# Relationship between silent cerebral infarcts and quality of anticoagulation in patients with prosthetic mitral valves

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## ABSTRACT

**Objective:** Although patients with prosthetic heart valves have an increased risk of clinically overt cerebrovascular events, evidence for the risk of silent cerebral infarction (SCI) is scarce. Serum neuron-specific enolase (NSE) is suggested to be a valid biomarker that allows for the quantification of the degree of neuronal injury. We aimed to assess whether NSE is elevated as a marker of recent SCI in patients with a prosthetic mitral valve.

**Methods:** We measured the NSE levels in 103 patients with a prosthetic mitral valve (PMV), admitted to our outpatient clinics for routine evaluation. International normalized ratio (INR) and time in target therapeutic range (TTR) were noted as anticoagulation quality measures.

**Results:** Most of the patients were females (58%), and a mean age was 65 years. NSE values of >12 ng/mL, suggesting a recent SCI, was detected in 25 patients (24%). NSE was negatively correlated with admission INR (r=–0.307, p=0.002). Multivariate analyses demonstrated subtherapeutic INR (INR <2.5) and suboptimal TTR as independent predictors of SCI [odds ratio (OR) 5.420; 95% confidence interval (CI) 1.589 to 18.483; p=0.007, and OR 4.149; 95% CI 1.019 to 16.949; p=0.047, respectively]. Being a current smoker (OR 10.798; 95% CI 2.520 to 46.272; p=0.001), large left atrium (OR 6.763; 95% CI 2.253 to 20.302; p=0.001), and not using aspirin (OR 10.526; 95% CI 1.298 to 83.333; p=0.027) were other independent predictors.

**Conclusion:** Our data suggest that silent brain infarcts are very prevalent among patients with a PMV, as one fourth of them had the event during their routine outpatient visit. Poor quality of anticoagulation partly explains the increased prevalence.

**Keywords:** neuron-specific enolase, prosthetic heart valve, silent cerebral infarct

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## Introduction

Mechanical heart valve prosthesis is an important risk factor for thromboembolic complications. It is estimated that an embolic stroke occurs in approximately 20% of these patients in 15 years of valve replacement, mitral valve prosthesis possessing a higher risk (1). In addition, asymptomatic neurologic injury may account for a greater percentage of thromboembolic complications (2, 3). Silent cerebral infarct (SCI) is defined as the evidence of cerebral infarction in the absence of a clinically apparent stroke or transient ischemic attack (4). Cranial magnetic resonance imaging (MRI) has been the gold standard method for establishing the diagnosis of cerebrovascular injury (5). However, serum neuron-specific enolase (NSE) is suggested to be a valid biomarker that allows for the quantification of the degree of acute neuronal injury (6). NSE is a sensitive neuronal ischemia marker that is detectable in the serum after 2 to 4 hours of ischemia and can remain positive for approximatey 2–3 days (7, 8). This current study aimed to assess whether NSE is elevated as a marker of recent SCI in patients with a prosthetic mitral valve (PMV).

## Methods

We recruited 172 consecutive PMV patients admitted to our outpatient clinics for routine evaluation. Physical examination, ECG, and echocardiography were performed in all patients.

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**HIGHLIGHTS**

- Serum neuron specific enolase (NSE) is a biomarker for neuronal injury, even for silent cerebral infarcts (SCI).
- We assessed NSE as a marker of recent SCI in patients with prosthetic mitral valve.
- Recent SCI was detected in 24% of patients, all asymptomatic, at their routine outpatient controls.
- We suggest that silent brain infarcts are so prevalent among prosthetic valve patients that one fourth of them had the event during their routine visit.
- Poor anticoagulation quality partly explains this results prevalence.

Blood sample was collected for complete blood count, glucose, alanine transaminase, aspartate transaminase, lactate dehydrogenase, billirubine, creatinine, sodium, potassium, International normalized ratio (INR), and NSE analyses.

The NSE analysis was performed on an immunologic automated analyzer using h-NSE kits (Diametra, Foligno, Italy). It was performed using the direct immunoenzymatic colorimetric method. Intra and interassay coefficient variables were ≤4.4% and 11.2%, respectively and 0.12 µg/L was defined by the manufacturer as the upper limit of normal for NSE. Patients with serum NSE levels >0.12 µg/L (12 ng/mL) were defined as having SCI.

