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# Subtype Reclassification and Cardioembolic Tendency in Patients with Recurrent Ischemic Stroke: A Retrospective Study

## Tekrarlayan İskemik İnme Hastalarında Alt Tip Değişiklikleri ve Kardiyoembolik Eğilimler: Retrospektif Bir Çalışma

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**ABSTRACT**

**Background:** Recurrent ischemic stroke is defined as a new event in a different vascular territory at least 24 hours after onset, or in the same territory at least 21 days later. These events challenge secondary prevention and are complicated by changes in etiologic subtypes over time. We aimed to analyze subtype evolution in recurrent ischemic stroke and its relationship with recurrence interval.

**Methods:** This retrospective study included 94 patients with recurrent ischemic stroke. Clinical and radiological data were reviewed. Initial and recurrent subtypes were compared, and patients were categorized by lesion localization and recurrence interval. Associations were tested using chi-square methods, with McNemar's test applied for paired comparisons of initial and recurrent TOAST subtypes.

**Results:** Subtype reclassification occurred in 43 patients (45.7%). The most frequent change was from cryptogenic to cardioembolic or possible cardioembolic stroke (29.8%). McNemar's test showed significant asymmetry, with 28 cryptogenic-to-cardioembolic reclassifications and none in the opposite direction ($P<.001$). Among initially cryptogenic patients, 63% recurred within the first year, mostly reclassified as cardioembolic. In the cardioembolic group, subtype consistency was 100%. Recurrence tended to occur earlier in this group, but without statistical significance ($P = .629$)

**Conclusion:** Cryptogenic-to-cardioembolic reclassification was the most common pattern, indicating that many cryptogenic cases may conceal underlying cardioembolic mechanisms. These findings emphasize the need for long-term cardiac monitoring and periodic reassessment of etiology in recurrent ischemic stroke.

**Keywords:** Stroke, brain ischemia, recurrence, cardiogenic embolism, cryptogenic stroke.

**ÖZ**

**Amaç:** Tekrarlayan iskemik inme, inme başlangıcından en az 24 saat sonra farklı bir vasküler bölgede veya ilk inmeden en az 21 gün sonra aynı bölgede ortaya çıkan yeni bir iskemik olay olarak tanımlanır. Bu olgular, sekonder koruma stratejilerinin etkinliğini sınırlamakta; etiyolojik alt tiplerde zamanla gözlenen değişimler ise altta yatan patofizyolojik mekanizmaların anlaşılmasını güçleştirmektedir. Bu çalışmanın amacı, tekrarlayan iskemik inme hastalarında etiyolojik alt tiplerin zaman içindeki değişimini ve bu değişimin tekrarlama süresiyle ilişkisini analiz etmektir.

**Yöntemler:** Bu retrospektif gözlemsel çalışmaya, tekrarlayan iskemik inme tanısı almış 94 hasta dahil edildi. Klinik ve radyolojik veriler geriye dönük olarak incelendi. İlk ve sonraki inme alt tipleri karşılaştırıldı; hastalar lezyon lokalizasyonu ve tekrarlama sürelerine göre kategorize edildi. İlişkiler ki-kare yöntemi kullanılarak test edildi ve başlangıç ile rekürren TOAST alt tiplerinin eşleştirilmiş karşılaştırmaları için McNemar testi uygulandı.

**Bulgular:** Toplam 43 hastada (%45,7) alt tip değişikliği görüldü. En sık geçiş kriptojenik inmeden kardiyoembolik inme grubunaydı (%29,8). McNemar testi bu geçişin anlamlı olduğunu gösterdi ($P < .001$). Başlangıçta kriptojenik olanların %63'ü ilk yıl içinde tekrarladı ve çoğu kardiyoembolik olarak yeniden sınıflandı. Kardiyoembolik grupta alt tip sabit kaldı (%100 tutarlılık). Bu grupta rekürrens daha erken olma eğilimindeydi ancak anlamlı değildi ($P = .629$).

