

**Incidence of seizures following initial ischemic stroke in a community-based cohort: The Framingham Heart Study.**

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**Highlights**

- The incidence of seizures following an ischemic stroke is 5%.

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- The majority of post-stroke seizures occur within the first 24 hours after a stroke.
- Lower rates of seizure-free survival are seen with higher disability after stroke.

**Abstract:**

**Purpose:** We examined the incidence of seizures following ischemic stroke in a community-based sample.

**Methods:** All subjects with incident ischemic strokes in the Framingham Original and Offspring cohorts between 1982 and 2003 were identified and followed for up to 20 years to determine incidence of seizures. Seizure-type was based on the 2010 International League Against Epilepsy (ILAE) classification. Disability was stratified into mild/none, moderate and severe, based on post-stroke neurological deficit documentation according to the Framingham Heart Study (FHS) protocol and functional status was determined using the Barthel Index.

**Results:** An initial ischemic stroke occurred in 469 subjects in the cohort and seizures occurred in 25 (5.3%) of these subjects. Seizure incidence was similar in both large artery atherosclerosis (LAA) (6.8%) and cardio-embolic (CE) (6.2%) strokes. No seizures occurred following lacunar strokes. The predominant seizure type was focal seizure with or without evolution to bilateral convulsive seizure. One third of participants had seizures within the first 24 hours from stroke onset and half of all seizures occurred within the first 30 days. On multivariate analysis, moderate and severe disability following stroke was associated with increased risk of incident seizure.

**Conclusions:** Seizures occurred in approximately 5% of subjects after an ischemic stroke. One third of these seizures occurred in the first 24 hours after stroke and none followed lacunar strokes. Focal seizures with or without evolution in bilateral convulsive seizures were the most common seizure type. Moderate and severe disability was predictive of incident seizures.

## **Introduction:**

Stroke is the leading cause of neurological disability in the United States and ranks third behind cancer and cardiovascular disease as a cause of death (1). Stroke is a major cause of seizures in midlife and in the elderly (2); in Rochester, Minnesota, over a 33-year follow up period, cerebrovascular disease was identified as the etiology of epilepsy in about 25% of patients with an identified cause to their seizures (3) and in the National General Practice Study of Epilepsy in the UK, stroke accounted for about half of all cases among older individuals (4). Seizures immediately following stroke, are associated with increased resources utilization, prolonged length of hospital stay and increased mortality (5). Furthermore, seizures in older individuals have a negative impact on quality of life through driving restrictions, increased risk of falls and fractures and increased susceptibility to adverse effects from the use of anti-epileptic drugs (6, 7).

Numerous studies have evaluated seizure occurrence following stroke and have reported varying estimates of seizure incidence (8-25). The wide variance in the reported incidence of post-stroke seizures has been attributed to methodological differences among studies that include prospective vs retrospective study designs, heterogeneous source populations, stroke subtypes (hemorrhagic, ischemic, lacunar strokes and transient ischemic attacks), timing of seizures (early vs late), ambiguities in seizure classification and varying length

of follow-up (22, 26). Stroke-related disability and seizure occurrence has been addressed infrequently (5, 25, 27, 28) and occasionally without the use of a validated functional status rating scale (17). In addition, some early studies were in the pre- computed tomography (CT) era and radiological confirmation of stroke was unavailable (29, 30). Most studies have reported higher seizure rates following cerebral hemorrhage compared to ischemic stroke (22, 31, 32); however ischemic infarctions are more common (26, 33), thus accounting for a large proportion of the seizures after stroke. We examined the incidence and risk factors for seizures after ischemic stroke in a prospective, longitudinal, community-based cohort with long follow-up.