INR level of <2.5 was defined as subtherapeutic on the basis of recent guidelines recommending target INR levels between 2.5 to 3.5 for PMV patients (9). Time in target therapeutic range (TTR) was calculated by the traditional method, as the percentage of INRs in the therapeutic range (10, 11). In our protocol, the last five INR results, which had to be within the range of 2–8 weeks intervals, were taken into account. The TTR value of <60% was considered as suboptimal (10, 12, 13).

Exclusion criteria were as follows: having a bioprosthetic mitral valve or more than one prosthetic valve, patients who had their valve surgery in the past six months, need of further evaluation with detailed imaging modalities for valvular dysfunction, possible valvular hemolysis (as it can itself increase serum NSE levels), significant paravalvular leaks or severe mitral regurgitation, patients with left ventricular ejection fraction (EF) <40%, absence of previous INR results needed for TTR calculation, end-stage renal failure (glomerular filtration rate <15 ml/min/1.73 $m^2$) or dialysis patients, known valvular, apical or left atrial thrombus, any type of cancer, history of stroke, transient ischemic attack (TIA) or brain tumor, and head trauma within the past six months.

### Statistical analysis

All analyses were performed using the SPSS version 20.0 software (SPSS Inc., Chicago, IL, USA). Categorical variables are expressed in frequencies and percentages, while continuous variables are expressed as means ± standard deviations and as median (interquartile range), if not normally distributed. The Kolmogorov–Smirnov test for normality was used to examine the data distribution. The chi-square test was used to compare categorical variables, while for the continuous variables, the Student's t test or Mann-Whitney U test, if not normally distributed, were used to compare the SCI positive and SCI negative patients. Bivariate Pearson correlation analysis was performed to measure the association of NSE with admission INR and TTR values. The relationship between elevated NSE levels and possible independent predictors was assessed by binary logistic regression analysis. A probability value of $p < 0.05$ was considered significant.

Our study was conducted in accordance with the Declaration of Helsinki. All our patients gave their written informed consents and our study protocol was approved by the Local Ethics Committee.

## Results

Of 172 consecutive outpatients with PMV, 69 were excluded for following reasons: missing INR values to calculate TTR (22 patients), EF <40% (16 patients), more than one prostethic valve (12 patients), end-stage renal failure (9 patients), history of stroke or TIA (5 patients), suspicion of thrombus on the prosthetic valve (3 patients), and cancer (2 patients). The remaining 103 patients (58% female) with a mean age of 65 years were included in the study.

An NSE level >12 ng/mL, suggesting a recent SCI, was detected in 25 patients (24%). The baseline clinical characteristics of the patients in this study according to the presence of SCI are shown in Table 1. Patients with SCI were more likely to be current smokers and to have a larger left atrium in the echocardiography, while they were less likely to have used aspirin. Admission INR and mean TTR values were significantly lower in the SCI group. NSE level was negatively correlated with admission INR, such that NSE level was lower in patients with higher INRs (r=–0.307, p=0.002) (Fig. 1). The Correlation of NSE level with TTR was not significant (r=–0.171, p=0.084). While SCI was significantly more common in patients with subtherapeutic INR, this difference was not observed in those with suboptimal TTR (Fig. 2). Multivariate analyses demonstrated that subtherapeutic INR and TTR were independent predictors of SCI [odds ratio (OR) 5.420; 95% confidence interval (CI) 1.589 to 18.483; p=0.007, and OR 4.149; 95% CI 1.019 to 16.949; p=0.047, respectively). Being a current smoker (OR 10.798; 95% CI 2.520 to 46.272; p=0.001), having a larger left atrium (OR 6.763; 95% CI 2.253 to 20.302; p=0.001), and not using aspirin (OR 10.526; 95% CI 1.298 to 83.333; p=0.027) were other independent predictors (Table 2).

