Temporal relationship between infective endocarditis and stroke

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ABSTRACT

Objective: Stroke frequently complicates infective endocarditis (IE). However, the temporal relationship between these diseases is uncertain.

Methods: We performed a retrospective study of adult patients hospitalized for IE between July 1, 2007, and June 30, 2011, at nonfederal acute care hospitals in California. Previously validated diagnosis codes were used to identify the primary composite outcome of ischemic or hemorrhagic stroke during discrete 1-month periods from 6 months before to 6 months after the diagnosis of IE. The odds of stroke in these periods were compared with the odds of stroke in the corresponding 1-month period 2 years earlier, which was considered the baseline risk of stroke.

Results: Among 17,926 patients with IE, 2,275 strokes occurred within the 12-month period surrounding the diagnosis of IE. The risk of stroke was highest in the month after diagnosis of IE (1,640 vs 17 strokes in the corresponding month 2 years prior). This equaled an absolute risk increase of 9.1% (95% confidence interval 8.6%–9.5%) and an odds ratio of 96.5 (95% confidence interval 60.1–166.0). Stroke risk was significantly increased beginning 4 months before the diagnosis of IE and lasting 5 months afterward. Similar temporal patterns were seen when ischemic and hemorrhagic strokes were considered separately.

Conclusions: The association between IE and stroke persists for longer than previously reported. Most diagnoses of stroke and IE are made close together in time, but a period of heightened stroke risk becomes apparent several months before the diagnosis of IE and lasts for several months afterward. *Neurology*® 2015;85:512–516

GLOSSARY

CI = confidence interval; **ED** = emergency department; **ICD-9-CM** = *International Classification of Diseases, Ninth Revision, Clinical Modification*; **IE** = infective endocarditis; **OR** = odds ratio.

Infective endocarditis (IE) occurs in 1.7 to 6.2 per 100,000 people per year in the United States and Europe.¹ Stroke often complicates IE, affecting approximately 16% to 25% of patients with IE.^{2,3} Cerebral embolism heralding or following a diagnosis of IE substantially increases morbidity and mortality.^{3–5} However, knowledge is limited regarding the time period during which patients with IE face a heightened stroke risk, with reports ranging from as early as 40 days before IE is recognized to as late as 5 weeks after the start of antibiotic treatment.^{3,4,6–8} Recent data suggest that IE may increase stroke risk for even longer periods of time, as one European cohort study reported that patients had a moderately increased risk of embolic events up to 180 days after community-acquired bacteremia.⁹ We hypothesized that the risk of stroke in the setting of IE persists for longer than current data suggest. Therefore, we sought to better delineate the time period during which patients diagnosed with IE face an increased stroke risk.

METHODS Study design. We performed a retrospective study of the temporal relationship between IE and stroke diagnoses using administrative claims data from California. The California Office of Statewide Health Planning and Development collects data about all emergency department (ED) visits and hospital stays at nonfederal acute care hospitals in California. After quality checking, these data are provided in a deidentified format to the Agency for Healthcare Research and Quality for its Healthcare Cost and Utilization

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Project.¹⁰ A unique record linkage number for each patient allows longitudinal tracking of ED encounters and hospitalizations.¹¹ Because this publicly available database includes only deidentified data, our institutional review board certified our study as exempt from review.

Patients. We identified all patients hospitalized with IE between July 1, 2007, and June 30, 2011, using the following previously validated *ICD-9-CM* codes for infective endocarditis: 421.0 (acute and subacute infective endocarditis), 421.1 (endocarditis, valve unspecified, in diseases classified elsewhere), 421.9 (acute endocarditis, unspecified), and 424.9 (endocarditis, valve unspecified). These codes have been frequently used in prior studies of endocarditis and have a positive predictive value of 81% and a sensitivity of 93%^{12–16} for IE based on the modified Duke criteria.¹⁷ Patients younger than 18 years of age were

excluded because IE in children has been recognized as a different clinical entity from IE in adults, associated with different predisposing factors (e.g., congenital heart disease) and presenting far less often with extracardiac manifestations.¹⁸ To maximize our ability to assess follow-up ED visits and admissions, we excluded patients who were not California residents.