## Methods

**Study Population:** Subjects were recruited to the Framingham Heart Study, a longitudinal, community-based cohort, in two phases. The Original Cohort, was recruited in 1948 (34) while their offspring and spouses were recruited in 1971 as the Offspring Cohort (35). The Original Cohort was evaluated biennially and the Offspring every 4-8 years since recruitment. Our study population included all subjects who were alive and stroke-free as of January 1982, in both the Original (n= 2,858; 1774 female; mean age: 73 years) and Offspring Cohorts (n= 4,291; 2267 female; mean age: 53 years). All subjects who suffered an ischemic stroke between 1982 and 2003 were identified (n=472) and those with a history of seizures predating their stroke were excluded (n=3). A total of 469 subjects (287 female; mean age: 82 years) were included in our analyses.

The study was approved by the institutional review board at Boston University and all subjects provided informed consent.

**Subtypes of ischemic strokes and seizures:** Ischemic stroke was defined as a focal neurological deficit of presumed vascular cause with a sudden onset and lasting for at least 24 hours, in the

absence of an intracranial hemorrhage (diagnosed by CT when available, or laboratory results, clinical information or autopsy findings when CT was not available) or other brain disorder that could cause focal neurological deficits. When a CT scan was available and demonstrated an ischemic infarction, the location of the lesion was correlated with the documented clinical deficit. Ischemic stroke subtypes were categorized into atherosclerotic brain infarction further divided into a) large-artery atherothrombosis (LAA) and b) lacunar infarction and infarctions secondary to cerebral embolus (CE) from a documented cardiac source (36) .

Seizure was defined as “a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain” (37) and seizure types were divided into focal and generalized, according to the 2010 ILAE Commission on Classification and Terminology report (38) based on their documented semiology. Early seizures (ES) were defined as occurring within 30 days and late seizures (LS) as occurring 30 days or more after the initial ischemic infarction.

**Post-stroke disability/functional status:** Disability was based on the observed deficits at the initial examination post-stroke and was stratified into three categories according to a protocol used in the FHS over the past 4 decades. “None/mild”: Lack of any deficit or an isolated deficit in visual, communication, motor, and/or sensory domains that does not affect functional independence; “moderate”: deficits requiring assistance in any one of the aforementioned domains, and “severe”: functional dependence on others in 2 or more domains. Functional status was assessed based on performance in activities of daily living (ADL) with the use of the Barthel Index [BI] (39), a scale that utilizes a 100 point rating, with zero reflecting the least favorable and 100 the most favorable outcome.

**Case ascertainment:** FHS stroke assessment and surveillance has been detailed elsewhere (40) but will be briefly outlined here. All persons with an incident clinical stroke between 1982 and 2003 were identified by surveillance of both clinic visits and hospital admissions. Clinicians used structured questionnaires to elicit a history of stroke symptoms at each examination. If participants reported a history suggestive of stroke a FHS neurologist evaluated them. Hospital-based surveillance was also maintained by daily monitoring of hospital admissions at the sole acute care hospital in Framingham, Massachusetts. Additional stroke surveillance was obtained by annual telephone health updates, as well as by collaboration with primary care physicians and local emergency departments.

At least one cranial CT scan was obtained in 85% of all participants with an incident stroke (41). A panel of three investigators, of whom at least two were vascular neurologists, made a final determination regarding the diagnosis and classification of stroke.

To identify seizures in participants with an incident ischemic stroke, a neurologist reviewed the charts, the FHS stroke review cards, follow-up visit and clinic examination histories, standardized questionnaires and emergency department documentation to identify any history of a seizure or seizure-like episode. If such a history was present, all additional clinical information available at the time of this event was also reviewed including laboratory, neuroimaging, and EEG studies. Data regarding antiepileptic medication administration were also obtained. Based on the above information the neurologist made a clinical diagnosis of seizure.

**Follow-up:** Since January 1982 all participants with incident stroke have been followed utilizing a standardized assessment protocol: in-hospital assessment within 48 hours of stroke onset whenever feasible, and thereafter follow-up assessments at 3, 6, 12 and 24 months post-stroke.

A detailed history (including history regarding incident seizures), neurological examination, and assessments of neurological and functional status were completed at each evaluation.