**Table 1. Baseline clinical characteristics of study patients**

| | Silent cerebral infarct (+) (n=25) | Silent cerebral infarct (-) (n=78) | *P* value |
|---|---|---|---|
| Age (years), mean±SD | 66±13 | 64±12 | 0.511 |
| Female sex, n (%) | 15 (60%) | 45 (57%) | 0.840 |
| Body mass index (kg/m$^2$), mean±SD | 29.8±6.3 | 29.5±6.4 | 0.842 |
| Hypertension, n (%) | 18 (72%) | 46 (59%) | 0.238 |
| Diabetes mellitus, n (%) | 11 (44%) | 27 (35%) | 0.402 |
| Current smoking, n (%) | 12 (48%) | 9 (12%) | <0.001 |
| Hyperlipidemia, n (%) | 11 (44%) | 22 (28%) | 0.137 |
| Glomerular filtration rate (mL/min/1.73 m$^2$), mean±SD | 68.3±21.9 | 72.1±23.4 | 0.483 |
| Hemoglobin (g/dL), median (IQR)* | 12.3 (1.8) | 12.5 (2.2) | 0.290 |
| Lactate dehydrogenase (U/L), mean±SD | 293.8±159.3 | 287.7±159.3 | 0.879 |
| Indirect billirubin (mg/dL), mean±SD | 1.1±0.6 | 0.9±0.7 | 0,323 |
| Coronary artery disease, n (%) | 6 (24%) | 15 (19%) | 0.608 |
| Atrial fibrillation, n (%) | 16 (64%) | 39 (50%) | 0.222 |
| Time after valve replacement (years), mean±SD | 6.3±4.1 | 4.9±3.9 | 0.161 |
| TTR (%), mean±SD | 51±20 | 64±20 | 0.008 |
| Admission INR, mean±SD | 2.60±0.57 | 3.16±0.68 | <0.001 |
| Use of aspirin, n (%) | 2 (8%) | 20 (26%) | 0.064 |
| Use of statin, n (%) | 11 (44%) | 36 (46%) | 0.847 |
| **Echocardiographic parameters** | | | |
| Moderate/severe spontaneous echo contrast, n (%) | 7 (28%) | 14 (18%) | 0.280 |
| Ejection fraction %, mean±SD | 49±9 | 53±10 | 0.153 |
| Left atrium diameter (cm), mean±SD | 5.6±0.6 | 5.1±0.6 | 0.001 |
| Moderate mitral regurgitation, n (%) | 2 (8%) | 15 (19%) | 0.182 |

*Median (IQR) value used for non-normally distributed parameters.
INR - international normalized ratio, IQR - interquartile range, NSE - neuron-specific enolase, SD - standard deviation, TIA- transient ischemic attack, TTR - time in target therapeutic range

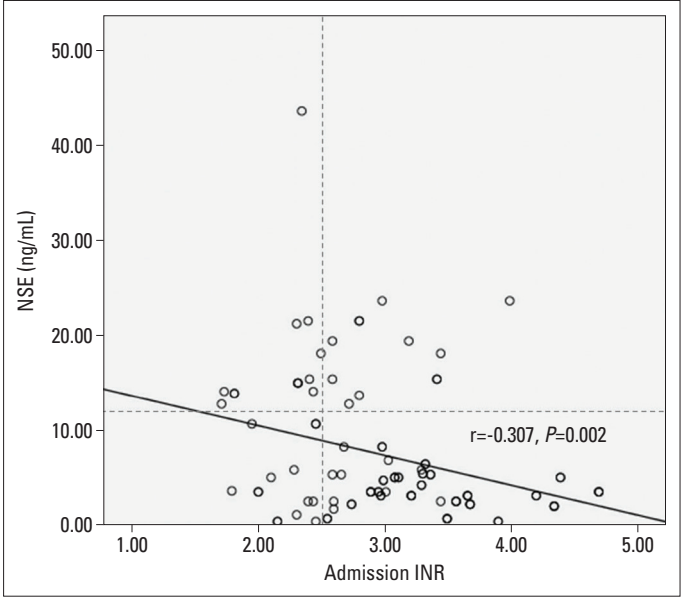


**Figure 1.** Scatterplot analysis of admission INR against NSE level. The perpendicular dotted line represents the cut-off value of 2.5 for INR and horizontal dotted line represents the cut-off value of 12 ng/mL for NSE
NSE - neuron-specific enolase, INR - international normalized ratio

