# Prognosis of Cryptogenic Ischemic Stroke: A Prospective Single-Center Study in Chile

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Approximately 25%-40% of ischemic strokes are considered of unknown cause (ie, cryptogenic). The available information on associated risk factors, functional outcome, and recurrence of this subtype of stroke is limited, especially for the Chilean population. We conducted a prospective cohort study of 380 patients aged ≥18 years admitted consecutively to a stroke unit with demonstrated ischemic stroke. The stroke subtypes were classified according to the Trial of Org 10172 in Acute Stroke Treatment criteria. The modified Rankin Scale score and Barthel Index were used to assess functional outcome. The Kaplan–Meier product-limit method and Cox proportional hazards regression analysis were used to identify predictors of recurrent stroke during the follow-up period (mean, 2.1 years). Cryptogenic stroke (CS) was diagnosed in 76 patients (20%), 55.2% of them male, with a mean age of 62 ± 17 years. CS was the third most common stroke subtype after the large-artery disease (29%) and cardioembolic (24.4%) subtypes. After adjustment for age and sex, no vascular risk factors or laboratory parameters assessed at the time of admission were found to be predictive of CS. The CS subtype had the lowest rate of stroke recurrence at the end of the follow-up period (n = 4; 2.5% per year; odds ratio, 0.32; 95% confidence interval, 0.11-0.91; $P = .022$), a favorable functional outcome (mean modified Rankin Scale score, 2; mean Barthel Index, 77), and no increase in mortality risk (odds ratio, 0.73; 95% confidence interval, 0.29-1.77; $P = .48$). Our findings demonstrate that patients with no definite etiology identified after an extensive workup are at lower risk of recurrence and more likely to have a favorable outcome. No risk factors distinguish CS from other stroke subtypes in our study population. **Key Words:** Cryptogenic stroke—undetermined stroke—stroke classification.


The cause of ischemic stroke is unknown in 25%-40% of cases.[1] These cases are identified as cryptogenic stroke (CS) when no clearly definable cause can be detected after an extensive workup.[2,3] At present, some conditions, including arterial hypertension,[4,5] current smoking,[4,5] low high-density lipoprotein cholesterol level,[5] high factor VIII activity (in men),[6] and low plasma folate level (in women),[5] have been associated with CS at different times. In patients aged >60 years, increased age and prevalence of atherosclerotic plaques in the aortic arch and the carotid and vertebral arteries remain potential etiological mechanisms, whereas in patients aged <55 years, the atherosclerotic burden is usually low, and the finding of patent foramen ovale has been suggested as a putative risk factor.[7]

CS is a diagnosis of exclusion. Since the first report on CS by Sacco et al[8] in 1989, several studies have been published of which some do not consider CS as a separate group of ischemic strokes and sometimes refer to CS as "ischemic stroke of unknown cause."[9,10] Most registries fail to identify a definite cause of stroke in 25%-40% of

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cases, depending on the design of study, the completeness and precocity of the etiologic source search, and the definition used for the CS subtype.[1,5,9-11]

The objectives of the present study were to compare risk factors, outcome, and recurrence between Chilean patients with the CS subtype and those in whom a definitive cause had been found, and to evaluate our results in the context of other results available in the literature.

## Subjects and Methods

### *Study Population*

This is a prospective cohort study of 380 (aged ≥18 years) male and female patients admitted consecutively to the Stroke Unit of the Hospital Clínico de la Universidad de Chile, Santiago, with a confirmed first ischemic stroke between October 2007 and December 2009. Data were obtained from the hospital's stroke registry as approved by the Neurology/Neurosurgery Department Scientific Committee. Only the Stroke Unit's attending neurologists (A.J. and S.I.) had access to this registry, to protect patient identity and confidentially. The diagnosis of ischemic stroke was established according to the National Institute of Neurological Disorders and Stroke Classification III criteria.[8] All patients were evaluated by a vascular neurologist (J.V., J.A., S.I., J.M., or V.D.) according to local protocol. This evaluation included the collection of demographic data, medical history day, vascular risk factors, National Institute of Health Stroke Scale (NIHSS) score determined on admission, and biochemical and hematologic laboratory test results. Control visits were scheduled every 6 months after the onset of symptoms and were done by telephone contact or clinical examination by a vascular neurologist (J.V., A.J., S.I., or V.D.) or a neurology resident (R.G., P.G.). All brain images (computed tomography [CT], magnetic resonance imaging [MRI], and magnetic resonance angiography [MRA]) were evaluated by a single neuroradiologist (P.O.).