Participants who had recurrent strokes continued to be followed. All new-onset seizure events that occurred after the date of stroke were recorded through December 2003. Non-events were censored at the last available study examination or health status update at date of death, or in December 2003 if still alive and seizure-free.

### **Statistical Analysis**

Our primary outcome variable was incidence of seizure following ischemic stroke. We also abstracted age at stroke and at seizure onset, sex, hemispheric lateralization of the vascular lesion, and level of disability/functional status. Ischemic strokes were classified as detailed above. Using Kaplan- Meier techniques we calculated years of seizure-free survival post-stroke by level of disability, based on the stratification detailed above. Using incident seizures as our primary dependent variable we used a Cox- regression model, adjusted for age and sex, to assess the impact of age, sex, stroke type, hemispheric lateralization, level of disability and functional status based on stratified BI (>60 mild/moderate dependence, < 60 severe dependence) on the risk of developing seizures. All analyses were performed on PC-SAS software 9.1 (SAS Institute, Inc).

### **Results:**

A total of 469 participants developed an ischemic stroke during the study period. Large artery atherosclerosis was the most frequent stroke mechanism, accounting for just over half of all strokes (n= 242, 51.5%), followed by CE (n= 148, 31.5%,) and lacunar (n=79, 17%) strokes. The follow-up ranged between 1 and 20 years (mean 12 years) during which 25 (5.3 %) participants had a first-time seizure.

### **Seizure incidence by stroke type**

Data regarding overall, early, and late seizure incidence by stroke type is presented in Table I. No seizures occurred following lacunar strokes. The rate of seizure occurrence after CE (n= 10, 6.2%) and LAA strokes (n=15, 6.8%) was similar and there was no significant associations seen when the subgroups of early and late seizures were further analyzed.

### **Seizure type by stroke type**

The most common overall seizure type was focal onset seizure, with or without evolution in bilateral convulsive seizure (n=18, 72%). In the LAA group 13 out of 15 seizures (n=10) were focal at onset, while in the CE group equal number of patients had focal at onset and generalized seizures (Figure 1).

### **Seizure incidence relative to time from initial stroke**

Nine participants (36%) had seizures within the first twenty-four hours with an additional 3 participants (12%) having a seizure within the first month. Of the remaining 13 seizures, 5 subjects had a seizure within one and twelve months (20%) and 8 participants experienced seizures more than a year after stroke (32%). Figure 2 demonstrates seizure incidence relative to time after the initial stroke.

### **Disability from stroke and seizure incidence**

Lower rates of seizure-free survival are seen with higher levels of disability after stroke. Seizures were significantly associated with moderate (hazard ratio (HR): 4.33; 95% CI: 1.28-14.64; p= 0.019) and severe disability (HR: 9.71; CI: 3.01-31.34; p<0.001), as well as with BI scores less than 60 (HR: 5.39; CI: 2.14- 13.56; p<0.001). No other risk factors were significantly associated with seizure incidence. Figure 3 provides information regarding Kaplan- Meier



analysis of seizure-free survival based on level of disability. Table II provides information regarding Cox regression analysis (adjusted for age and sex) with incident seizure as the dependent variable.

### **Discussion:**

Our community-based, prospective cohort study demonstrated a 5% seizure incidence after ischemic stroke, concordant with previous findings in both older (8, 9, 32) and younger individuals (ages 18-55 years)(42).