**Sonuç:** Kriptojenik inmeden kardiyoembolik inmeye geçiş en sık gözlenen değişimdi ve bu durum, başlangıçta kriptojenik olarak sınıflanan vakaların önemli bir kısmında gizli kardiyoembolik nedenler bulunabileceğini düşündürmektedir. Bulgular, uzun süreli kardiyak izlem ve tanısal sınıflandırmaların zaman içinde yeniden değerlendirilmesinin önemini vurgulamaktadır.

**Anahtar Kelimeler:** İnme, beyin iskemisi, tekrarlama, kardiyoembolik inme, kriptojenik inme

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## INTRODUCTION

A recurrent stroke can be defined as a new stroke occurring in a different vascular region within 24 hours of stroke onset or a stroke occurring in the same region within 21 days of the initial stroke.[1] Approximately half of patients who experience an ischemic stroke or transient ischemic attack are at high risk of stroke, particularly in the first one to two days after the initial event.[2] The risk of stroke recurrence begins to decrease after the third month, and this risk ratio stabilizes between the 6th and 12th months.[3,4] Studies have reported that the risk of ischemic stroke recurrence is 7-20% in the first year, while this rate ranges from 16-35% over a 5-year period 5. Recurrent stroke leads to prolonged hospital stay, worsened functional outcomes, and increased mortality.[4,5] The risk of ischemic stroke recurrence may be related to stroke subtype or previously unidentified risk factors. The Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria are frequently used for ischemic stroke subtype classification.[6] While some studies found no association between stroke subtype and the frequency of stroke recurrence,[7–9] others found a significant difference (cardioembolic stroke and strokes resulting from large-vessel atherosclerosis had a higher risk of recurrence).[10–14] Even with adequate examination, the stroke subtype cannot be determined in most patients. In some of these cases, the stroke subtype is updated to cardioembolic based on advanced cardiological examination methods (long-term electrocardiographic monitoring, transesophageal echocardiography) or examinations performed in cases of ischemic stroke recurrence.[15,16] In this study, we investigated whether there was a difference between the first stroke subtype and the second stroke subtype in cases of recurrent ischemic stroke and the time to recurrence of ischemic stroke.

## MATERIAL AND METHODS

This study included 94 patients diagnosed with recurrent ischemic stroke who were followed up in our hospital's Neurology Clinic and Stroke Center between January 2024 and January 2025. A retrospective analysis was performed.

Recurrent ischemic stroke was defined as a new stroke occurring in a different vascular region within 24 hours of stroke onset or a stroke occurring in the same region 21 days after the initial stroke.

Patient data were obtained from the electronic patient record system. Demographic and clinical information for each patient, including age, gender, comorbidities, stroke subtype of the first and second stroke according to TOAST criteria, lesion location, medical treatment and interventional methods (thrombolysis/thrombectomy), and treatment administered at discharge (antiplatelet/anticoagulant), was recorded. Patients with missing data were excluded from the study.

To determine stroke subtype, we perform diffusion magnetic resonance imaging (MRI), brain and neck computed tomography angiography (CT), including the aortic arch, electrocardiography, and transthoracic echocardiography in all eligible patients. All patients under 55 years of age are evaluated for stroke in the young. In cases of cryptogenic stroke, 24-48 hours of electrocardiographic monitoring is performed, and in appropriate cases, transesophageal echocardiography (TEE) is performed.

Stroke subtypes were determined according to TOAST criteria (small vessel disease, large vessel atherosclerosis, cardioembolism, cryptogenic, and other). We included patients we considered to have embolic stroke of undetermined origin (ESUS) in the cryptogenic stroke group.

If the stroke subtype could not be determined in further evaluation of our recurrent ischemic stroke cases and one or both of the following two (***) features were present, we considered a possible cardioembolic stroke:

***Appearance suggestive of acute infarction in the right and left hemispheres or anterior and posterior systems on diffusion MRI.

***Left atrium or biatrial dilatation on transthoracic echocardiography. Patients who did not have TEE or long-term electrocardiographic monitoring recordings at the time of the second stroke were excluded from the study.