### *Inclusion Criteria*

The CS subtype was defined in accordance with the Trial of Org 10172 in Acute Stroke Treatment (TOAST) study criteria.[2] In brief, cases were designated as CS when no cause for the stroke was found despite a systematic etiologic workup that included the clinical features of the stroke, routine blood tests, a detailed coagulation study in selected patients, brain imaging (CT scan and/or 1.5-T MRI), vascular imaging (extracranial Doppler ultrasonography, transcranial Doppler [TCD], CT, and/or magnetic resonance and/or digital subtraction angiography [DSA]), 12-lead electrocardiography (ECG) and/or 24-hour Holter ECG, and transesophageal echocardiography (TEE), with a contrast study and Valsalva's maneuver in all cases. In patients with a negative initial follow-up, we performed a complete coagulation analysis (i.e., homocysteine, protein C, protein S, antithrombin III, lupic anticoagulant, anti-nuclear antibody, extractable nuclear antigens, anti-neutrophil cytoplasmic antibody, anti-DNA, rheumatoid factor, anti-cardiolipin antibodies, protein electrophoresis, β2 glycoprotein 1, factor V Leiden, prothrombin gene), and 24-hour Holter ECG for paroxysmal atrial fibrillation. These investigations were performed within 5 days after stoke onset. Patients with transitory ischemic attack (defined according to the National Institute of Neurological Disorders and Stroke Classification III[8]), patients with intracranial hemorrhage confirmed by brain neuroimaging, and all patients whose etiologic study was incomplete and could not be classified into any TOAST subtype were excluded from this study.

### *Vascular Risk Factors*

Arterial hypertension was defined as a history of treated hypertension or of blood pressure >140/90 mm Hg on 2 independent measurements before stroke, or the use of antihypertensive medication. Diabetes mellitus was defined as a fasting blood glucose level >126 mg/dL on 2 independent measurements before stroke, a glycosylated hemoglobin level >6.5%, or use of an antidiabetic medication at the time of admission. Hypercholesterolemia was defined as a history of total cholesterol >200 mg/dL on 2 independent measurement or the use of a lipid-lowering medication. Smoking habits were coded as current smoker, ex-smoker, or nonsmoker based on smoking behavior at the time of the stroke. Coronary artery disease was defined as a history of angina pectoris, myocardial infarction, or coronary angioplasty, stent, or bypass. Carotid stenosis and intracranial stenosis were defined as an estimated luminal diameter reduction of >50% by CT angiography or DSA due to arteriosclerotic plaques. Asymptomatic atherosclerotic burden was defined as the presence of atherosclerotic plaques, <50% stenosis on intracranial or extracranial arteries (demonstrated by extracranial Doppler ultrasonography and/or MRA and/or DSA), or <4-mm-thick aortic arch plaques on TEE.

### *Patient Follow-Up*

Recurrent stroke was defined as a new ischemic stroke occurring after the acute phase of the index stroke that could not be attributed to brain edema, mass effect, brain shift syndrome, or hemorrhagic component at the CT/MRI examination. A neurologic examination and brain imaging (CT and/or MRI) were conducted to support the diagnosis of recurrent stroke. Information about deceased patients was obtained directly from family members. The modified Rankin Scale (mRS)[12] and Barthel Index (BI)[12] were used by a vascular neurologist (J.V., A.J., S.I., J.M., or V.D.) to measure functional status during the follow-up period after the index stroke. Data from the BI were divided into 2 classes with a cutoff at 60, to rank

functional status as either slight to moderate or severe disability.