Prior studies have divided seizures after stroke into early (ES) and late onset seizures (LS). ES were defined as those occurring within 24-48 hours (9, 43), 1 week (11, 22, 27, 42, 44), 2 weeks (8, 17, 18, 45) and 30 days (18) after stroke. Reported ES incidence ranges from 2.2 to 33% (8, 9, 11, 17, 19, 31, 42-46), reflecting the different ES definitions used. In our study, ES incidence was 2.5% and two thirds occurred in the first 24 hours. Greater stroke severity at presentation has been linked to a higher risk of ES (25, 28) and the presumed mechanism is enhanced cortical excitability within a larger penumbra (46) and is supported by evidence of peri-infarct electrical depolarizations recorded in the stroke penumbra in animal models (47). LS have been defined as those occurring at least a week after the initial stroke, but exact definitions differ and subsequently reported incidence varies between 3% and 67% in the literature (8, 9, 11, 17, 42-45). LS occurred in 2.7% of our cases. Dichotomizing seizures after stroke into early and late seizures has a biological basis. Early seizures are thought to occur secondary to a cascade of pro-excitatory cellular changes that follow acute ischemic neuronal injury and include glutamate release (26) and accumulation of intracellular  $\text{Ca}^{++}$  and  $\text{Na}^{+}$ , that promote membrane depolarizations and lower seizure threshold (22). Pathophysiological processes underlying late onset seizures are less well understood and may include development

of a cortico-meningeal or post-stroke gliosis (48). Other suggested mechanisms include the pyramidal or interneuron cells (49), altered GABAergic transmission (50), axonal sprouting (49, 51), and effects of hemosiderin.

In our study the majority of seizures were focal in onset 72% (n=18), regardless of stroke type or time of seizure occurrence in concordance with prior studies, (19, 32, 42, 44). These findings are not surprising given the accepted hypothesis that the focal lesion following an infarction acts as the seizure focus and it is argued that even in the case of generalized, by semiology, seizures a fast bilateral spread from a focal seizure generator cannot be ruled out.

We classified strokes using the Framingham Heart Study criteria (36) and there was no difference in total seizure incidence between the LAA and CE groups. There is conflicting evidence in the literature and several studies have suggested that strokes of a cardio-embolic etiology carry a higher risk (20, 52, 53) compared to atherosclerosis. Among the few population-based studies this was only confirmed in the Rochester, Minnesota cohort, where embolic stroke was an independent risk factor ( $p=0.03$ ) for early post-stroke seizures (11). Other studies have not shown an increased risk (8, 31, 54-56) and our study offers further evidence in that direction, even when long follow-up is available. No seizures occurred following lacunar strokes, which by definition occur in areas remote from the cerebral cortex, the likely site of epileptogenesis, a finding also previously reported (21).

Stroke severity, disability and functional status after stroke have been studied as a predictor of subsequent seizures. We found that moderate and severe disability after stroke predicted a higher risk of seizure. In the Copenhagen Stroke Study, subjects with ES had more severe stroke than those without ES (53), and Arntz et al. showed that high NIHSS was a significant predictor of post-stroke epilepsy among young stroke survivors (24). Kilpatrick et al

demonstrated no significant difference in functional status between those with and without early seizures, however the authors used a non-standardized neurological index to determine functional status (17). The correlation of neurological disability with post-stroke seizure incidence may represent a proxy measure for the size of an ischemic stroke. Although we did not evaluate size of ischemic lesion, prior studies have demonstrated a significant correlation between lesion volume and seizure incidence (8, 25, 26, 45).

The strengths of our study include the documentation of all strokes in a community-dwelling population-based cohort study and long duration of follow-up of the participants with thorough and established surveillance. The diagnosis and classification of stroke and seizures, and the determination of the level of disability post-stroke were all completed using validated instruments and classification systems. The main limitation of this study is the ethnic homogeneity of our population of primarily European descent, thus precluding generalizability of our conclusions, and the overall low number of incident seizures. Another limitation of an observational cohort study design, like the FHS, is that certain diagnostic procedures, like EEGs to rule out subclinical seizure activity (57), or serial CTs to rule out hemorrhagic transformation of an ischemic stroke (22), were not routinely obtained based on a specific post-stroke diagnostic protocol. This data was overall sparse in our sample and we have not included it in our analysis of post-stroke seizure predictors.

