platelet responses,⁸ more arrhythmia in depressed patients with premature ventricular contractions,³⁸ as well as behavioral pathways, such as poorer compliance with cardiac treatment and a less healthy lifestyle.³⁹ At the same time, the vascular depression hypothesis suggests that subclinical underlying cerebrovascular disease can cause depression in cardiac patients.¹³ The relationship between depression and vascular diseases seems to be reciprocal.^{40,41} This reciprocal relationship could be synergistic in cardiac patients but not in patients without cardiac disease. This would explain the interaction between cardiac disease and depression found in our study.

An alternative explanation for our findings is that depressive symptoms are an indicator of a poor prognosis in cardiac patients because the number of depressive symptoms is (partly) associated with the severity of underlying cardiovascular disease.⁴² We chose to use the CES-D to score depressive symptoms because, when LASA was designed, studies showed that the overlap with physical illness was limited.^{43,44} A more recent study⁴⁵ of patients undergoing cardiac surgery showed that the CES-D detected change after this intervention, not only shortly after surgery but also later during follow-up, which suggests that depressive symptoms, as measured with the CES-D, benefit from an improvement in cardiovascular status. Moreover, trials of antidepressants in depressed patients after myocardial infarction do not consistently report less long-term depression or a better cardiac prognosis, which suggests that depressive symptoms may in part be due to the severity of the underlying cardiac disease.⁴⁶⁻⁴⁹

In conclusion, cardiac disease moderates the association between CRDSs and incident stroke. This moderating effect of cardiac disease could be explained not only by a synergistic effect of the reciprocal mechanisms between vascular disease and depression but also by depressive symptoms being an indicator of the severity of underlying cardiac disease. Both explanations deserve more attention in further research because they have implications for targeting effective interventions. At least, depression in cardiac patients seems to be an indicator of a poorer prognosis to some extent because of the higher incidence of stroke among these patients, as this study showed.

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