In cases of recurrent stroke, the first and second stroke subtypes were recorded, and any differences were noted. The duration of recurrence was examined by dividing it into four temporal groups, taking into account the time elapsed between the first and second strokes. (0–6 months, 6 months–1 year, 1–5 years, and >5 years). Based on brain imaging findings, lesion locations were classified into four main groups: Middle cerebral artery (MCA) superior division, MCA inferior division, posterior system (mesencephalon, pons, bulb, cerebellum) and multiple lesions. Any relationship between infarct locations, stroke subtype, lesion location, and time to stroke recurrence was noted.

The study was approved by Samsun University Non-Interventional Clinical Researches Ethical Committee (Date: July 9, 2025, Decision No:2025/14/8). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Statistical analyses were performed using IBM SPSS Statistics (Version 27.0; IBM Corp., Armonk, NY, USA). For descriptive statistics, mean ± standard deviation or median (minimum–maximum) values were reported for numerical data, and frequency and percentage (%) distributions were reported for categorical data. The Pearson chi-square test was used to assess relationships between qualitative variables. When necessary, if the expected cell frequencies were low, Fisher's exact test or the chi-square test supported by Monte Carlo simulation was preferred. For paired categorical data, such as the comparison of TOAST classification subtypes between the first and recurrent strokes, McNemar's chi-square test was applied. In

### MAIN POINTS

- Subtype change occurred in 43.9% of recurrent ischemic strokes.
- Most frequent subtype reclassification was from cryptogenic to cardioembolic subtype.
- Cardioembolic strokes showed 100% consistency at recurrence.
- Recurrence was earlier in cardioembolic than in other subtypes.
- Findings support early long-term cardiac monitoring in recurrence.

comparisons where cell counts were too small for McNemar's test, Fisher's exact test was used as an alternative. Possible relationships between variables such as change in stroke subtype, lesion location, and time to recurrence were evaluated separately. In all analyses, a P value of <.05 was considered statistically significant.

## RESULTS

A total of 94 patients (62.7% male, 37.2% female) diagnosed with recurrent stroke were included in the study. Hypertension was the highest risk factor in both genders (77.3% male, 68.3% female). 53 patients (56.4%) were receiving Antiplatelet therapy, including 3 (3.2%) on dual antiplatelet therapy. 12 patients (12.8%) were on Anticoagulant therapy.

Additionally, 5 patients (5.3%) reported irregular use of anticoagulants and 2 (2.1%) reported irregular use of antiplatelet agents (Table 1).

**Table 1.** Demographic and clinical characteristics of the study population

| Variable | Category | n | % |
|---|---|---|---|
| **Sex** | Male | 59 | 62.8 |
| | Female | 35 | 37.2 |
| **Age** | 65–75 years | 38 | 40.4 |
| | >75 years | 36 | 38.3 |
| | <65 years | 20 | 21.3 |
| **Comorbidities** | Hipertansiyon | 70 | 74.5 |
| | Hypertension + Diabetes mellitus | 13 | 13.8 |
| | Hypertension + Coronary artery disease | 11 | 11.7 |
| **Antiplatelet therapy** | None | 83 | 88.3 |
| | ASA | 7 | 7.4 |
| | Clopidogrel | 1 | 1.1 |
| | Dual | 3 | 3.2 |
| **Anticoagulant therapy** | None | 81 | 86.2 |
| | Yes | 7 | 7.4 |
| | Irregular | 6 | 6.4 |
| **ECG** | NSR | 63 | 67.0 |
| | ECG | 31 | 33.0 |
| **Echocardiography** | Not significant | 87 | 92.6 |
| | Significant | 7 | 7.4 |
| **Acute treatment** | None | 88 | 93.6 |
| | Mechanical thrombectomy | 4 | 4.3 |
| | Acute treatment | 2 | 2.1 |

When we examined the patients' initial stroke subtypes, the most common was cryptogenic stroke (n=65, 69.1%), followed by cardioembolic (CE) (n=14, 14.9%), small vessel disease (SVD) (n=9, 9.6% ) and large artery atherosclerosis (LAA) (n=6, 6.4% ).