In conclusion, we documented a 5% rate of post ischemic stroke seizures. The majority of seizures was of focal onset and occurred within 24 hours of stroke. Stroke severity was associated with a higher risk of subsequent seizures. Although seizures may occur in a small proportion of patients after ischemic stroke, these patients are likely to have more severe disability and worse functional status during post-stroke rehabilitation

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Conflicts of Interest/ Disclosures: Nothing to disclose for all authors

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**List of Figures:**

**Figure 1:** Seizure Incidence by Seizure and Stroke Type.

LAA= large artery atherosclerosis, CE= Cardio Embolic

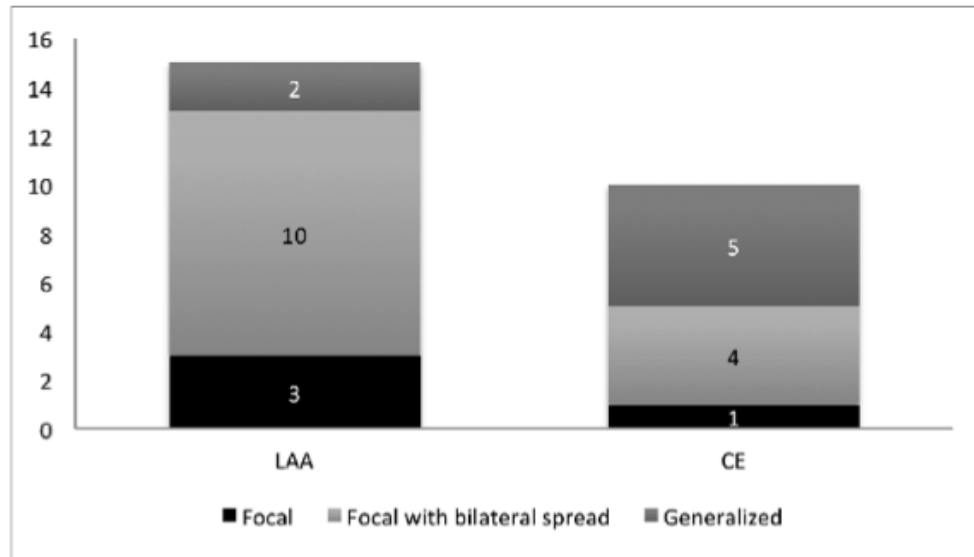
**Figure 2:** Seizure Incidence by Time after Stroke and Type of Stroke.