Outcomes. In accordance with a validated algorithm, ischemic stroke was defined as *ICD-9-CM* codes 433.x1, 434.x1, or 436 in any diagnosis code position in the absence of a primary discharge code for rehabilitation (V57) or any codes for subarachnoid hemorrhage (430), intracerebral hemorrhage (431), or trauma (800–804 and 850–854).¹⁹ Hemorrhagic stroke was defined by the presence of discharge codes for intracerebral hemorrhage (431) or subarachnoid hemorrhage (430) in the absence of a primary discharge code for rehabilitation (V57) or trauma (800–804 and 850–854). This algorithm has been validated to have a sensitivity of $\geq 82\%$ and a specificity of $\geq 93\%$ for both ischemic and hemorrhagic stroke subtypes.¹⁹ To focus on incident diagnoses, we included only the first recorded diagnosis of IE or stroke. In our primary analysis, we included all ischemic and hemorrhagic strokes; in secondary analyses, we considered ischemic strokes separately from hemorrhagic strokes.

Statistical analysis. We determined the odds of first-recorded stroke hospitalizations during 1-month periods from 6 months before to 6 months after IE as compared with the corresponding 1-month period 2 years earlier. In a sensitivity analysis, we used the corresponding 1-month periods starting 1 year earlier. This design allowed us to compare the risk of stroke during the period surrounding the diagnosis of IE in relation to each patient's baseline risk of stroke well before developing IE. Since we had data from January 1, 2005, through December 31, 2011, we excluded patients with a first-recorded IE diagnosis before July 1, 2007, or after June 30, 2011, so as to have full data on the 6 months before and after the IE diagnosis and the accompanying time period 2 years prior. Absolute risks and odds ratios (ORs) were calculated using a Mantel-Haenszel estimator for matched data. The *p* values were not adjusted for multiple comparisons. All statistical analyses were performed with Stata/MP, version 13 (StataCorp, College Station, TX).

RESULTS Among 17,926 patients with IE, 2,275 developed a stroke during the 12-month period surrounding the diagnosis of IE. Of these patients, 1,877 (82.5%) had an ischemic stroke diagnosis, 312 (13.7%) had a hemorrhagic stroke diagnosis, and 86 (3.8%) had a concurrent ischemic and hemorrhagic stroke diagnosis. Patients with stroke more often had vascular risk factors and markers of more severe IE (table 1). Stroke risk was highest in the month following the diagnosis of IE as compared with the same 1-month period 2 years earlier (1,640 events vs 17). This corresponded to an absolute increase in risk of 9.1% (95% confidence interval [CI] 8.6%–9.5%) and an OR of 96.5 (95% CI 60.1–166.0) (table 2). The risk of stroke was significantly elevated from the fourth month before the IE diagnosis (OR 3.1; 95% CI 1.6–6.5) through the fifth month afterward (OR 2.6; 95% CI 1.4–5.2) (figure) (table 2).

Table 1 Baseline characteristics of patients with infective endocarditis, stratified by the occurrence of stroke^a

Characteristic	Stroke (n = 2,275)	No stroke (n = 15,651)	<i>p</i> Value
Age, mean (SD), y	65.2 (16.0)	65.9 (17.5)	0.08
Female	1,031 (45.3)	7,024 (44.9)	0.69
Race			0.05
White	1,326 (60.7)	9,540 (63.4)	
Black	258 (11.8)	1,501 (10.0)	
Hispanic	404 (18.5)	2,647 (17.6)	
Asian	165 (7.6)	1,108 (7.4)	
Other	33 (1.5)	249 (1.7)	
Payment source			<0.001
Medicare	1,301 (57.2)	9,549 (61.0)	
Medicaid	319 (14.0)	2,153 (13.8)	
Private insurance	533 (23.4)	2,868 (18.3)	
Self-pay	62 (2.7)	437 (2.8)	
Other	60 (2.6)	644 (4.1)	
Vascular risk factors			
Hypertension	1,483 (65.2)	9,845 (62.9)	0.04
Diabetes	839 (36.9)	5,366 (34.3)	0.02
Coronary heart disease	816 (35.9)	5,358 (34.2)	0.13
Congestive heart failure	793 (34.9)	6,097 (39.0)	<0.001
Peripheral vascular disease	313 (13.8)	1,658 (10.6)	<0.001
Chronic kidney disease	720 (31.7)	4,731 (30.2)	0.17
Chronic obstructive pulmonary disease	272 (12.0)	2,677 (17.1)	<0.001
Atrial fibrillation	720 (31.7)	4,330 (27.7)	<0.001
Markers of illness severity			
Sepsis	1,381 (60.7)	7,679 (49.1)	<0.001
Valve surgery	193 (8.5)	687 (4.4)	<0.001
Mechanical ventilation	584 (25.7)	1,880 (12.0)	<0.001
Elixhauser comorbid conditions, mean (SD), no.	4.6 (2.1)	4.2 (2.2)	<0.001

Data are presented as no. (%) unless otherwise specified.