**Table 2. Independent predictors of SCI in binary logistic regression analysis**

| | OR (95%, CI) | *P* value |
|---|---|---|
| Age | 1.017 (0.956-1.083) | 0.585 |
| Female sex | 2.254 (0.524–9.700) | 0.275 |
| Acetyl salicylic acid use | 0.095 (0.012–0.770) | 0.027 |
| Smoking | 10.798 (2.520–46.272) | 0.001 |
| TTR <60% | 6.896 (1.388–34.482) | 0.018 |
| Ineffective INR at the NSE control visit | 7.725 (1.966–30.347) | 0.003 |
| Left atrium diameter | 6.763 (2.253–20.302) | 0.001 |

CI - confidence interval, OR - odds ratio, NSE - neuron-specific enolase, EF - ejection fraction, INR - International normalized ratio, TTR - time in target therapeutic range

## Discussion

In the current study, we evaluated 103 outpatients with a mechanical PMV and found that a substantial number of them (24%) had an NSE elevation, suggestive of a recent SCI. The presence

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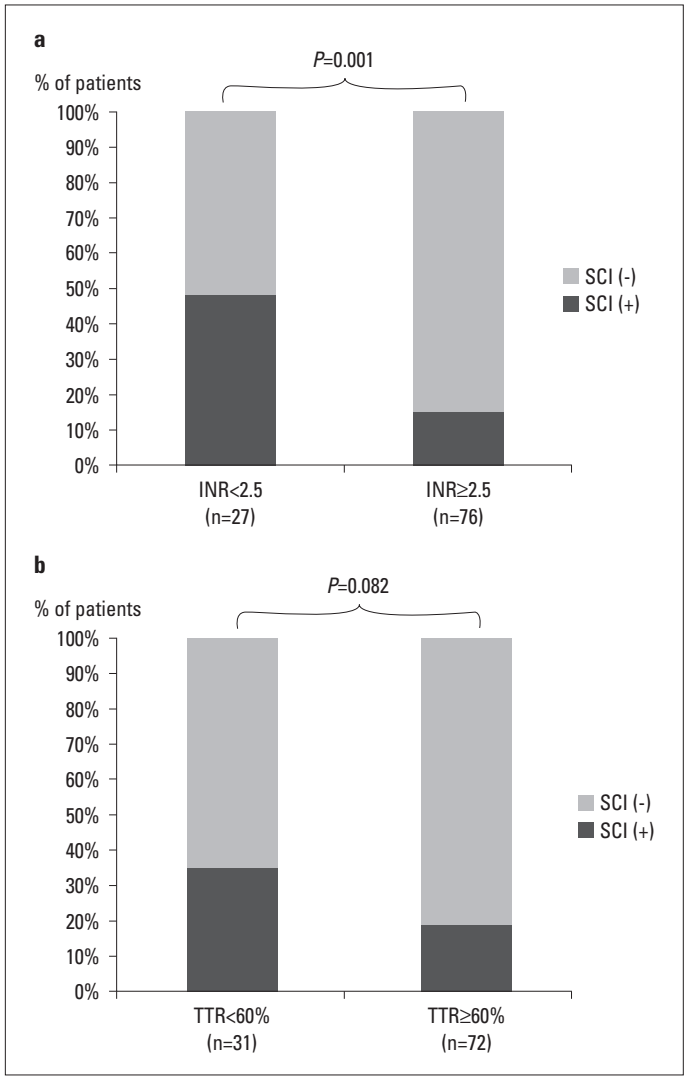


**Figure 2.** Presence of SCI with regard to the quality of anticoagulation. (a) with regard to admission INR. (b) with regard to TTR
SCI - silent cerebral infarct, INR - international normalized ratio, TTR - time in target therapeutic range

of SCI was significantly associated with poor quality of anticoagulation determined by the lower INR and TTR values in this group. To the best of our knowledge, this is the first study showing evidence of recent SCI in patients with PMV.