### *Statistical Analysis*

Differences in continuous variables between groups were examined by the $\chi^2$ test, Fisher's exact test, or analysis of variance. The Kaplan–Meier product-limit method was used to estimate rates of survival and recurrence. The long-rank test was used to compare rate estimates, and the Cox proportional hazards model was used to identify predictors of recurrent stroke. Numerical values are reported as mean ± standard deviation (SD), and odds ratios (ORs) with 95% confidence intervals (CIs) are used to estimate relative risks. A $P$ value $<.05$ was considered significant in univariate and multivariate analyses. Statistical analyses were performed using Stata 9.2 for Windows (StataCorp, College Station, TX).

## Results

### *Study Population*

A total of 380 patients were admitted into the study. The basal characteristics are enumerated in Table 1. The mean patient age was 66 ± 15 years (range, 21-97 years), and 219 of the patients were men (57.6%). Among the different stroke subtypes, CS (n= 76; 20%) was the third most frequent after large-artery disease (LAD; n = 110; 29%) and cardioembolism (CE; n = 93; 24.4%). The small-artery disease (SAD; n = 56; 14.7%) and other cause (OC; n = 45; 11.8%) subtypes were observed at lower frequencies.

All patients underwent cerebral imaging consisting of cranial MRI (356 patients; 93.3%), cranial CT scan (93 patients; 24.7%), or both (74 patients; 19.4%). A total of 307 patients (80.3%) were examined by TCD; 312 (82.1%) underwent CT, MRA, or DSA; 235 (61.8%) were examined by extracranial Doppler sonography; and 358 (94.2%) underwent TEE. All 380 patients (100%) underwent 12-lead ECG, and 82 patients (34.7%) had a 24-hour Holter ECG. A detailed coagulation study, including complete thrombophilia tests, was performed in 61 patients aged <50 years in whom no cause for stroke was documented after cardiac and extracranial–intracranial arterial exploration. Cerebrospinal fluid analysis and a basic blood rheumatology battery, including antinuclear antibodies, extractable nuclear antigen antibodies, antiphospholipid antibodies, and rheumatoid factor, were performed in the 28 patients (7.3%) with vasculitis as a suspected origin. Before admission, 18 patients (24%) in the CS group were taking an antiplatelet agent, aspirin alone in all cases (100 mg/day in 16 patients and 250 mg/day in 2 patients). The use of an oral antihypertensive drug was reported by 32 patients (42.7%); the most commonly used drugs were angiotensin-converting enzyme inhibitors (n = 16; 21.3%) and diuretics (n = 12; 16%). Only 1 patient, who had hypercholesterolemia, was using a statin. At the end of follow-up (mean, 2.1 years; range, 0.5-3.5 years), 35 patients (9.2%) were lost from the study (2 patients with CS, 19 with LAD, 9 with CE, 3 with SAD, and 2 with OC).

### *Risk Factors*

The distribution of the ratios for age, but not for sex, differed significantly among the stroke subtypes. The highest mean age was for the CE group (73 ± 12 years), and the lowest was for the OC group (45 ± 13 years). The mean age of patients with the CS subtype was intermediate (62 ± 17 years). However, when subgroups were created based on age, higher proportions of patients aged <50 years were found in the OC (n = 30; 49.1%) and CS (n =22; 3%) groups ($P$ = .001). This finding suggests a lower probability of discovering the source of cardioembolism, atherosclerotic origin, or lacunar etiology in young patients. The NIHSS score at admission differed signofocantly among the subtypes (mean of all groups, 6.76 ± 5.8; $P$ = .0003), with the highest score for the CE group (9.1 ± 7.3) and the lowest score for the SAD group (3.8 ± 2.3), with the CS in between (6.4 ± 4.9) (Table 1). A history of hypertension, diabetes mellitus, and/or hypercholesterolemia showed significant differences for all subtypes of stroke ($P$ = .019, .013, and .033, respectively), with values for the CS group between those for the LAD (highest frequency) and OC (lower frequency) groups. Smoking and past history were not associated with any subtype of stroke.