^aStroke was defined as the first occurrence of a diagnosis of ischemic or hemorrhagic stroke within 6 months before or after the first occurrence of a diagnosis of infective endocarditis.

Table 2 OR and absolute risk of stroke for 1-month intervals before and after the diagnosis of IE

Time interval from IE, mo	OR (95% CI)			Absolute risk of stroke (%) (95% CI)		
	All strokes	Ischemic strokes	Hemorrhagic strokes	All strokes	Ischemic strokes	Hemorrhagic strokes
−6	1.8 (0.9–3.5)	1.8 (0.9–4.1)	1.8 (0.4–8.2)	0.07 (−0.01–0.15)	0.06 (−0.01–0.13)	0.02 (−0.03–0.06)
−5	1.5 (0.8–3.0)	1.4 (0.7–2.9)	3.0 (0.5–30.4)	0.05 (−0.03–0.13)	0.03 (−0.04–0.10)	0.02 (−0.01–0.06)
−4	3.1 (1.6–6.5)	2.9 (1.5–6.2)	3.0 (0.2–157.5)	0.14 (0.06–0.22)	0.13 (0.05–0.21)	0.01 (−0.01–0.03)
−3	4.8 (2.6–9.9)	4.0 (2.1–8.3)	12 (1.8–514.0)	0.26 (0.16–0.35)	0.20 (0.11–0.29)	0.06 (0.02–0.10)
−2	6.9 (3.9–13.5)	7.3 (3.8–15.9)	6.3 (1.9–33.4)	0.43 (0.31–0.55)	0.35 (0.25–0.46)	0.09 (0.03–0.15)
−1	11.6 (7.1–20.4)	11.9 (7.0–21.6)	9.0 (2.8–46.4)	1.0 (0.84–1.17)	0.90 (0.75–1.06)	0.13 (0.07–0.20)
+1	96.5 (60.1–166.0)	80.9 (50.4–139.4)	321 (57.2–12,712)	9.05 (8.62–9.48)	7.58 (7.18–7.98)	1.79 (1.59–1.98)
+2	8.1 (3.9–19.6)	6.8 (3.2–16.4)	20 (3.2–829.0)	0.32 (0.22–0.42)	0.26 (0.17–0.35)	0.11 (0.05–0.16)
+3	2.5 (1.3–5.3)	2.3 (1.1–4.9)	12.0 (1.8–513.0)	0.11 (0.03–0.19)	0.08 (0.01–0.16)	0.06 (0.02–0.11)
+4	2.2 (1.2–4.0)	1.9 (1.0–3.7)	6.0 (1.3–55.2)	0.12 (0.03–0.21)	0.08 (0–0.16)	0.06 (0.01–0.10)
+5	2.6 (1.4–5.2)	2.2 (1.1–4.5)	12.0 (1.8–513.0)	0.12 (0.04–0.21)	0.08 (0.01–0.16)	0.06 (0.02–0.11)
+6	1.5 (0.8–2.9)	1.2 (0.6–2.4)	6.0 (0.7–276.0)	0.04 (−0.03–0.12)	0.02 (−0.06–0.09)	0.03 (−0.01–0.6)

Abbreviations: CI = confidence interval; IE = infective endocarditis; OR = odds ratio.

Similar to all strokes, the risk of ischemic stroke was highest in the month after the IE diagnosis (1,376 events vs 17), corresponding to an absolute increase in risk of 7.6% (95% CI 7.2%–8.0%) and an OR of 80.9 (95% CI 50.4–139.4) (table 2). Ischemic stroke risk increased in the fourth month before the IE diagnosis (OR 2.9; 95% CI 1.5–6.2) and persisted through the third month afterward (OR 2.3; 95% CI 1.1–4.9) (table 2). A similar temporal pattern was found for hemorrhagic stroke, although the peak increase in absolute risk during the month after IE was more modest (1.8%; 95% CI 1.6%–2.0%)

than for ischemic stroke (table 2). Similar patterns were seen in sensitivity analyses in which the likelihood of stroke was compared with the same period 1 year earlier.