In recurrent stroke presentations, 88 patients (93.6 %) received no intervention, while 4 patients (4.2%) underwent mechanical thrombectomy, 2 patients (2.1 %) underwent intravenous thrombolytic therapy (IV-tPA).

Two of the four patients who underwent mechanical thrombectomy experienced subtype changes. Their initial stroke subtypes were cryptogenic; one patient was diagnosed with cardioembolic stroke after AF was detected on the ECG, and the other patient was diagnosed with possible cardioembolic stroke due to echocardiographic findings (biatrial dilatation). One patient whose stroke subtype changed and who underwent mechanical thrombectomy initially had a cryptogenic stroke but was reclassified as another stroke after carotid artery involvement was identified. Only one of the two patients who received IV-tPA experienced a subtype change. In this case, the subtype reclassification from cryptogenic to cardioembolic stroke occurred due to AF detected on the ECG.

There were 51 patients with the same first and second stroke subtypes (31 cryptogenic, 1 SVD, 5 LAA, 14 CE ), and 43 patients with different subtypes (34 cryptogenic, 8 SVD, 1 LAA). The most common subtype reclassification in the different subtypes was from cryptogenic stroke to CE (n=18) or possible cardioembolic (n=10) stroke (total n=28, 29.8%).

Seventeen of the patients who converted to the cardioembolic subtype were identified on routine ECGs, and one patient was identified with AF on 24-hour Holter ECG. While ECHO findings were detected in 4 of the patients considered to have a possible cardioembolic subtype, the remaining 6 were considered to have a possible cardioembolic stroke due to the lesion localization.

Among cryptogenic stroke patients, 34 of 65 (52.3%) patients showed a change in TOAST classification subtype; 18 of them had CE and 10 had conversion possible CE. In contrast, 9 of 29 (31.0%) patients in the other baseline subtype groups showed a change. This difference was not statistically significant ($\chi^2$ = 2.85, (P =.091). Of the 43 patients who changed in TOAST classification subtype, 28 (65.1%) were initially classified as having Cryptogenic stroke and were reclassified as CE (n=18) or possible CE (n=10) at recurrence. This represents the most frequent pattern of subtype change observed in the cohort. McNemar's test demonstrated a significant asymmetry in paired subtype classifications: 28 patients were reclassified from cryptogenic to CE, whereas no patients changed in the opposite direction (P<.001, Table 2).

**Table 2.** Cross-tabulation of initial and recurrent ischemic stroke subtypes

| Initial \ Recurrent | SVD | LAA | Cryptogenic | CE | Possible CE |
|---|---|---|---|---|---|
| **SVD** | 1 | 1 | 2 | 3 | 2 |
| **LAA** | 0 | 5 | 1 | 0 | 0 |
| **Cryptogenic** | 3 | 3 | 31 | 18 | 10 |
| **CE** | 0 | 0 | 0 | 14 | 0 |

*SVD: Small Vessel Disease, LAA: Large Artery Atherosclerosis , CE: cardioembolic

**The most frequent change was from Cryptogenic subtype) to Cardioembolic stroke.

This change was found to be statistically significant using the McNemar test (P<.001)

All other subtype reclassification were seen in 10 patients (4.2% LAA, 3.1% SVD, 3.1% cryptogenic) (Figure 1).