No association was found between the arteriosclerotic burden on extracranial vessels and CS in cases with no intracranial vascular plaques (Table 1). In addition, there were no significant differences in the mean levels of basal total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, or triglycerides or in the Castelli Index among all patients ($P > .05$). After adjustment for age and sex, no risk factors were predictive for CS (Table 2); however, a history of arterial hypertension and diabetes mellitus was significantly related to SAD (OR, 5.38; 95% CI, 1.85-15.62; $P$ = .02 and OR, 3.55; 95% CI, 1.73-7.28; $P$ = .001, respectively) and LAD (OR, 2.22; 95% CI, 1.07-4.58; $P$ = .03 and OR, 3.18; 95% CI, 1.41-7.15; $P$ = .05, respectively). Hypercholesterolemia was significant only in the LAD group (OR, 3.25; 95% CI, 1.51-6.98; $P$ = .002). All patients with the CS subtype were discharged from the hospital on an antiplatelet regimen, along with a statin regimen in patients with a basal low-density lipoprotein cholesterol level >110 mg/dL. Strict control of vascular risk factors was reemphasized at discharge and during control visits to help reduce the risk of stroke recurrence and the systemic complications associated with each risk factor.

### *Recurrent Stroke*

Table 3 and Figure 1 present estimates of recurrent stroke for the different stroke subtypes. Recurrent

**Table 1.** *Basal characteristics of 380 patients by stroke subtype*

| Characteristics | Subgroup of ischemic stroke | | | | | Total group | *P* value |
|---|---|---|---|---|---|---|---|
| | CS (n = 76; 20%) | LAD (n = 110; 28.9%) | CE (n = 93; 24.5%) | SAD (n = 56; 14.7%) | OC (n = 45; 11.9%) | | |
| Age, years, mean ± SD | 62 ± 17 | 69 ± 11 | 73 ± 12 | 68 ± 13 | 45 ± 13 | 63 ± 15 | <.001 |
| Women | 61 ± 21 | 70 ± 12 | 75 ± 12 | 69 ± 14 | 42 ± 12 | 66 ± 18 | |
| Men | 64 ± 15 | 67 ± 10 | 72 ± 12 | 68 ± 12 | 47 ± 13 | 66 ± 14 | |
| Sex, n (%) | | | | | | | |
| Male | 42 (19.18) | 65 (29.68) | 52 (23.94) | 37 (16.89) | 23 (10.5) | 219 (57.6) | .578 |
| Female | 34 (21.25) | 44 (25.50) | 41 (25.62) | 19 (11.88) | 22 (13.75) | 161 (43.40) | .578 |
| Risk factors, n (%) | | | | | | | |
| Hypertension | 47 (17.09) | 90 (34.7) | 75 (27.27) | 51 (18.55) | 12 (4.36) | 275 (72.36) | .019 |
| Diabetes | 13 (11.93) | 46 (42.2) | 22 (20.18) | 22 (20.18) | 6 (5.5) | 109 (28.6) | .013 |
| Hypercholesterolemia | 11 (12.22) | 38 (42.22) | 22 (24.44) | 14 (15.56) | 5 (5.56) | 90 (23.68) | .033 |
| Smoking | 30 (21.9) | 41 (29.93) | 31 (22.73) | 24 (17.52) | 11 (8.03) | 137 (36.05) | .488 |
| Previous stroke history | 10 (12.5) | 25 (31.25) | 33 (41.25) | 8 (10.0) | 4 (5.0) | 80 (21.05) | .063 |
| NIHSS score on admission, mean ± SD | 6.4 ± 4.9 | 6.2 ± 4.7 | 9.1 ± 7.3 | 3.8 ± 2.3 | 7.2 ± 7.0 | 6.76 ± 5.8 | .0003 |
| Blood pressure, mm Hg, mean ± SD | 106.2 ± 18 | 108.8 ± 16 | 108.3 ± 18 | 110.5 ± 16 | 101.4 ± 16 | 107.5 ± 17 | .110 |
| Artheriosclerotic burden, n (%) | | | | | | | |
| Intracranial plaques | 0 | 17 (73.91) | 4 (17.39) | 1 (4.35) | 1 (4.35) | 23 (6.0) | — |
| Carotid plaques | 13 (12.68) | 54 (53.47) | 16 (16.84) | 12 (11.88) | 6 (5.94) | 101 (26.5) | .039 |
| Aortic arch plaques | 10 (11.24) | 53 (59.55) | 16 (17.98) | 8 (8.99) | 2 (2.25) | 89 (23.43) | .021 |
| Treatment at admission, n (%) | | | | | | | |
| Antiplatelet agents | 18 (24) | 47 (42.7) | 33 (35.5) | 20 (37.5) | 6 (13.3) | 124 (32.6) | .003 |
| Anticoagulation | 1 (1.3) | 3 (2.7) | 22 (23.7) | 1 (1.8) | 1 (2.2) | 1 (7.1) | <.001 |
| Hypolipemiant agents | 1 (1.3) | 20 (18.2) | 12 (19.2) | 2 (3.6) | 1 (2.2) | 36 (9.5) | <.0001 |
| Antihypertensive agents | 32 (42.7) | 79 (71.8) | 64 (68.8) | 45 (84) | 10 (22) | 230 (60.6) | <.001 |