LAA= large artery atherosclerosis, CE= Cardio Embolic

**Figure 3:** Post-Stroke Seizure-Free Survival by Level of Disability.

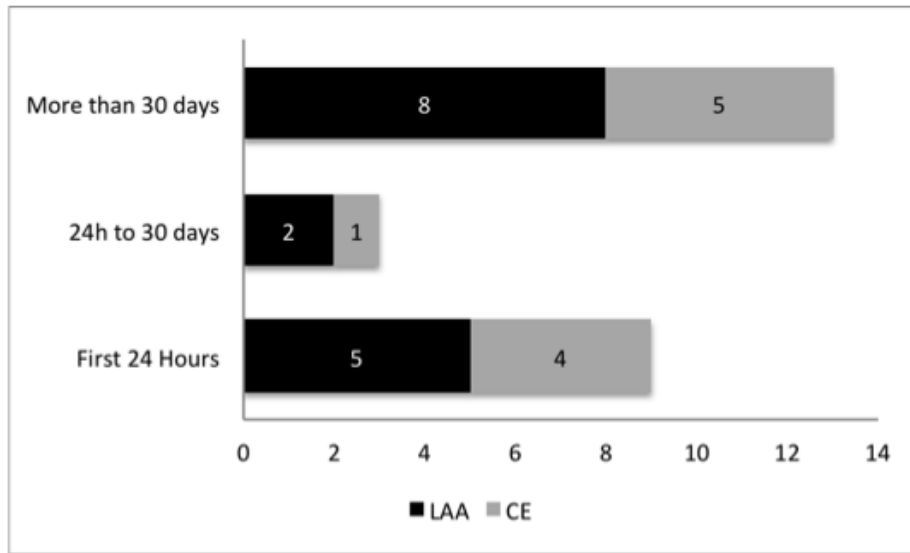


Figr-1



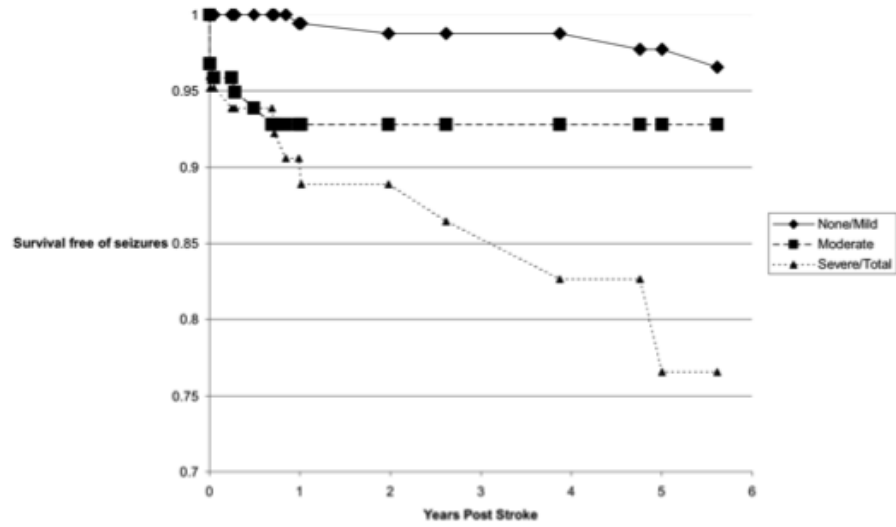
**Figure 1** Seizure Incidence by Seizure and Stroke Type.  
LAA= Large artery atherosclerosis, CE= Cardio Embolic

Figr-2



**Figure 2** Seizure Incidence by Time After Stroke and Type of Stroke.  
LAA= Large artery atherosclerosis, CE= Cardio Embolic

Figr-3

**Figure 3** Post-Stroke Seizure-Free Survival by Level of Disability

**Table 1:** Seizure Incidence by Stroke Type

<b>Stroke Subtype</b>	<b>Subjects with seizures/No of strokes (%)</b>	<b>Subjects with early seizures</b>	<b>Subjects with late seizures</b>
<b>Large artery atherosclerosis</b>	15/242 (6.2%)	7/242 (2.8%)	8/242 (3.3%)
<b>Cardio-embolic</b>	10/148 (6.8%)	5/148 (3.3%)	5/148 (3.3%)
<b>Lacunar</b>	0/79 (0%)	0/79 (0%)	0/79 (0%)
<b>Total</b>	25/469 (5.3%)	12/469 (2.5%)	13/469 (2.7%)

**Table 2:** Association Between Post-Stroke Disability and Seizure Incidence

Variable	Subjects with Seizures/ Total Number of seizures	Percentage (%)	p	Cox regression adjusted for age and sex	
				HR (95% CI)	p
<b>Sex:</b>					
Male	9/182	5.0	0.767		
Female	16/287	5.6			
<b>Age:</b>					
< 75 yrs	6/147	4.1	0.416		
≥ 75 yrs	19/322	5.9			
<b>Stroke Type:</b>					
LAA*	15/242	6.2	0.067		
CE†	10/148	6.8			
Lacunar	0/79	0.0			
<b>Stroke Hemisphere:</b>					
Left	14/216	6.5	0.783		
Right	11/189	5.8			

<b>Disability:</b>					
None/ Mild	4/199	2.0			
Moderate	8/123	6.5	0.005	4.33 (1.28-14.64)	0.019
Severe	13/124	10.5		9.71 (3.01-31.34)	<0.001
<b>Barthel Index</b>					
> 60	7/248	2.8			
			0.003		
≤ 60	18/193	9.3		5.39 (2.14-13.56)	< 0.001

\* LAA= Large artery atherosclerosis

†CE= Cardio embolism