Embolic stroke is a devastating complication for patients with PMV (1). On the other hand, clinically overt thromboembolic complications may be the tip of the iceberg and these patients could be facing a significant burden of asymptomatic embolic complications, known as SCI. Accumulating evidence suggests that SCIs may lead to cognitive decline, dementia, and depression (14). Furthermore, several studies have demonstrated the important prognostic implication of SCIs for future stroke risk, which was more than threefold in the Rotterdam Scan Study (15). Recent studies claim that SCI is common among patients with underlying heart diseases such as atrial fibrillation, heart failure, and coronary artery disease (16-18). However, we were not able to find any study regarding the prosthetic heart valves, except one computed tomography trial suggesting a 37.5% prevalence of SCI in patients presenting with mechanical heart valve thrombosis (19). In our trial, where patients with valve thrombosis were excluded, one fourth of patients with PMV had an NSE elevation, suggestive of SCI. However, since NSE does not provide any information conerning SCIs older than 2–3 days, we were able to only detect recent SCIs. Thus, these results do not rule out the possibility that some of our patients without an NSE elevation may have had SCIs in the past.

Our data revealed that the quality of anticoagulation was significantly associated with SCI occurence. TTR is a quality measure for relatively long-term anticoagulation care, whereas admission INR provides information about the level of anticoagulation at a given point. It is therefore not surprising for us to observe that TTR was not a strong predictor of recent SCI, while admission INR was a strong predictor. On the other hand, nearly half of our patients with SCI had therapeutic INR levels on admission. Thus, the recommended INR levels for preventing clinically overt stroke may not be optimal for preventing silent thromboembolic events. Apart from the level of anticoagulation, other mechanisms are involved in the etiopathogenesis of valve thrombosis. Corpuscular blood components and plasma interact at the molecular level with prosthetic surfaces, and a turbulent flow and an increase in shear stress may lead to thrombosis (20). In our trial, patients with hemodynamically significant valvular dysfunction were excluded to minimize the potential impact of this mechanism. It has been previously shown that aggregates of red blood cells and platelets on mechanical valves may lead to chronic exposition to microemboli, and aspirin was shown to reduce these microembolic events (2, 21, 22). Recently, Maestrini et al. (23) postulated that low-dose aspirin might improve cerebrovascular outcomes in patients with silent brain infarcts. In line with this data, we found that using aspirin was significantly associated with a lower prevalence of SCI. Indeed, recent guidelines recommend the addition of aspirin to warfarin only in cases with TIA or stroke, despite the therapeutic levels of anticoagulation (9). Currently, there are no suggestions regarding the treatment of silent infarcts.

The findings of this study have to be interpreted in the light of some limitations. First of all, NSE is known to be a surrogate marker, and our diagnosis of SCI was not confirmed by an imaging modality. However, NSE is suggested to be a valid biomarker for the degree of neuronal injury and has a good correlation with MRI, which is the gold standard for the diagnosis of SCI (6, 24, 25). The patients in our study had their standard transthoracic echocardiographic controls in the outpatient clinics and those needing further evaluation with transesophageal or 3D echocardiography for valvular dysfunction were excluded. Therefore, we could not obtain further detailed echocardiographic valvular parameters because of the design of our trial. Another limitation of our study was the relatively small sample size.

## Conclusion

In conclusion, our study suggests that silent brain infarcts are very prevalent among patients with PMV, as one fourth of them had the event during their routine outpatient visit. Poor quality of anticoagulation partly explains this increase in prevalence.

**Conflict of interest:** None declared.

**Peer-review:** Externally peer-reviewed.

**Authorship contributions:** Concept – N.Ö., S.G.; Design – N.Ö., S.G., H.G.; Supervision – S.G., E.T.; Fundings – N.Ö., S.G., E.T.; Materials – N.Ö., H.G., K.E.; Data collection and/or processing – N.Ö., H.G., K.E.; Analysis and/or interpretation – N.Ö., S.G., H.G., K.E.; Literature search – N.Ö., K.E.; Writing – N.Ö., S.G., E.T.; Critical review – S.G., E.T.

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