**Table 2.** *Risk factors and comorbidity among groups*

| Risk factor | CS (n = 76) | Well-established etiology (n = 304) | OR (95% CI)* | *P* value |
|---|---|---|---|---|
| Previous stroke | 10 | 70 | 0.55 (0.26-1.13) | .108 |
| Hypertension | 45 | 229 | 0.60 (0.33-1.09) | .097 |
| Diabetes mellitus | 13 | 97 | 0.45 (0.23-0.87) | .018 |
| Hypercholesterolemia | 11 | 80 | 0.48 (0.24-0.97) | .042 |
| Active smoking | 30 | 107 | 1.14 (0.67-1.93) | .619 |
| Carotid artery plaque | 13 | 88 | 0.55 (0.28-1.08) | 1.084 |
| Aortic arch plaque | 10 | 79 | 0.44 (0.23-0.98) | .046 |

*Logistic regression analysis adjusted by age and sex.

ischemic strokes were detected in 40 patients (10.5%) during the follow-up period. Of these, the recurrence rate was lowest in the CS group (n = 4; 5.3%), followed by the LAD (n = 8; 7.3%), OC (n = 5; 11.1%), SAD (n = 7; 12.5%), and CE (n = 16; 17.2%) subtypes ($P$ = .022 for all subtypes). In patients with CE stroke, recurrence was observed primarily after 12 months from the original stroke, whereas in the CS subtype, no cases of recurrence were documented earlier than 6 months poststroke. In this last group, cases occurred between 6 (2 cases) and 12 (2 cases) months after the index stroke and corresponded to SAD (1 case), CE (1 case, attributed to an embolism from patent oval foramen associated with interatrial septal aneurysm, which was not demonstrated in a previous echocardiography performed 8 months earlier), and LAD (2 cases, both associated with the first demonstration of an atherosclerotic plaque >4 mm thick on the aortic arch region). Of the CE patients, 58 (62.3%) were taking an oral anticoagulation agent during the follow-up period. The earliest recurrence occurred in 15 patients in the CE group, with 3 recurrences within 3 months of initial stroke onset. Nine of 15 patients were taking an oral anticoagulation agent (acenocumarol; International Normalized Ratio <2). However, in the LAD