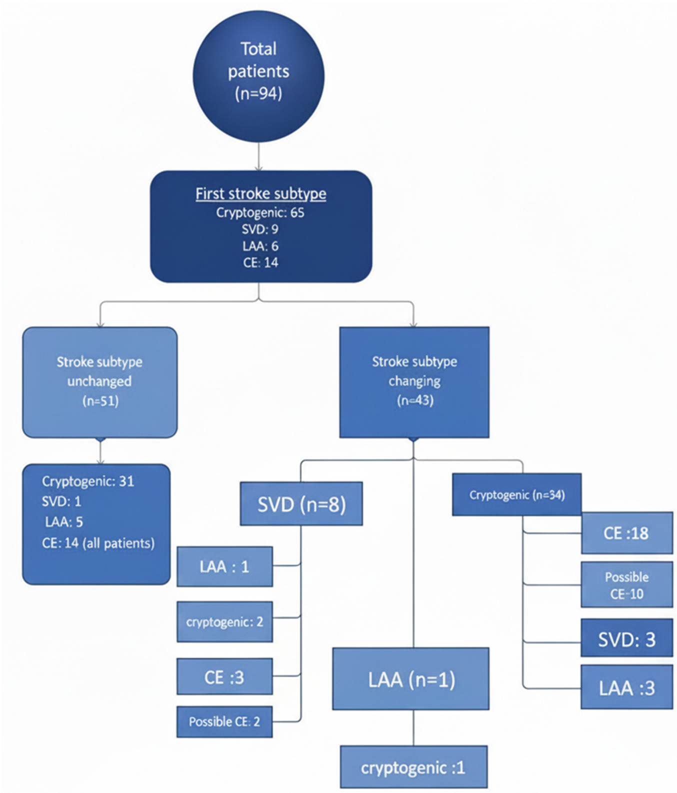


**Figure 1.** Flow Diagram Depicting Etiological Subtype Changes and Subtype Reclassification Patterns.
SVD: Small Vessel Disease, LAA: Large Artery Atherosclerosis , CE: cardioembolic

In patients with strokes due to SVD, 33.3% of second strokes were determined to be CE, 22.2% were considered possible CE, and 22.2% were considered cryptogenic. Subtype reclassification was less common in first strokes with a LAA etiology; 83.3% of patients continued with the same subtype in their second stroke. There was no subtype reclassification in patients whose first stroke was CE (100% consistency) (Figure 2).

The Sankey diagram illustrates the distribution of patients according to TOAST classification at the time of the initial ischemic stroke (left) and at recurrence (right). The most frequent reclassification pattern was from cryptogenic stroke to cardioembolic or possible cardioembolic stroke.

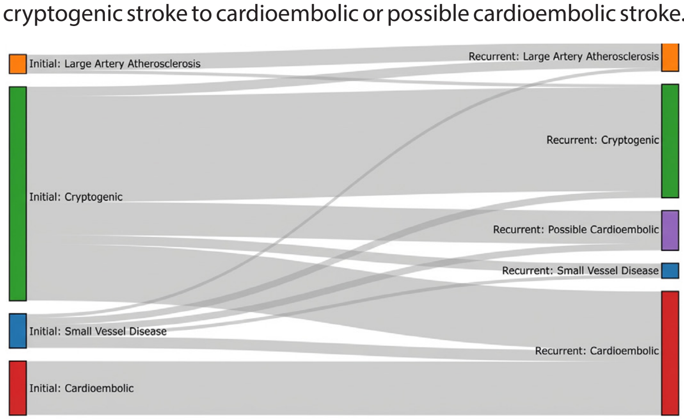


**Figure 2.** Flow of patients between initial and recurrent stroke subtypes.

According to the recurrence time, 27 patients (28.7%) had a stroke recurrence within the first 6 months, 18 patients (19.1%) within 6 months to 1 year, 26 patients (27.7%) between 1 and 5 years, and 23 patients (24.5%) after more than 5 years.

No statistically significant relationship was found between the first stroke subtype and the recurrence interval ($\chi^2$=3.59, df=9, P=.936, Table 3). Similarly, analysis of subtype reclassification showed no significant association with recurrence interval ($\chi^2$=3.18, df=3, P=.364, Table 4). Moreover, the distribution of recurrent stroke subtypes across different recurrence intervals did not demonstrate a statistically significant difference ($\chi^2$=4.27, df=9, P=.556, Table 5). Collectively, these findings indicate that the timing of recurrence was not significantly influenced by either the initial stroke subtype or subsequent subtype reclassification.