DISCUSSION Using a large, population-based cohort, we found that stroke risk began to increase approximately 4 months before a diagnosis of IE, peaked in the 1-month period after IE, and then attenuated and normalized by 5 months afterward. Ischemic stroke was much more common than hemorrhagic stroke, although both were dramatically increased (more than 80-fold) in the 1-month period after IE. The heightened stroke risk in the 1-month period after IE is consistent with the results of prior studies, which show that the majority of IE-related strokes occur in the immediate period surrounding IE diagnosis and treatment.³

Our results build on prior studies regarding the temporal association between stroke and IE. Previous reports describe strokes occurring up to 40 days before the diagnosis of IE and as late as 5 weeks after the initiation of antibiotics, but these studies were from significantly smaller cohorts.^{3,4,6} More recently, a European cohort study found a substantially increased risk of myocardial infarction or ischemic stroke within 30 days of community-acquired bacteremia and a modestly increased risk from 31 to 180 days after bacteremia.⁹ Although not all patients with bacteremia develop endocarditis, these results support our finding that IE increases stroke risk for longer periods of time than previously considered.

In addition to a prolonged period of increased stroke risk after the diagnosis of IE, we found that the stroke risk began to increase approximately 4

Figure Temporal relationship between infective endocarditis and stroke

Absolute increases in stroke risk during the 6 months before through 6 months after a diagnosis of infective endocarditis.

months before the IE diagnosis was established. In some cases, strokes occurring before the diagnosis of IE may be a manifestation of occult IE, particularly the subacute form.^{6–8} Other cases of stroke that precede IE may reflect the presence of shared risk factors for both stroke and IE, such as cardiac valve surgery, or poststroke risk factors that may predispose to IE, such as poststroke immunodepression or use of central venous catheters after stroke.^{20–25} The nature of our data prevents us from determining the mechanistic basis for these findings, but future analyses should aim to delineate the specific pathophysiologic processes underlying the complex relationship between IE and stroke.

The increased stroke risk before the diagnosis of IE supports a potential causal link between inflammation and stroke. Research has shown that inflammatory mechanisms contribute to the pathogenesis and progression of atherosclerosis, plaque rupture, and thrombotic events.^{26,27} Furthermore, inflammatory biomarkers such as high-sensitivity C-reactive protein have been identified as predictors of stroke in various populations.²⁸ Infections may contribute to inflammation and subsequently increase stroke risk. In addition, hospitalization for infection is associated with an elevated short-term risk of stroke,²⁹ and serologic evidence of chronic infection has been correlated with stroke risk.³⁰ In our cohort, preceding infections such as dental caries or sinusitis may have directly led to IE, but also could have increased stroke risk via inflammatory mechanisms.

Our study has several important limitations. First, our study design and the nature of our data precluded us from resolving the causal direction of the relationship between IE and stroke. Our results indicate that the temporal relationship between IE and stroke is more complex than currently appreciated, but further work is needed to elucidate the mechanisms at play. Second, our matched design relied on estimates of baseline stroke risk from 2 years before the diagnosis of IE, and it is therefore possible that our estimates of stroke risk were confounded by the interim effects of aging or the development of other illnesses unrelated to IE. We think this is unlikely to explain our findings because our results were not substantially changed in sensitivity analyses in which stroke risk was compared to a period 1 year before IE. Third, we lacked data on ambulatory visits, and therefore captured only cases of IE or stroke resulting in hospitalization. However, these serious illnesses would typically result in hospitalization, and therefore it is unlikely that we misascertained a significant number of diagnoses. Fourth, we were unable to resolve the temporal association of cases of IE and stroke that were diagnosed during the same hospitalization, and therefore the temporal extent of the association between IE and stroke may

be even more dispersed than we have found. Finally, because patients were identified using administrative claims data, we were unable to account for certain clinical information such as stroke mechanism, type and duration of antibiotic usage, type of valve replacement (bioprosthetic vs mechanical), temporal relationship between valve surgery and stroke, type of microorganism, and vegetation location and size.

We have found that the association between IE and stroke persists for longer than previously reported. The highest risk of stroke is in the 1 month following a diagnosis of IE, but a period of increased stroke risk becomes apparent several months before the diagnosis of IE and lasts for several months afterward.

AUTHOR CONTRIBUTIONS

Alexander E. Merkler conceived and designed the study, analyzed and interpreted the data, and drafted and revised the manuscript for intellectual content. Stacy Y. Chu designed the study, analyzed and interpreted the data, and drafted and revised the manuscript for intellectual content. Michael P. Lerario analyzed and interpreted the data, and revised the article critically for important intellectual content. Babak B. Navi designed the study, analyzed and interpreted the data, and revised the article critically for important intellectual content. Hooman Kamel designed the study, analyzed and interpreted the data, and revised the article critically for important intellectual content.

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DISCLOSURE

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