**Table 3.** *Recurrence and long-term outcome of subtype stroke*

| Evolution of patients | Subgroups of ischemic stroke | | | | | Total group |
|---|---|---|---|---|---|---|
| | CS | LAD | CE | SAD | OC | |
| Recurrence | | | | | | |
| No recurrence | 70 | 83 | 68 | 46 | 38 | 305 |
| Recurrent stroke, n (%)* | 4 (5.3) | 8 (7.3) | 16 (17.2) | 7 (12.5) | 5 (11.1) | 40 (10.5) |
| Recurrence time | | | | | | |
| <3 months | 0 | 0 | 1 | 0 | 0 | 1 |
| 3-6 months | 0 | 1 | 1 | 1 | 1 | 4 |
| 7-12 months† | 2 | 2 | 5 | 1 | 0 | 10 |
| 1-2 years | 2 | 3 | 8 | 5 | 4 | 22 |
| 2-3 years | 0 | 2 | 1 | 0 | 0 | 3 |
| Long-term outcome | | | | | | |
| BI, mean ± SD | 77 ± 18 | 76 ± 9 | 64 ± 19 | 88 ± 15 | 85 ± 13 | 76 ± 16 |
| mRS score, mean ± SD | 2 ± 1 | 2 ± 1 | 3 ± 1 | 1 ± 1 | 1 ± 1 | 2 ± 2 |
| Without disability, n‡ | 20 | 28 | 26 | 21 | 16 | 111 (29.2) |
| Mild disability, n§ | 20 | 24 | 20 | 13 | 8 | 85 (22.3) |
| Moderate disability, n¶ | 5 | 10 | 10 | 6 | 3 | 39 (8.9) |
| Severe disability, n‖ | 3 | 2 | 5 | 0 | 1 | 11 (2.9) |
| Death, n (%)** | 6 (8.0) | 8 (7.3) | 15 (16.1) | 0 | 2 (4.4) | 31 (8.1) |
| Lost to follow-up, n | 2 | 19 | 9 | 3 | 2 | 35 (9.2) |

*$P$ = .022, Fishers exact test.
†$P$ = .020, Fishers exact test.
‡mRS, 0; BI, 100.
§mRS, 1 or 2; BI, ≥60.
¶mRS, 3; BI, 40-55.
‖mRS, 4 or 5; BI, ≤35.
**$P$ = .006, Fishers exact test.

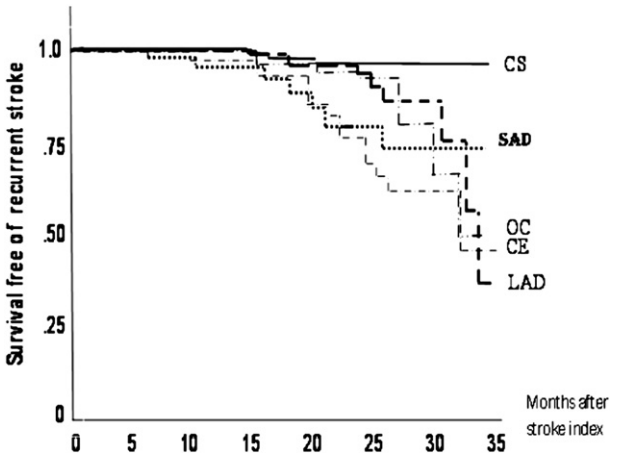


**Fig 1.** *Kaplan–Meier analysis showing the cumulative proportion of patients surviving free of recurrent stroke stratified by subtype of ischemic stroke in 380 patients. In the CS subtype, no cases of recurrence were documented before 6 months. The LAD subtype reached the highest recurrence rate at the end of follow-up period (P = .022).*

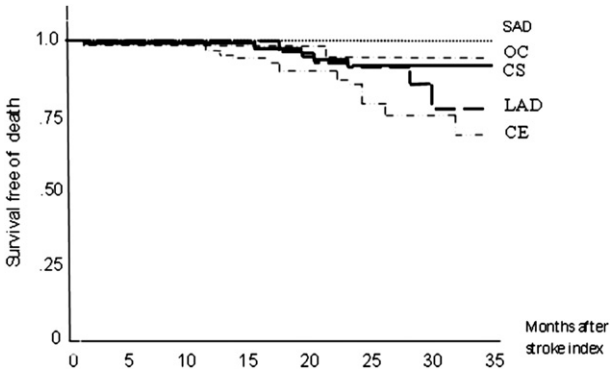


**Fig 2.** *Kaplan–Meier analysis showing the cumulative proportion of patients surviving after follow-up period stratified by subtype of ischemic stroke among 380 patients. The mortality rate was different during the later period of follow-up, with the greatest number of events in the CE group (P = .006). No fatal cases were reported for SAD subtype.*

group, the last recurrence event occurred 26 months after the index stroke. For all ischemic stroke subtypes, recurrence rates were significantly related to a major risk factor for over 70 years before and after adjustment for age ($P$ = .003), but not for sex ($P$ = .90). Cox proportional hazards regression analysis showed that only the SAD subtype was a significant predictor of long-term recurrence (OR, 2.23; 95% CI, 1.14-4.22; $P$ = .013), and the CS subtype showed a low risk of recurrence (OR, 0.32; 95% CI, 0.11-0.91; $P$ = .03).