**Table 3.** Distribution of initial TOAST subtypes by recurrence interval

| Recurrence interval | SVD | LAA | Cryptogenic | CE | Possible CE |
|---|---|---|---|---|---|
| 0–6 months | 1 | 0 | 7 | 4 | 2 |
| 6–12 months | 2 | 2 | 7 | 5 | 2 |
| 1–5 years | 4 | 3 | 14 | 6 | 3 |
| >5 years | 2 | 1 | 10 | 4 | 3 |

*SVD: Small Vessel Disease, LAA: Large Artery Atherosclerosis , CE: cardioembolic
Chi-square test: $\chi^2$ = 3.59, df = 9, P = .936
No significant association was found between initial stroke subtype and recurrence interval.

**Table 4.** Association of etiologic subtype reclassification with recurrence interval

| Recurrence interval | No reclassification | Reclassification | Cryptogenic |
|---|---|---|---|
| 0–6 months | 13 | 14 | 7 |
| 6–12 months | 10 | 8 | 7 |
| 1–5 years | 15 | 11 | 14 |
| >5 years | 13 | 10 | 10 |

Chi-square test: $\chi^2$ = 1.34, df = 3, P = .72
No significant association was found between subtype reclassification and recurrence interval.

**Table 5.** Distribution of recurrent subtypes by recurrence interval

| Recurrence interval | SVD | LAA | Cryptogenic | CE | Possible CE |
|---|---|---|---|---|---|
| 0–6 months | 1 | 0 | 7 | 4 | 2 |
| 6–12 months | 2 | 2 | 7 | 5 | 2 |
| 1–5 years | 4 | 3 | 14 | 6 | 3 |
| >5 years | 2 | 1 | 10 | 4 | 3 |

*SVD: Small Vessel Disease, LAA: Large Artery Atherosclerosis, CE:cardioembolic
** Chi-square test: P=.556
There was no significant association between the recurrent TOAST subtype and the recurrence interval.

Recurrent strokes within the first year occurred more frequently in patients classified as having CE or possible CE than in patients with other TOAST classification subtypes; however, this difference was not statistically significant ($\chi^2 = 5.70$, P=.127).

Patients were classified into four main groups according to the lesion localization detected at the time of their initial stroke: middle cerebral artery (MCA) upper division (n=38), MCA lower division (n=25), posterior system (n=5), and multiple lesions (n=32).

The chi-square test performed to evaluate the relationship between lesion localization and time to recurrence revealed no statistically significant difference (x2=17,97 df=9, P=.458).

Specifically, in the MCA upper division group, 27.7% of patients experienced recurrence within the first 6 months, 26.2% between 6 months and 1 year, 27.7% between 1 and 5 years, and 18.5% after >5 years. In the MCA lower division group, these rates were 25.0%, 25.0%, 25.0%, and 25.0%, respectively.

Stroke recurrences were observed more than three times in four patients. The first stroke subtype in these cases was cryptogenic. The second stroke subtype was considered a possible cardioembolic stroke due to multiple acute infarctions in three different regions (both anterior and posterior systems). Malignancy was detected in all four patients evaluated for malignancy after the third or fourth recurrence.

## DISCUSSION

This study investigated stroke subtype reclassification and recurrence timing in patients with recurrent ischemic stroke. Nearly half of the cohort (45.7%) showed a different TOAST subtype at recurrence compared with the initial event. The most common reclassification pattern was from cryptogenic stroke to cardioembolic (CE, n=18) or possible CE (n=10), accounting for 29.8% of the entire cohort and 65.1% of all reclassifications. Seventeen patients were diagnosed with atrial fibrillation (AF) on routine ECG, one on 24-hour Holter monitoring, and six based on lesion localization. McNemar's test confirmed a significant asymmetry in paired classifications, with 28 patients reclassified from cryptogenic to CE and none showing the reverse pattern (P<.001). This finding emphasizes the likelihood of underlying cardioembolic mechanisms in a subset of initially cryptogenic strokes.