### *Functional Outcome and Survival*

Functional disabilities assessed by the mRS and BI were different across stroke subtypes at the end of the follow-up period (all groups, $P$ = .003 for mRS and $P$ = .001 for BI). Major functional disabilities were found in the CE subtype, which had a mean mRS score of 3 ± 1 and a mean BI of 64 ± 19, whereas the CS group demonstrated mild to moderate functional disabilities (mean mRS score, 2 ± 1; mean BI, 77 ± 18). The SAD and OC groups had the lowest functional disability scores (Table 3).

Thirty-one patients died during the follow-up period. Figure 2 presents Kaplan–Meier estimated death rates for the different stroke subtypes. Mortality was different among the subtypes, with a high frequency in the CE group (n = 15; 16.1%), no fatal cases in the SAD group, and an intermediaye value in the CE group had an intermediate value (n = 6; 7.8%; $P$ = .006 for all stroke subtypes) (Table 3). Cox proportional hazards regression analysis showed that CE subtype was predictive of long-term mortality (OR, 3.14; 95% CI, 1.55-6.37; $P$ = .001) without a risk for CS (OR, 0.73; 95% CI, 0.29-1.77; $P$ = .48). The mortality rate for all ischemic stroke subtypes was significant before and after adjustment for age, with a major risk seen in those aged >70 years ($P$ = .007), Mortality rate was not significant after adjustment by sex ($P$ = .85).

## Discussion

To the best of our knowledge, this is the first study of CS performed in Chilean population. Our results suggest that patients with ischemic stroke, in which no definite etiology can be found after an extensive workup, had the lowest rate of stroke recurrence at the end of follow-up period (n = 4; 2.5% per year; OR, 0.32; 95% CI, 0.11-0.91; $P$ = .022) a favorable functional outcome (mean mRS score, 2; mean BI, 77) and no increase in mortality risk (OR, 0.73; 95% CI, 0.29-1.77; $P$ = 0.48).

The TOAST classification system has demonstrated that stroke prognosis, risk of recurrence, and choices of management are influenced by ischemic stroke subtypes.[10] "Ischemic stroke of undetermined cause (UC)" constitutes the most heterogeneous group, grouping patients having at least two definite potential causes together with those who had an incomplete etiological study. In our study, we separated CS from UC. Data on long-term follow-up and type of recurrent stroke in this group of patients have seldom been reported. Thus, to further define the cryptogenic subtype, more exhaustive etiological searches, including standard blood test, neuroimaging (CT and MRI), vascular imaging (angiography, Doppler ultrasonography, or MRA) and cardiologic structural and electrophysiological studies (transthoracic echocardiography [TEE]), need to be done. This constitutes the most important limitation among series. In our study, a brain MRI was available in 93.9% of the 380 patients (CT scan in 25% and both in 74%); a cardiologic exploration was done in 94.2%; and any cerebral and/or cervical vascular imaging was done in 82.1%. Testing for any acquired or congenital thrombophilia (including protein S, protein C, antithrombin III, antiphospholipid antibodies, factor V Leiden, and prothrombin variant G20210A) was done in 16% of patients aged <50 years (including

**Table 4.** *Comparative cryptogenic stroke studies*

| Author (year) | Stroke subtype | | | Follow-up | Rate of recurrent stroke, % | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | All, n | UC, n (%) | CS, n (%) | | UC | CS | LAD | CE | SAD | OC |
| Cryptogenics | | | | | | | | | | |
| Moroney et al (1998)[14] | 297 | — | 81 (28) | 3 month | — | 4 | 13 | 11 | 1 | NA |
| Bang et al (2003)[10] | 204 | — | 37 (18) | 1 year | — | 30 | 16 | 14 | 2 | NA |
| Present study | 380 | — | 76 (20) | 2 years | — | 4 | 8 | 16 | 7 | 5 |
| Undeterminated | | | | | | | | | | |
| Petty et al (2000)[9] | 454 | 164 (36 | — | 2 years | 21 | — | 29 | 17 | 12 | NA |
| Kolominsky-Rabas et al (2001)[4] | 752 | 188 (25) | — | 2 years | 14 | — | 10 | 22 | 11 | NA |
| Grau et al (2001)[11] | 5017 | 1137 (23) | — | 1 week | 4 | — | 8 | 3 | 3 | NA |
| Murat Sumer et al (2002)[15] | 356 | 87 (33) | — | 6 months | 9 | — | 9 | 6 | 5 | NA |