The predominance of cryptogenic-to-CE reclassification in our study is consistent with prior literature. The limitations of the TOAST classification in defining cryptogenic stroke have long been debated.[16] The concept of embolic stroke of undetermined source (ESUS) was introduced to capture cases lacking a clear etiology.[17] ESUS represents a heterogeneous entity, often later attributed to covert cardioembolism following long-term monitoring or advanced cardiac imaging.[18,19] In NAVIGATE-ESUS, more than half of recurrent events occurred in patients initially classified as cryptogenic, many of whom were later reclassified as CE after extended evaluations.[18] Similarly, meta-analyses indicate that AF can be detected in up to 30% of ESUS patients during long-term follow-up, highlighting the importance of comprehensive rhythm surveillance.[20]

The growing recognition of covert AF is supported by large trials such as TRENDS and RE-SPECT ESUS, which showed that embolic events frequently occur independently of documented AF episodes and that the risk of CE stroke increases with age.[21,22] Advanced modalities, including prolonged cardiac rhythm monitoring and transesophageal echocardiography, are therefore critical in detecting paroxysmal AF and structural cardiac abnormalities. According to the TOAST classification, the rate of CE stroke is approximately 25%.[23] Recent bibliometric analyses further demonstrate the rising prevalence and scientific focus on CE stroke, underscoring its clinical importance.[24,25]

In our cohort, CE strokes showed complete consistency between first and recurrent events, while LAA and SVD subtypes more frequently changed at recurrence, often toward a CE classification. Only one patient with an initial LAA etiology was reclassified, and in SVD cases, one-third converted to CE or possible CE. These findings suggest that initial non-CE classifications may obscure covert cardioembolic mechanisms that manifest at recurrence.

We did not observe a statistically significant relationship between initial stroke subtype, subsequent reclassification, or recurrent subtype and the timing of recurrence. Although cardioembolic and possible cardioembolic strokes tended to occur earlier—particularly within the first year—this pattern did not reach statistical significance. This aligns with prior studies, such as the Oxford Vascular Study, which reported that early recurrence was more common in cardioembolic strokes but that the association weakened after adjustment for age and comorbidities.[2] Similarly, pooled European data showed heterogeneous recurrence intervals across subtypes, suggesting that baseline classification alone cannot reliably predict recurrence.[1] These findings emphasize that recurrence risk stratification should not depend solely on initial subtype, but rather incorporate prolonged cardiac monitoring and comprehensive vascular evaluation.[20]

Four patients in our cohort experienced more than three recurrences. All were initially classified as cryptogenic but later reclassified as possible CE based on multiple infarctions across anterior and posterior circulations. Importantly, malignancy was identified in all four cases. This observation supports previous reports linking cancer with recurrent ischemic events and multifocal infarcts suggesting that occult malignancy should be considered in patients with multiple unexplained recurrences.[26,27]

The rising prevalence of CE stroke has been attributed not only to aging populations but also to improved diagnostic recognition of hidden AF.[28] Emerging technologies—including wearable devices and artificial intelligence—offer promising tools for detecting paroxysmal arrhythmias that underlie many strokes previously classified as cryptogenic.[29,30] Histopathological studies of thrombi retrieved during mechanical thrombectomy further support this perspective, showing similarities between clots in cryptogenic and cardioembolic cases.[19] Taken together, these findings reinforce the growing need to reconsider cryptogenic stroke as a potential marker of covert cardioembolic disease.

Our study has limitations. It was a single-center retrospective analysis with a relatively small sample size. Comprehensive cardiac evaluations, including prolonged ambulatory ECG monitoring and transesophageal echocardiography, were not feasible in all patients at the time of the initial event. These limitations may have led to underdetection of cardioembolic sources and misclassification of some cryptogenic strokes.

## CONCLUSION

Long-term cardiac monitoring and the use of advanced imaging methods are crucial for identifying a cardioembolic etiology, particularly in strokes where the cause is initially unknown. A recurrent stroke without any other etiological cause can be considered a possible cardioembolic stroke if there is a patent foramen ovale, left atrial dilatation, left ventricular disease, atrial cardiopathy, or valvular heart disease.

**Ethics Committee Approval:** Ethical committee approval was received from the Ethics Committee of Samsun University Non-Interventional Clinical Research Ethics Committee. (Date: July 9, 2025; Decision No: 2025/14/8). The study was conducted in accordance with the principles of the Declaration of Helsinki.

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