the CS subtype). In the Grau study,[11] a large, multicenter, hospital-based stroke study conducted in Germany, neuroimaging was done in all patients (CT scan in 97% and MRI in 29%). Extracranial Doppler ultrasound was done in 83% of patients, TCD in was done 90% of patients, and CT angiography, MRI, or DSA was performed in 20% of patients. TTE was done in 63.2% of the patients. In the study of Petty et al,[9] a population-based study conducted in Rochester, Minnesota, carotid Doppler ultrasound, TCD, or cerebral angiography was done in only 54% of the patients, whereas TTE and TEE were done in 50%. In a Chilean population-based study, CS was included with all strokes of UC, and brain CT scan was done in 86% of the patients and MRI was done in only 3%.[13] In this study, extracranial Doppler ultrasound was done in 25% of patients, TTE in 36%, and TEE in 3%. No patient underwent intracranial vessel assessment.

The distribution of stroke subtypes is a controversial subject in the literature, especially when considering the UC stroke subtype. In our study, the proportion of patients with CS (20%) was similar to that reported by Bang et al (18%)[10] and lower than that reported by Moroney et al (28%).[14] These are the only previous studies that separated CS from UC.The proportion of LAD found in our study (29%) was higher than that reported by Bang et al (17%) or Maroney et al (20%). A possible reason for these differences may be the high frequency of hypercholesterolemia in our study (23% of all patients and 42% of those with LAD), compared with the 5.5% of all patients and 4% of those with LAD reported by Bang et al (Table 4).

We failed to find any direct association between arterial hypertension, diabetes mellitus, or hypercholesterolemia and the occurrence of CS. Similarly, Bang et al[10] reported a lower rate of diabetes mellitus in the CS group compared with the other groups, along with no differences in hypertension and hypercholesterolemia among the groups. Interestingly, we found that these risk factors were highly prevalent in all stroke subtypes except OC.

Endothelial disturbances, microangiopathic damage and/or cardiac dysfunction are reported more directly associated with CS, LAD, SAD, and CE than with the OC subtypes. In our study, the prevalence of these risk factors in the CS group were intermediate, likely due to the younger age of or our CS group (mean age, 62 ± 17 years; 49% aged <50 years) compared with the SAD (mean age, 68 ± 13 years), LAD (mean age, 69 ± 11 years), and CE (mean age, 73 ± 12 years) groups. We hypothesize that this younger group had less exposure to these risk factors; however, this hypothesis requires further study for confirmation.

Consistent with other hospital-based reports,[10,11,14] we found a low rate of ischemic stroke recurrence (3.5% by year). We found that patients with CE had high rates of early stroke recurrence (15%), high mortality, and the worst functional outcomes at the end of the follow-up period. This differs from the existing literature, which reports the highest recurrence rate in the LAD subtype[9,11,14] (range, 8%-13% at 3 months). In our study, the patients with CS had a significantly lower rate of recurrence (4 patients; 1.7% by year) than reported previously (range, 4% at 3 months and 15%-30% by year 10). In our study, recurrences were observed in 2 patients with SAD, in 1 patient with CS, and in 1 patient with LAD. These discrepancies might be linked to differences among the studies in terms of cohort size, methodology, follow-up period (1 week to 2 years), and definitions of CS.

This study has some limitations. It was hospital-based, not population-based, conducted in the oldest stroke unit in Chile, which serves as a primary care site for acute stroke patients in a semipublic hospitality region. However, the baseline characteristics of our population are in line with those expected for the general Chilean population.[13] Because this was a single-center study using a hospital-based stroke data bank, future population-based studies are needed to confirm our findings, which reflect the practices and local demographic characteristics of our center.

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